Advanced Drug Delivery Reviews 191 (2022) 114590

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/adr

Surface modification of two-dimensional layered double hydroxide nanoparticles with biopolymers for biomedical applications

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ARTICLE INFO

Article history:
Received 6 December 2021
Revised 24 May 2022
Accepted 25 October 2022
Available online 29 October 2022

Keywords:
Layered double hydroxide
Biopolymer
Nanocomposite
Surface modification
Carrier material

ABSTRACT

Layered double hydroxides (LDHs) are appealing nanomaterials for (bio)medical applications and their potential is threefold. One can gain advantage of the structure of LDH frame (i.e., layered morphology), anion exchanging property towards drugs with acidic character and tendency for facile surface modification with biopolymers. This review focuses on the third aspect, as it is necessary to evaluate the advantages of polymer adsorption on LDH surfaces. Beside the short discussion on fundamental and structural features of LDHs, LDH-biopolymer interactions will be classified in terms of the effect on the colloidal stability of the dispersions. Thereafter, an overview on the biocompatibility and biomedical applications of LDH-biopolymer composite materials will be given. Finally, the advances made in the field will be summarized and future research directions will be suggested.

Contents

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https://doi.org/10.1016/j.addr.2022.114590
0169-409X/

1. Introduction

Due to their variable, but well-defined structures, layered double hydroxides (LDHs) have been in the focus of research since the nineties, clearly proven by the over ~30,000 articles published to date. Recent reviews and other high impact papers [1–9] indicate the widespread contemporary interest in these materials in academic research and in more applied disciplines.

LDHs can incorporate basically every stable element of the periodic table. Their framework consists of smaller metal cations, while their interlayer space is a host for non-metallic elements in their anionic form or complexes of metal ions. Consequently, their physico-chemical properties move on a wide range, which was summarized from different aspects, for example in catalysis [10,11], sensing [12,13] and energy related applications [4,7,14,15]. Owing to their structural diversity, ease of synthesis, possibility of inner and outer surface immobilization (i.e., intercalation and surface adsorption) of various bioactive molecules and high biocompatibility, LDHs are popular subjects in medical research. This field includes imaging, cancer therapy, delivery of small drug substances, bone repair, and battling oxidative stress, to name a few. Such topics regarding LDH-biopolymer composites are discussed in detail later in the article. Due to the extensive research activity, the progress in the field of LDH chemistry should be regularly discussed. This review covers the synthesis and basic features of LDH clay, LDH-biopolymer interaction, biocompatibility of the LDH-biohybrids and biomedical applications (Fig. 1). Note that the present article heavily focuses on both fundamental and practical aspects of LDH-biopolymer hybrids emphasizing the results of colloidal and surface chemistry studies reported on these systems so far. Therefore, it significantly differs from other review articles [16] discussing LDH-based biomaterials in general.

2. Pristine LDH materials

2.1. Basic features of LDHs

The most generic formula of the LDH structure is $[M(II)_xM(III)_{1-x}(OH)_2][A^{m-}_{x/m}\cdot nH_2O]$, where M(II) and M(III) are metal cations in the octahedral positions and A is the anion [17]. The composition can be derived from brucite ($Mg(OH)_2$) by isomorphous substitution of M

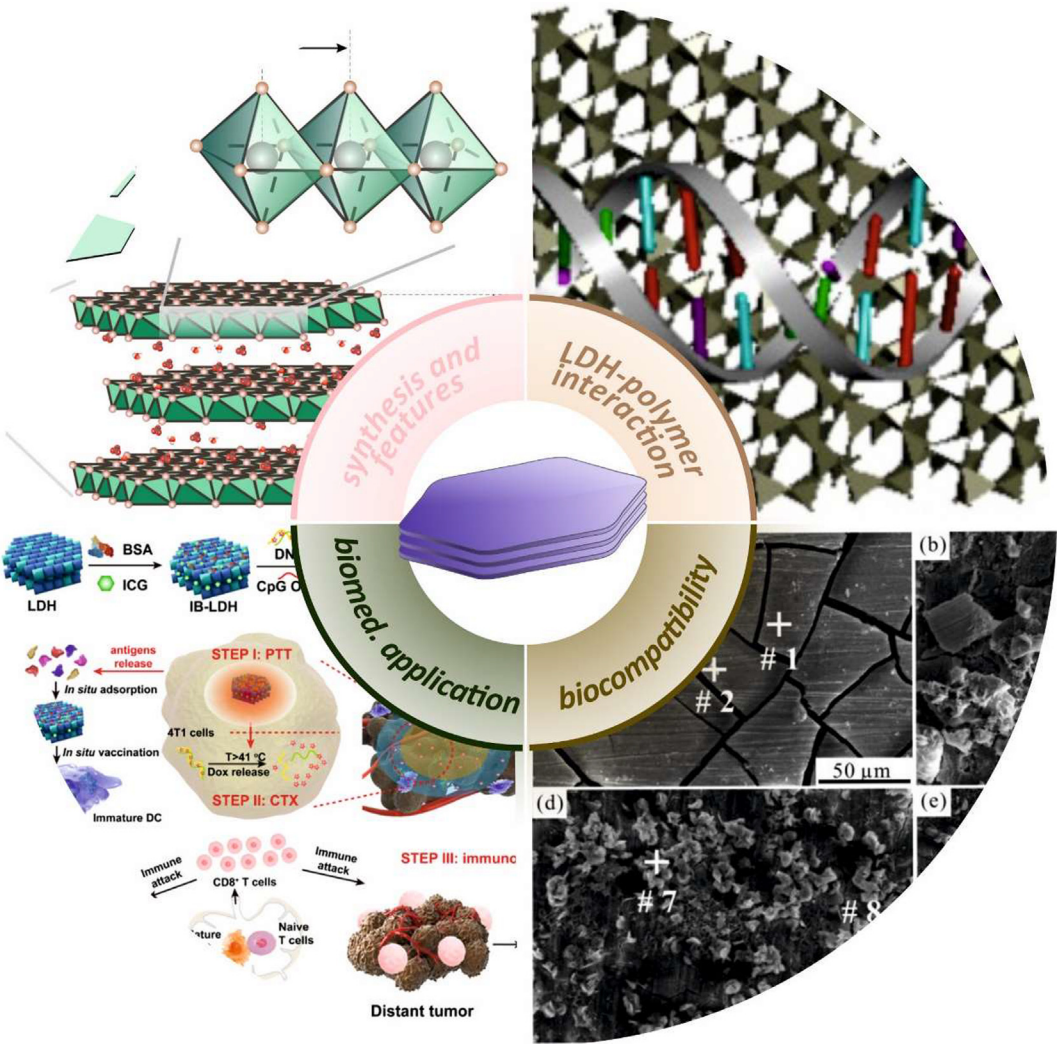

Fig. 1. Schematic representation of topics covered by the present review. Reprinted from (Study on the adsorption of DNA on the layered double hydroxides (LDHs), 121, B. Li, P. Wu, B. Ruan, P. Liu, N. Zhu, Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 2014, 387–393). Copyright (2022), with permission from Elsevier. Reprinted (adapted) with permission from (Development of Multifunctional Clay-Based Nanomedicine for Elimination of Primary Invasive Breast Cancer and Prevention of Its Lung Metastasis and Distant Inoculation, 11, L.-X. Zhang, X.-M. Sun, Z.P. Xu, R.-T. Liu, ACS Applied Materials & Interfaces, 2019, 35566–35576). Copyright (2022) American Chemical Society. Reprinted from (Biocorrosion resistance and biocompatibility of Mg-Al layered double hydroxide/poly-L-glutamic acid hybrid coating on magnesium alloy AZ31, 147, W. Wu, X. Sun, C.-L. Zhu, F. Zhang, R.-C. Zeng, Y.-H. Zou, S.-Q. Li, Progress in Organic Coatings, 2020, 105746). Copyright (2022), with permission from Elsevier.

(II) metal ions to M(III) [18–20]. The detailed structure of the LDH is presented in Fig. 2 [21].

For charge compensation, the positive layer charge is balanced with exchangeable hydrated/solvated interlayered/outer anions creating a bi-dimensional lamellar composite structure arranged with 1:1 sequential blocks to build ABAB type heterostructure [22–25]. Various divalent (Ca(II), Mg(II), Ni(II), Fe(II)) and trivalent (Al(III), Fe(III), Cr(III)) as well as other (Li(I), Zr(IV), Sn(IV)) cations are referred to as layer building constituents of the LDH classifying it into various groups such as hydrocalumites and hydrotalcites, for instance [26–33]. In the LDH nomenclature, hydrotalcite is the name of the supergroup, which, beside the name-giving substance, consists of LDHs with various structures and properties as well as many other isomorphous and polytype varieties [34]. Non-conventional LDHs of Al-excess compositions are also known ([M(II)$Al_4(OH)_{12}$]$(A^{n-})_{2/n}\cdot mH_2O$), but without significant applications compared to their conventional counterparts [35].

LDHs are well-known anion exchanging materials [36] and have numerous applications in different areas such as electrochemistry [37], drug delivery [38] or heterogeneous catalysis [39,40] due to their several advantages such as ease of preparation [41], chemical stability [42], resistance against mechanical energy [43] and compatibility with biological systems [44]. By utilizing their anion exchanger capacities, various structures of different interlayer galleries or outer surfaces, morphologies [45,46], dimensions [47] and compositions [48] were produced, exhibiting wider physico-chemical properties compared to their parent structures. The platelet-like 2D morphology of LDHs facilitates the preparation of composite materials for various applications. LDH crystals typically possess high aspect ratio and, as a result, readily form thin films ideal for high performance capacitors [15,49], electrocatalysts [50] or electrode materials [51]. Large platelets can often serve as hosts for smaller nanomaterials, e.g., noble metals for electroanalytics [52,53], or photoactive compounds for energy applications [54]. The platelets of LDH can be combined with polymeric materials to enhance their physical properties, e.g., tensile strength and wear resistance [55,56], while also improving their flame retardancy, partially owing to the decreased gas permeability of oxygen through the self-organized elongated LDH particles [57,58]. Moreover, the morphology of pristine LDHs are also tuneable to obtain porous platelets of higher specific surface area used as catalysts for water oxidation [59] or organic transformations [60]. Additionally, exotic, hollow structures can also be synthesized, suitable for adsorption of pollutants [61,62]. The chemical composition of the interlayer/adsorbed anions largely determines the ion-exchange capacity of LDHs. Considering the thermodynamic stability with respect to the anions, the $CO_3^{2-} > SO_4^{2-} > OH^- > F^- > Cl^- > Br^- > NO_3^- > I^-$ order can be given [63].

Complex or large anions were successfully intercalated. Accordingly, amino acids [64], phthalocyanine metal complexes [65], porphyrin derivatives [66], DNA [67,68], ATP [69], nucleosides [70] or polymers [71,72] were introduced within the interlayer gallery. In addition, biologically active specimens such as enzymes [73], cofactors [74] and RNA [75] have been also immobilized in/on LDHs without losing their activities. Syntheses of bio-LDH composites and controlled drug release have become the fastest growing trends in this field. To produce these composites, classical methodologies such as coprecipitation (see details in next section) or direct anion exchange method based on electrostatic interactions proved to be useful tools, however, beneficial modifications are often required in the procedures.

It became fully evident that for the optimal operation of a bio-LDH composite under biological/industrial reaction conditions, some basic properties of LDHs must be improved to ensure (i) high surface area, (ii) well-controlled particle size, (iii) molecular dimensions of the pores, (iv) remarkable adsorption capacity as well as (v) possibility of modulating the electronic and structural properties of the active sites [76]. Systematically varying the synthesis conditions [77] or using organic solvent treatment [78] gave rise to significant increase in surface area. Notable progress was made to produce attractive composites, however, with some limitations with respect to the sorption capacity or structural stability.

To avoid the above limitations, exfoliation into unilamellar nanosheets is a straightforward approach [75,79,80]. However, the ordinarily used delamination processes include lengthy step-by-step procedures and costly utilization of toxic organic solvents (e.g., DMSO, DMF and *N*-methyl-pyrrolidone) [7]. Furthermore, the exfoliated LDH nanosheets suffered from the strong adsorption of solvent molecules, which significantly decreased their anion exchange capacity [81]. Alternatively, from a green and economical point of view, synthetic strategies were built up to produce hierarchically ordered LDHs of porous 3D structures [82]. Three different

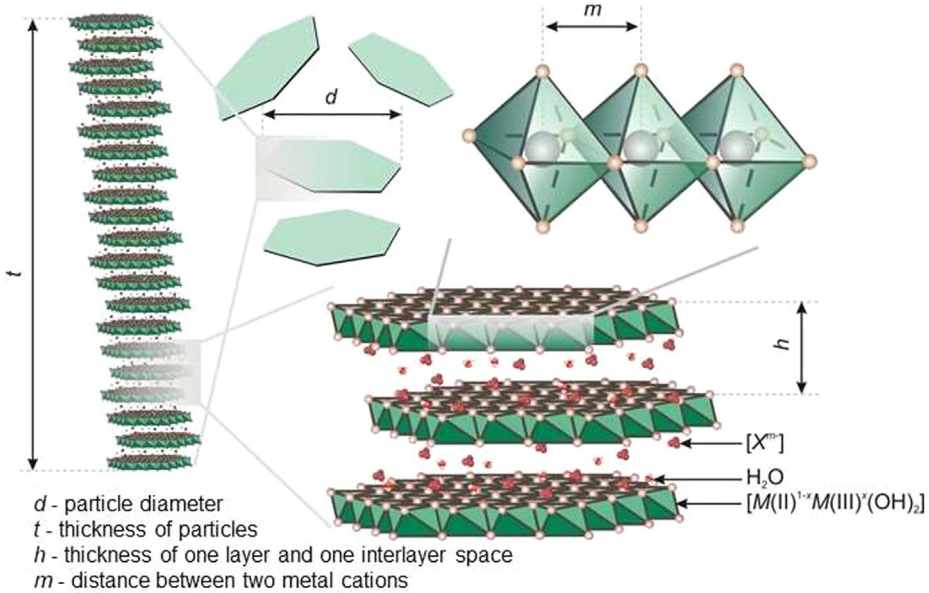

Fig. 2. Schematic representation of different levels of LDH nanoclay structure, ranging from octahedral complexation until platelet form.

methodologies can be applied to achieve this target. Namely self-assembly, templating and deposition methods. Template methods, combining with post synthetic treatments to remove the template molecules, seemed to be one of the most efficient strategies producing hollow nanosphere composites, which enables incorporation of biologically active centres without leaching or diffusion limitations [83–85].

2.2. Preparation of LDH materials

Owing to the facts that size-controlled syntheses widen the applicability of the lamellar LDH structures [86], new synthetic routes were designed and developed, while novel applications became possible from sorption chemistry to LDH-based biological utilizations [87]. LDHs are usually prepared by coprecipitation of metal containing mother liquors at constant [88] or non-controlled pH values [89].

Clear dependence of the level of supersaturation on the morphology and particle size distribution of LDHs has been determined [90]. This dependence may help size-controlling syntheses of LDHs, however, significant limitations of this method in the tuneable range of particle size have been observed [54]. To broaden this range, novel sol–gel methods have been introduced including the hydrolysis of alkoxide precursors followed by their solidification under mild reaction conditions [91,92]. By using these methods, various types of LDH nanoparticles were produced, nevertheless, with significantly polydisperse feature in both lateral dimension and thickness [93]. Similarly to these syntheses, salt-oxide method [94] (a version of coprecipitation route) and preparation by separate nucleation and aging steps (in colloid mills) led to the formation of LDH particles of wide size distribution [95]. Lately, via simple solid-state approach using ambient pressure and room temperature, mechanochemical/-sonochemical synthetic routes provided an adequate way to tackle the problem of polydispersity [96–98].

It can be noticed from this information that low size polydispersity of LDHs is an important parameter to achieve during synthesis. It was pointed out that the distribution of the lateral LDH size affects intercalation yield, cellular uptake as well as improves efficiency in biomedical therapies [99]. Therefore, polydispersity in the lateral dimension should be measured and controlled during preparation of LDH-based delivery vehicles. Regarding measurement techniques, dynamic light scattering offers a powerful tool to determine polydispersity indices in dispersions, through the analysis of the intensity correlation functions with the cumulant method [100]. Concerning size control, the hydrothermal treatment of raw LDH materials was developed to obtain fine particle dispersions of low polydispersity index [87].

Noticeably, because of theoretical reasons related to the mechanical power transmission, the above methods are far from optimal for preparing nano-sized LDHs [101]. It also became clear that the application of post synthetic treatment such as dehydration-rehydration [8,19] as well as hydrothermal treatment [42,102] cannot be an option from biological application point of view because the presence of organic additives is essential for building LDH nanoparticles. More recently, monodisperse LDH nanoparticles at the 50–100 nm length scale could be prepared by means of a reverse micelle/microemulsion method [103]. By encapsulating aqueous solutions of reactants with the surfactant molecules such as oleyl amine, LDH nanoplates with finetuned particle size could be obtained. Additionally, the dimensions of the LDHs are linearly depended on the surfactant-to-water ratio.

2.3. Biomedical applications of pristine LDHs

The so-called pristine LDHs contain small inorganic anions (generally OH^-, Cl^-, NO_3^- or ClO_4^-) in the interlamellar space that are taken up from the mother liquor during synthesis. However, these anions are also attracted by the outer surface on crystallites through Coulombic interactions owing to the intrinsic positive structural layer charge of LDH [21,33,87,104–115]. Its low magnitude of charge or the lack of other stabilizing factors manifests in aqueous colloids with low stability, which may prevent applications in bio-relevant media.

Although this review is dedicated to surface modified LDH substances, we briefly summarize the importance of pristine and small biomolecule intercalated LDHs in bio-related applications. LDHs as basic compounds reacting with acids, which is a potential application area of MgAl-LDH as antacid. Since neither Mg(II) nor Al(III) is poisonous [116], their applicability as vaccine adjuvants was also demonstrated [117]. Furthermore, pristine transition metal-bearing LDHs are potential substitutions for traditional biomedicines in imaging therapies. It was shown that Mn-based LDHs possess favoured properties for magnetic resonance imaging (MRI), specifically as T_1, i.e., positive contrast, longitudinal relaxation agents. Compared to existing Gd complexes used in human diagnostics, LDHs with incorporated Mn had lower cytotoxicity, better relaxation properties, while accumulated in tumour cells with remarkable efficiency [118]. Ruan et al. showed that MnFe-LDH exhibits photothermal effect suitable for thermal imaging and photodynamic cancer therapy [119]. Xie et al. further improved the concept of Mn-based MRI by immobilizing iron oxide nanoparticles, which are known for their T_2-type (negative contrast) transverse relaxation traits, leading to formulation of a composite material with dual mode of MRI relaxation. This may provide the diagnostic teams to better differentiate between diseased and healthy tissues to deliver more accurate results [120]. Another dual mode MRI contrast agent LDH was prepared by Andrade et al., who co-incorporated T_1-type Gd(III) and T_2-type Dy(III) within the LDH lamellae [121].

Similarly intriguing for applications are LDHs with radioisotopes in their framework. Kim et al. synthesized MgAl-LDH that was hydrothermally treated with $^{57}CoCl_2$ to dope the structure with the radioisotopes. It was shown that the LDH enters several types of tissue cells and the γ radiation following the electron capture decay of ^{57}Co was followed by a suitable detector, proving that the LDH can be used as an imaging agent in cancer patients [122].

Imaging is a bridge territory between pristine and intercalated LDHs, since trivalent metal cations are building constituents of the layers, but they can be immobilized in the interlayer after complexation. The most common T_1-type MRI agent Gd is trivalent, and it was used as a dopant in a MgAlGd-LDH prepared by Wang et al [123]. The material was modified by intercalation of cytotoxic and antiproliferative doxorubicin (DOX), surface Au nanoparticles (for CT imaging) and heparin coating for proper colloidal stability under in vivo conditions. The results showed that the composite fulfilled its multifold role in cancer imaging and treatment in mice. On the other hand, the intercalation of the MRI active $[Gd(DTPA)]^{2-}$ (DTPA is diethylene triamine pentaacetate [124]) was also achieved. Another type of cancer treatment was possible through a carborane intercalated LDH demonstrated by Ay et al. The lighter natural isotope of boron, ^{10}B has impeccable cross section towards thermal neutrons followed by the emission of degrading radiation to the surrounding unhealthy tissues after targeted adelivery [125]. Imaging was also possible utilizing the intercalation of anionic fluorescent dyes. Musumeci et al. used four dye molecules, concluding that fluorescein was an ideal candidate for cell fluorescent labelling owing to the high fluorescent response of the intercalant [126]. The intracellular pathway of LDH was investigated using a fluorescein intercalated LDH. It was shown that LDHs are effortlessly taken up by endocytosis, and a 30–60 min timeframe was demonstrated indicating the rapid uptake of LDHs, which is ideal for delivery of pharmaceuticals [127]. LDHs

intercalated with pharmaceuticals are important cornerstone in the chemistry of 2D nanomaterials. This topic is well-covered in other review papers previously released in the literature [128–130].

3. Fundamentals of LDH-biopolymer interactions at the interface

LDHs are considered as efficient delivery agents for various biomolecules into cells during treatment of different diseases [3,131,132]. Conjugation of bio-active compounds with the LDH carrier involves interfacial interaction between the host and guest, i.e., adsorption on either the outer surface or within the layers. These scenarios are illustrated in Fig. 3 for LDH-(bio)polymer systems.

Adsorption mechanism and possible structural changes upon immobilization are key issues in development of effective LDH-based drug delivery systems. In addition, biomolecule adsorption may affect the surface charge properties and subsequently, the colloidal stability of the particles. Note that aggregation of the LDH-biopolymer hybrid (i.e., formation of dimers, trimers, or higher ranked particle aggregates) either during preparation or in biofluids leads to several disadvantages including decrease in surface area, prevention of drug release or blocking veins by the aggregated clusters. For this reason, adsorption and aggregation processes in LDH-based delivery systems were explored for various biopolymers by several research groups in the past and an overview on these data is given in this section.

3.1. Interaction of LDHs with nucleic acids

Application of nucleic acids (RNA or DNA) in gene therapies is a promising method in treatments of various sicknesses including cancer, Alzheimer, and Parkinson disease [2,133,134]. Unfortunately, the use of bare DNA or RNA is limited in these biomedical processes due to their net negative charge, which retards their penetration through the like-charged cell membrane. Therefore, delivery agents are needed and LDHs were widely applied for such purposes owing to their advantageous surface properties for DNA or RNA immobilization. The fact that nucleic acid-LDH hybrids entered successfully into cells was confirmed in several studies [2,134,135].

In their pioneering works, Choy et al. internalized DNA biopolymers within the layers of MgAl-LDHs [136,137]. Such an intercalation was performed by exchanging the nitrate ions to DNA in the interlayer gallery, which resulted in a significant increase in basal spacing leading to the formation of pillared materials. It was also assumed that the double helix conformation oriented parallel to the double hydroxide layers. Besides, preparation and application of other nucleic acid-LDH hybrids were also reported by this research group [134,138].

Li et al. shed light on the fact that DNA has greater affinity to MgAl-LDHs of higher divalent-to-trivalent metal ion ratios [139]. Under such circumstances, the adsorption took place within reasonable timeframe and the obtained hybrids were not so sensitive to the pH of the medium compared to traditional LDH structures of 2:1 Mg(II)-to-Al(III) ratio. Moreover, spectroscopic characterization of the adsorbed DNA molecules revealed that no significant damage occurred in the DNA structure upon immobilization (Fig. 4).

Ren et al. comprehensively explored the adsorption mechanism of different DNA biopolymers through identifying the functional groups responsible for the attachment [140]. Once phosphate groups were located inside the helix, the double strand DNA was

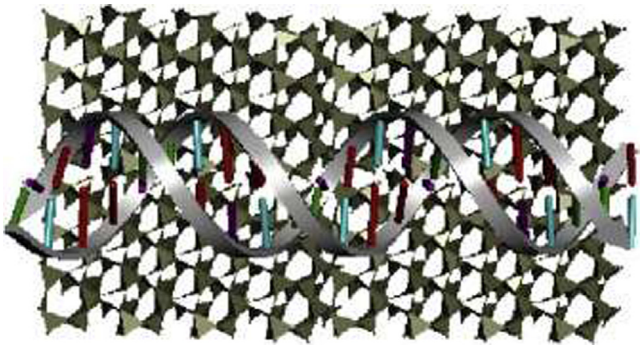

Fig. 4. Schematic representation of equilibrium interfacial structure for DNA on LDH surface: top view of the initial configuration for DNA adsorption on LDH. Reprinted from (Study on the adsorption of DNA on the layered double hydroxides (LDHs), 121, B. Li, P. Wu, B. Ruan, P. Liu, N. Zhu, Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 2014, 387–393). Copyright (2022), with permission from Elsevier.

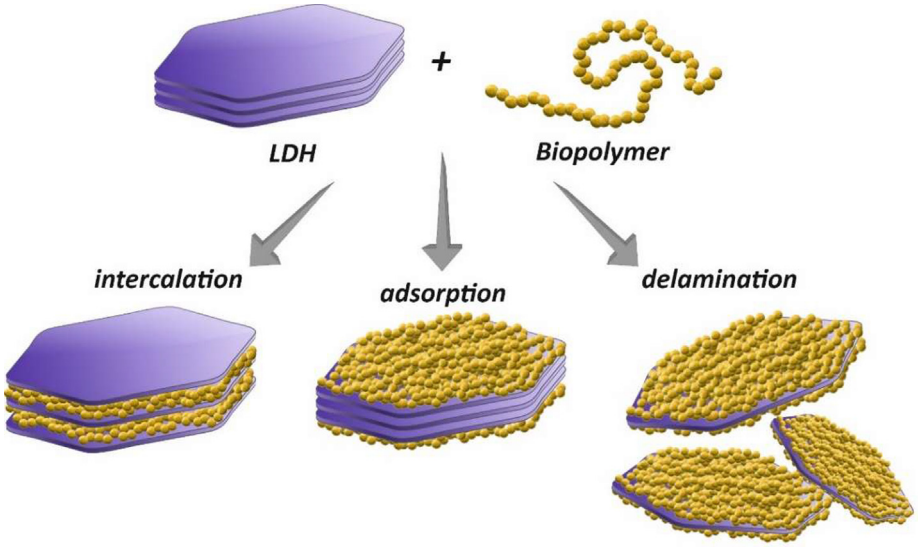

Fig. 3. Schematic representation of LDH-biopolymer composites obtained by intercalation or adsorption.

not fully bonded to the surface, i.e., partitioning took place between the surface and the bulk. Nevertheless, in case of single strand DNA, the phosphates were exposed to the surface and thus, strong adsorption occurred on the LDH. This effect was utilized in the development of DNA sensors.

In two consecutive papers [141,142], Thyveetil and co-workers published the results of molecular dynamics simulations on double stranded, linear and plasmid DNA intercalated MgAl-LDH materials. In line with findings of previous experimental studies, they found that phosphate functional groups of DNA are responsible for the strong immobilization within the layers, however, hydration of the biopolymer plays also a major structure determining role. In addition, DNA structure is less sensitive to the environmental conditions, such as temperature and pressure, once intercalated in the interlayer space, where surface diffusion of the biopolymer was also assumed.

Along with this research line, Lu et al. extensively studied the chemisorption of DNA on MgFe-LDH using various experimental techniques [143]. They concluded that apart from the above discussed electrostatic attraction, the phosphate groups of the DNA coordinates to the metal cations of the LDH layers via ligand-exchange processes giving rise to rapid and strong interaction between the surface of the host particle and guest biopolymers. It was also found that both Mg(II) and Fe(III) ions acted as binding sites for the phosphate backbone.

Different approaches were applied to prepare MgGa-LDH-DNA hybrids [67]. The presence of DNA during the coprecipitation process, i.e., in the mixture of the metal ions before increasing the pH, resulted in intercalation of the nucleic acid between the layers. In addition, labile LDH-DNA composites were obtained by ion exchange and direct self-assembly of the components.

While there is a chance of cellular uptake of LDH non-viral vectors by unspecific micropinocytosis or caveolae-mediated uptake, in most of the cases, uptakes occur through clathrin-mediated endocytosis [144]. It is important to note that the size of the vectors critically determines the mechanism of the uptake, therefore, hydrodynamic diameter of LDH-biohybrid is more important than the type of interaction employed for loading DNA into the LDH interlamellar space. In other words, LDH nanoparticles adhere to the membrane interface and enter the cell mainly through clathrin-coated vesicles those further matures to the early endosome and subsequently, to the late endosome. Late endosomal stage is characterized by an acidic pH condition that dissolves LDH vectors, which causes increase in osmotic pressure driving water molecules into the endosomes. This is followed by a burst of endosome and releases of DNA to the cellular matrix. This buffering capacity of LDH remains the most important LDH feature of an efficient DNA release [145]. Other routes of uptake, including micropinocytosis, depend on the exchange of DNA with ions, where its strong interaction with LDH layers, especially in a case of chemisorption, can significantly harm the process of release.

The role of the functional groups of single stranded RNA was investigated in the adsorption mechanism on MgAl-LDH particles differing in the Mg(II)-to-Al(III) ratio, i.e., in their structural surface charge [146]. Results of large-scale computer simulations revealed that RNA adsorbed strongly through electrostatic attraction between the phosphate groups and the Al(III) charge sites, in agreement with findings of experimental studies. Moreover, the base groups were exposed to the bulk solution (Fig. 5).

The Xu group extensively studied the interaction of RNA compounds with various LDHs to develop efficient gene delivery strategies. For instance, siRNA was loaded into CuAl-LDHs, however, this process did not affect the zeta potential and the size of the host particles [147]. In addition, coating the obtained hybrid with poly (ethylene glycol)-poly(2-aminoethyl methacrylate hydrochloride) copolymer modified with dimethylmaleic acid (PEG-PA/DM) resulted in pH sensitive surface charge being positive and negative in slightly acidic and alkaline solutions, respectively. This pH tunable charge played an important role in delivery of the hybrid into tumor cells. They also reported that the size of the nanoparticulate support is a crucial parameter to enhance RNA intercalation, i.e., MgAl-LDHs of smaller size could internalize significantly larger amounts of biopolymers [99]. The zeta potential of the obtained hybrids was negative indicating the fact that the RNA adsorption on the LDH reversed the original sign of charge in this case. Besides, the structural and dynamical features of siRNA within the interlayer space of LDHs were studied with molecular dynamics simulations [148]. The results indicated that significant differences exist between the structure of the intercalated compounds in crystalline forms and in the presence of water. More information on the nucleic acid-LDH conjugation protocols and on the potential biomedical applications can be found in recent reviews published by the Xu group [2,3].

Furthermore, DNA [149] and RNA [79] immobilization on delaminated NiIn-LDH was also investigated, where the adsorption of the biopolymer took place on the outer surface via electrostatic attraction. It was found that the DNA can be released once the hybrid was added to phosphate solutions. Nucleic acids were also immobilized on LDH-based composite materials. As an example, Konari et al. carried out functionalization of CNT-ZnCr-LDH (CNT stands for carbon nanotube) nanocomposite with DNA aptamers [150]. The developed immobilization protocol resulted in vertical

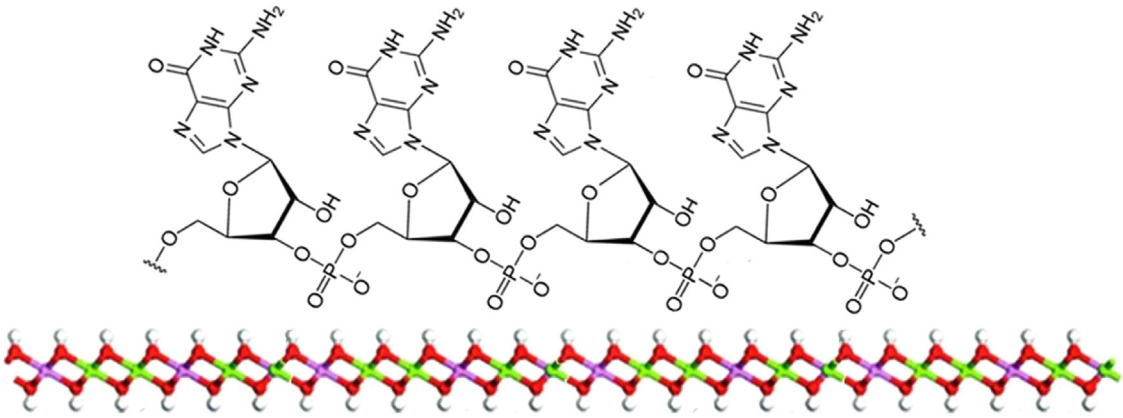

Fig. 5. Schematic diagram displaying the orientation that the RNA adopts when interacting with the LDH surface. Reprinted (adapted) with permission from (Influence of surface chemistry and charge on mineral-RNA interactions, 29, J.B. Swadling, J.L. Suter, H.C. Greenwell, P.V. Coveney, Langmuir, 2013, 1573–1583). Copyright (2022) American Chemical Society.

conformation of the biopolymer on the solid substrate. Finally, covalently grafted DNA to LDHs was also reported [151]. The main novelty of this work was the optimization of the grafting reaction through calcination-rehydration of MgAl-LDH.

3.2. Adsorption of poly- or oligosaccharides on LDHs

Synthesis of LDH composites with heparin, a natural sulfonated polysaccharide having one of the highest line charge densities among the known biopolymers, was frequently reported for various purposes. Therefore, interfacial interactions within LDH-heparin composites deserve a discussion.

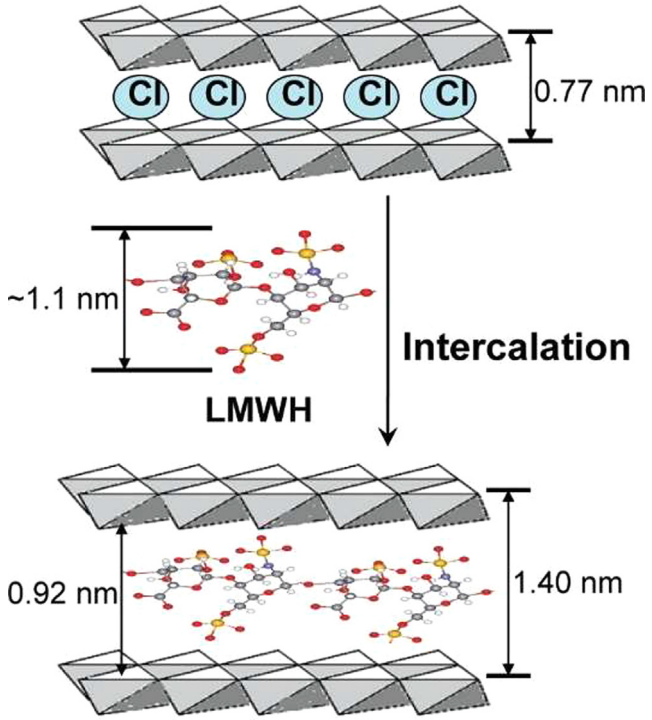

Fig. 6. Schematic representation of LDH structure before and after heparin intercalation. Reprinted (adapted) with permission from (In Vitro Sustained Release of LMWH from MgAl-layered Double Hydroxide Nanohybrids, 20, Z. Gu, A.C. Thomas, Z.P. Xu, J.H. Campbell, G.Q. Lu, Chemistry of Materials, 2008, 3715–3722). Copyright (2022) American Chemical Society.

Gu et al. intercalated low molecular weight heparin by adding the polyelectrolyte to the mixed Mg(II) and Al(III) salt solution during coprecipitation [27]. The determined interlayer distance was significantly larger than for chloride intercalated LDH (Fig. 6). Release tests pointed out that anion exchange between the heparin and the bulk anions occurred, while diffusion of the polyelectrolyte was also assumed on the surface.

In a follow-up study, intercalation of heparin into MgAl-LDH was investigated by molecular dynamics simulation [152]. The nature of the interlayer space was modeled and thus, the arrangement of the biopolymer and water molecules as well as the gallery spacing were determined. Heparin adsorption took place on the LDH surface by strong electrostatic forces, while the intermolecular hydrogen network changed upon intercalation allowing the self-diffusion of the polyelectrolyte within the LDH structure. Besides, the self-diffusion coefficients of both an interlayer model surfactant of sulfonate head group and water were estimated, and the results adequately supported the theory developed for the self-diffusion of heparin, whose sulfonated part plays a major role in the adsorption and mobility on the surfaces, inside LDH materials [153].

Such a strong adsorption of heparin on LDH surface was utilized in preparation of ultrathin films using the layer-by-layer technique [154]. Electrostatic attraction and hydrogen bonding network provided good structural stability, enhanced mechanical properties and blood compatibility for the film, which holds great promise in future biomedical applications, for instance as replacement of conventional plastics.

Apart from heparin, other polysaccharides were also used to modify the surface of LDHs and to prepare composite materials. For example, pristine LDH surface was grafted with 3-(aminopropyl)-triethoxysilane (APTES) and intercalation of dexamethasone-carboxymethyl-β-cyclodextrin (DEX-CM-β-CD) took place via anion exchange (Fig. 7) [155]. The cyclodextrin loading resulted in a decrease in zeta potential and increase in size compared to the pristine LDH indicating the successful intercalation of the guest macromolecules. This finding was further confirmed in X-ray diffraction (XRD) measurements, as an increased interlayer distance was determined upon intercalation.

Alginate and chitosan were also interleaved in the interlayer gallery or adsorbed on the outer surface of LDHs, however, these studies did not focus on the fundamental aspects of the interactions between the LDH surface and the functional groups of the biopolymers, but rather on the utilization of these hybrids for various applications [12,156,157]. Therefore, we do not discuss these findings in this section in detail.

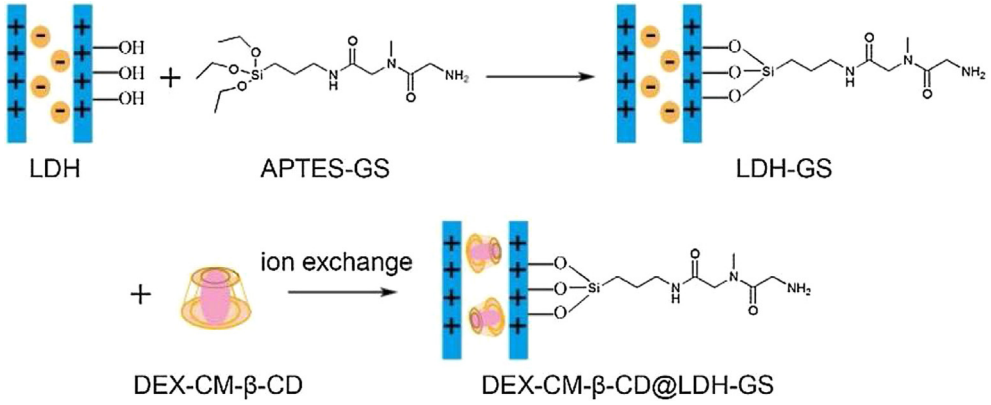

Fig. 7. Two steps synthesis of DEX-CM-β-CD@LDH-GS nanocomposites (GS: glycylsarcosine) including surface grafting and intercalation. Reprinted from (Multifunctional nanocomposite eye drops of cyclodextrin complex@layered double hydroxides for relay drug delivery to the posterior segment of the eye, 260, C. Xu, J.H. Lu, L. Zhou, J. Liang, L. Fang, F. Cao, Carbohydrate Polymers, 2021, 117800). Copyright (2022), with permission from Elsevier.

3.3. LDH interaction with miscellaneous biopolymers

Studying interaction between other biopolymers and LDHs or their derivatives was studied in the past decades, as the immobilized substances may provide enhanced surface properties to host drug molecules, good colloidal stability and biocompatibility for the hybrid materials used in biomedical processes. Like the above discussed biopolymers, adsorption on the outer surface or intercalation between the LDH layers were both reported as immobilization methods.

Accordingly, Shi et al. published results on the synthesis of Fe_3O_4@NiFe-LDH hybrid material and investigated the affinity of histidine-rich proteins to these particles [6]. The composite showed excellent selectivity for bovine hemoglobin making it a promising candidate for separation of such proteins from blood samples.

Yang et al. reported on the synthesis and characterization of an LDH-polydopamine (PDA) hybrid material used for sensing purposes [158]. The dopamine monomer was adsorbed on the outer surface of prefabricated MgAl-LDH and self-polymerization took place under alkaline conditions. The resulting LDH-PDA hybrid possessed negative charge probably due to the deprotonation of the hydroxyl groups of the adsorbed monomers under the synthetic conditions.

ZnAl-LDH was intercalated with lignosulfonate via direct coprecipitation [159]. The biopolymer adopted a bilayer molecular arrangement giving rise to the formation of a pillared composite material. The obtained LDH-lignosulfonate hybrid was used as filler for bio-related polyesters and decreased the water/polymer contact angle as well as increased the viscosities of the polyesters in certain cases. The obtained hybrid can be a potential candidate to modify plastics used in biomedical devices.

Although systems containing LDHs intercalated with drugs or other bioactive molecules were internalized in various biopolymeric matrices [160–163], this topic was not in the focus of this review, as we intend to discuss the adsorption or intercalation of single biopolymer chains on/in LDH materials.

3.4. Tuning particle aggregation in LDH-biopolymer systems

Adsorption processes often modify the surface properties of LDHs that the extent of interparticle forces responsible for the colloidal stability of the samples changes significantly. They can be of different nature depending on the physicochemical features of the host, guest and the surrounding bulk. Tendency to aggregation for charged particles dispersed in electrolyte solutions can be predicted by the classical theory developed by Derjaguin, Landau, Verwey and Overbeek (DLVO) [164,165]. This theory assumes point-like charges dispersed in dielectric media and the presence of repulsive electrical double layer and attractive van der Waals forces. The strength of the former ones strongly depends on the charge of the particles, while the latter one originates from the material composition [166]. An important parameter involved in this theory is the ionic strength, whose increase weakens the electrical double layer repulsion giving rise to diffusion-controlled aggregation of the particles above the critical coagulation concentration (CCC). Consequently, the CCC can be derived from the DLVO theory and its value is equal to the electrolyte concentration, which separates slow and rapid particle aggregation regimes [166]. For example, the ionic strength is about 150 mM in blood serum [167] and thus, the CCC of the applied LDH-biopolymer composite must significantly exceed this value in order to avoid rapid particle aggregation and subsequent destabilization of the dispersion. Note that aggregation of LDH-based particles means the formation of dimers or larger clusters of the lamellar particles and not the development of multilayered materials. However, the conformation of the adsorbed biopolymer chains, complex nature of biofluids and the application of various stabilizing agents usually give rise to the development of additional (non-DLVO) repulsive and attractive interactions. They include steric, patch-charge and depletion forces [166,168,169], for instance.

Since the generic colloidal stability of LDHs in the presence of ionized species has been recently reviewed [33], we only focus here on the aggregation processes taking place in samples containing biopolymers. Special attention has been paid to identify the connection between the surface properties (both charge and structure) and the aggregation rate of the LDH-biopolymer hybrid particles.

Results of fundamental studies performed with MgAl-LDH materials and heparin biopolymer shed light on the relation between adsorption and aggregation processes in aqueous dispersions [108]. It was found that adsorption of heparin on the oppositely charged particles resulted in charge neutralization, while overcharging and formation of saturated (bio)polyelectrolyte layer occurred at higher doses. Overcharging (also known as charge reversal) is a typical phenomenon upon adsorption of charged macromolecules on oppositely charged surfaces leading to reversal of the original sign of the particle charge [33,169]. The presence of DLVO type forces was assumed in the above MgAl-LDH-heparin system, since the neutral particles rapidly aggregated, while LDHs fully coated with heparin were stable due to their significant charge. Nevertheless, additional steric repulsion (originating from the overlap of adsorbed polyelectrolyte chains and subsequent rise of osmotic pressure [166,170]) was also identified in the latter case leading to remarkably high colloidal stability, as indicated by the extremely high CCC determined in salt-induced aggregation measurements. Accordingly, a tremendous increase in the CCC from 39 mM (bare LDH particles) to 1100 mM (heparin coated LDH) was determined due to surface functionalization [108]. Considering the ionic strength of about 150 mM in the blood stream [167], the developed heparin-LDH hybrid is expected to resist against electrolyte-induced aggregation in bio-delivery processes. These findings indicated that LDH-heparin composites are of great potential in biomedical applications once the surface properties are properly tuned to avoid particle aggregation.

Vasti et al. performed a comprehensive study on the adsorption of serum proteins on MgAl-LDHs intercalated with different anions and its effect on the colloidal stability [171]. The adsorption of albumin, which is the main protein in human blood plasma, led to corona formation and consequently, to high colloidal stability of the nanocarriers. The strong adsorption of albumin was accompanied with overcharging of the LDH particles, and the stabilizing forces were of electrostatic and steric origin. Despite the relatively high biopolymer concentration, attractive depletion forces [166,168] were not detected. The protein corona prevented dissolution of the LDH support under acidic conditions, which is often a major drawback of its applications. It was pointed out that LDHs of intercalated small inorganic anions tend to form more stable colloids upon protein adsorption compared to the one intercalated with surfactant molecules between the layers of the host particles [171].

Xu et al. performed comprehensive studies on the adsorption of bovine serum albumin (BSA) on various LDHs and its effect on the colloidal stability of the particles. In their comprehensive work [106], a strategy was developed to coat MgAl-LDH particles with BSA via physical adsorption to prevent aggregation during in vivo drug delivery processes. They shed light on the importance of several factors during the coating procedure. These factors include the experimental conditions (e.g., sequence and speed of reagent addition as well as concentration of BSA and LDH) and certain features of the particles (e.g., size and type of intercalated anions). It was concluded that MgAl-LDHs of 110 nm in diameter coated at 5:2

BSA-to-LDH ratio showed the highest colloidal stability in PBS and cell culture media. The resistance of the developed LDH-BSA hybrid against salt-induced aggregation was further improved by crosslinking the proteins with glutaraldehyde (GTA) on the particle surface (Fig. 8) [172]. It was assumed that crosslinking immobilized BSA on the surface leads to strong steric repulsive forces, which act together with the electrical double layer forces (so-called electrosteric stabilization) to prevent the aggregation of the particles. This method made the developed nanocarriers excellent candidates for use in a wide variety of bio-applications in vitro and in vivo.

Apart from the above studies carried out to explore LDH-BSA interactions in aqueous dispersions, Zhao et al. prepared LDH-MoS_2 composite with adsorbed BSA on the outer surface [173]. Based on the observable Tyndall effect, the authors concluded that the dispersions contained homogeneously distributed particles, i.e., functionalization with BSA led to an improved colloidal stability of the composite.

4. Biocompatibility and biodegradability of LDH-based hybrids

Recent years have brought large progress in nanomedicine science, especially in the fields of bioimaging, drug and gene delivery, by co-application of hydrotalcite-like compounds with biopolymers. The ease of LDH functionalization by polymers and macromolecules, either by straightforward physical adsorption or more complex intercalation and covalent grafting, remains one of the highest motivations for this widespread usage. Although easily manufactured and often highly efficient, LDH-based hybrids need to be sufficiently biocompatible to reach the final goals. In addition, biodistribution and biodegradability are also crucial factors influencing the performance of the utilized materials. It is important to note that there are numerous studies in the literature demonstrating the adequate biocompatibility of bare LDH material [174–178], nevertheless, only the biocompatibility of LDH-based biohybrids will be in the focus of this review.

Magnesium alloys, like AZ31 alloy, are very promising cardiovascular stent material with advantageous physical properties and degradation. However, there is a significant room for improvements in the areas of corrosion resistance, endothelialization and hemocompatibility. The recent study by Li et al. [115] demonstrates the advantageous properties of LDH coated with PDA with or without addition top layer of heparin. Number of adherence and proliferation rate of human umbilical vein endothelial cells (HUVECs) on the LDH/PDA sample was comparable to the titanium samples, and significant improvement over bare AZ31 alloy was observed. Additional coating by heparin (LDH/PDA/HEP) slightly decreased corrosion resistance and long-term proliferation of HUVECs, but further improved HUVEC migration rate. The initial cell adhesion and cytoskeleton formation of HUVECs cultured on different samples were observed by confocal laser scanning microscope. This strong effect can be explained by enhanced corrosion resistance and improved hydrophilicity due to the introduction of bioactive functional groups. Similarly, high effectiveness was demonstrated by coating of AZ31 alloy with LDH-polyglutamic acid (LDH/PGA) hybrid. Such a coating of LDH was performed by immersing in PGA solution for different times followed by freeze-drying [179]. Out of all prepared materials, LDH/PGA-30 (30 min immersion time) demonstrated the highest corrosion resistance with a relatively low cytotoxicity (Fig. 9).

Beside usage of LDH hybrids in materials science, these nanoparticles are often employed, as discussed earlier and in the next section, in imaging and delivery processes. For these applications, impact of LDH hybrids on vascular or blood cells and their overall blood compatibility are crucial factors. High biocompatibility was confirmed by a hemolytic assay [180]. In other words, red blood cells were treated with different concentrations of several LDH hybrids containing PEG, acidic or basic amino acids. It was found that LDH functionalization determined the in vivo biodistribution of the hybrid. Positive amino-LDHs preferably accumulated in lungs, while there was a rapid clearance of negatively charged LDHs from the blood flow to liver. Interestingly, decoration of LDH by a neutral PEG5000 polymer demonstrated very low accumulation in any major organs with an enhanced blood circulation time [180]. Moreover, MTT assays also proved a low to nonexistent toxicity of LDH-carboxymethylcellulose (LDH-CMC) [181] and LDH- poly(vinyl chloride) [182]. Comprehensive studies are still needed to be performed in order to improve biocompatibility of biodistribution, however, LDH hybrids definitely present a very promising material for a numerous biomedical applications discussed in the following section.

5. Biomedical applications of LDH-biopolymer hybrids

High biodegradability and biocompatibility, in combination with a high compositional and morphological diversity, made LDH-based hybrids promising candidates for numerous biomedical applications. The basic strategy for preparing LDH nanoparticles of advantageous functional features is either isomorphous substitution of divalent magnesium ion from the brucite-like structure with another, functional divalent cation, like Cu(II) [183] or Mn (II) [118], or post-functionalization of LDH nanomaterial by intercalation [176] or immobilization [184] of functional molecules, like drugs or polyelectrolytes. The first route is easily achievable due to ability to exchange layer forming cations with other ones of a similar radius, while the latter is feasible due to elevated LDH ion-exchange capacity. Applications of LDH substances and their derivatives include bioimaging [121,147,185], cosmetic [186] and therapeutic applications [77,173], development of novel drug and gene delivery platforms [155,187], tissue engineering [188–190], material science [1,4,191] and various sensing schemes based on LDH nanoparticles [192–194]. Below, we will focus on those involving LDH-biopolymer hybrids during materials preparation or functionalization.

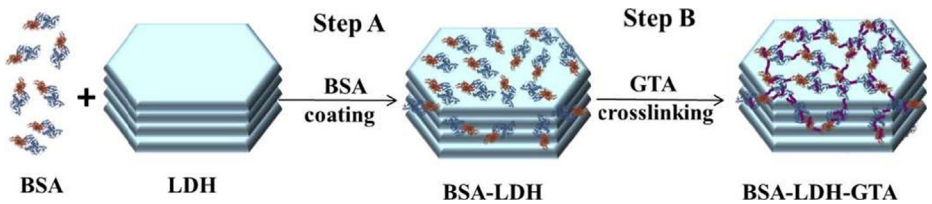

Fig. 8. Schematic illustration of BSA-coating onto LDH nanoparticles and subsequent GTA crosslinking. Reprinted from (Crosslinking to enhance colloidal stability and redispersity of layered double hydroxide nanoparticles, 459, H. Zuo, Z. Gu, H. Cooper, Z.P. Xu, Journal of Colloid and Interface Science, 2015, 10–16). Copyright (2022), with permission from Elsevier.

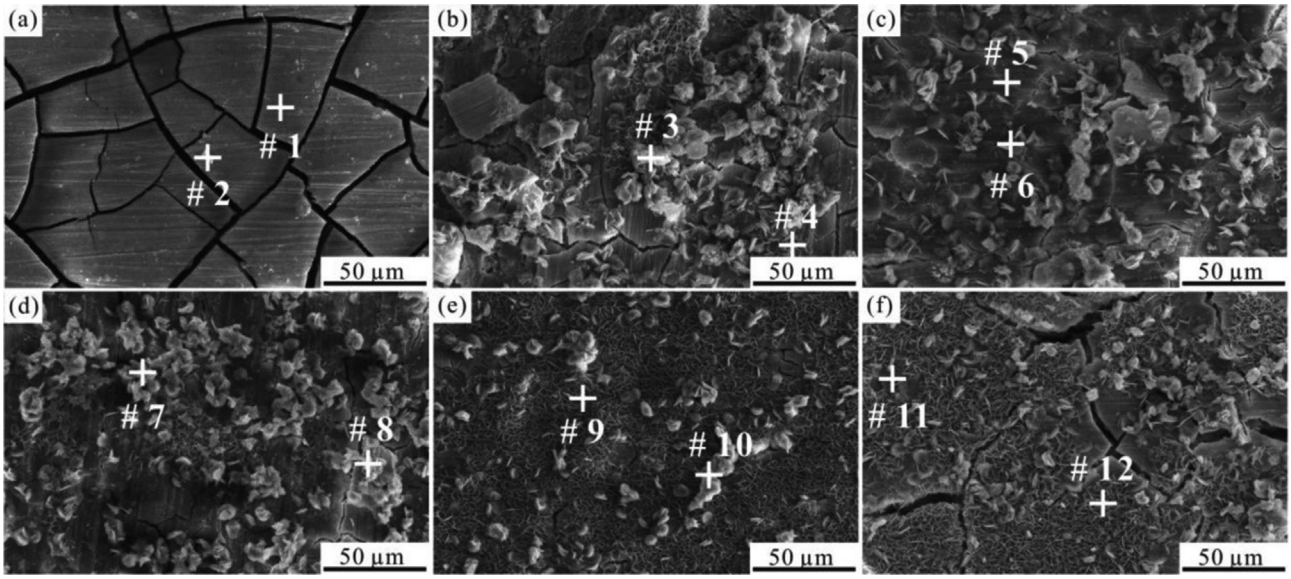

Fig. 9. Scanning electron microscopy (SEM) images of AZ31 (a), LDH coating (b), LDH/PGA-10 coating (c), LDH/PGA-20 coating (d), LDH/PGA-30 coating (e) and LDH/PGA-60 coating (f) after 230 h immersion in Hank's solution. Reprinted from (Biocorrosion resistance and biocompatibility of Mg–Al layered double hydroxide/poly-L-glutamic acid hybrid coating on magnesium alloy AZ31, 147, W. Wu, X. Sun, C.-L. Zhu, F. Zhang, R.-C. Zeng, Y.-H. Zou, S.-Q. Li, Progress in Organic Coatings, 2020, 105746). Copyright (2022), with permission from Elsevier.

5.1. Bioimaging and therapy

Implementation of LDH materials in the processes of bioimaging and therapy, in addition to the novel theranostic approach, dated from the time when DNA-LDH biohybrids were reported in 1999 by Choy et al [136]. This pioneering work demonstrated that herring testis DNA, together with adenosine-5′-monophosphate, guanosine-5′-monophosphate, and cytidine-5′-monophosphate, can successfully be intercalated in the interlayer space of the two-dimensional lamellar material, such as LDH. Note that the intercalated biomolecules were conformationally and functionally intact. This study opened an entire new field, which interconnected material science, pharmacy and medicine, and utilizes LDH as a host lattice for gene and drug reservoirs. In addition to intercalation, covalent grafting of a single strain DNA molecules was also demonstrated by Adok-Sipiczki et al [151].

LDH-biopolymer hybrids have been used as contrast agents for fluorescent imaging [195], optical imaging [196] and magnetic-resonance imaging [9]. Furthermore, these types of materials were frequently employed for gene delivery, chemotherapy, photodynamic therapy, combinatory therapy or vaccine vectors. Bioimaging and therapy applications are often combined and thus, LDH-based materials are used as a theranostic agent that can simultaneously detect the presence of certain conditions and immediately react, like in the case of joint tumor cell detection and chemotherapy. Previously reported theranostic applications have been recently reviewed by Xu [197] and Choy [198]. These articles put a strong emphasis on the development of pH sensitive LDH nanoparticles for MRI contrasts or positron emission tomography (PET) imaging agents in combination with co-delivery of therapeutic antitumor agents.

LDH-based materials are widely used as bioimaging agents, however, quite often functionality is simply introduced by isomorphous substitution and not biopolymer decoration. Such a case of imaging application of LDHs without biopolymers involved has already been briefly discussed in section 2.3. Nevertheless, there are several papers that demonstrate how utilization of polymers can introduce or further improve monohybrid functions. In a recent study by Zhang et al., LDH nanoparticles were combined with a fluorinated biopolymer that gave a material of a superior MRI imaging capabilities [9]. Signal from ^{19}F NMR/MRI present in the obtained material was quenched at physiological conditions but gets promoted following the reduction under mild acidic conditions. Mechanism of this behavior was based on a partial dissolution of Mn(II) from the Mn-LDH nanoparticles and subsequent reduction in the effect of paramagnetic relaxation.

Another potential application of LDH nanoparticles as a support is near-infrared (NIR) in vivo optical imaging [196]. It has been demonstrated that amine modified LDH can successfully intercalate fluorescent dye or indocyanine green (ICG) by electrostatic interactions. Furthermore, GTA was used as a cross-linking agent to coat amine modified LDH with different amount of chitosan. This hybrid material exhibited numerous advantageous properties over the sole fluorescent dye. Accordingly, dye molecules were intercalated among the LDH layers that prevented leaching and metabolizing under physiological conditions. Cytotoxicity of the obtained agent was at low level. Coating functional fluorescent LDH-based nanoparticles with chitosan did not result only in an improved stability and bioavailability, but also brought advantageous biodistribution. In other words, important outcome of the study is also an organ-specific delivery system that is based on the different amount of covalently bonded chitosan. Uncoated LDH-ICG targeted liver and spleen, while particles coated with higher biopolymer content preferable accumulated in lung and liver [196].

As mentioned above, in vivo PET imaging represents another opportunity of utilization of advantageous LDH properties. Chelator-free labeling of BSA modified Mg_2Al-LDH has been successfully achieved by simply mixing LDH with a variety of PET isotopes [183]. BSA modification tremendously increased colloidal stability of the material in a culture medium but also influenced in vivo biodistribution of radio labelled LDH nanoparticles making them more suitable for the targeted applications.

Beside utilization of LDH-biopolymer hybrids for bioimaging purposes, investigations related to the therapeutic application of these materials are the most reported studies in the literature. These cover a wide range of applications such as anticancer agents [77,199,200], anti-restenosis drug [201], hybrids against reactive

oxygen species (ROS) [184], anti-microbial agent [202–204] and photodynamic therapy [205]. Cancer remains still the most investigated topic when therapeutic purposes of LDH-biopolymer composites are discussed. Different approaches were presented in the literature, namely intercalation of an anti-cancer drug with a subsequent biopolymer decoration [199], multifunctional LDH-based nanomedicine that combines different therapies in one process [5] and the most advanced nano-vaccine approach [77] that has also been recently reviewed by Zhang et al [2].

The utilization of advantageous properties of LDH nanoparticles was demonstrated by Minnelli et al. in a study that exhibits encapsulation of a natural drug, stilbenoid polyphenol of confirmed antitumor activity (resveratrol, RES), between LDH nanosheets that were further coated by BSA. This study successfully combined molecular dynamic simulations with experimental studies showing an efficient intercalation of RES in the interlamellar space of LDH-BSA hybrid clay. The obtained material was stabilized by intermolecular interactions. Further characterization of the developed composite was performed by attenuated total reflection Fourier transform infrared spectroscopy, XRD and transmission electron microscopy. In addition to encapsulation efficiency, drug release of LDH-RES and LDH-BSA-RES was also probed. Both hybrids demonstrated no burst effect due to strong interaction of the hydrophobic RES molecule with the LDH nanosheets. Interestingly both materials exhibited a release of half amount of the active compound in the first 7 h of the experiments, which was followed by an almost complete drug release within 24 h in the case of non-coated LDH-RES. Finally, anticancer ability of the obtained nanohybrid was evaluated in human lung cancer cell line (A549). This proved the higher activity of the intercalated drug in comparison to the free compound that is characterized by a poor water solubility and bioavailability [199].

Challenges related to the cancer recurrence and metastasis are more difficult that the elimination of the primary tumor. Strategies tackling with this issue are often bimodal and use combined radiotherapy and chemotherapy (CTX) and photothermal therapy (PTT) in addition to immunotherapy. A recent study by Zhang et al. [5] represents a pioneering work that demonstrate a multimodal approach that utilized a nanomedicine composite, which integrates three therapeutics, namely, indocyanine green (for PTT), DOX (for CTX) and CpG (for immunotherapy) (Fig. 10). This unique combinational therapy granted a full elimination of primary tumor, prevention of lung metastasis and promoted in situ immunity that further inhibited distant reinoculated tumor growth in 4 T1 breast cancer model. This LDH-based biohybrid demonstrated high efficiency at significantly lower doses than three Food and Drug Administration (FDA)-approved drugs providing an alternative cancer treatment that can be more effective and low-cost compared to traditional therapies [5].

Combination of a tumor growth inhibition with a long-lasting continuous protecting immunity represents most wanted goal for modern medicine. One of the possibilities is the utilization of LDH-based nano-vaccines against cancer. Recent study by Zhang et al. demonstrated the formation of nanovaccines composed of a model antigen ovalbumin (OVA) and bioadjuvant CpG. LDH was prepared with the same composition, but different average sizes ranging from 77 to 285 nm. In addition, these vaccines were applied intravenous instead of traditional subcutaneous vaccination. Interesting observation was that the larger LDH particles of 215 nm promoted dendritic cells to present the most antigen and

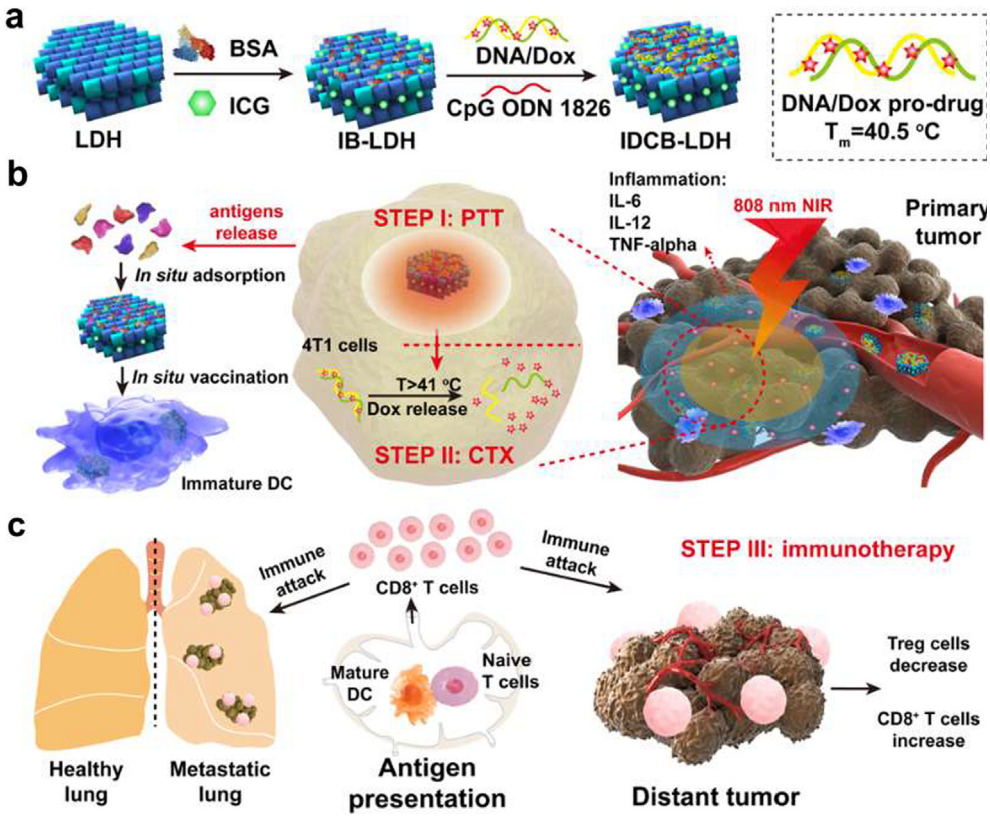

Fig. 10. Schematic representation of functional material preparation and operation that can combine chemotherapy and photothermal therapy in addition to immunotherapy. Reprinted (adapted) with permission from (Development of Multifunctional Clay-Based Nanomedicine for Elimination of Primary Invasive Breast Cancer and Prevention of Its Lung Metastasis and Distant Inoculation, 11, L.-x. Zhang, X.-m. Sun, Z.P. Xu, R.-t. Liu, ACS Applied Materials & Interfaces, 2019, 35566–35576). Copyright (2022) American Chemical Society.

showed the elevated spleen enrichment. In addition, in vivo immunologic experiments proved that the same vaccine induced the most potent antitumor immune response and a complete prevention of tumor growth. Another conclusion arising from the study highlights the advantage of an intravenous injection over the subcutaneous application in terms of vaccine efficiency [77].

Surgical removal of atherosclerotic lesions and blood flow restoration can lead to a restenosis of the artery. These conditions can often be treated by low molecular weight heparin (LMWH). However, disadvantages were discovered, and they are mostly related to the low cellar uptake and inaccurate treatment by elevated drug concentration due to inability to act locally and precisely. LDH nanocarriers can ultimately present a vector for a heparin delivery either by intercalation [201] or immobilization on the LDH outer surface [108]. In a study by Gu et al, low cytotoxicity LDH nanoparticles were used as carriers for LMWH that was intercalated and tested in vitro [201]. Successful synthesis of a novel anti-restenotic drug was confirmed by inhibition of a smooth muscle cell proliferation and migration by more than 60 % over the period of 3 to 7 days in comparison to the control. Moreover, LMWH-LDH hybrid demonstrated different cell uptake mechanism than LMWH alone. Although the underlying mechanism needs further investigation and clarification, it inevitably provided more rapid drug absorption by muscle cells as well as long and sustained uptake [201]. The following study used all previous advantages of LMWH-LDH hybrid but went one step further by introducing a specific antibody for a local targeting [206]. Successful conjugation of the antibody recognizing cross-linked fibrin D-dimer to LDH nanoparticles was achieved. Heparin conjugation with a desired antibody was performed by an initial activation of hydroxyl groups of heparin molecules by maleimide, while thiol functionalities were introduced to 1D2 antibody through the existing amino groups. The resulting (bio)nanocomposite 1D2-LMWH-LDH showed high efficiency in targeting the injured artery wall and subsequent reduction of restenosis and thrombus formation [206].

ROS are inevitable sub-product of cell metabolism, but still represent a major treat to the health of a living organism. In addition, ROS level is elevated in many cancer cells. One possibility to lower the level of these dangerous species is the supplementation of antioxidant enzymes. However, this raises numerous issues related to the low stability (or high sensitivity to environmental conditions) of these biocatalysts. A potential way of overcoming previously mentioned obstacles is enzyme immobilization on the surface of carriers, like LDH [184,207]. ROS-scavenging hybrid materials was recently developed by sequential adsorption of heparin and poly-L-lysine as oppositely charged polyelectrolytes of high charge density. Superoxide dismutase and horseradish peroxidase enzymes were embedded between the polyelectrolyte layers. The resulting hybrid material possessed high colloidal stability without enzyme leakage and most importantly, high enzymatic activity of the immobilized enzyme cascade. Furthermore, in vitro tests were performed demonstrating high degradation of ROS generated in human cervical adenocarcinoma cells [184]. Unique combination of excellent colloidal stability and effectiveness to consume ROS made this material a promising candidate for further drug trials.

LDH-biopolymer hybrids have also been utilized for antimicrobial purposes related to the wound healing or oral application. In several recent studies, LDH nanoparticles were loaded by different antimicrobial drugs, namely ciprofloxacin and silver sulfadiazine [203,204,208]. The obtained LDH-drug complex was furthermore combined with different (bio)polymeric structures, like hyaluronan [204], alginate [208] or polylactic acid [203], in order to obtain functional antimicrobial material that can successfully cover a wound and enhance its healing by protection from Staphylococcus aureus or Escherichia coli. Beside wound healing application, LDH-CMC bio-nanocomposite hydrogel proved to be an efficient controlled-release nanocarriers for colonic bacterial infections treatment [202]. The swelling results of the obtained hydrogel beads exhibited strong pH-dependent properties, which made them a promising future candidate for amoxicillin oral delivery [202].

FDA agency approved a NIR fluorescent dye, ICG, to be intercalated inside the LDH interlayer spacing, which granted a novel hybrid material with advantageous properties for photothermal therapeutic applications [205]. Photosensitizer ICG stabilization in the LDH nanostructure demonstrated superior properties for a photodynamic therapy due to low leaching and prevented ICG metabolization in the physiological conditions. The best performing material was the one coated with two layers of chitosan by applying GTA as a spacer for a covalent grafting of biopolymer to the nanoparticle surface. A recently published follow-up study went one step further by addition of an acid-responsive BSA-DOX prodrug to the already reported ICG intercalated LDH nanoparticles [76]. Accordingly, natural clay-based photochemotherapeutic agent (ICG/LDH@BSA-DOX) was obtained. The synthesized material possessed synergistic features to induce skin cancer apoptosis that was induced by acid-triggered release of DOX followed by a simultaneous heat generation and local production of ROS upon laser irradiation. This work provided a novel strategy to design anticancer drugs to significantly decrease applied drug dosages and therefore, to decrease the side effects in clinical applications [76].

Another promising field for application of LDH nanoparticles and their polymer functionalized derivatives is the usage as biomedical implants, as it was discussed in a recent review by Rojas et al. [209]. Accordingly, advantageous morphological properties of LDH particles in combination with their functionalization with various biopolymers, like chitosan and gelatin, were exploited to produce novel biomedical implants. These implants can adequately replace a missing part of a tissue, e.g., bone engineering [210], or simply represent a biodegradable implant that resorbs after performing its therapeutic task, such as the case of antimicrobial wound dressing [203,204].

5.2. Gene delivery platforms

Viral vectors remain the most efficient gene delivery vehicles, but their application is often followed by elevated cytotoxicity and activation of an immune response. Some non-viral vectors are also quite common, as reported in the literature. Accordingly, lipid nanoparticles, liposomes, and different polymeric and nanoparticle carriers were extensively used. Relatively high surface charge density and ion-exchange capabilities of LDH nanoclays granted them a promising spot in gene delivery applications as non-viral vector. Interactions among biopolymeric structures, like DNA, have already been discussed in the previous sections of this review. Nevertheless, physisorption of negatively charged DNA or RNA molecules on the positively charged LDH surface remains just one of the possibilities for the formation of DNA-LDH or RNA-LDH hybrids, beside covalent linkage, and intercalation.

A study from 2014 by Balcomb et al. demonstrates the ability of LDH to adsorb different amounts of DNA molecules by electrostatic attraction [211]. LDH nanocarriers also provided a certain level of protection of DNA molecules from nuclease digestion. Moreover, all DNA-LDH hybrids caused significant promotion of luciferase gene expression, while maintaining low cytotoxicity towards human embryonic kidney (HEK293), cervical cancer (HeLa) and hepatocellular carcinoma (HepG2) cell lines.

Approaches based on the physical adsorption on the particle surface is the least labor-intensive approach, but often suffers from

increased leakage. For this purpose, it is also possible to covalently bound DNA molecules, which would not present disadvantage during delivery due to dissolution of LDH particles at lower pH values [151]. This was achieved through the salinization of LDH surface that introduced amino groups, which were able to react with a C-terminal part of a single stranded DNA (ssDNA). In most previously published studies, only the outer surface of the LDH nanoparticle has been exploited. For that reason, LDH can also be delaminated prior to functionalization, which can further provide better cell membrane penetration, beside the evident lower amount of the utilized carrier for the same amount of adsorbed DNA [212].

The most promising approach to obtain DNA that is protected from enzymatic and thermal degradation is to intercalate DNA into the interlayer gallery of LDH. Recently published work by Senapati et al. successfully proves this hypothesis [145]. Intercalation of DNA was proved by comparing XRD patterns of pristine LiAl-LDH with a DNA-LiAl-LDH, where a strong shift of the 003 peak, which confirms the change in interlayer distance. The LDH-based nanovehicle demonstrated low cytotoxicity with a high cellular uptake and pH-sensitive cargo release (Fig. 11).

5.3. Bone tissue engineering

Engineering of novel bone tissue scaffolds has recently become a hot topic in the scientific community and therefore, it is covered in several review articles [213–215]. These scaffolds need to possess a specific pore size between 100 and 150 μm, but in some cases even larger pores are essential for osteogenesis and angiogenesis. Beside porous structure, significant mechanical strength, biodegradability, cell penetration ability and osteoconductivity are vital features. It is clear from all previously mentioned prerequisites that LDH clay solely would hardly be able to perform this task, nevertheless, LDH-biopolymer hybrids represent a promising class of material to deal bone tissue engineering challenges [210,216,217].

The most evident approach in bone tissue scaffold engineering is to use natural bone mineral hydroxyapatite (HA) and try to com-

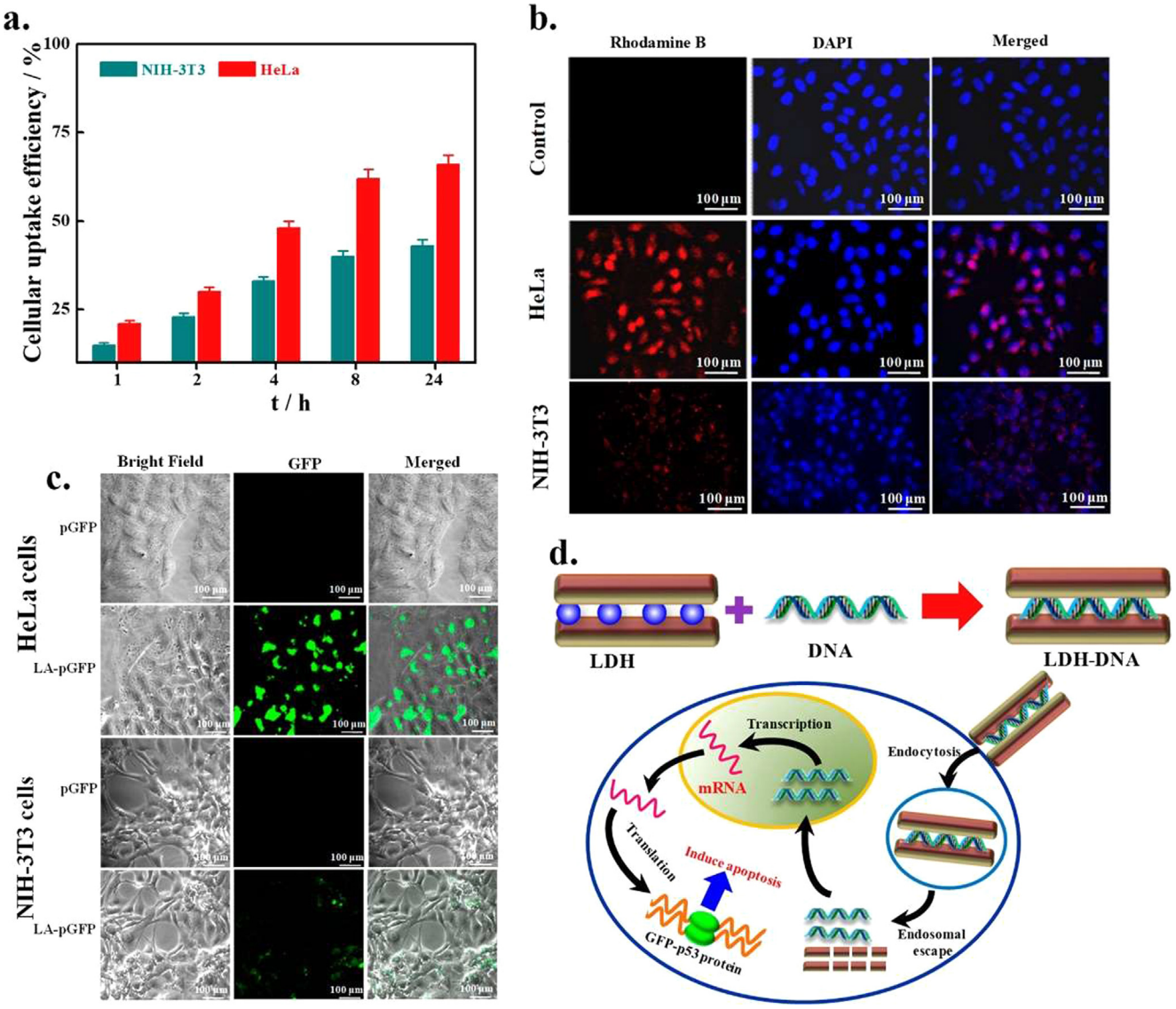

Fig. 11. Cellular uptake kinetics of rhodamine-B labeled LDH nanoparticles in NIH-3 T3 and HeLa cells (a), fluorescence images of two cell types demonstrating successful cellular uptake with a control experiment (b), fluorescence images of HeLa and NIH-3 T3 cells transfected with naked GFP-p53 and LDH-(GFP-p53) (c) and schematic illustration of DNA intercalation and gene transfection (d). Reprinted (adapted) with permission from (Layered Double Hydroxide Nanoparticles for Efficient Gene Delivery for Cancer Treatment, 30, S. Senapati, T. Sarkar, P. Das, P. Maiti, Bioconjugate Chemistry, 2019, 2544–2554). Copyright (2022) American Chemical Society.

bine it with LDH and diverse biopolymers to get desired material properties [210,218,219]. LDH nanoplates were successfully combined with HA and gelatin (G) by layer solvent casting combined with freeze-drying and lamination techniques. The obtained material demonstrated a microstructure of high porosity (ranging from 82 % to 92 %) similar to the natural spongy bone [218,219]. Mechanical properties of the materials were also satisfying with an adequate Young's modulus. SEM micrographs, in addition to the alkaline phosphatase activity and Alizarin red staining results, suggested an advantageous performance of LDH-HA/G in comparison to LDH/G. Rabbit adipose stem cells (ASCs) were also seeded on the LDH-HA/G scaffolds. Moreover, different scaffolds with or without ASCs were planted on the critical damage made on the left radius, which after 12 weeks demonstrated accelerated bone regeneration with a significantly improved quality of new bone formed in the presence of ASCs [219]. The immediate follow-up study by Fayyazbakhsh et al. also revealed the potential application of vitamin D3 that can be encapsulated within gelatin through one-step dissolution method [210]. Vitamin D3 encapsulation gave rise to controlled release without burst effect, which further had a strong signaling effect and caused improved biomineralization and cellular response. As a result, several scaffolds were obtained, namely, LDH/G, LDH-HA/G, LDH/G-D3 and LDH-HA/G-D3. Three properties were measured and compared, scaffold porosity, secondary HA crystal formation after treatment with simulated biological fluid (SBF) and cellular interactions with scaffolds (Fig. 12) [210].

Beside usage of HA, several studies demonstrated excellent osteogenic performance of LDH-based hybrid material by combination with polycaprolactone (PCL) [220] or β-tricalcium phosphate [221]. Although they are chemically different, both materials exhibited similar porosity and presented a possible alternative to a typical HA-based bone tissue scaffold. Furthermore, a novel poly(lactide-*co*-caprolactone) copolymer-LDH hybrid network was proposed as controlled ion release agent for artificial bone tissue regeneration [188].

5.4. Detection schemes based on LDH

Immobilization or intercalation of various biopolymers (alginate, chitosan, etc.) and biomolecules (enzymes, DNA, etc.) often resulted in a promising LDH biohybrid used for sensing purposes of numerous analytes. Majority of sensing schemes involving LDH substances are electrochemical sensors [150,156,193], but there are few examples of fluorescence-based assays [140]. Extensively investigated electrochemical sensors utilize the advantageous properties of LDH materials that can easily be deposited in the form of thin films on the electrodes, together with a certain biopolymer. These films are manufactured using several methods

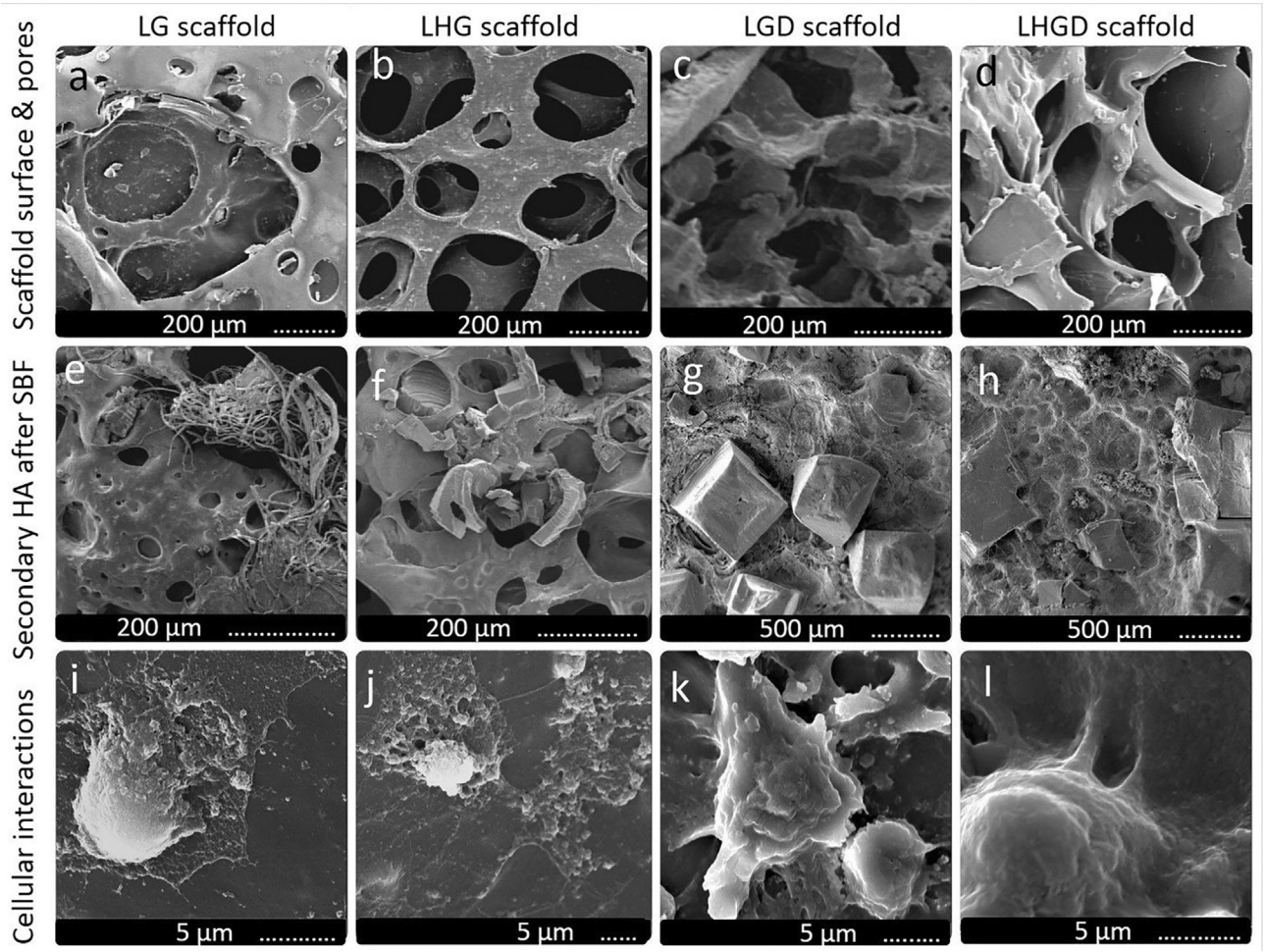

Fig. 12. SEM micrographs of various scaffolds demonstrating surfaces and pores (first row), formation of secondary HA crystals after SBF (middle row) and scaffold's cellular adhesion (bottom row). Reprinted from (Release behavior and signaling effect of vitamin D3 in layered double hydroxides-hydroxyapatite/gelatin bone tissue engineering scaffold: An in vitro evaluation, 158, F. Fayyazbakhsh, M. Solati-Hashjin, A. Keshtkar, M.A. Shokrgozar, M.M. Dehghan, B. Larijani, Colloids and Surfaces B: Biointerfaces, 2017, 697–708). Copyright (2022), with permission from Elsevier.

including solvent casting, layer-by-layer (LbL) assembly, and electrodeposition [12].

Advantageous properties of these films are related to the increased sensitivity of the amperometric probes. For instance, coating an electrode with an LDH-glucose oxidase composite can lower the limit of detection with a few orders of magnitudes [222]. For this reason, LDH-enzyme biohybrid coated electrodes are very abundant throughout the literature. The applied biohybrids include electrogeneration, adsorption or chemical grafting of various oxydoreductive enzymes at LDH interface, such as polyphenol oxidase [223], glucose oxidase [224], lactate oxidase [225], horseradish peroxidase [50], cytochrome *C* [51], to name a few. Large variety of analytes (catechol, phenol, cresol, DOPA, tyrosine, glucose, choline, lactate, cholesterol, etc.) could be successfully detected and quantified. In addition, enzyme substrates and enzyme inhibitors were also among the targets.

Nevertheless, it is important to note that efficient enzyme adsorption procedure is crucial for sensor performance. Simple physical adsorption of the biocatalysts provides a higher loading, which is directly reflected in a lower limit of detection, while covalent grafting grants higher limits of detection, but possibly longer lasting electrodes owing to the prevented enzyme leakage.

Adsorption of nucleic acid aptamers on LDH nanoclay can also provide sufficient sensing platforms for detection of proteins, such as thrombin [150]. Development of this type of sensor, so-called aptasensor, was just recently reported exhibiting very low limits of detection for this model protein, with a relatively wide linear range.

Beside electrochemical sensors, LDH based hybrids were also used in a fluorescence quenching scheme for a DNA detection [140]. The quenching efficiency of LDH to 5(6)-carboxyfluorescein attached to single ssDNA (FAM-ssDNA) was about 88 % and after FAM-ssDNA hybridization with a complementary DNA oligonucleotide was about 33 %. These values are very similar to the more expensive ZIF-8-La sensing material, which is also complicated to prepare [226].

6. Conclusions and outlook

To conclude, LDHs are versatile materials applied in different areas of biomedical science. Their interaction with biopolymers such as nucleic acids, bio-polyelectrolytes and proteins are widely utilized to prepare hybrid substances with improved structural stability, biocompatibility, and cellular uptake. Such composites may act themselves as therapeutic agents or building blocks in more complex biomaterials, which are being developed to address and mitigate multiple bottlenecks to deal with unmet clinical needs in tissue engineering, design of artificial organs, implants, bioinks for bioprinting platforms, microfluidics, bioactive scaffolds, wearable, and implantable devices as well as in-vitro diagnostics, for instance.

Despite the large number of results disseminated to date, several fundamental and practical features must be reconsidered or improved on a path of their clinical translation. For example, although numerous research groups made considerable advances in the synthetic strategies of LDH-biopolymer-based materials, only a handful scientists addressed the issue of colloidal stability of such systems. Given the fact that these bioactive materials are used in biofluids, possible aggregation processes not only hinder the activity, but also induces undesirable effects such as blocking veins or cellular transport channels. Therefore, comprehensive studies dealing with the determination and analysis of surface charge properties and interparticle forces must be carried out to improve the resistance against particle aggregation in biologically relevant media. This type of studies will also need to be performed in biofluids or using biofluid models to facilitate the clinical translations. However, the complexity of such biofluids often, at the same time, hinders the probing of colloidal stability of LDH nanoparticles, therefore, methodological development is also needed. This is of a crucial importance for any future delivery applications, where LDH particles are used as a non-viral vector. These delivery applications are often linked to the detection of biochemical markers that grant information regarding the target efficacy. However, especially colorimetric assays are prone to failure caused by strong adsorption of organic chromophores on LDH surface.

Besides, reproducibility of LDH synthesis protocols is often questionable, especially once complex structures are required to form for specific applications. To further improve preparation techniques, several experimental parameters must be considered and optimized. This requires extended synthetic studies involving experimental and theoretical approaches. Fundamental investigations on the interfacial structure of LDH-biopolymer composites are also needed to better understand the function and structure of the hybrid materials. Prior to these studies, previous results from different disciplines must be combined and understood to develop more effective LDH-biopolymer hybrids for future use.

Nevertheless, such LDH-biopolymer composites represent an important class of materials in biomedical applications and show great potential in more applied disciplines. For instance, immobilized antioxidant enzymes are becoming powerful candidates to reduce ROS level in product manufacturing processes in the textile, food, and cosmetic industry.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

The authors thank for the financial sources to the National Research, Development, and Innovation office (SNN131558) and to the Ministry of Innovation and Technology of Hungary (TKP2021-NVA-19). The support from the University of Szeged Open Access Fund (5767) is gratefully acknowledged.

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