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Article

Comparative Study on the Effect of Transition Metal (Zn^{2+}) and Alkaline Earth Metal (Mg^{2+}) Ions on Adsorption-Release of Diclofenac and Ibuprofen on Nano M-Al-LDH as Drug Carriers

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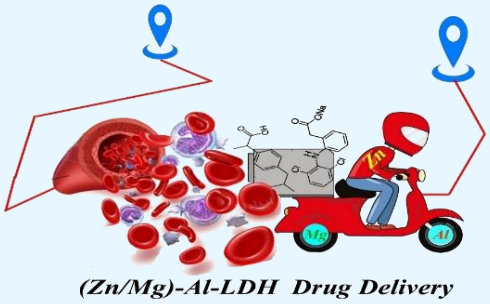
Abstract: In this project, three nanoscale M-Al LDHs, which M is a divalent metal (Mg^{2+}, Zn^{2+} and/or a mixture of them and LDH = Layered Double Hydroxide) were synthesized by co-precipitation and characterized by general techniques, such as FTIR, XRD, FESEM, and EDS. LDHs have got different physical properties, such as; crystal size, lattice parameters, morphology and drug delivery. These M-Al LDHs were used as drug carriers for diclofenac and ibuprofen, which adsorption and release percentages of drugs by them were studied and compared. The results showed that Al-LDHs including transition metal (Zn^{2+}) are suitable for drug delivery purposes. As the mixed divalent (Zn/Mg)-Al LDHs are more efficient drug carriers for both diclofenac and ibuprofen drugs.



Keywords: Nanomaterial, Drug delivery, Diclofenac, Ibuprofen, *In vitro*, Layered double hydroxides, Transition metal, Mg

1. INTRODUCTION

Drug delivery is the method or process of administering a pharmaceutical compound to achieve a therapeutic effect in humans or animals.[1] Drug carriers or delivery systems (DDS) are important research subjects as attracted the attention of many scientists, because, by DDS the release of drugs is controlled. Therefore this controlled release, provides prolonged delivery of a drug, and it also has the following advantages: affected the pharmacological activity, increases patient agreement, reduced local and systemic side-effects, and thus a reduced toxicity profile.[2] Drug delivery systems (DDS) were commonly categorized in 3 groups, such as organic, inorganic, and organic-inorganic hybrids DDS.[3] Organic-based DDS include polymers such as Chitosan,[4] amphiphilic copolymers,[5] micelles,[6] hydrogels,[7] cellulose,[8] polysaccharides,[9-10] lipids[11] and others (pathogens).[12] Organic-inorganic hybrids DDS are as follows; silica-based[13] such as poly(butyl acrylate)/silicon dioxide,[14] metal-based (MOF: Metal-Organic Framework), and magnetite-based[15] such as Chitosan-Fe_3O_4, poly lactic acid-Fe_3O_4 (PLA-Fe_3O_4). Organic-based and organic-inorganic hybrid DDS have got some disadvantages such as high toxicity, low loadings, and easy leakage of drugs which reduce their drug-delivering efficiency.[16-17] Inorganic-based DDSs are including silica, quantum dots, gold, carbon nanoparticles, metal, metal oxides-based nanostructures[18] and layered double hydroxides (LDHs).[19-20]

Inorganic based DDS show much better properties than organic-based DDS. They have stable mesopores structure, large surface area, good biocompatibility, and tailored size of mesopores. All these requisites exhibited promising application as an immediate and controlled drug delivery system.[21] Also, the general advantages of inorganic DDS is easy to prepare with a defined size. More interestingly, they often exhibit multiple functions useful in medicine, for example as exothermic reactors and contrast agents, whereas organic DDS such as liposomes and microspheres serve only as drug reservoirs.[22]

Among the inorganic DDS compounds, layered double hydroxides have received much attention in the past decade and are introduced as a new drug carrier, because of convenient synthesis, structural and morphological customizable, and their low toxicity and good biocompatibility.[23-28] Layered Double Hydroxides (LDHs) are the hydrotalcite-type inorganic compounds (Figure 1).

LDHs are famous as anionic clay. The general formula of the LDHs materials can be described as $[M^{II}_{1-x}M^{III}_{x}(OH)_2^{x+}(A^{m-})_{x/m}nH_2O]$ (x = 0.2-0.4; n = 0.5-1), where M^{II} is a divalent metal cation such as Mg^{2+}, Zn^{2+} or Ni^{2+}, M^{III} a trivalent metal cation such as Al^{3+}, Ga^{3+}, Fe^{3+} or Mn^{3+}, and A^{m-} is an anion. Anions A^{m-}, e.g., CO_3^{2-}, NO_3^-, Cl^-, SO_4^{2-}, or RCO_2^-, located between two layers and balance the positive charge of cations via electrostatic interaction, and x is the mole fraction of M^{3+}.[28-35]

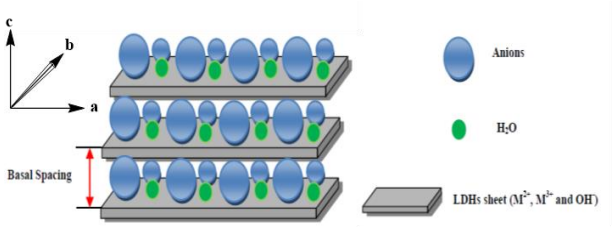


Figure 1. General representation of the structure of LDHs.

Some literatures have been reported the study of adsorption and release of different drugs by different LDHs; example being Nisin,[36] aspirin,[37] acetylsalicylic acid (ASA),[38] methotrexate (MTX),[39] gemfibrozil, captopril, heparin, pravastatin (prava), fluvastatin(fluva), fibrates, and non-steroidal anti-inflammatory drugs (NSAIDs).[35]

Non-steroidal anti-inflammatory drugs (NSAIDs) are aromatic organic compounds with easily ionizable carboxylic groups, thus permitting their intercalation as anions between the layers of LDH hosts.[40,49,50] It has been shown that many common NSAIDs, such as ibuprofen, naproxen, diclofenac, and some other drugs can be rapidly intercalated in LDH hosts using a variety of methods, mainly co-precipitation, ion-exchange, and reconstruction.[35,49,50]

Diclofenac and ibuprofen belong to the family of non-steroidal anti-inflammatory drugs or cyclo-oxygenase inhibitors. It is an effective anti-inflammatory, analgesic, and antipyretic agent. It is commonly used in the treatment of acute and chronic pain, rheumatoid and osteoarthritis.[41]

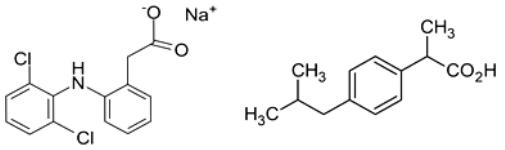


Figure 2. Chemical structure of diclofenac sodium (left) and ibuprofen (right).

In this project, we chose Al-based LDHs for the study of adsorption and release of diclofenac and ibuprofen drugs (Figure 2) because of their high chemical versatility, anionic exchange capacity, and low toxicity. Anionic form of diclofenac and ibuprofen were selected based on the anionic exchange properties of LDHs. In following, we designed three M-Al-LDHs with a different divalent metal ion such as Mg, Zn, and the mixture of these two metals together (Mg/Zn, 3:1). On the other hand, we intend to evaluate the effect of different divalent metal ions (alkaline earth and transition metals) with different physical and chemical properties, on the adsorption and release of diclofenac and ibuprofen in vitro conditions.

2. EXPERIMENTAL

All chemicals were of reagent grade (Merck and/or Aldrich). All compounds were used without further purification. FTIR spectra were recorded as pressed KBr discs using a PerkinElmer RXI, FT-IR instrument. The XRD data of the synthesized nanoparticles were obtained with PHILIPS PW 3830 X-ray diffractometer (Advanced-D8) using Cu-Ka radiation. FESEM and EDS data were obtained by field emission SEM model Mira 3-XMU instrument. The Absorption data were collected by UV-vis spectrophotometer Cintra 2020.

Synthesis of Mg-Al-CO_3 LDHs

The Mg-Al-CO_3 LDH was synthesized by the co-precipitation method at constant pH under low super-saturation conditions. Solution A was prepared by mixing with 0.045 mol (11.3 g) $Mg(NO_3)_2{\cdot}6H_2O$ and 0.015 mol (5.62 g) $Al(NO_3)_3{\cdot}9H_2O$ in 60 mL of deionized water. Solution B was prepared by mixing with 0.108 mol (4.32 g) NaOH and 0.008 mol (0.79 g) Na_2CO_3 in 60 mL of deionized water. Solution B was added slowly to a 250 mL flask of solution A under vigorous stirring maintaining pH 10 at room temperature. The resulting white precipitate was aged for 24 h at 60 °C.

Synthesis of Zn-Al-CO_3 LDHs

This compound was synthesized with the same method as mentioned above. Solution A was mixed with 0.045 mol (13.38 g) $Zn(NO_3)_2{\cdot}6H_2O$ and 0.015 mol (5.62 g) $Al(NO_3)_3{\cdot}9H_2O$ in 60 mL of deionized water. Solution B was mixed with 0.108 mol (4.32 g) NaOH and 0.008 mol (0.79 g) Na_2CO_3 in 60 mL of deionized water. Solution B was added slowly to a 250 mL flask of solution A under vigorous stirring maintaining pH 10 at room temperature. The resulting white precipitate was aged for 24 h at 60 °C.

Synthesis of (Zn/Mg)-Al-CO_3 LDHs

To a solution of 0.005 mol (2.08 g) $Al(NO_3)_3{\cdot}9H_2O$ in 30 mL of deionized water, a solution of the mixture of 0.007 mol (1.79 g) $Zn(NO_3)_2{\cdot}6H_2O$ and 0.021mol (6.21 g) $Mg(NO_3)_2{\cdot}6H_2O$ in 30 mL deionized water, was added. Then, solution B was mixed with 0.108 mol (4.32 g) NaOH and 0.008 mol (0.79 g) Na_2CO_3 in 60 mL of deionized water. Solution B was added slowly to a 250 mL flask of solution A under vigorous stirring maintaining pH 10 at room temperature. The resulting white precipitate was aged for 24 h at 60 °C.

Adsorption of drugs in the synthesized LDHs

Drug-LDHs compounds were synthesized with the insertion of the desired drug on any synthesized LDHs by co-precipitation and anion exchange methods. In the desired aqueous solution of Mg or Zn and Al nitrate salts, as described above, and a solution of 0.5 g diclofenac sodium (1.42×10^{-3} M) and/or 1.0 g of

ibuprofen (4.8×10^{-3} M) in a mixture of water/methanol solvents, was added slowly to the desired alkaline solution. The mixture was stirring for 4 h by magnetic stirring. The progress of the drug loading process was investigated by UV-Vis spectroscopy. The resulting white precipitate was aged for 24h at 60 °C.

Release of Drugs

Diclofenac and ibuprofen drugs were released from any synthesized LDHs-diclofenac and LDHs-ibuprofen carriers in two different conditions such as stomach (pH = 2) and blood (pH = 7.5) condition. The mixture was stirred at different time and then filtered off by centrifuge. In stomach condition: 20 mg of any desired LDHs were added to 10 mL of an aqueous solution of 0.03 M HCl. The absorption of diclofenac (at 276 nm) and ibuprofen (at 222 nm) were recorded by UV-Vis spectroscopy at different times. In blood condition: 20 mg of any desired LDHs were added to the 10 mL of 0.05 M phosphate buffer solution. The absorptions of diclofenac and ibuprofen were also recorded by UV-Vis spectroscopy at different times.

3. RESULTS AND DISCUSSION

Characterization of LDHs carriers

The synthesized LDHs in the present work were characterized by general techniques such as FT-IR, powder XRD, FESEM, and EDS. The results are discussed as follows.

FT-IR

The FT-IR spectra of Mg-Al-LDH-CO_3, Zn-Al-LDH-CO_3 and (Zn/Mg)-Al-LDH-CO_3 compounds are shown in Figure 3. All compounds show the same spectra containing four types of absorption bands at around 3400, 1600, 1300 and 800 cm^{-1}. The broadband in the region between 3700-3100 cm^{-1} can be attributed to the stretching vibrations of the hydroxyl groups from the inorganic layer and the hydrogen-bonded water molecules. The peak around 1600 cm^{-1} region is assigned to the in-plane bending vibration of H_2O. The bands of carbonate ions are observed in the region of 1354 cm^{-1} (anti-symmetric stretching), 860 cm^{-1} (out of plane) and 680 cm^{-1} (in-plane bending). In the region below 1000 cm^{-1}, the spectra show bands attributed to the lattice vibrations modes of the M-O-M and HO-M-OH (M = Zn^{2+}, Mg^{2+}, Al^{3+}). In all of the spectra of the synthesized nanoparticles, stretching bands corresponding to the nitrate group were not observed.[42-43]

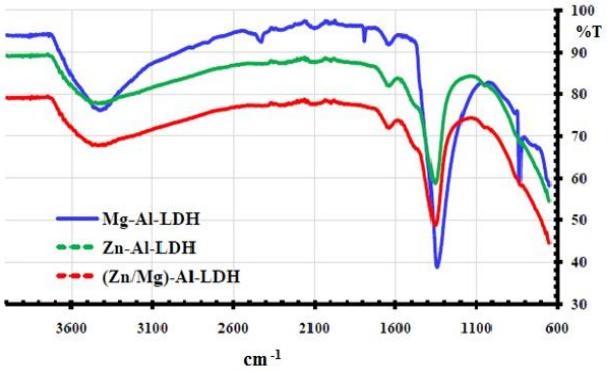


Figure 3. The FT-IR spectra of synthesized M-Al-LDH-CO_3, M = Mg, Zn, Zn/Mg.

XRD

The XRD patterns and lattice parameters of all the synthesized compounds are shown in Figure 4 and Table 1. The reflections observed at 2θ values below 30˚ are assigned to the (003) planes that are related to interlayer distance (d_{basal}) and the cell parameter c (Figure 4). The d_{003} is 0.738, 0.759 and 0.756 nm for Mg-Al, Zn-Al and (Zn/Mg)-Al LDHs, respectively (Table 1, Entry 1). Accordingly, the basal distance is increased by replacing of Mg metal ion with Zn transition metal ion, the reason for this result can be related to the ionic radius of the divalent metal (r_{Mg2+} = 0.86 and r_{Zn2+} = 0.88 Å).[44] The reflection observed in 2θ values in the region of 60˚ is attributed to the (110) plane related to the cell parameter a that gives the average distance between metal ions in the layer.

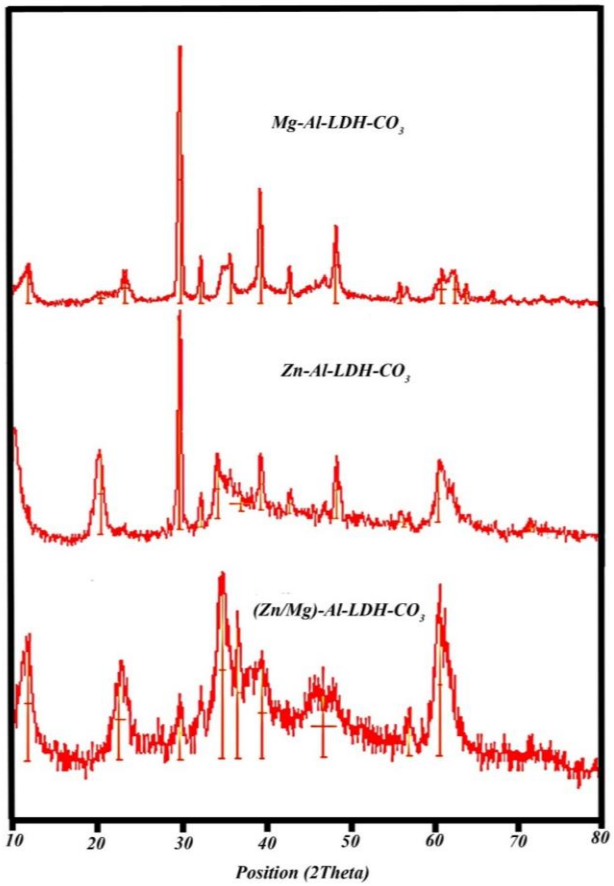


Figure 4. The XRD patterns of the synthesized LDHs.

Table 1. The Lattice parameters and Scherrer's average crystal size of the synthesized LDHs

Entry	2 Theta (º)	Lattice parameters (nm)	Mg-Al	Zn-Al	(Zn/Mg)-Al
1	~ 10	d_{003}	0.738	0.759	0.756
		$c = 3d_{003}$	2.214	2.277	2.268
2	~ 60	d_{110}	0.1518	0.1538	0.1531
		$a = 2d_{110}$	0.3036	0.3076	0.3062
3	~ 30	$D_{(nm)} = K\lambda /(\beta \cos\Theta)$	29.76	30.15	30.00

According to the result shown in Table 1, Entry 2, the parameter's *a*, like parameter's *c*, has a gradual increase with the change from magnesium to zinc. The average crystal sizes, based on Scherrer's equation, are 29.76, 30.15 and 30.00 nm for Mg-Al, Zn-Al, and (Zn/Mg)-Al synthesized LDHs, respectively (Table 1, Entry 3). (Zn/Mg)-Al LDHs has got broad XRD peaks against both Mg-Al and Zn-Al LDHs, which indicates the crystal dimensions are reduced in mixed divalent metals in comparison to the Mg-Al and Zn-Al LDHs.[45] So, the XRD patterns of Mg-Al and Zn-Al LDHs are fine and they haven't got noisy, showing that their structures are more crystalline. The fine XRD pattern shows that the ratio of the crystalline structure is higher than to bulk (amorphous structure), but the XRD patterns of (Zn/Mg)-Al LDHs has got some noisy, thus, the mixed divalent metals compound tends to have amorphous structure. The XRD data show that the materials are nanometer-sized.

FESEM

The FESEM images of Mg-Al, Zn-Al and (Zn/Mg)-Al LDHs nanocompounds are presented in Figure 5. According to the images, the Mg Al-LDH particles are densely spaced together in a spherical shape with an average diameter of 26 nm. The FESEM image of Zn-Al LDHs is different in comparison to Mg-Al LDHs; it has got a mixture of worm-like and sphere shapes. The average size of the sphere shape is about 20 nm and the length of the worm-like is about 32 nm. Mg-Al LDHs particle looks more compact than Zn-Al LDHs particles. The more interesting result is that the image of the mixture of divalent metals-Al LDHs is different in comparison to the other both LDHs. The morphology of (Zn/Mg)-Al LDHs is similar to a bunch of flowers. It consists of several circular petals or coins with an average size of 120 nm. Nanometer size has been mentioned as an important factor for cell endo-cytosis for drug delivery so that sizes below 200 nm are well-known for drug carriers.[46] Therefore, all three compounds have got sizes below 150 nm that would be suitable for drug carriers due to the ease of crossing the body's biological and defense barriers. Also, FESEM shows that the physical properties of M-Al LDHs have been changed by changing the divalent metal cation from Mg to Zn.

EDS

Figure 6 is containing the energy dispersive X-ray spectrum and elemental analysis table of the synthesized LDHs. According to this figure, the synthesized Mg-Al LDHs sample has got C, O, Mg, and Al elements, that it's consistent with the formula of this nanocompound. The weight percentage (atom%) of these elements was obtained 3.35 (5.07), 60.57 (68.81), 24.64 (18.42) and 11.44 (7.70)%, for C, O, Mg, and Al, respectively. Also, according to the EDS data of Zn-Al LDHs, C, O, Al and Zn elements have the weight percentage (atom%) of 2.96 (4.58), 71.60 (83.08), 12.65 (8.71) and 12.78 (3.63)%, respectively.

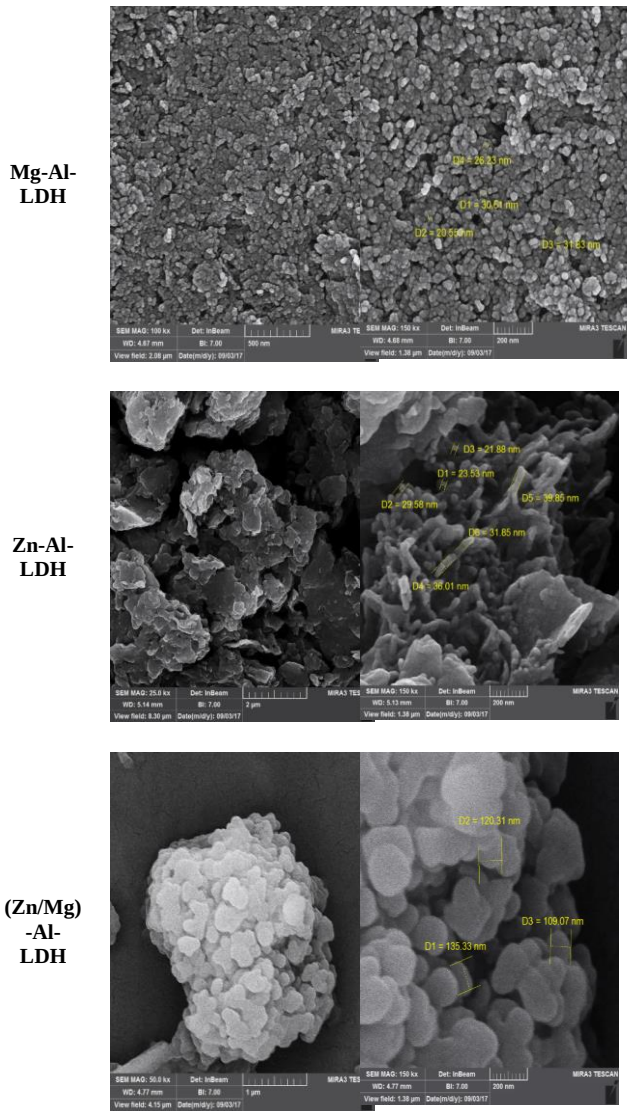


Figure 5. The FESEM images of the synthesized M-Al LDHs.

This data confirmed the proposed Zn-Al LDHs with carbonate anion. The EDS data of mixed divalent metals showed that it is containing C, O, Mg, Al, and Zn

elements with weight (atom%) of 5.86 (9.16), 51.90 (60.91), 28.34 (21.89), 9.89 (6.89) and 4.00 (1.15)%, respectively. The presence of Mg and Zn elements confirmed the synthesis of mixed divalent metal in this nanocompound. Also, the %weight or %atomic of the Mg element is more than the Zn element following the molar ratio in the synthesis route. Any N element was not observed in all EDS data of synthesized nanocompounds, which is in agreement with the FTIR results.

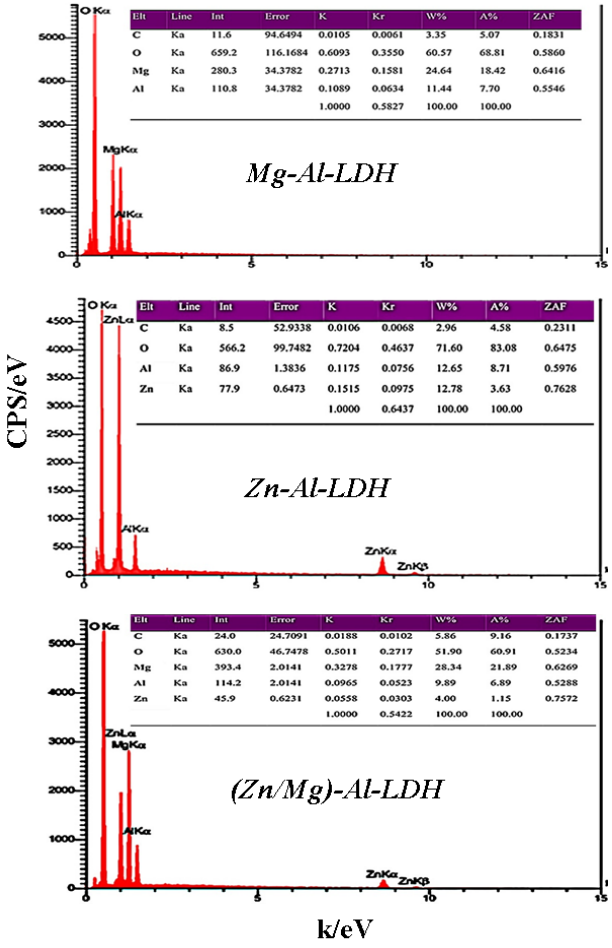


Figure 6. Energy dispersive X-ray spectrum of the synthesized LDHs.

Adsorption-desorption of intended drug by M-Al-LDHs

The study of adsorption-desorption of diclofenac and ibuprofen drugs on every synthesized Al-LDHs was done based on UV-Vis spectroscopy and the change in the maximum absorption peak of any drug, which was 276 nm for diclofenac and 222 nm for ibuprofen. Efficiency adsorption percentage (%A) of any drug on the synthesized Al-LDHs was calculated by:

$$\%A = [(C_0 - C_t)/C_0] \times 100$$

C_0 is the initial concentration of drug (C_0 of diclofenac = 14.2×10^{-3} M and ibuprofen = 48.4×10^{-3} M) and C_t, is the concentration of drug at any time, which was obtained based on changing the maximum absorption peak of each drug over time.

Adsorption of drug by M-Al-LDHs

a) Adsorption of diclofenac on M-Al-LDHs

Figure 7 shows diagram of the adsorption percentage of diclofenac over time (from zero to 4 h) on the tree LDHs. The amount of drug absorbed on all LDHs is different, following the order of %adsorption as: (Zn/Mg)-Al > Zn-Al > Mg-Al. The amount of diclofenac adsorption on the (Zn/Mg)-Al is more than 50% in the first hour, and is almost completed after 3 h. But the absorption percentages of the other two LDHs in the first hour were less than 50% and were not complete after 4 h. Consequently, the mixed divalent metals Al-LDHs are more efficient than Mg-Al and Zn-Al LDHs for adsorption of diclofenac drug. Also, the important point in this comparison is that a transition metal (Zn) instead of alkaline earth metal (Mg) in Al-LDHs causes increased drug adsorption. Various factors may cause this difference in the %adsorption of this drug on carriers. First, the morphology of the drug carriers: based on FESEM results, Mg-Al LDHs has got high-density morphology but other LDHs have got highly porous morphology. The differences in morphology can affect the contact surface between the drug and the carriers. Second, the lattice parameters such as c or d_{003} represent the interlayer space or basal spacing. It seems that the intercalation of the drug is easier between the layers when the greater interlayer space is used. As discussed in the XRD section, the interlayer space in Zn-Al LDHs is greater than that in Mg-Al LDHs, which is why the drug carrier containing Zn has got a higher adsorption percentage than Mg. Third, hard-soft acid-base theory[47] (Pearson concept = hard prefers binding hard and soft prefers binding soft but soft not prefers binding to hard), Zn^{2+} is a soft acid and Mg^{2+} is a hard acid because zinc ion has greater radius than magnesium ion. On the other hand, CO_3^{2-} is a hard base and anionic form of diclofenac is a soft base, therefore, Zn-CO_3 (soft-hard) is unstable binding than Mg-CO_3 (hard-hard) and in the opposite, Zn-diclofenac (soft-soft) is stable binding than Mg-diclofenac (hard-soft). Due to these three factors, (Zn/Mg) is a more suitable carrier for the diclofenac drug.

b) Adsorption of ibuprofen on M-Al-LDHs

Adsorption of ibuprofen drug on three Al-LDHs was compared as shown in Figure 8. Again, (Zn/Mg)-Al LDHs performs better than other carriers, similar to diclofenac adsorption. By comparing the adsorption percentage of each drug on these carriers, it can be concluded that Al-LDHs with zinc ions is better adsorbent for adsorbing of drugs and diclofenac is more adsorbed on carriers than ibuprofen.

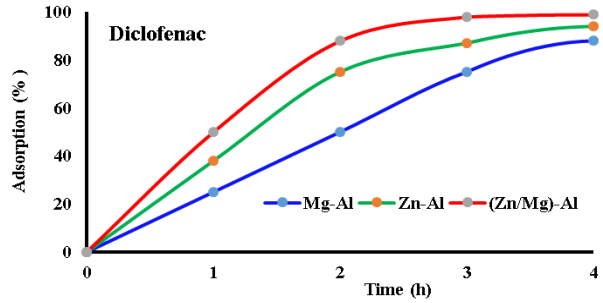


Figure 7. The adsorption percent of diclofenac on the synthesized LDHs over time.

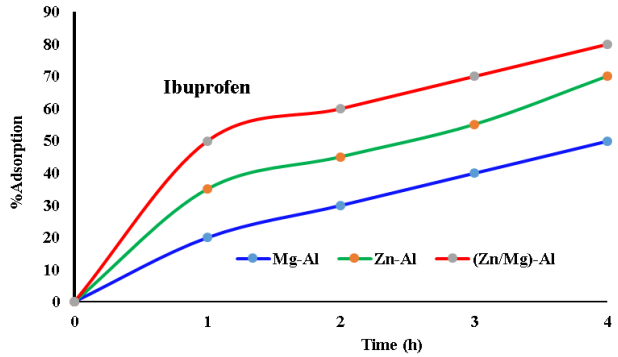


Figure 8. The adsorption of ibuprofen on the synthesized LDHs over time.

Kinetic adsorption of drugs

The kinetic data of adsorption reactions of both drugs on three synthesized M-Al LDHs are showed in Figures 9 and 10. In these diagrams, $-\ln(C_t/C_0)$ were plotted versus the adsorption time. The kinetic behavior of all carriers for both drugs is similar. As shown, a good linear relationship exists between $-\ln(C_t/C_0)$ versus time according to the following equation representing the adsorption rate of both drugs on the carriers:

$$\ln(C_t/C_0) = -kt$$

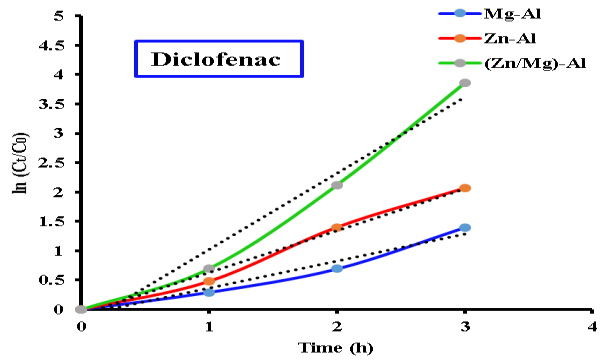


Figure 9. Relationship between $-\ln(C_t/C_0)$ and Adsorption time for kinetic data of Diclofenac by M-Al-LDHs.

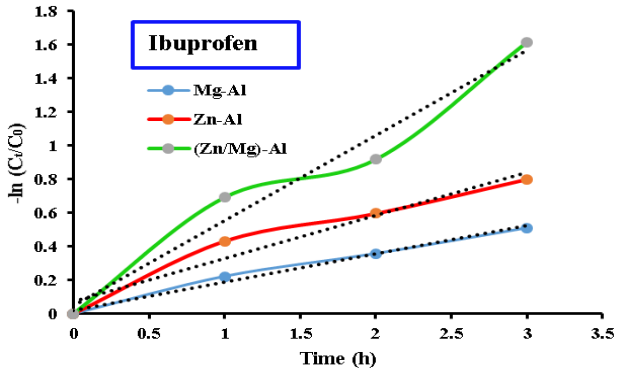


Figure 10. Relationship between $-\ln(C_t/C_0)$ and adsorptiontime for kinetic data of ibuprofenby M-Al-LDHs.

This equation demonstrated that the adsorption process of both drugs on any LDHs is kinetically a *pseudo*-first-order reaction. Also, the rate constant of M-Al-LDHs containing the mixed divalent transition and alkaline earth metals is higher than the other carriers. It seems that the reason for the difference in the rate of drug adsorption is attributed to the *lability* of metal ions.[48] Three main factors that affect whether a complex is labile or inert are: 1) size, smaller metal ions tend to be more inert, then against Zn^{2+} ion, Mg^{2+} is an inert metal ion,2) charge on metal ion, the greater the charge on the metal ion, the greater the tendency towards being inert, this factor is ineffective between zinc and magnesium ions,3) the number of *d* electrons and configuration: d^{10} is an electronic configuration of Zn^{2+} that is labile, then, LDHs containing Zn^{2+} metal ions is a labile complex and has got high adsorption speed.

Release of diclofenac and ibuprofen

Efficiency release percentage (%R) of any drug on the synthesized Al-LDHs was calculated by:

$$\%R = (C_t/C'_0) \times 100$$

C'_0 is the initial concentration of drug in adsorption process (C_0 of diclofenac = 14.2×10^{-3} M and ibuprofen = 48.4×10^{-3} M) multiplied by %adsorption of an adsorbent, ($C'_0 = C_0 \times \%A$) and C_t, is the concentration of drug at the time in two different conditions (stomach and blood), which was obtained based on changing the maximum absorption peak of each drug over time.

The release of both drugs by all drug carriers, in stomach condition, is fast (less than 10 min) because LDHs are destructed rapidly in the acidic medium at pH = 2. But in blood condition (pH = 7.2), drug carriers behavior are different (Table 2). As shown in Table 2, these results were obtained based on the %R:

1) Diclofenac: Mg-Al > (Zn/Mg)-Al > Zn-Al
2) Ibuprofen: (Zn/Mg)-Al > Zn-Al > Mg-Al
3) For Mg-Al drug carrier: Diclofenac > Ibuprofen
4) For Zn-Al drug carrier: Ibuprofen > Diclofenac

5) For (Zn/Mg)-Al Drug carrier: Diclofenac ≈ Ibuprofen

According to the above results from 1 to 5, release of diclofenac in blood by Mg-Al LDHs are more than Al-LDHs containing transition metal (zinc). Also, mixed divalent Al-LDHs is better than Zn-Al LDHs. Contrary to previous observations, the release of ibuprofen in blood by Al-LDHs with transition metal (zinc) is more than Mg-Al LDHs, also mixed divalent Al-LDHs is better than Zn-Al LDHs. Based on %release, Mg-Al LDHs is suitable for diclofenac but Zn-Al LDHs is beneficial for ibuprofen. The important point is (Zn/Mg)-Al LDHs is lucrative for both drugs.

Table 2. The %release of both drugs in the blood condition

		%R					
		1 (h)	2 (h)	3 (h)	4 (h)	5 (h)	6 (h)
Diclofenac	Mg-Al	22	25	36	43	58	65
	Zn-Al	10	19	25	31	35	39
	(Zn/Mg)-Al	24	26	28	35	39	42
Ibuprofen	Mg-Al	13	21	24	29	33	38
	Zn-Al	17	20	27	35	38	42
	(Zn/Mg)-Al	27	39	46	58	67	70

4. CONCLUSIONS

Based on reported results from this project, three Al-based LDHs with different divalent metal ions from the main metals (Mg) and transition metals (Zn) and mixed of both them, as nano drug carriers were synthesized and characterized. Along with the change of the divalent metal from Mg to Zn, different physicochemical properties observed in LDHs based on Al. All synthesized Al-LDHs are suitable for drug delivery purposes in blood. The mixed divalent included Zn and Mg with Al-LDHs is the best carriers, due to high adsorption and release percentage, while Mg-Al LDHs is useful for ibuprofen and Zn-Al LDHs is for diclofenac drugs.

CONFLICTS OF 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. No animal or human studies were carried out by the authors for this article.

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