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Original Article

Layered double hydroxides-indomethacin nanohybrids: intercalation, pH influence, stability and release properties

Silvia N. Mendieta[1*], Marcos I. Oliva [2, 3], Celso F. Pérez[1], Patricio Reyes Nuñez[4], Marcela Longhi[5], Gladys Granero[5] and Mónica E. Crivello[1]

[1]Centro de Investigación y Tecnología Química, CITeQ-CONICET-UTN. Universidad Tecnológica Nacional, Facultad Regional Córdoba, Ciudad Universitaria. Córdoba, X5000HUA, Argentina.
[2]FAMAF, "Facultad de Matemática, Astronomía y Física" Universidad Nacional de Córdoba, Ciudad Universitaria. Córdoba, X5000HUA, Argentina.
[3]Instituto de Física Enrique Gaviola – CONICET – Universidad Nacional de Córdoba. Ciudad Universitaria. Córdoba, X5000HUA, Argentina.
[4]Departamento de Físico-Química, Universidad de Concepción, Facultad de Ciencias Químicas. Concepción, Chile.
[5]Unidad de Investigación y Desarrollo en Tecnología Farmacéutica, UNITEFA CONICET-UNC. Departamento de Farmacia, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba. Ciudad Universitaria, Córdoba, X5000HUA, Argentina.

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ABSTRACT

In this work, three pH values (8, 9 and 10) were studied for the insertion of Indomethacin (Indo) molecules into Layered Double Hydroxides (LDHs). The obtained results showed that the LDH materials have been a good storage for the drug. LDHs provide thermal stability with an increase in the thermal decomposition of the drug around 100°C more. Indo into LDHs exhibited higher photostability to UV light irradiation. In vitro drug release experiments in a phosphate buffer solution (pH = 7.4) have been carried out. The loading amount of intercalated Indo was increased to 66 % at pH 8, and showed a profile of sustained release of 97 % in 8h. The release profiles were fitted by mathematical models, which describe various kinetic models that served to investigate the drug release mechanism, being the Bhaskar kinetics model the most appropriate. The results showed that the nanohybrids can be used as an effective drug delivery system.

Keywords: layered double hydroxide, stability properties, indomethacin, drug delivery system.

INTRODUCTION

Layered Double Hydroxides (LDH), also known as hydrotalcite like compounds or anionic clay, are a class of host-guest layered solids and they are usually represented by the general formula $[M^{2+}_{(1-x)} M^{3+}_{x} (OH)_2]^{x+} (A^{n-}_{x/n}). mH_2O$, where M^{2+} and M^{3+} are the di-, trivalent metal cations, A is an organic or inorganic anion, *m* is the number of interlayer water and *x* is the layer charge density of LDH. Their structure consists of brucite-like layers, where the substitution of M^{2+} for M^{3+} cations, leads to an excess of positive charge, which is balanced by anions located together with water molecules in the interlayer [1]. Through direct synthesis it is possible to introduce any type of anion between its layers. These anions can be replaced by others, via ion-exchange, with subsequent variation of the interlayer distance that depends on the size of the intercalated anions.

Nanobiohybrids are based on a layered inorganic host that can intercalate various biological materials in the nanometer size galleries between the layers. In particular, the combination of the synthesis of nanobiohybrids and the intercalation technique offers a new area for developing nanohybrids with a desired functionality. Consequently, the interlayer region of a laminate host may be considered a micro vessel in which an anionic drug may be stored and successively released as an effect of an intercalation process [2]. The ability of LDH to exchange the interlayer anion has been clearly proven in the consulted

***Corresponding Author Address: Silvia N. Mendieta,** Centro de Investigación y Tecnología Química, CITeQ-CONICET-UTN. Universidad Tecnológica Nacional, Facultad Regional Córdoba, Ciudad Universitaria. Córdoba, X5000HUA, Argentina.*
E-mail: smendieta@frc.utn.edu.ar

literature and, thus, they may be used as biocompatible hosts for several drugs [3, 4].

The applications of MgAl-LDH in Medicine and Pharmacy have been almost exclusively restricted to its role as antacid or anti-pepsinic. Recently, anionic, drug molecules have been intercalated into a variety of LDH [2, 5-11]. Moreover, they may act as stable host matrices for storage and delivery of various intercalated bioactive molecules and drugs [12-16]. One important feature they exhibit is that the labile, bioactive substances intercalated into LDH could be effectively protected against rapid degradation by light, temperature, oxygen, alkali metals, etc., [17-19]. In their recent studies, Wei et al. [20] have demonstrated that the intercalation of the chiral drug L-dopa into MgAl LDH enhanced significantly its chemical stability. Kura et al. [21] found that the layered hydroxide nanocomposite containing the Levodopa anti-Parkinsonian agent is a possible alternative choice for a nano delivery system for chronic Parkinson's disease treatment rather than conventional Levodopa.

Choy et al. [22] first developed the DNA-LDHs nanohybrids for efficient gene delivery, and it was shown that the DNA molecules could be easily intercalated into LDHs by anion exchange. Lun Dong et al. [23] studied the incorporation of Camptothecin into LDH by reconstruction methods, profiles and kinetics release. On the other hand, a variety of pharmaceutical, anionic materials were intercalated into the LDH, some examples of non-steroidal, anti-inflammatory drugs (NSAIDs) are: Ibuprofen, Diclofenac, Naproxen, etc. [24, 25]. The release properties of the NSAIDs have been investigated by adding their intercalation compounds to samples of simulated gastrointestinal and intestinal fluids. Ambrogi et al. [2] have reported on the intercalation of Diclofenac, finding that the microencapsulation of drugs immobilized on Mg-Al-LDH was successively achieved in order to obtain a new, enteric, composite system for a potential, colonic drug delivery. Li et al. [26] have studied Fenbufen-intercalated LDH as the core was coated with enteric polymers, Eudragit® S 100 or Eudragit® L100 as a shell, resulting in a composite material which showed controlled release of the drug under in vitro conditions.

Among the members of the NSAIDs, there is Indomethacin. It is used to reduce pain caused by osteoarthritis, rheumatoid arthritis, bursitis, gout, etc. [27], however, it has well known side effects including gastrointestinal disturbances. The drug is described as poorly soluble and highly permeable (class II). Given that water-insoluble drugs often show low absorption and weak bioavailability, improvements in dissolution rates and/or solubility are important for the development of drug preparations. The successful formulation of poorly water-soluble drugs is one of the major problems in pharmaceutical manufacturing. Indo exists in two stable polymorphic forms, termed γ-form and α-form. The γ form, with the highest point of fusion and consequently, the least soluble is thermodynamically the most stable. El-Brady et al. [28] have reported on the study about solid-state properties of the solid, dispersion system of Indo in PEG400 (polyethylene glycol 4000) and Gelucire 50/13. Gelucire is a family of vehicles derived from the mixtures of mono-, di- and triglycerides with polyethylene glycol esters of fatty acids. Del Río [29, 30] has studied the polymorphism phenomenon in the formulation of Indo tablets, and their behavior during the study of dissolution. Del Arco et al. [31] have studied LDH synthesized at a wide range of pH (8-9), by reconstruction methods of LDH and have focused on the gastric, membrane damage. On the other hand, Indo is sensitive to the exposure to strong, direct sunlight [32] and photolabile in organic solvents [33]. Under UV light, the primary degradation products are alcohol, aldehyde and decarboxylation [34]. Regarding solid stability during storage, it should be stored in closed containers protected from light, as it is photosensitive.

Thus, the purpose of this work is to study the intercalation of Indo by direct synthesis into LDH using a coprecipitation method at different pH (between 8 and 10 ±0.2), and then to determine the recommended pH value to achieve a greater incorporation - release. The drug release from the obtained nanohybrids was analyzed in a simulated intestinal media (pH 7.4). The release profile data were fitted by mathematical models which describe various kinetic mechanisms. Furthermore, the photostability to UV light irradiation and thermal decomposition of the drug are studied to infer whether the host-guest structure (LDH-drug) provides some benefits.

EXPERIMENTAL

Synthesis of the samples: The LDH with intercalated Indomethacin (LDH-Indo) have been prepared by direct co-precipitation from Mg and Al chlorides, a similar method to the one described by Dupin et al. [35]. Two aqueous solutions of $AlCl_3.6H_2O$ and $MgCl_2.6H_2O$ were dissolved in 100 mL of decarbonated water, with the relationship M^{2+}/M^{3+} = 2. The aqueous solution was slowly added to 50 mL of decarbonated water with Indomethacin, and the suspension was stirred magnetically. The co-precipitation was carried out at 35 °C under nitrogen atmosphere, to avoid the incorporation of CO_2. For the synthesis, three pH values were studied (8, 9 and 10) ± 0.2, the pH was

maintained constant by continuously adding NaOH 0.1 M, which made also the drug gradually solubilize. The resulting suspension was stirred for 20 h at 60 ºC under nitrogen atmosphere. The product was filtered, washed with decarbonated water at 60 ºC and finally dried at room temperature. The sample without drug was prepared to compare it with the incorporated host. This sample was called LDH-Cl.

Characterization of the samples: Powder X-ray diffraction (XRD) data were collected on a X´Pert Pro-PANalytical diffractometer using Cu K_α radiation (λ = 1.54 Å) in a scan range between 1.5º and 70º at a scan speed of 3º/min in 2θ and step size 0.02º.

FT-IR spectra were recorded on a Jasco FT/IR 5300 spectrometer in air at room temperature. The sample was pressed into a disc with KBr. The spectrum of each sample was recorded by accumulating 48 scans at 2 and 4 cm^{-1}, resolution between 400 and 4000 cm^{-1}.

The scanning electron microscopy (SEM) study of the parent LDH, were obtained in a JEOL JSM-6380 LV. Gold Coverage was applied to make samples conductive. The acceleration voltage was 20 kV.
Moreover, the solids were analyzed by transmission electron microscopy (TEM) with a JOEL JEM-1200 EX II. A small drop of the dispersion (sample in solution water-ethanol 50%) was deposited on a copper grid and then evaporated in air at room temperature.

Drug loading was determined by UV absorption spectrophotometer using a Jasco 7800 at λ=320 nm. The measurements of the calibration curve obtained from five solutions were analyzed in fivefold by UV absorption at λ=320 nm. These measurements were analyzed through a linear regression method, in which the correlation coefficient (R^2= 0,999) and the equation of a straight line were calculated. A specific amount of LDH-Indo was dissolved in 10 mL of HCl 1M solution under magnetic stirring for 2 h to dissolve the LDH matrix and then it was diluted with phosphate buffer at pH 7.4 [36]. Precision was examined by the standard deviation (S.D.) of recovery data (*n*=3).

Thermogravimetric analyses (TG) and differential scanning calorimetry analyses (DSC) were performed by means of an automatic thermal analyzer (TA SDT Q600) Thermal analyses were conducted at a scanning rate of 10 °C/min from 20 to 600 °C. The degradation study was carried out with a model PHILIPS TL 8W/05 lamp, which has a maximum energy emission of 365 nm, in the region of UV-A and UV-B. Exposure took place directly on the LDH-Indo into an enclosure, during certain periods, from 30 minutes to 16 hours; the changes in the solid were analyzed by UV-visible diffuse reflectance (UV-vis-DR) with a Jasco V-650 spectrophotometer in the range of 200-900 nm.

Drug release studies were performed in the dissolution apparatus Hanson Research SR6 serie II baskets type. The baskets rotation speed was 50 rpm and the vessels were kept in a thermostatically controlled circulation water bath at 37.0±0.5 °C. The dissolution media were simulated, intestinal fluids at pH 7.4±0.05. The release studies were done by placing a given amount of LDH-Indo in 750 mL of medium under sink conditions. The samples of 7 mL were withdrawn at predetermined intervals, followed by replenishment after each withdrawal with the same volume of fresh medium equilibrated at 37.0±0.5 °C. They were appropriately filtered (filter type: 0.45 μm, Milipore 13 mm) and analyzed by UV absorption spectrophotometer Jasco 7800 at λ=320 nm. The measurements were analyzed through a linear regression method, in which the correlation coefficient (R^2= 0,999) and equation of a straight line were calculated. The percentage released at each point in time was expressed as a fraction of the total amount of Indo. Drug release was monitored for 8 hours; Indo concentration was reported as an average of three determinations and the error expressed as standard deviation (S.D.).

RESULTS AND DISCUSSION

X-ray powder diffraction (XRD): The "c" lattice parameter values for the studied samples have been included in Table 1. This parameter is calculated from the position of the first peak, plane 003 (hexagonal packing is assumed) and $c = 3d_{003}$. The interlayer distance value of d_{003}, represents the summation of thickness of the brucite-like layer and the gallery height, which is a function of the number, the size and the orientation of intercalated anions. For the hydrotalcite interlayer with chlorides, the d-spacing for planes (003) with a hexagonal packing is in the range of 7.66 Å, which represents a value of 11.54 at 2θ. Since the brucite-like layer thickness of LDH is 4.8 Å [1], the interlayer space is 2.86 Å (Fig. 1A).

Successful intercalation of Indo into the LDH host is demonstrated by the XRD diagrams of the nanohybrids. During the coprecipitation, the layers of LDH expand to host the pharmaceutical anions and this expansion is reflected by the values of d_{003} which are also given in Figure 1B, such a swelling of the layers being due to the intercalation of the drug molecules.

The interlayer distance increased from 2.86 to 18.00 Å (22.8-4.8 Å) for the sample synthetized at pH 8 and from 2.86 to 19.25 Å (d=24.05 Å) for the samples synthetized at pH 9 and 10.

In samples synthesized at pH 9 and 8 (Fig.1B b-c), peaks corresponding to the pure drug were observed which would indicate that it is adsorbed on the solid surface. The observed peaks indicate that γ-Indomethacin suffers a transformation due to the thermal treatment performed during synthesis and the observed peaks corresponding to α-Indomethacin polymorph [30, 37]. At pH 9, both structures can be seen, LDH-Indo as well as the peaks belonging to absorbed drug α-Indomethacin. In contrast, in the synthesis performed at pH 8, the incorporated drug can be observed in the plane 003 in a disordered manner. This is due to that at low values of 2θ, it has different peaks, indicating that the position in the interlayer is not arranged, as at higher pH. The peaks are less intense and wider, indicating a more disordered disposition after intercalation [16]. At pH 10, they show a higher order crystalline LDH structure (Fig.1B a). Given that, the incorporation is partial; there are two types of the interlayer sizes, corresponding to the LDH-Indo and the LDH-Cl host. The peak at 11.35 at 2θ in Figure 1B (a), corresponds to the planes (003) reflection of LDH-Cl, overlapped whit the (009) reflection of LDH–Indo; that was observed at pH 9 and 10 [38, 39].

The symmetric reflections (110) and (113) merged in the sample synthesized at pH 10, indicating a disturbance of the brucite-like layer structure. These reflections were not observed in the samples synthesized at pH 8 and 9 which would reveal the presence of brucite-like layers in thin films [16, 39-40].

Fourier Transform Infrared Spectroscopy (FTIR): Figure 2 shows FTIR spectra for α-Indomethacin and γ-Indomethacin, which have different absorption bands in the carbonyl region. As Chen et al. [41] proposed, the γ-Indomethacin has characteristic absorption bands at 1717 and 1692 cm^{-1}. The 1717 cm^{-1} absorption band is assigned to the carbonyl stretch of the acid dimmer. The 1692 cm^{-1} absorption band is assumed to be the carbonyl stretch of non-protonated amide. The α-Indomethacin has characteristic absorption bands at 1735, 1692, 1680 cm^{-1}, which is related to its crystal structure. The 1735 cm^{-1} adsorption band is assigned to the non-dimer involved carboxylic acid carbonyl, while the adsorption band for the carboxylic acid dimer is presumed to be the unresolved shoulder near 1717 cm^{-1}. The 1692 cm^{-1} adsorption band in both forms is assumed to be the carbonyl stretch of non-protonated amide, while the adsorption band at 1680 cm^{-1} is assigned to the protonated amide.

The FT-IR spectra of LDH-Cl and intercalated LDH-Indo materials synthesized at different pH values are shown in Figure 3. In Figure 3 (b to d), a decrease in the characteristic bands of the pure drug is observed, when the pH increases from 8 to 10. At pH 10, the pure drug bands are less intense; this reveals a lower incorporation, which corresponds to the diffraction pattern obtained. The band at 1560 cm^{-1} corresponds to the carboxylate group, so it can be inferred that the drug is in its anionic species and incorporated into the LDH. The band at 1680 cm^{-1}, indicates that the γ-Indomethacin suffers a transformation during the incorporation to α-Indomethacin.

Scanning Electron Microscopy (SEM): As shown in Figure 4, the SEM of the LDH-Indo materials synthesized at different pH values is different. The LDH-Indo synthesized at pH 8 (Fig. 4-a) shows a structure of threads, this morphology is characteristic of the α-Indomethacin polymorph [30, 42]. The presence of this structure confirms the findings of DRX. When the pH of synthesis is increased, the wire structure disappears and the characteristic, layered structure of the LDH is observed. In the samples synthesized at pH 9, amorphous grains of different size and smaller needles were observed (Fig. 4 (b)). In the LDH-Indo synthesized at pH 10, similarly sized, uniform particles (Fig. 4c) were observed. In this case, sheets are well-formed, resulting in the aggregate which takes the form of rosettes. Figure 4 (d) shows an enlarged area of LDH to pH 10 (marked area), which displays, with more detail, the structure similar to a rosette. This structure is favored by the heat treatment, aging temperature and pH synthesis mainly, which coincides with the observations made by Faour et al. [43, 44].

Transmission Electron Microscopy (TEM): TEM of LDH-Indo were illustrated in Figure 5. The differences observed are mainly due to the ordering of the lamellar structure. In the sample synthesized at pH 8 (Fig. 5 (a)), individual, thin and disordered sheets are observed, while in the sample synthesized at pH 10 (Fig. 5(b)), a high order of the layer is noticed (demarcated area). This structure corresponds to that observed by XRD.

Drug Loading: Table 1 shows the percentage of incorporation for each LHD synthesized. It can be observed that the incorporation of the drug decreases with increasing pH of synthesis. This behavior may be due to the increase in the crystalline structure of solids, as it was previously discussed. The materials synthesized at lower pH

(8 and 9) showed a more disordered layer structure which favors the incorporation of the drug, either in the interlayer or being adsorbed on the external surface. More importantly, the LDH-Cl showed no absorption at 320 nm.

Thermal Analysis: Thermal behaviour was determinate by TG and DSC, the curves of LDH-Cl and LDH-Indo synthesized at different pH values, are illustrated in Figures 6 and 7. For LDH-Cl, the host solid, (Fig. 6-a) three weight loss stages can be observed. The first stage, whose weight loss is below 160 °C, was produced due to physically adsorbed water. The second stage corresponds to the loss of interlayer water (180 – 250 °C). Finally, the third stage (250 – 600 ºC) is attributed to the dehydroxylation of the brucite-like sheets and the loss of interlayer ions in the form of HCl and Cl_2 indicating that the layer has disappeared.

The TG curves of LDH-Indo synthesized at pH 8 and 9 are illustrated in Figure 6 (b) and (c), the total weight loss (Table 2) for both solids was similar (about 85%). These values, in both cases, are higher than the obtained at pH 10 (66,70%), Figure 6 (c). This behavior is related to the capacity to incorporate each of them. The first stage, from room temperature (RT) to 230 ºC, exhibits that the weight loss in the three samples is about 12%; however, at temperatures above 230 °C, the samples synthesized at pH 8 and 9 show a higher weight loss than the sample synthesized at pH 10. This indicates the greatest interaction of the drug with the brucite layer and the increase in the formation of the lamellar structure, as was observed by DRX.

The DSC curves for LDH-Cl and the LDH-Indo synthesized at pH 8, 9 and 10 are shown for comparison in Figure 7. Indo displayed an endothermic peak at 161.26 °C which corresponds to its melting point [29, 36]. The samples with incorporated Indo showed an endothermic peak at 112 ºC due to loss of surface adsorbed and interlayer water. The first exothermic peak corresponding to the possible decomposition of Indo is approximately 270 °C in the samples synthesized at pH 9 and 10 (curve (c) and (d)); at the same temperature, in the LDH-Indo synthesized at pH 8, an endothermic peak was observed. This indicates that there is little interaction between the drug and the brucite layer as well as there is also drug on the surface, this result is consistent with what is observed by XRD. It can be inferred that the LDH host provides thermal stability to Indo up to 270°C, since the decomposition temperature of the pure drug is 161.26 °C. The last exothermic zone (350-650°C) could correspond to the removal of the interlayer drug and the dehydroxylation. The decomposition process occurs in multi-steps [16, 17, 35, 45-46], forming CO_2, NO_2, and water vapor; unfortunately, the gases evolved during decomposition could not be analyzed. The stronger exothermic effects due to combustion probably masked the expected endothermic peaks between 300 and 500 °C, due to dehydroxylation of the LDH, finally the complete decomposition occurred at 550 °C [8].

UV-visible diffuse-reflectance spectroscopy (UV-vis-DR): Photochemical tests : Figure 8 shows the UV-vis RD of LDH-Indo synthesized at different pH, without irradiation and with irradiation at different times (0.5, 7, 16 and 73 h). The host LDH did not present any remarkable absorption, as showed in Figure 8 I-(g). The samples synthesized at pH 9 and 10 did not present any significant changes until 16 hours of irradiation, which may suggest a stabilization of the drug in front of the light provided by the LDH host [13]. However, the sample synthesized at pH 8 showed a shoulder around 450 nm (marked zone), suggesting a possible degradation of products. Since these products have not been identified, this area is still under study. It should be noted that, by XRD, laminar formation and a higher interaction with the interlayer at high pH was observed, whereas in the sample at pH 8, a greater adsorption of the drug on the surface was observed. In Figure 8, the (e) curve represents the UV-vis RD spectra for each pH, while (f) signals pure Indo irradiated for 73 h. At 360 nm, the pure drug exhibits a shoulder (☼), which can be caused by the decomposition after irradiation time. This variation is not observed in the LDH-Indo at any synthesis pH. This would indicate that Indo into LDH exhibited higher photostability to UV light irradiation since after 73 hours of irradiation the drug is not significantly affected.

Drug release: In vitro drug releases were performed in a phosphate buffer at pH 7.4±0.1, in order to mimic the small intestine environment. The profiles, at different pH are reported in Figure 9. The profile was characterized by 8 hours. The sample synthesized at pH 8 exhibited the highest drug release, with 97%. At pH 9 and 10, the release was 92% and 67% respectively. In the initial 15 minutes, at pH 8 and 9, the drug release was similiar (17-14%) and at pH 10, the release was slower with 5%. At lower pH, the initial burst probably arose from the release of the drug absorbed on LDH matrix surface.

The kinetic drug release was characterized by fitting standard release equations to experimental data. First order, Higuchi's, Bhaskar's, Ritger-Peppas's, and Kressman and Kitchener's equations

were applied [17, 47-48] and the relative correlation coefficients are reported in Table 3. The Bhaskar equation fitting produces the highest R^2 values for drug diffusion through LDH which is strictly controlled by matrix. L. Pieroli et al. [48] proposed that LDH is a particular matrix; it could be able to control guest release by two processes: 1) chemical, due to the selectivity towards different anions and ion-exchange mechanism, or 2) physical, due to the length of the obliged ways of galleries. In this case, the first process plays the key role for all release time.

The cause of slow release at pH 10 may be attributed to the fact that the drug diffusion out of the LDH matrix is controlled by the rigidity of the structure layers, diffusion path length and the stronger electrostatic interaction between the Indo anions and LDH host layer [49]. However, at pH 8, the film type structure (observed by XRD) provides Indo with an easy access to the surface so a quick release in the first two hours is achieved and then, a controlled release is observed. Subsequently, at pH 9, the release was much lower and sustained compared to pH 8. By comparing the Higuchi model, which presented low values of correlation, to the Bhaskar, it can be concluded that the release process is not due to the concentration of the drug.

CONCLUSIONS

Indo has been successfully incorporated into LDH at different pH of synthesis. The materials synthesized at lower pH (8 and 9) show a more disordered layer structure which favors the incorporation of the drug, either in the interlayer or by being adsorbed on the surface. At pH 10, the highest order of structure and the lowest incorporation can be observed.

Indo suffers a morphological change due to the thermal treatment used. By DRX and SEM, it has been observed a progressive drug incorporation into the LDH layers with increasing pH. At lower pH, the formation of needles is observed (Indo own structure) which disappeared with increasing pH. The LDH provides thermal stability, with an increase in the thermal decomposition of the drug, around 100°C more. When Indo is intercalated into the LDH exhibited higher photostability to UV light irradiation since after 73 hours of irradiation the drug is not significantly affected. The LDH-Indo synthesized at different pH provides a good support for controlled release. The ability to incorporate and release behavior can be controlled by the coprecipitation pH. The release profiles were fitted by mathematical models, being the Bhaskar kinetics model the most appropriate. It can be concluded that the release process is not due to the concentration of the drug. The host-guest interactions play an important role in the drug stability and release performance.

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Table 1: pH of synthesis, interlayer distance and drug loading.

LDH synthesized	pH of synthesis	d (Å)	Drug Loading [%] ± S.D
LDH - Cl	10	7.66	----
LDH-Indo	8	22.80	66 ± 2
	9	24.05	60 ± 3
	10	24.05	56 ± 4

Table 2: Weight lost mass of LDH-Indo synthesized.

LDH-Indo pH synthesized	Weight lost [%]			Total Weight lost [%]
	RT-230 °C	230-400 °C	400-600 °C	RT -600 °C
8	11.56	33.98	40.99	86.53
9	11.94	22.45	50.82	85.21
10	11.24	18.86	36.60	66.70

Table 3: Mathematical model fitting of release data.

LDH-Indo pH synthesized	Model kinetics - R^2					
	Higuchi	Ritger-Peppas n= 0.7	n=1	Bhaskar	1st Order	Kressman and Kitchener
8	0.9292	0.8365	0.7327	0.9821	0.9432	0.9488
9	0.9581	0.9056	0.8191	0.9960	0.9763	0.9763
10	0.9873	0.9797	0.9161	0.9975	0.3966	0.9739

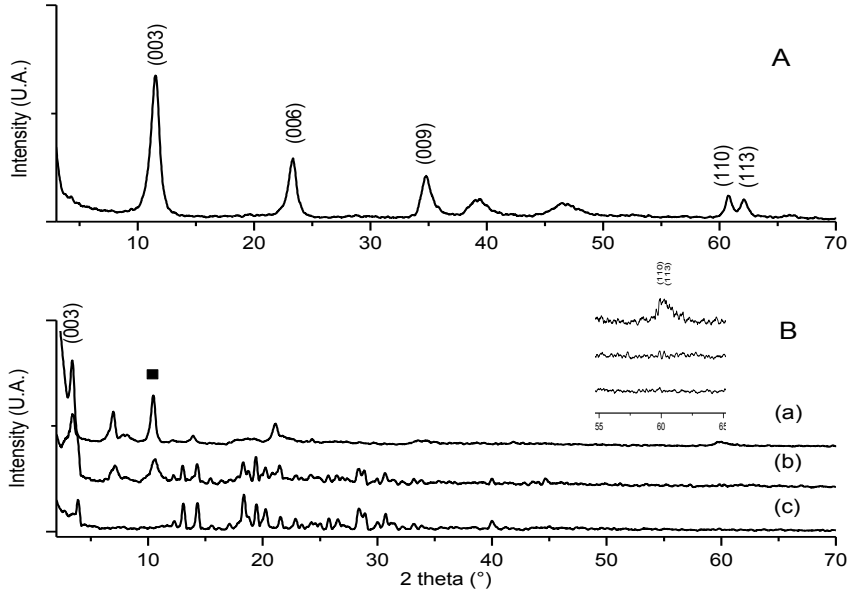

Figure 1 A: DRX of LDH-Cl. **B:** DRX LDH-Indo, (a) pH=10, (b) pH=9, (c) pH=8.

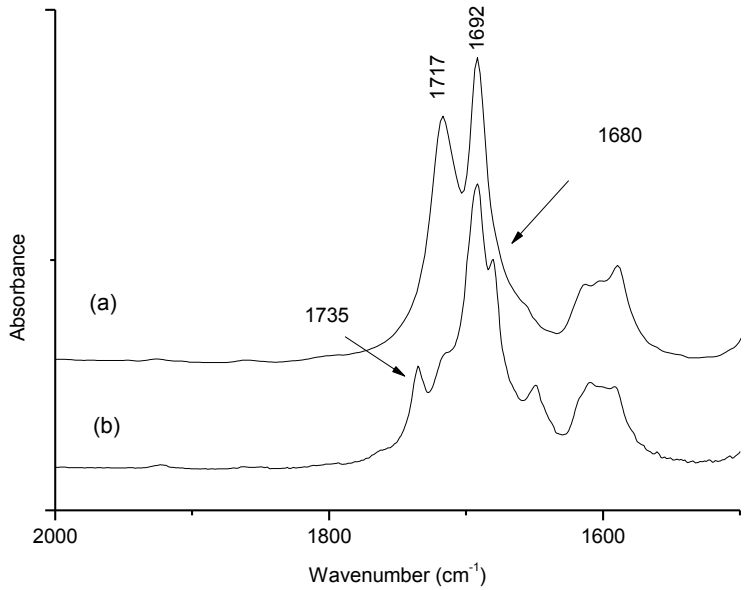

Figure 2: FT-IR of (a) γ-Indomethacin and (b) α-Indomethacin.

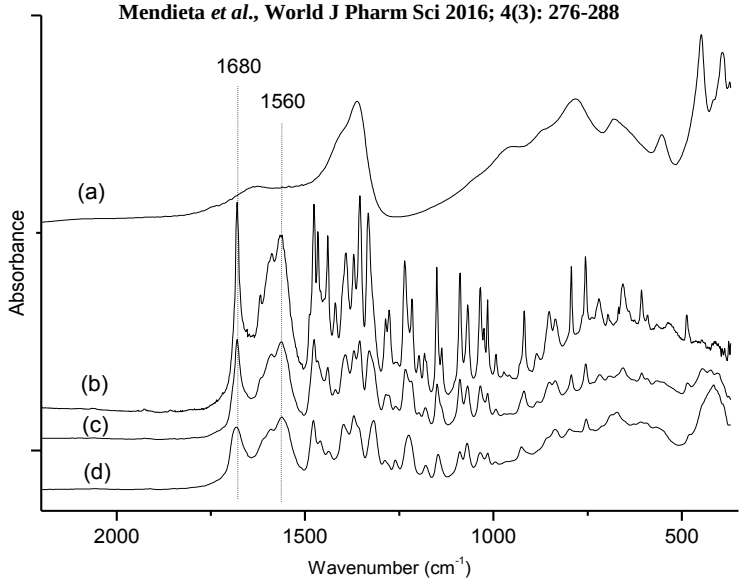

Figure 3: FT -IR of (a) LDH-Cl and LDH-Indo, (b) pH=8, (c) pH=9, (d) pH=10.

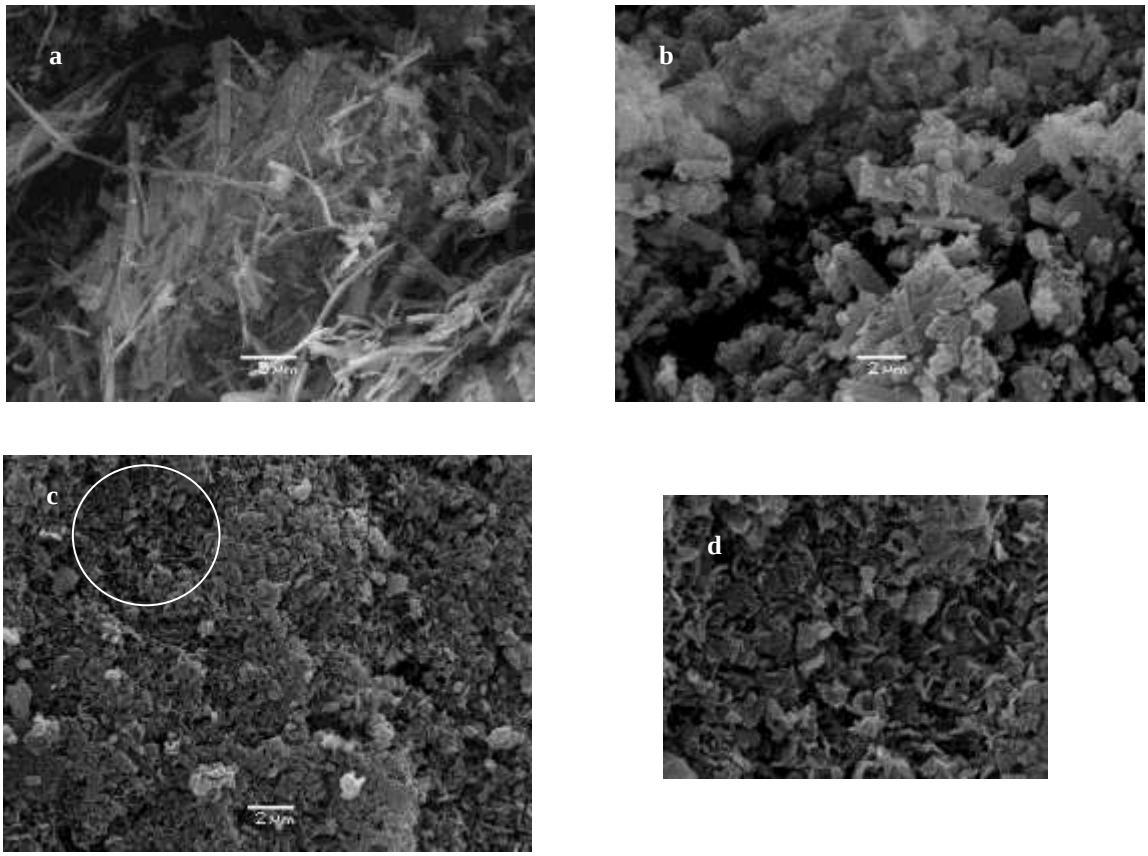

Figure 4: SEM of LDH-Indo. (a) pH=8, (b) pH=9, (c) pH=10 , (d) magnified image of pH=10.

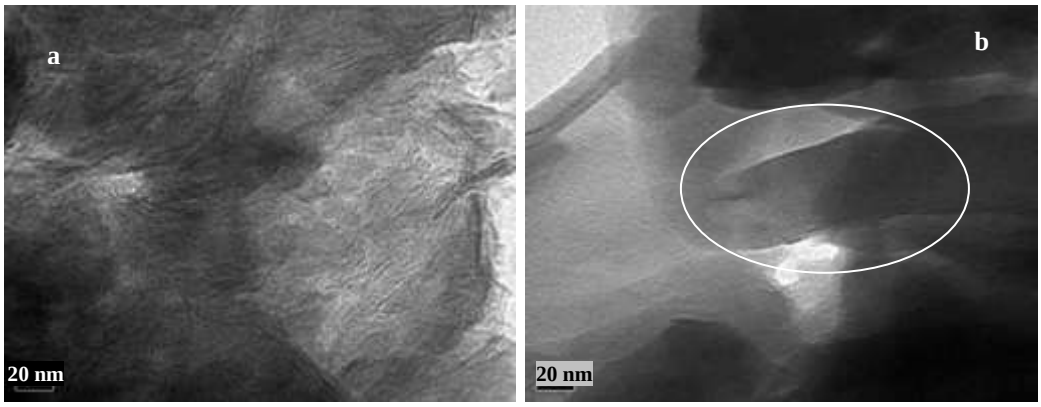

Figure 5: TEM of LDH-Indo. (a) pH=8, (b) pH=10.

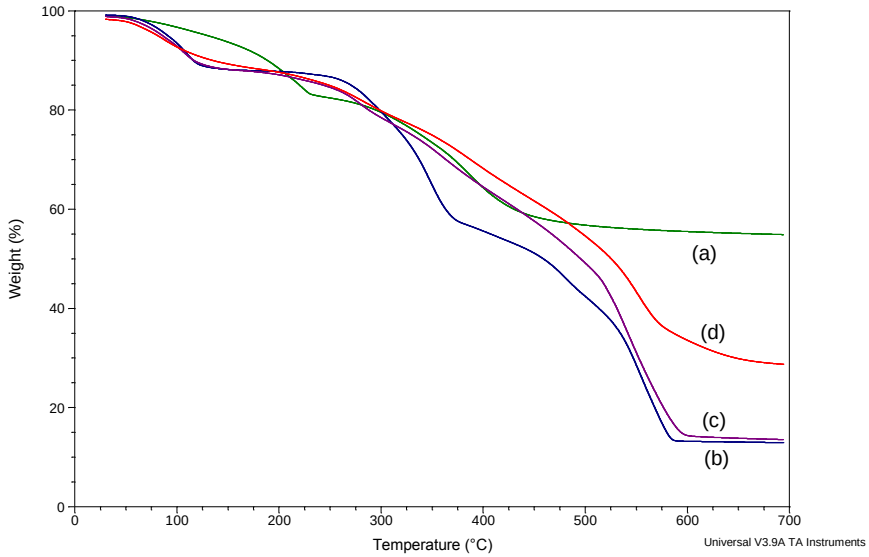

Figure 6: TG of (a) LDH-Cl and LDH-Indo, (b) pH=8, (c) pH=9, (d) pH=10.

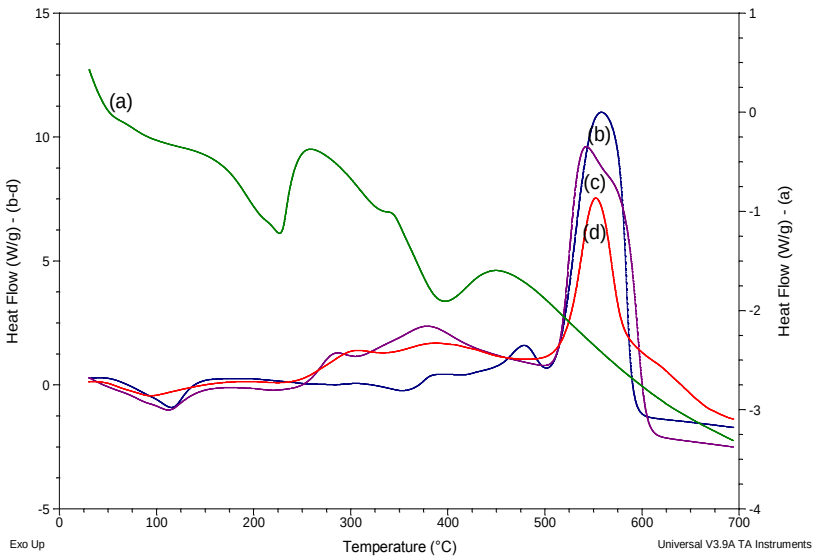

Figure 7: DSC of (a) LDH-Cl and LDH-Indo, (b) pH=10, (c) pH=9, (d) pH=8.

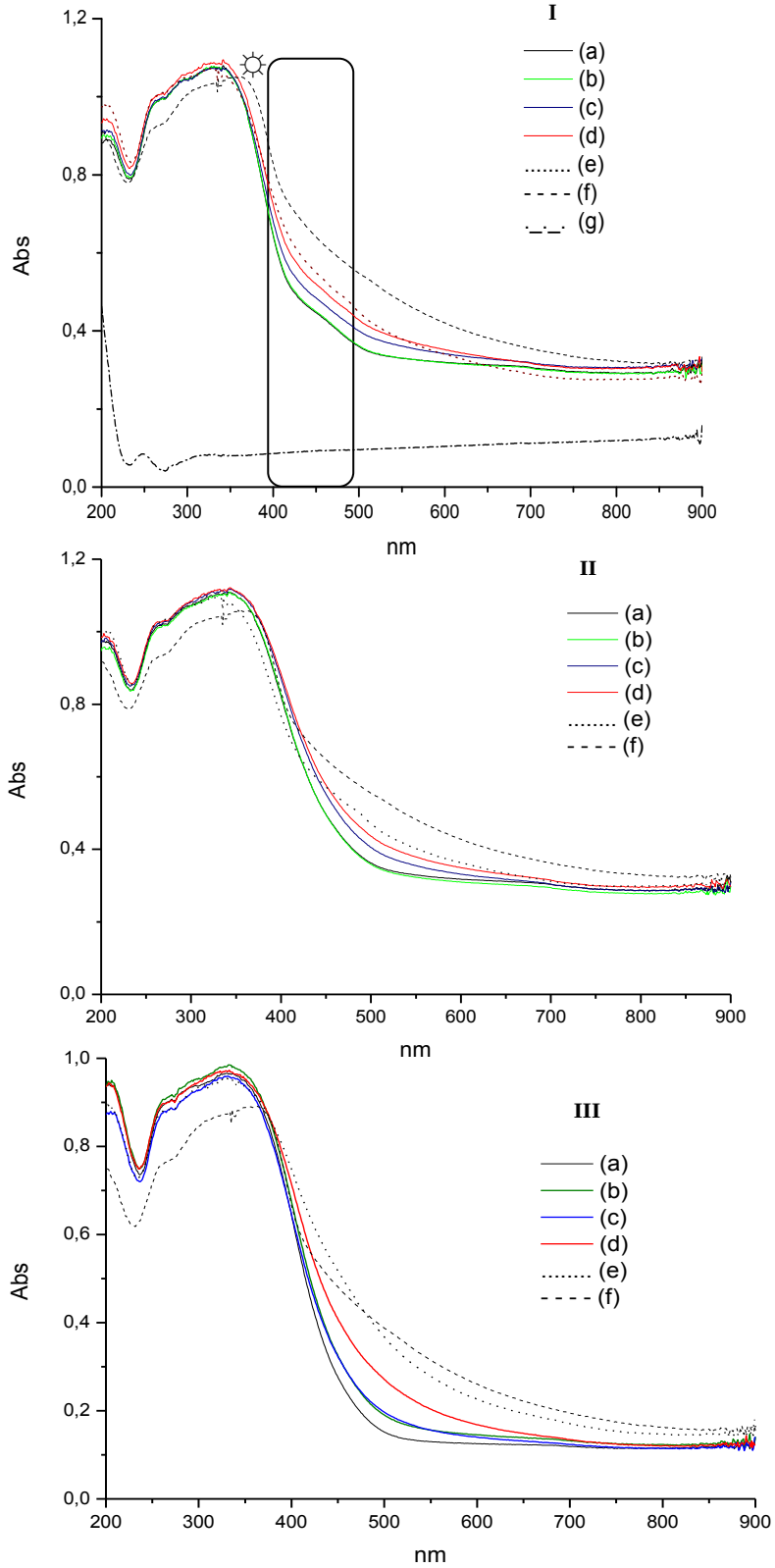

Figure 8: UV-vis-RD of LDH-Indo, (I) pH=8, (II) pH=9, (III) pH=10, (a) without irradiation, (b) 30 min of irradiation, (c) 7 h of irradiation, (d) 16 h of irradiation, (e)73 h of irradiation, (f) Indo 73 h of irradiation, (g) LDH.

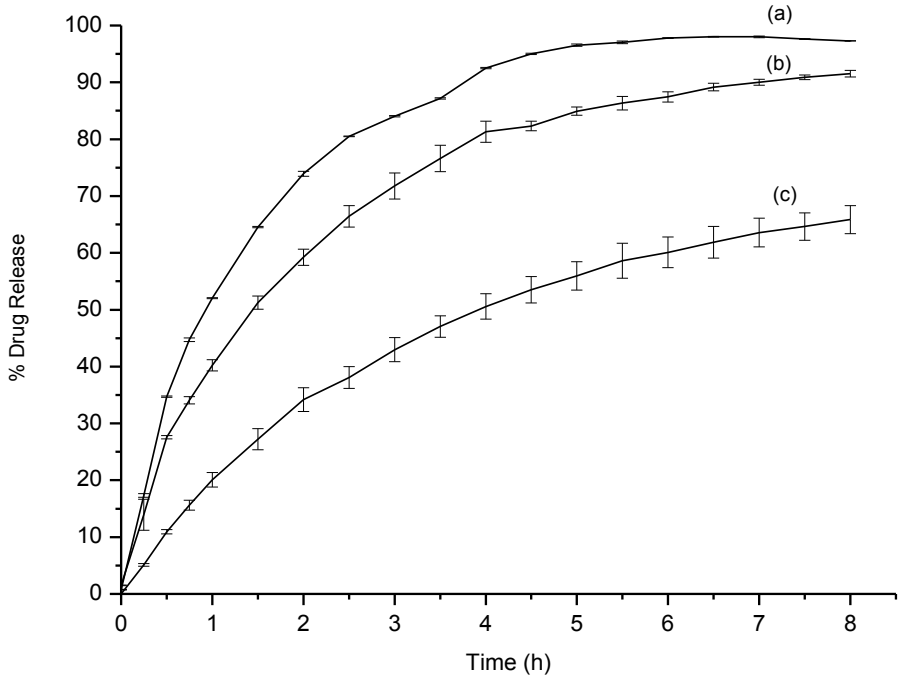

Figure 9: Release behavior of Indo from HDL-Indo of buffer simulated 7.4: (a) pH=8, (b) pH=9, (c) pH=10.

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