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Mechanochemical Loading of Doxorubicin on the Surface of Magnesium and Zinc-Based Layered Double Hydroxides

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Abstract: In the search for technologies and materials to improve the safety and efficacy of active ingredients used in treating diseases, layered double hydroxides (LDHs) have been proposed as drug carriers since they can enhance the effects of active ingredients and even reduce toxicity. Doxorubicin (DOX) is one of the most widely used and studied antitumor drugs due to its broad spectrum; however, due to its low plasma bioavailability and slow systemic clearance, only a small fraction of the drug reaches and acts on the tumor, so LDHs have been proposed as vehicles to solve these disadvantages. The most used method to load the drug is incubating LDH particles in DOX solutions. In this work, two additional methods, co-precipitation, and mechanochemical reaction, were explored to evaluate the structural stability of the vehicle and the amount of DOX retained by LDHs structured by magnesium/aluminum and zinc/aluminum cations, which are the two most common compositions to design materials for biomedical applications. The zinc/aluminum LDH structure degraded in the loading process, whereas the magnesium/aluminum LDH particles were stable against the three loading processes. The mechanochemical procedure, a green and sustainable technology, loaded the highest content of DOX.

Keywords: hydroxide; doxorubicin; vehicles; loading process

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Academic Editor: Keith J. Stine

Received: 11 February 2025
Revised: 18 March 2025
Accepted: 19 March 2025
Published: 21 March 2025

Citation: Ventura Muñoz, M.G.; Lara Cerón, J.A.; Gallegos Saucedo, M.d.J.; Carbajal Arizaga, G.G. Mechanochemical Loading of Doxorubicin on the Surface of Magnesium and Zinc-Based Layered Double Hydroxides. *Processes* **2025**, *13*, 931. https://doi.org/10.3390/pr13040931

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1. Introduction

One strategy to improve therapies and treatments against diseases is the development of vehicles or forms of administration of known drugs. Liposomes are one of the most efficient routes for the transport of poorly soluble drugs. However, micelles can become destabilized when in contact with different chemical environments during the trajectory within the body. A proposal that has been explored by several research groups is the use of layered double hydroxide (LDH) nanoparticles as transport vehicles [1,2].

These particles can tune the release rate of drugs [3] and even control the release in the stomach or intestine environments, depending on their chemical composition [4]. Layered double hydroxides are inorganic structures whose composition is represented by the general formula $M(II)_{1-x}M(III)_x(OH)_2]^{x+}A^{n-}{}_{x/n}$, where M(II) and M(III) are metal cations organized in a two-dimensional structure upon coordination with -OH ions. The resulting layer retains a charged residue (x+) that is stabilized by interlayer anions, $A^{n-}{}_{x/n}$ [5]. A particle of LDH results from an alternate stacking of cationic layers and anions.

The popularity of LDHs lies in the wide range of compositions enabled by the large number of metal cations that can be combined, the different values of X, and the interlaminar anions that can be selected. Additionally, the exchangeability of the A^{n-} anion is exploited

on many occasions for substitution by the drug to be transported. This exchange approach is preferable for compounds that form stable anions, such as carboxylates, resulting in LDH particles retaining the drug within the crystal lattice. However, LDHs can also transport drugs on external surfaces, i.e., without intercalation, with the same advantages as that of a drug transported by a nanovehicle. The external adsorption phenomena occur in molecules like doxorubicin (DOX) [6]. In addition to the flexibility of its chemical composition, there is also the diversity of structures, shapes, and sizes, enabling several applications [5]. One example of its use is as a lubricant. It can act as a matrix to hold organic gasses and allow their carbonization. They are also environmentally friendly by reducing the amount of inorganic waste from synthesis processes, as occurred with the formation of NiAl-CO_3 LDH particles, which has significantly improved the tribological performance of in situ carbon layers that can be used as lubricants under extreme loads and high shear stresses without the need for inspection and reworking of coatings [7].

LDHs are also used as delivery systems for cosmetic active ingredients due to their potential to stabilize them and improve rheological properties, specifically in emulsions.

Cinnamic acid and its derivative, p-methoxy cinnamic acid, have been inserted into the interlayer space of an LDH. LHDs show a great capacity for attenuating UV rays while being transparent in the region of visible light. It has also been reported that the oxidation of castor oil added to cosmetic and nutritional formulations caused by the air decreases when cinnamic acids are intercalated in the LDHs [8,9].

A novel application is the use of LDHs as an alternative to the white pigments currently used in the food, cosmetic, and pharmaceutical industries. To this end, LDHs were prepared with magnesium and aluminum, and surface-modified with casein and carboxymethylcellulose (CMC), and compared with currently used whiteners such as food-grade titanium dioxide (E171), rice starch, and silicon dioxide (E551). The experiment showed that the aqueous suspension of LDH is heat and pH-stable and outperforms current alternatives such as rice starch and silicon dioxide (E551) [10].

Likewise, strategies for recovery from spinal cord injury have been explored using magnesium and aluminum LDH, evaluating the functions of neuronal regeneration and immune regulation in mice. The experiment achieved significant performance in accelerating neural stem cell (NSC) migration, neural differentiation, L-Ca^{2+} channel activation, and the generation of inducible action potentials [11].

The bottom-up synthesis of LDHs from soluble salts of M(II) and M(III) cations, and the addition of the drug to this solution, producing particles when alkalinized with sodium hydroxide, is another common procedure for drug loading in LDHs. This procedure retains the drug inside the particles during crystal formation. This method, known as co-precipitation, is efficient for molecules with carboxylate groups, such as ibuprofen [12]. However, in some cases, the co-precipitation is not successful for the intercalation of some molecules, especially those that do not produce stable anions, like polyphenols. In this case, the retention occurs by adsorption onto the external surfaces, and the formed particles retain the activity of the organic compounds [13]. Therefore, it can be concluded that there is no absolute method of synthesis and that for each molecule to be loaded into or onto an LDH particle, different methods must be explored to select the most appropriate one.

In the case of DOX, the synthesis method to produce the loading is achieved by dispersing LDH nanoparticles in a DOX solution, which is a wet impregnation [6]. This work aims to compare the traditional wet synthesis methods and include the mechanochemical process, which to date has been widely explored for LDH synthesis, but not for forming intercalation products [14]. This method has the advantage of avoiding the use of solvents during the synthesis and reducing energy consumption.

In this article, we explore the traditional "exchange" process to incorporate DOX in LDH particles and compare it with the co-precipitation and mechanochemical procedures. The assays were conducted with the magnesium and zinc-based compositions of LDHs, which are proposed for biomedical studies owing to their null or low toxicity [15,16].

2. Materials and Methods

All reagents were of analytical grade and no additional purifications were performed.

2.1. Magnesium (MgAl-NO_3) and Zinc (ZnAl-CO_3) Layered Double Hydroxides

A 100 mL solution was prepared with magnesium nitrate and aluminum nitrate in a Mg:Al molar ratio of 2.5:1. The suspension was stirred and 12% NH_4OH was added until pH 9.5 was reached. The suspension was stirred for 24 h. Then, the product was recovered by centrifugation, washed with deionized water, and dried for 72 h at 55 °C. The solid obtained was ground in an agate mortar and identified as MgAl-NO_3. The reaction with zinc nitrate was prepared with a solution of zinc nitrate and aluminum nitrate in the ratio of 2.5:1 following the above procedure. The product was identified as ZnAl-NO_3.

2.2. Loading Attempt by Anion Exchange

In a beaker containing 25 mL of deionized water, 0.030 g of doxorubicin (DOX) was added. The solution was stirred until DOX dissolution was achieved. Subsequently, 0.104 g of MgAl-NO_3 (or ZnAl-NO_3) was added, and the mixture was stirred until homogenized. A drop of 1 M NaOH was added to adjust the pH to 7. The suspension was stirred for 24 h. Then, the solid was recovered by centrifugation and dried in an oven for 24 h at 50 °C. The resulting purple powder was pulverized in an agate mortar until a fine powder was obtained. The samples were labeled as MgAl-DOX/Exch and ZnAl-DOX/Exch.

2.3. Loading Attempt by Co-Precipitation

20 mL of solution containing the metal cations Mg(II) and Al(III) were prepared by dissolving the mass of salts indicated in Section 2.1. To this solution, 0.010 g of DOX was added and stirred until homogenized. Then, 6% NH_4OH was added to pH 8.5 to induce the formation and precipitation of LDHs with doxorubicin.

The zinc-based sample was prepared by switching to a solution of Zn(II) and Al(III) cations. Both experiments were left in agitation for one day. They were then centrifuged to separate the solid. The products were washed with deionized water and dried for 24 h at 55 °C. They were then pulverized in agate mortar until a fine powder was obtained and labeled as MgAl-DOX/Exch and ZnAl-DOX/Exch.

2.4. Loading Attempt by Mechanochemical Reaction

A mixture was prepared with 0.100 g of MgAl-NO_3 (or ZnAl-NO_3) with 0.030 g of DOX. The mixture was placed in an agate mortar and ground for 20 min. A few drops of ethanol were added to form a paste to facilitate homogenization. Subsequently, the paste was transferred to a centrifuge tube, mixed with 25 mL of deionized water, and stirred to promote the release of DOX from the LDHs and ensure that the recovered powder contained exclusively DOX, chemically attached to the particles. The sample was then centrifuged at 5000 rpm for 5 min, and the washing process was repeated three times. The sample was transferred to a drying oven for 24 h at 55 °C and pulverized in agate mortar until a fine powder was obtained. The sample was labeled as MgAl-DOX/Mec (or ZnAl-DOX/Mec).

2.5. Solid-State Characterization

All powder samples were placed directly in a glass sample holder. The analysis was performed on a PANalytical diffractometer model Empyream (PANalytical, Malvern, UK); such equipment used a copper anode producing radiation with a wavelength of 0.154 nm. Reading was conducted in the 5 to 70 degrees (2θ) range with a step of 0.02 degrees and 25 s of exposure. The infrared data were collected, averaging 16 scans with a resolution of 4 cm^{-1} in the ATR mode with a Thermo Scientific apparatus model iS50 ATR (FTIR, Waltham, MA, USA).

Energy-dispersive X-ray spectroscopy (EDS) data were acquired with an OXFORD detector (Oxford model X-MaxN, High Wycombe, UK) assembled to a JEOL JSM-6610LV scanning electron microscope (SEM, Musashimurayama-shi, Tokyo, Japan) located at the Instituto Transdisciplinar de Investigación y Servicios—ITRANS, at the University of Guadalajara. The powder samples were adhered to a carbon tape. EDS data were obtained using SEM images acquired using a beam with 15 kV and 1 k magnification. The element content was measured in five zones for each sample and averaged manually. The computer program reports mass percentages, which are manually converted to moles per 100 g by dividing each percentage by the atomic weight.

3. Results and Discussion

3.1. Magnesium-Based LDH Loaded with DOX

The diffraction profile observed in the LDH MgAl-NO_3 sample mainly resembles the profile of a hydrotalcite structure [17] (Figure 1).

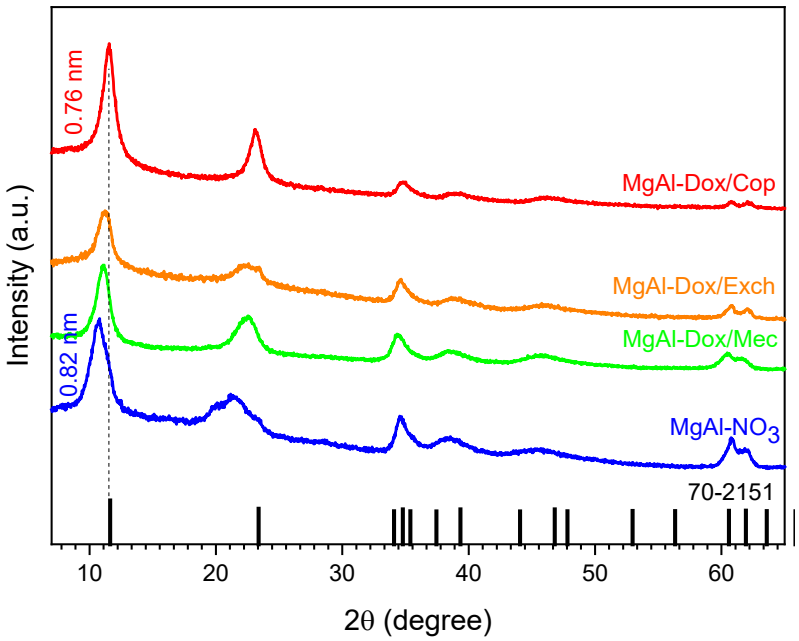


Figure 1. X-ray diffraction profiles of the MgAl-NO_3 pristine matrix and the doxorubicin (DOX) products processed by mechanochemical, exchange, and co-precipitation techniques.

However, in the diffractogram, a very broad peak is formed between 17 and 23 degrees (2 theta), which is not present in the card. In both structures, the most intense reflection appears in the same position, but the second reflection is shifted. Figure 2 shows the experimental diffractogram and the simulated profiles of hydrotalcite-type structures obtained with the MAUD (Version 2.9997) program based on two structures belonging to the space group P −6 2 m (space group 189) [18] and R −3 m (space group 166) [17]. This overlapping demonstrates the observed broadening of the MgAl-NO_3 profile.

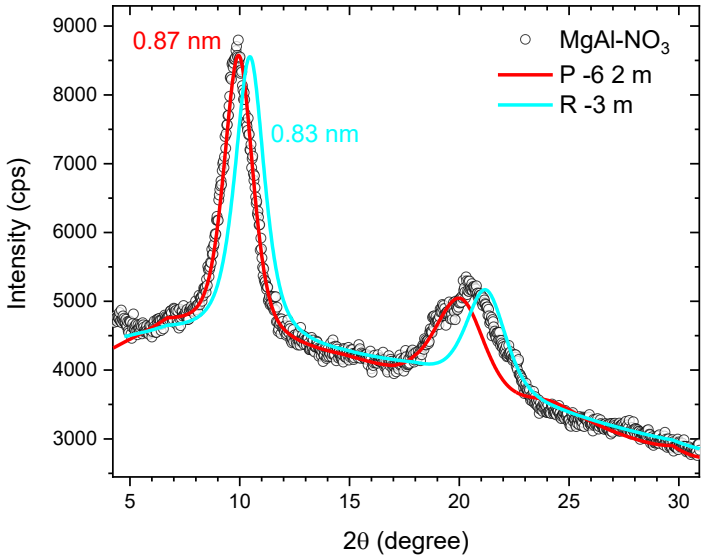


Figure 2. XRD profile of the basal reflections in the MgAl-NO_3 sample and the theoretical profiles of LDHs with two different crystal groups.

The most intense reflection in both profiles corresponds to crystal planes formed by the distance between two contiguous layers, called basal distance, and depends on the size of the anion intercalated between the layers [19]. The position of the peak transformed to a distance in the LDH Mg/Al-NO_3 sample, when calculated with the Bragg equation, corresponds to 0.87 and 0.83 nm for the P −6 2 m and R −3 m phase, respectively, which are consistent with the presence of interlayer nitrate [20,21].

When the DOX loading processes are carried out, the XRD profiles are maintained (Figure 1), especially the reflections above 30 degrees (2 theta). However, the basal reflection is slightly shifted to 0.76 nm. This lower value is associated with carbonate intercalated between the layers; this fact occurs by reaction with CO_2 from the atmosphere [22], and the aqueous medium favors it since it does not occur in the mechanochemical reaction.

IR spectroscopy analysis was performed to detect the presence of DOX in the samples (Figure 3). Firstly, MgAl-NO_3 presented a high intensity and width band around 3400 cm^{-1} related to the H-O stretching found in water and OH groups of the layers [23]. At 1360 cm^{-1}, bands related to the symmetric stretching of nitrate ions are observed [24]. Finally, below 680 cm^{-1}, bands of metal–oxygen or O-M-O stretching appear [23].

The control DOX spectrum is composed of several signals, but the bands that allow its identification in the other compounds stand out, such as the O-H and N-H and C-H signals between 3600 and 2900 cm^{-1}, C=O stretching at 1740 cm^{-1}, N-H stretching at 1650 cm^{-1}, and the high-intensity signal at 1050 cm^{-1} coming from C-O-C [25], which are shadowed in Figure 3. When evaluating the presence of this profile in the samples, the one prepared by the mechanochemical method presents the most pronounced signals at 2950, 1720, and 1050 cm^{-1}, indicating that it is the one that retained the highest amount of DOX. It is followed in intensity by the MgAl-DOX/Exch sample, with signals at 1720 cm^{-1} and slightly at 1020 cm^{-1}. It can be said that MgAl-DOX/Mec retains the greatest amount of DOX, while the MgAl-DOX/Cop sample has the least contribution to the DOX signal.

As inferred from the diffraction data, the interlayer space of the LDH particles treated with DOX is populated by carbonate anions, as represented in Figure 4. Then, the loading of the DOX molecules occurred over the external surface instead of the typical exchange reactions where the drug substitutes carbonate. The loading over the surface particles occurred regardless of the presence of two polytypes of LDH structures in the pristine sample.

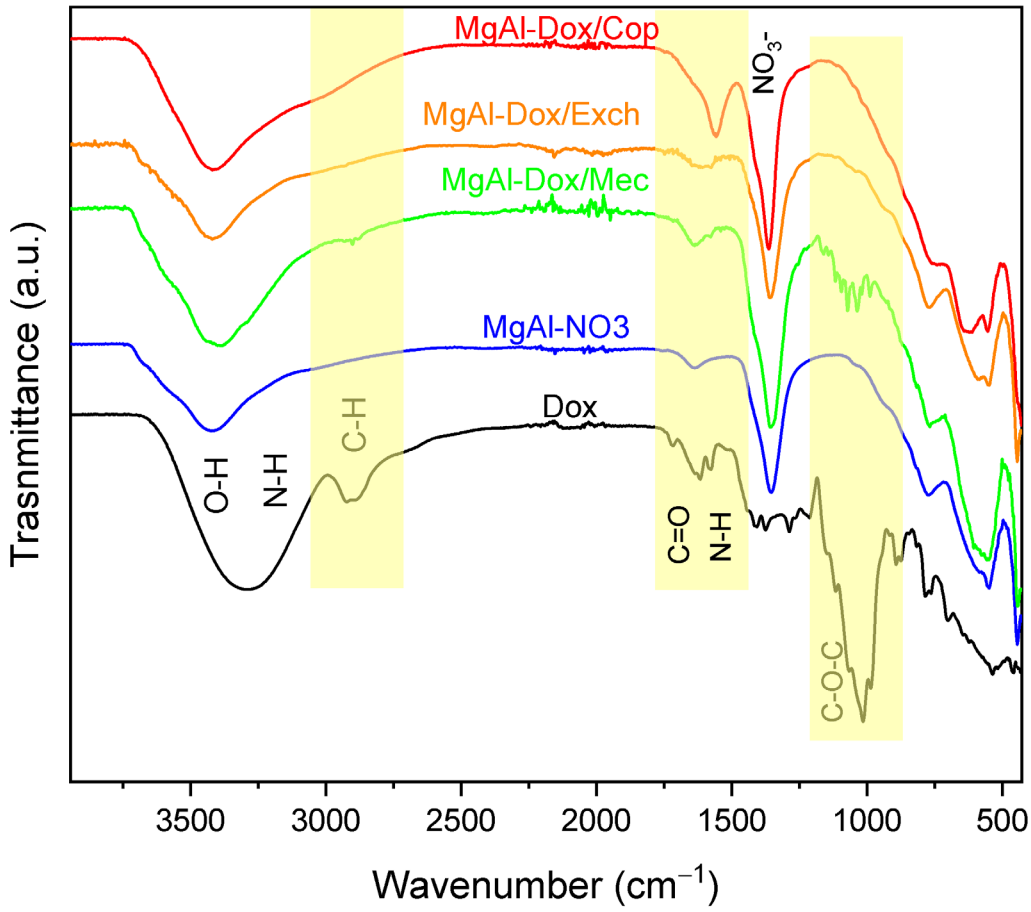


Figure 3. Infrared spectra of the Mg-NO_3 pristine matrix and the doxorubicin (DOX) products processed by mechanochemical, exchange, and co-precipitation techniques.

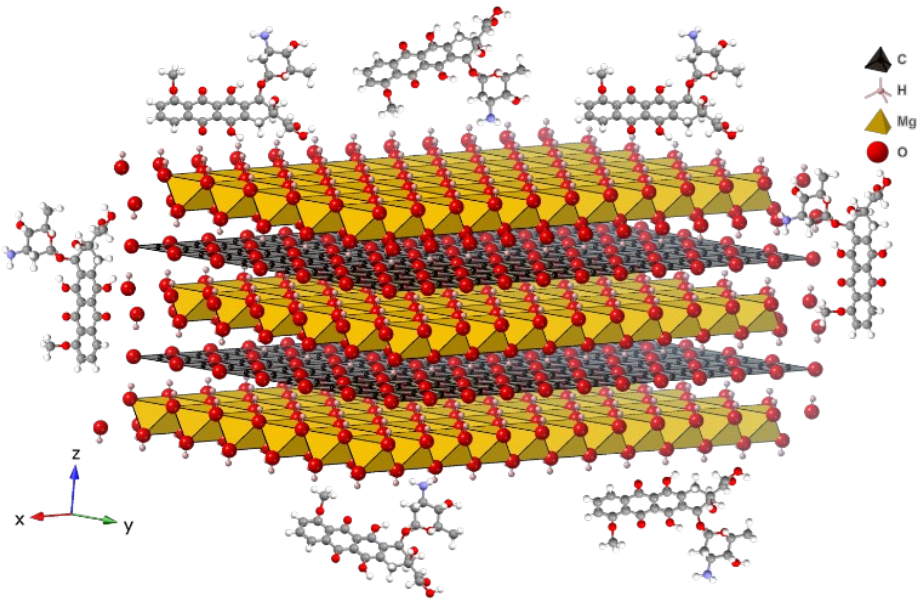


Figure 4. Representation of an LDH particle with the composition MgAl-NO_3 and DOX obtained by the mechanochemical procedure. Generated using CrystalMaker 11®. CrystalMaker Software Ltd., Oxford, UK (www.crystalmaker.com).

The data from element quantification using the EDS technique was treated to obtain the carbon content, which is an indicator of retained DOX (Figure 5a). The highest content in MgAl-DOX/Mec was 1.8 mol per 100 g of sample, which agrees with the infrared result

and confirms that the mechanochemical method is the most efficient procedure to load DOX in a LDH with hydrotalcite composition. The content of the other element taking as reference the aluminum (Figure 5b) also demonstrates the highest content of carbon in MgAl-DOX/Mec; additionally, this plot shows the molar ratio of Mg with respect to aluminum is close to 2.5:1 (dotted line in Figure 5b) indicating the chemical stability of the LDH structure.

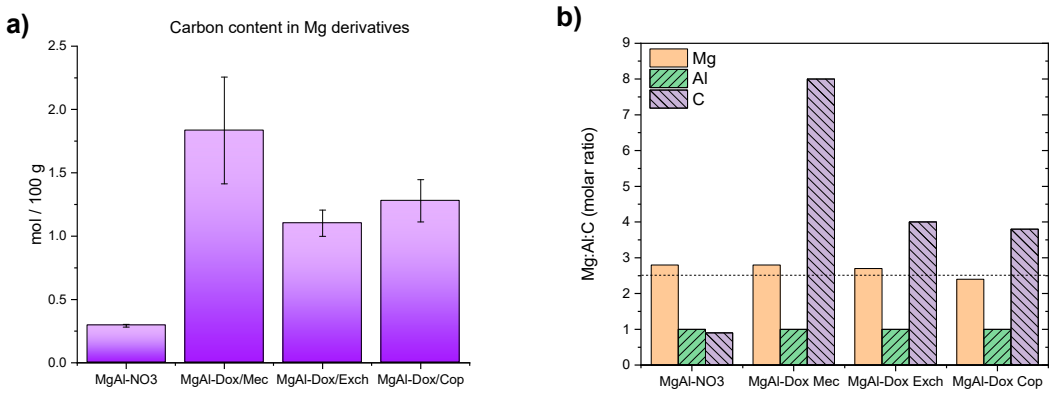


Figure 5. (**a**) Carbon content in the magnesium LDH loaded with DOX by the mechanochemical, co-precipitation and exchange procedures and (**b**) the magnesium:aluminum:carbon molar ratio in the same samples.

3.2. Zinc-Based LDH Loaded with DOX

The zinc-based matrix was analyzed by XRD (Figure 6); the profile of the ZnAl-NO_3 sample matches the profile of the 38-0486 card corresponding to an LDH of composition, $Zn_6Al_2(OH)_{16}CO_3{\cdot}4H_2O$ [26], and corresponds to a structure with R −3 m symmetry, similar to one of those found in the magnesium sample.

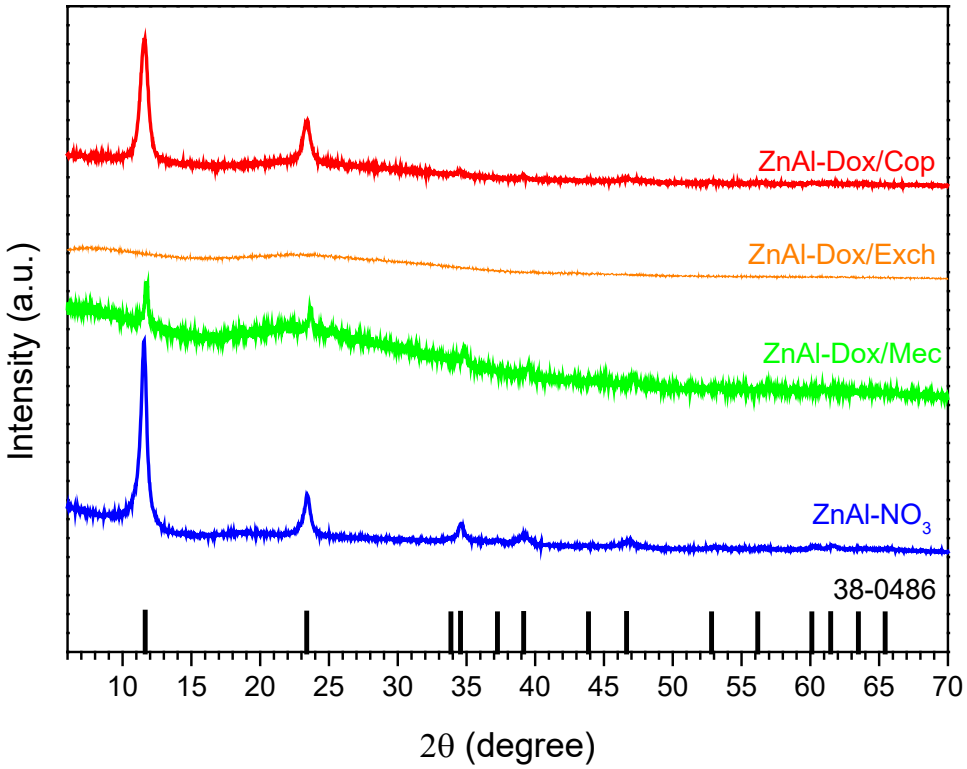


Figure 6. X-ray diffraction profiles of the ZnAl-CO_3 pristine matrix and the doxorubicin (DOX) products processed by mechanochemical, exchange, and co-precipitation techniques.

When evaluating the basal reflection, the distance between two contiguous layers is 0.76 nm, which suggests the presence of interlayer carbonate [22,27], so it can be said that a zinc-based LDH is more susceptible to carbonate contamination than a magnesium-based LDH.

Except for the ZnAl-DOX/Cop sample, where no diffraction signals were obtained indicating destruction of the crystalline arrangement, the products obtained from the mechanochemical and exchange methods present the initial LDH diffraction profile, indicating that these two methods do not destroy the LDH matrix.

Infrared spectroscopy shows that the spectrum of ZnAl-NO_3 is the same as that of the MgAl-NO_3 sample, thereby confirming the composition of an LDH (Figure 7). Even when the band at 1360 cm^{-1} is assigned to nitrate ions [23], carbonate vibrations also appear in the same wavenumber [22,27]; the presence of carbonate is corroborated by the high content of carbon (0.72 mol C/100 g) in ZnAl-NO_3 (Figure 8a) compared with MgAl-NO_3 (0.23 mol C/100 g). These data agree with the low basal space identified by XRD.

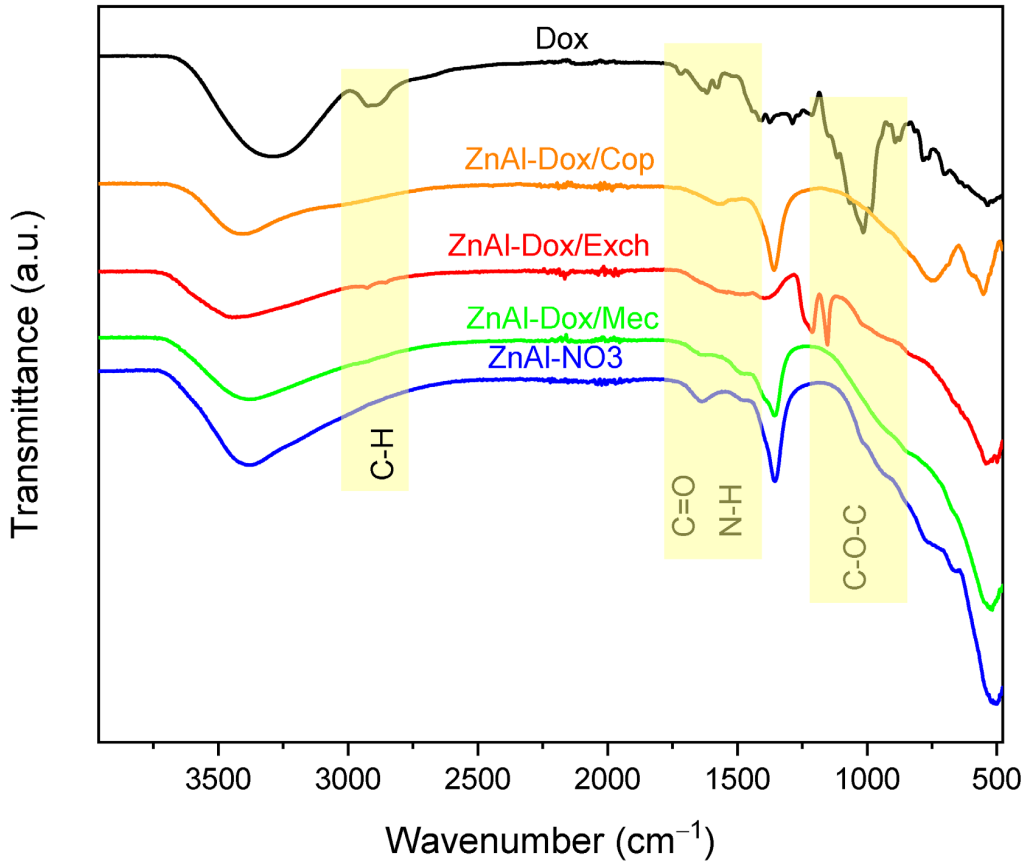


Figure 7. Infrared spectra of the ZnAl-NO_3 pristine matrix and the doxorubicin (DOX) products processed by mechanochemical, exchange, and co-precipitation techniques.

The presence of DOX in the loading products is suggested by the weak C=O and N-H signals in ZnAl-DOX/Mec and ZnAl-DOX/Exch; however, the ZnAl-DOX/Exch sample is not a layered material as inferred from XRD data. Then, ZnAl-DOX/Mec was the only sample loaded with Dox, probably causing the increase of carbon to 0.95 mol C/100 g (Figure 8a). However, the Zn:Al molar ratio in this sample is 0.5:1 instead of the expected 2.5:1, indicating a high content of aluminum (Figure 8b), then the carbon comes from a probable amorphous aluminum carbonate phase. Therefore, the zinc-containing LDH particles are less stable as vehicles for DOX compared to the magnesium LDH.

Among the novelties of our work was the addition of the mechanochemical method to the traditional synthesis methods used for LDHs. In the experimental design, three synthesis processes and two LDH compositions accepted in biological applications were tested. The expected result was not obtained in one of the compositions, ZnAl, once it was degraded, while the MgAl composition was stable.

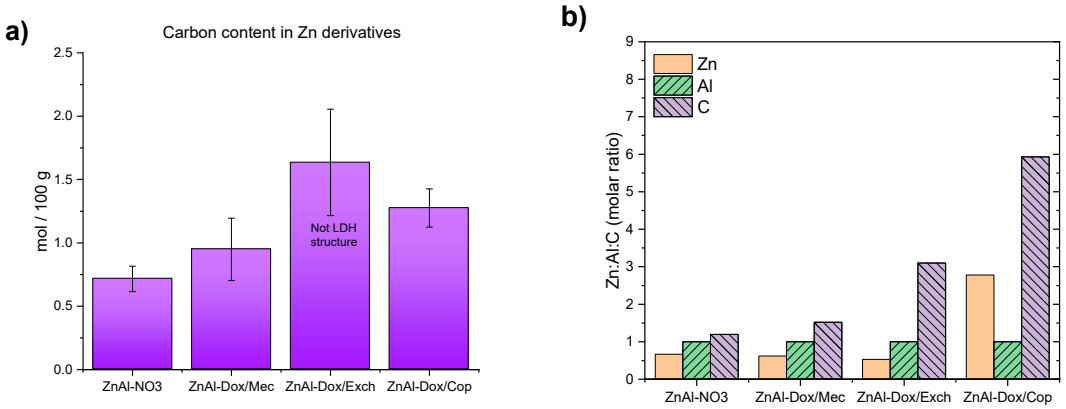


Figure 8. (**a**) Carbon content in the zinc materials loaded with DOX by the mechanochemical, co-precipitation, and exchange procedures and (**b**) the magnesium:aluminum:carbon molar ratio.

The novel result was in the product obtained by the mechanochemical process, which showed a higher DOX loading, allowing scaling-up since it is the least expensive, and does not require large amounts of sample, time, or sophisticated equipment. In these results, we demonstrate that certain compositions and synthesis methods are the most suitable in terms of cost, reaction, and operating time, as they are more efficient in loading complex or bulky drugs such as DOX in a more straightforwardly and economically, without causing any structural modification of the drug or LDHs. In addition, the environmental impact is reduced by not generating the waste of conventional synthesis processes, thus addressing some of the principles of green chemistry [28].

Solvents play an important role in conventional synthesis, and their toxicity is often the main challenge to overcome. Mechanochemical synthesis is more efficient because the reaction can be carried out by milling with or without a small amount of solvent [29,30].

Now, the further challenge is to evaluate the release profile of the most promising samples, and especially to choose a model of application. For example, it has recently been demonstrated that inorganic particles based on metal oxides have the potential for use as drug-eluting stents, especially, magnesium, and zinc oxides are used in the medical field, because they are bioabsorbable, inexpensive, and stable, and applied as alternatives in orthopedic implants in which they serve as delivery systems for anti-inflammatory drugs, antibiotics, growth factors, and antiresorptives. Little attention has been paid to metallic drug-releasing systems compared to polymeric systems. These systems are intelligent and sensitive and are increasingly popular in personalized medicine and pharmacotherapy as they can respond to key variables such as pH changes caused by inflammatory processes, thus allowing the system to release its bioactive load, reaching the desired site for the therapeutic effect [31–33].

One major problem is the rapid corrosion of magnesium-based biomaterials, which represents a significant obstacle to their application but can be reduced by adding elements such as aluminum and zinc [34]. The most effective way to improve the corrosion resistance of these biomaterials without impairing their mechanical strength is surface modification. For example, most metal-based drug delivery systems involve embedding drugs in polymeric or ceramic coatings applied to metal implants. There are also other methods for incorporating the drug itself into the metal surface through covalent bonds,

self-assembled layers, and silver nanoparticles [31]. Here, the LDHs loaded with drugs by the mechanochemical method could find an application.

4. Conclusions

The typical anions exchange reaction to load DOX on LDH particles was compared with the co-precipitation and mechanochemical processes. The MgAl LDH composition is stable and tolerates the three loading processes. The mechanochemical method retained the largest content of DOX. The ZnAl LDH was unstable against the exchange reaction since the structure was destroyed and the amount retained was low. The mechanochemical method was then the best procedure for the zinc-based composition. Therefore, the grinding process arises as a suitable green method to produce LDH vehicles for DOX, retaining the structural integrity of the LDH structure and reducing the use of reagents.

Author Contributions: Conceptualization, G.G.C.A.; data curation, M.d.J.G.S. and G.G.C.A.; formal analysis, M.G.V.M.; investigation, M.G.V.M., J.A.L.C., M.d.J.G.S. and G.G.C.A.; methodology, J.A.L.C.; writing—original draft, M.d.J.G.S.; writing—review and editing, G.G.C.A. All authors have read and agreed to the published version of the manuscript.

Funding: M.G.V.M. received fellowship (2021-000018-02NACF-08398, CVU number 891242) from "Secretaría de Ciencia, Humanidades, Tecnología e Innovación (SECIHTI)", Mexico, formerly "Consejo Nacional de Humanidades, Ciencia y Tecnología (CONAHCYT)". Funds were obtained from the Project "Ciencia de Frontera CF-2023-I-885" sponsored by the "Consejo Nacional de Humanidades, Ciencias y Tecnologías, CONAHCYT", Mexico.

Data Availability Statement: Data are available on request.

Conflicts of Interest: The authors declare no conflicts of interest.

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