

Controlled Release of Ibuprofen Using Mg Al LDH Nano carrier

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ABSTRACT

In the present study, NSAID (non-steroidal anti-inflammatory drugs) such as ibuprofen in anionic form has been intercalated *in-situ* into the interlayer space of Mg Al LDH nanoparticle during co-precipitation of hydroxides. LDH nanohybrids are characterized by XRD, FTIR and UV spectroscopy. $Mg_{1-x}Al_x(NO_3)_x(OH)_2 \cdot nH_2O$ nanoparticles were synthesized using co-precipitation method from an aqueous solution of $Mg(NO_3)_2 \cdot 6H_2O$ and $Al(NO_3)_3 \cdot 9H_2O$. Ibuprofen was intercalated in inter layer space of Mg-Al LDH during coprecipitation of drug LDH conjugate in nitrogen atmosphere. The nanopowders synthesised were in the size range between 25 to 90 nm with an average particle size of 55 nm. XRD analysis proved that there is an increase in d_{003} spacing from 7.89 Å for pristine LDH to 14.71 Å for ibuprofen intercalated LDH due to the intercalation of bigger ibuprofen molecule in the interlayer space of LDH. FTIR analysis showed hydroxyl and carbonyl stretching of ibuprofen in LDH-IBU sample confirming the intercalation of ibuprofen in the interlayer structure of LDH. The drug release study in phosphate buffer solution at pH 7.4 using UV-Vis spectroscopy demonstrated that 50 % drug molecules were released in 15 hours and more than 85 % release was achieved after 36 hours.

Keywords: - Layered double hydroxide (LDH), Ibuprofen intercalated LDH, Release rate, Phosphate buffer solution.

1. Introduction

Drug delivery using nanoparticles of layered double hydroxide (LDH) has been extensively studied in recent past due to its capacity of preserving drug molecules in the interlayer space, it easy endocytosis into the cellular compartment and controlled, but slow degradability to release intercalated drugs at a sustained rate in human cell. The structure of LDHs is comprised of positive charge compensating and exchangeable anion and water molecule. LDHs belong to the class of anionic lamellar compounds brucite like structure with positive charge. Bivalent and trivalent metal cations occupy shared octahedral through hydroxide ions present at the vertices to form the two-dimensional layers. Formula for LDHs containing multi valent cations is $[M^{2+}_{1-x}M^{3+}_x(OH)_2][A^{n-}]_{x/n} \cdot zH_2O$, where M^{2+} represents metal cations like Mg^{2+} , Zn^{2+} or Ni^{2+} , and M^{3+} stands for Al^{3+} , Ga^{3+} , Fe^{3+} or Mn^{3+} . A^{n-} is a non-framework charge compensating inorganic or organic anion, e.g., CO_3^{2-} , NO_3^- , Cl^- , SO_4^{2-} , or RCO_2^- , and x is the mole fraction of M^{3+} and M^{2+} that are orderly structured. The charge density of the structure can be disturbed if ordering of cation is not proper, which eventually affects the physiochemical parameters in the interlayer gallery and on the surface like bonding, reactivity, orientation and the mobility of chemical species. Negatively charged drugs, therapeutically active compounds and other bioactive molecules can easily be exchanged with interlayer exchangeable anions in LDH and be intercalated into LDH for controlled release of drug and biomolecules in the required areas of human body.

Due to their easy synthesis process, structural diversity and stability, a number of LDH-based drug carrier systems have been researched for that have shown potential practical applications for the controlled release of a different of pharmaceutically active agents. Choy *et al.* successfully intercalated methotrexate (MTX) [1,2] folinic acid (FA) [2] and 5-fluouracil (5-Fu) [3] into the interlayer space of Mg-Al-LDH and demonstrated efficacy of LDH in releasing anticancerous drugs in controlled and sustained manner. The authors showed that the intercalated molecules were stabilized in the tilted longitudinal monolayer mode by electrostatic forces [1]. In their study, the researchers found that proliferation of SaOS-2 (osteosarcoma) cell was suppressed more strongly by MTX-LDH nanohybrid than with MTX alone.[2] Guilherme et al [4] synthesized anionic mefenamic acid intercalated LDH and found an increase in the anti-inflammatory and antinociceptive potential of drug confined to LDH as well as its haemolytic effect. Intercalation of pharmaceutically active drug like diclofenac, ibuprofen, naproxen, tolfenamic acid etc. into layered double hydroxide (LDH) was studied by Khan et al and found the potential of LDH as tunable drug delivery system(DDS). Again, intercalation of non-steroidal anti-inflammatory drugs like diclofenac into LDH was studied elsewhere [6]. In another study, Gordijo et al reported the immobilization of ibuprofen and copper-ibuprofen drugs on layered double hydroxides [7] using ion exchange, reconstruction, and coprecipitation reactions.

Currently, the design of safe and efficient gene delivery systems possesses one of the key challenges in gene therapy. In this context, LDH materials have demonstrated its potential as a novel nonviral delivery systems [8]. The design and synthesis of *c-myc* antisense oligonucleotide (*As-myc*)-LDH hybrid by simple ion exchange method were executed by Xu *et al* [9]. The negative charge on *As-myc* molecule allows easy intercalation into LDH by ion exchange that thermodynamically forms stable structure due to increased electrostatic interaction. In their study, Xu et al [9] found that the movement of *As-myc* into HL-60 cells through endocytosis, enhanced due to the charge neutralization. Influence of LDH nanoparticles on cell viability and proliferation is negligible at concentrations $\leq 0.050 \text{ mg mL}^{-1}$ as reported by Ladewig et al [10]. They also discovered a pronounced down-regulation of protein expression upon LDH mediated siRNA transfection of HEK293T cells.

Though a lot of literature reports are available regarding controlled release of anti-inflammatory drugs from MgAl LDH nanocarrier, study on the mechanism of drug release from the interlayer space of Mg Al LDH nanohybrid has rarely been highlighted. Herein, we report synthesis of a MgAl-LDH- ibuprofen nanocarrier using simple co-precipitation method. The LDH-IBU composite was fully characterized using powder X-ray diffraction (XRD), Fourier transform infrared spectroscopy (FTIR), dynamic light scattering (DLS) technique and transmission electron microscopy (TEM). Ibuprofen loading in the formulation was determined using carbon hydrogen nitrogen (CHN) elemental analysis. The release kinetic of ibuprofen from the hybrid material was determined using UV Spectrophotometer after suspending the powders in phosphate buffer solution (PBS) at 7.4 for different time interval. The results reveal the potential efficacy of Mg Al LDH nanoparticles in releasing anti-inflammatory ibuprofen in controlled and sustained manner.

2. Experimental procedure

2.1. Materials

Magnesium nitrate hexahydrate [$\text{Mg}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$], aluminum nitrate nonahydrate [$\text{Al}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$], ammonium hydroxide [NH_4OH] were purchased from Sigma-Aldrich, USA. Ibuprofen was procured from Cipla, India. Deionized and decarbonated ultra-pure water (Millipore, specific resistivity $18 \text{ M}\Omega$) was used in all preparations and the chemicals utilized in this study were used as received without further purification.

2.2 Methods

Synthesis of Mg Al Layered double hydroxide

A solution of magnesium nitrate and aluminium nitrate in 2:1 molar ratio was prepared. The solution was vigorously stirred for 6 hours using magnetic stirrer. NaOH (1M) was added to the nitrate solution dropwise to maintain the pH of the solution at 10 with continuous stirring. The precipitate was centrifuged out at 6000rpm for 10 minutes. The centrifused solid residue was then washed twice with de-ionised water to remove nitrates associated with the sample. After that the solid sample was dried in oven at 90°C to obtain pure Mg Al LDH powders.

Synthesis of Mg Al LDH- IBU Nanohybrid

Intercalation of ibuprofen into interlayer space of LDH was also performed using the co-precipitation method. 0.4 (M) Mg ($\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ and 0.2 (M) Al ($\text{NO}_3)_2 \cdot 9\text{H}_2\text{O}$ with Mg: Al in molar ratio of 2:1, were dissolved in 150 ml of deionised water followed by addition of 0.1 gm of ibuprofen under nitrogen atmosphere with constant stirring. To maintain the pH of the mixed precursor solution at pH 10, NaOH solution (1 M) was used, along with magnetic stirring. The stirring was continued for further 24 hours in nitrogen atmosphere. The appearance of a white gelatinous precipitate indicated the formation of Mg-Al-LDH- IBU hybrids. The sample was then centrifuged, washed with distilled water thrice to remove nitrate and excess ibuprofen and then vacuum dried.

3. Characterizations-

3.1 X-Ray Diffraction Method

Powder X-ray diffraction (XRD) patterns for MgAl LDH and MgAl LDH –ibuprofen nanopowders were obtained with X'Pert High Score diffractometer (Rigaku, Japan) using $\text{CuK}\alpha$ (λ - 1.5418°A) radiation at 40 mA, 40 kV and Ni- filter. The samples were scanned from 2θ values varying between 1° and 80° using a step size of 0.005° .

3.2 Fourier Transform Infra Red Spectroscopy (FTIR)

FT-IR stands for Fourier Transform Infrared, the preferred method of infrared spectroscopy. FTIR was used to characterize the chemical functional groups present in materials, based on the characteristics of vibrational and rotational energies of different molecular bonds. Fourier transform infrared (FTIR) spectra of synthesized LDH-IBU nanopowders and pure ibuprofen were recorded at room temperature using KBr (Brooker, $\geq 99\%$) pellet method (sample: KBr = 1:100) on a F Varian 3600 (USA) spectrometer in the range of $400\text{--}4000 \text{ cm}^{-1}$ with an average of 10 scans.

3.3 Particle Size Analysis using dynamic light scattering

The particle size analyzer measures the size of the particle in a sample. It measures particle size in the size range of 1nm- 3 μ m. Average particle size and size distribution of prepared LDH-IBU nanohybrid was determined using dynamic light scattering technique at 90 degrees with an instrument Microtrac Zetatrac (PA, USA).

3.4 Transmission Electron Microscopy (TEM)

Particle size and morphology of LDH-IBU nanohybrid powders were further examined using a transmission electron microscope (TEM) (Tecnai G² 30ST FEI, Netherland) operated at an acceleration voltage of 120 KV.

3.5 CHN Analysis

A CHN analyser helps us to analyse the Carbon, Hydrogen, Nitrogen content of an unknown compound. The compound of interest was combusted in a furnace at a high temperature under oxygen stream. During the combustion process mostly the oxides of the concerned elements were formed which were then separated and directed to a detector consisting of inert gases like helium or argon as a carrier for quantitative analysis. Thus, measurement of carbon, hydrogen, and nitrogen contents of the LDH-IBU and LDH were obtained with fair accuracy. The amount of ibuprofen incorporated into LDH-IBU nanohybrid were determined using CHN analyser, Elemental Analysen Systeme (Germany / Vario EL).

3.6 Analysis using UV-Visible Spectrometer

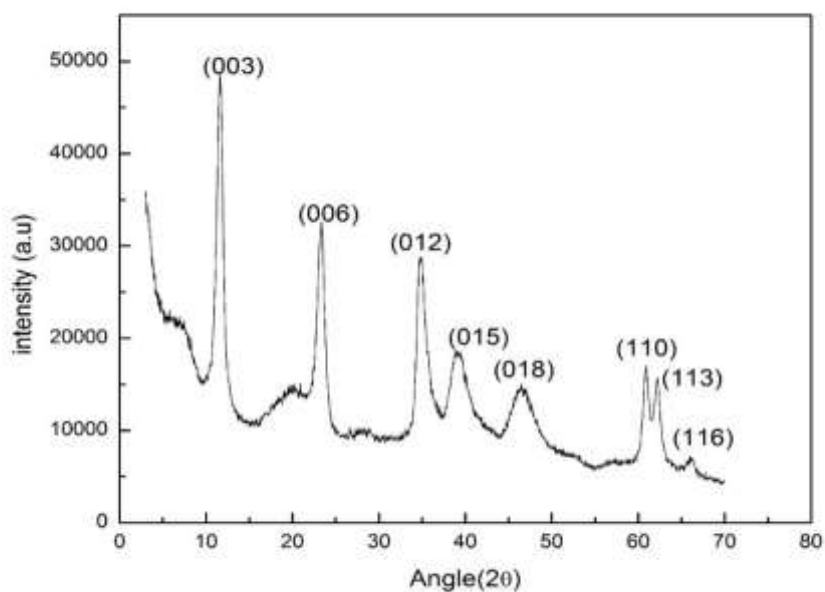
The process of identification and quantification of chemical species by measuring the absorption of monochromatic electromagnetic radiation having a wavelength in the UV-VIS range (200-900 nm) is referred to as UV- Visible spectroscopy. Ten mg of Mg Al LDH-ibuprofen formulation was dispersed in 5 mL of PBS at pH 7.4 in 8 different eppendorf, marked and kept for constant stirring for different duration of time. After definite time interval, one eppendorf was taken at a time and centrifuged at 3000 rpm for 5 mins to take out the supernatant solution containing released ibuprofen. The solution was then collected in a tube, filtered through 0.2 μ m filter paper and the filtrate was kept for analysis using a UV-visible spectrophotometer Lambda 35 (Perkin Elmer, USA).

4. Results and Discussion

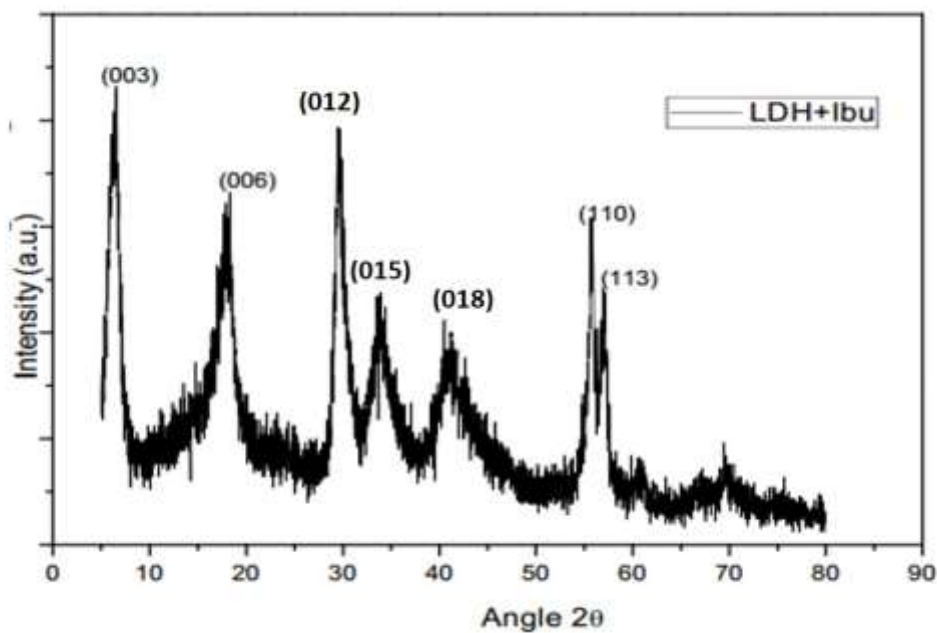
4.1 X-Ray Diffraction (XRD) Analysis

Phase evaluation of hydrotalcite-like LDH material was performed using XRD. The pristine MgAl-LDH (2:1) precursor was prepared using co-precipitation of the component hydroxides at constant pH with carbonate and exchangeable nitrate anions in the gallery space. Here Figure 1 (a) shows the powder XRD patterns of pristine Mg-Al LDH. The presence of both sharp and diffuse non-basal reflections in the XRD plot were taken as an indication of a partially disordered structure, resulted due to irregular stacking superposition of the regular unit layers. The pattern for MgAl-LDH was characteristic of the LDH structure with reasonably well crystallized hydrotalcite-like phase exhibiting rather sharp and symmetric 001 reflections. The basal spacing for (003) i.e. (d_{003}) was estimated to be 7.89 Å in pristine MgAl-LDH. The powder X -ray diffractogram of Mg Al LDH sample showed the structure of hydrotalcite displaying the characteristic reflection. Firstly with sharp and intense

basal 00l reflections of 003 and 006 planes appeared in the low angle region ($2\theta < 25^\circ$). Secondly broad 0kl reflections of 012, 015, and 018 planes appeared in the middle angle region ($2\theta = 30^\circ$ - 50°), followed by sharp hkl reflections of 110, 113, and 116 planes, in the high angle region ($2\theta = 55^\circ$ - 65°).



(a)



(b)

Fig -1: -XRD analysis of (a) pure Mg Al LDH and (b) LDH-IBU nanohybrid

The intercalation of ibuprofen into the MgAl-LDH matrix was confirmed by the shift of (003), (006) planes to higher d-values (Fig 1b). The interplanar spacing between (003) planes i.e. d_{003} in Mg Al-LDH- ibuprofen nanohybrid that is the gallery space for MgAl-LDH–ibuprofen nanohybrid material was found to be 14.71 Å, which was higher than the longitudinal molecular length of 13.72 Å for ibuprofen molecule. The basal spacing (d_{003}) increased from 7.89 Å in MgAl-LDH to that 14.71 Å in MgAl-LDH–ibuprofen nanohybrid because of intercalation of larger ibuprofen molecules into the interlayer space of LDH. Thus, intercalation of drug molecules in the interlayer space of Mg Al LDH caused expansion in the lattice structure. Ibuprofen being larger in size as compared to carbonates and nitrate ions in the interlayer space of pristine LDH, intercalation of ibuprofen increased the interlayer spacing of LDH-IBU nanohybrid significantly. Ibuprofen in anionic form was intercalated into the gallery space of MgAl-LDH because of anion exchange between nitrate and ibuprofen in the reaction solution that was favourable due to gain in enthalpy as well as entropy. Charge density of nitrate being higher than ibuprofen, it rather went into aqueous solution due to gain in solvation energy making place for ibuprofen in the interlayer space of Mg Al LDH. Also entropy gain in water because of removal of larger sized and predominantly hydrophobic ibuprofen from the aqueous environment in place of incoming smaller size and hydrophilic nitrate ions energetically favoured the intercalation of ibuprofen into Mg Al LDH.

4.2 Particle size distribution analysis

The particle size of ibuprofen intercalated LDH nanohybrid was determined using Dynamic Light Scattering (DLS) technique. If the particle size responsible for photon scattering increases by one order of magnitude, the scattered light intensity increases by about a million times. The intensity of photon signal is correlated to size by size measurement software through its inbuilt algorithm. The average particle size of the LDH-IBU nanoparticle was found to be ~ 55 nm with a poly dispersive index of 0.543 as evident from figure 2. Particle size is considered to be an important characteristic of LDH-IBU nanohybrid for exhibiting its efficacy as nanocarriers of pharmaceutically important drugs. The arte of transport of nanocarrier through the circulatory system depends on its size and morphology. Not only, that if the particle size falls above 200 nm, the particles would be arrested by reticuloendothelial system through phagocytosis and too small a particle would be very difficult for retaining inside cellular compartments. Particle size around 50 nm is ideal for cellular internalization by endocytosis and also for exhibiting controlled rate of dissolution in the cytoplasm to release the drug molecule. The particle size of LDH- IBU nanohybrid varied between 25- 90 nm which is ideal for its efficacy as carrier of drug. The particle size measured from DLS corroborated well with the particle size of LDH-IBU nanohybrid obtained from TEM micrograph in figure 3. Particle size in the range of 40-50 nm and spherical morphology of LDH-IBU nanohybrid as evident from TEM micrograph, is advantageous for its easy circulation inside human body.

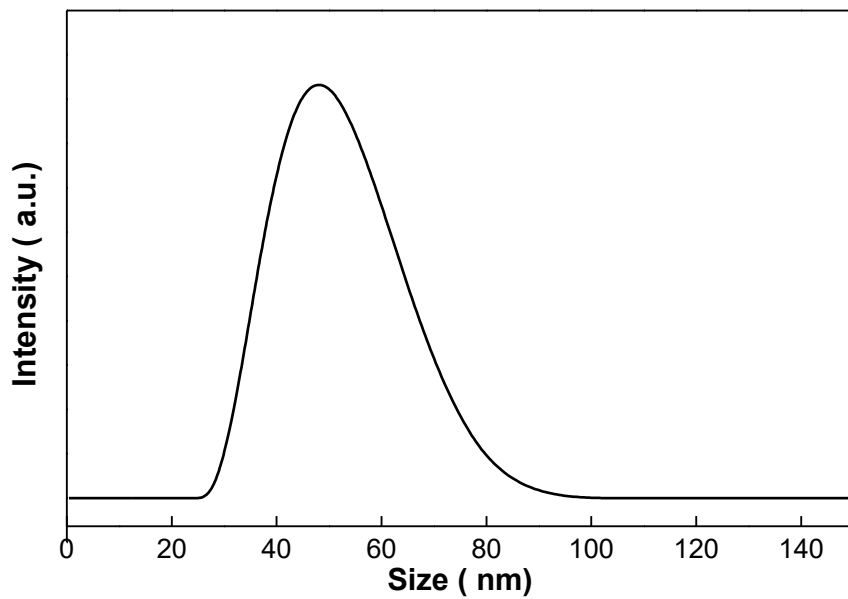


Fig 2 - Particle size distribution of synthesized LDH-IBU nanohybrid using DLS

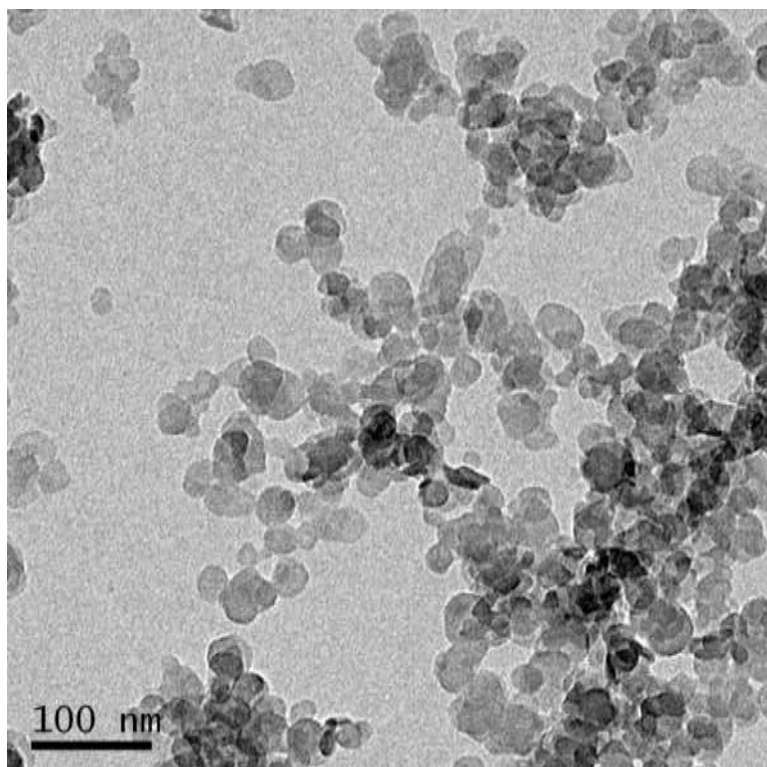
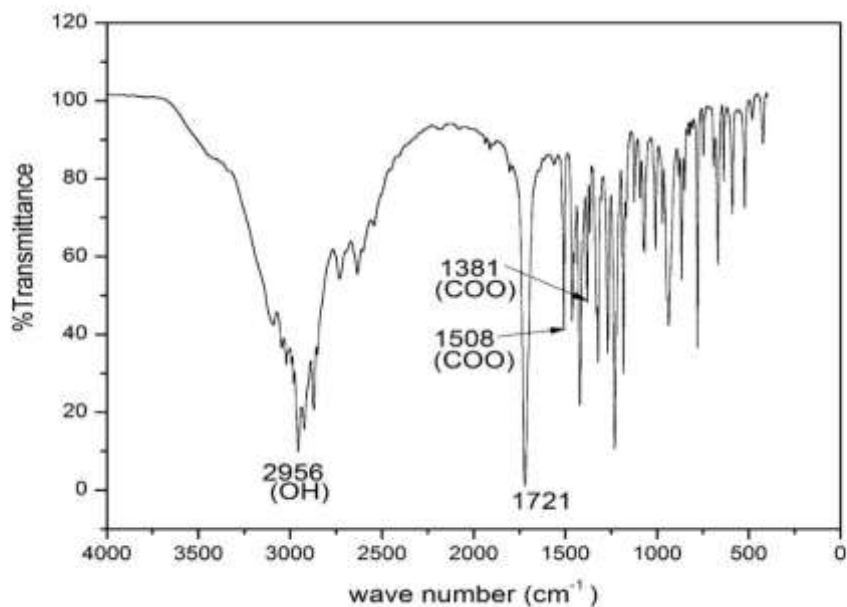
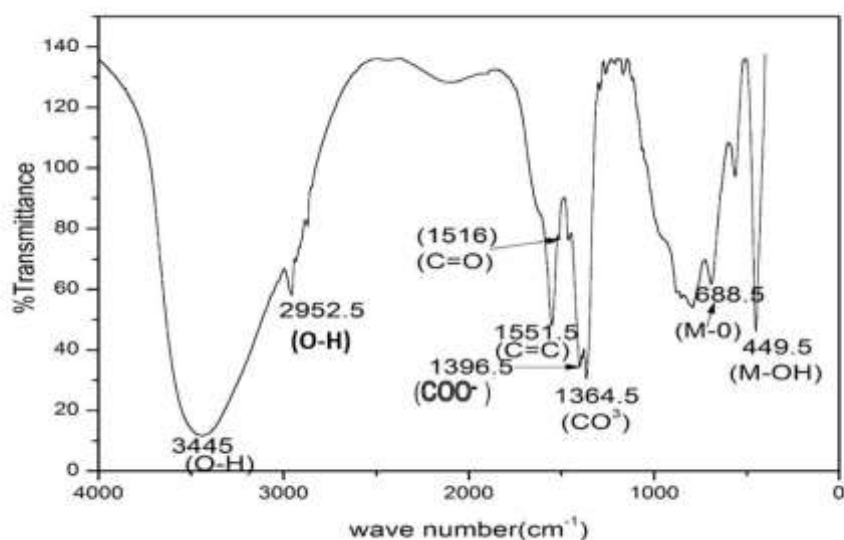


Figure 3: TEM micrograph of synthesized LDH-IBU nanohybrid

4.3 FTIR Analysis: -



(a)



(b)

Fig -4 :- FTIR spectra of (a) ibuprofen and (b) LDH- ibuprofen nanohybrids

The FTIR spectra of ibuprofen (IBU) molecule and LDH-IBU nanohybrids are shown in Fig. 4 (a) and 4 (b) respectively. The presence of several functional groups in ibuprofen gives rise to a spectrum with many absorption bands. In addition to bands at high wave number values

(2956, 2832 cm^{-1}) due to ν (OH) moieties, a band was recorded at 1381 cm^{-1} due to COO^- stretching [11]. The abnormally low value for the position of this band was due to intramolecular hydrogen bonds. The bands due to ν (C-C) of the aromatic ring were attributed to 1608, 1495, and 1462 cm^{-1} , while those due to mode ν (C=O) of the acid group was recorded at 1508 cm^{-1} .

FTIR spectra of LDH- IBU nanohybrid shows the presence of functional groups of both LDH and ibuprofen as in figure 4 (b). Two bands at 688 and 449 cm^{-1} arise due to the lattice vibrations of metal–oxygen and metal–hydroxyl bonds. The peak at 1396 cm^{-1} appeared due to COO^- stretching and the red shift observed due to bonding interaction between positive brucite layer and anionic COO^- of ibuprofen in the interlayer space [12- 14]. Further, the band at 1516 cm^{-1} was assigned to mode ν (C=O) of the acid group in LDH-IBU nanohybrid. The presence of C=C group of aromatic ring in LDH-IBU nanohybrid could be confirmed from band at 1605 cm^{-1} . The peaks at 3445 and 2952 cm^{-1} signify the stretching vibration of the labile hydroxyl group or chemically adsorbed water molecule in the interlayer space of LDH-IBU nanohybrids. The shifting of the hydroxyl stretching peak to a higher value clearly indicates that the drug, ibuprofen, was intercalated into the interlayer space of LDH. Existence of carbonate group in the nanohybrid could be confirmed from the peak observed at 1364 cm^{-1} .

4.4 CHN analysis

Element	Content (%)	
	LDH	LDH-SA (AE)
C	0.34	15.85
N	5.65	2.21
H	2.42	3.67

TABLE I: CHN analysis of LDH and LDH-IBU nanopowders

The CHN analysis of MgAl-LDH and MgAl-LDH-IBU nanohybrid are given in Table I. The amount of IBU intercalated into the interlayer space of MgAl-LDH was found to be 234.67 mg of IBU/g of LDH-IBU. Thus approximately 24. 21% of ibuprofen was present in LDH-IBU formulation. Small amount of nitrogen and carbon present in pristine LDH sample was due to the presence of nitrate and carbonate groups in the interlayer space of synthesized Mg Al LDH nanopowders.

4.5 Drug release study

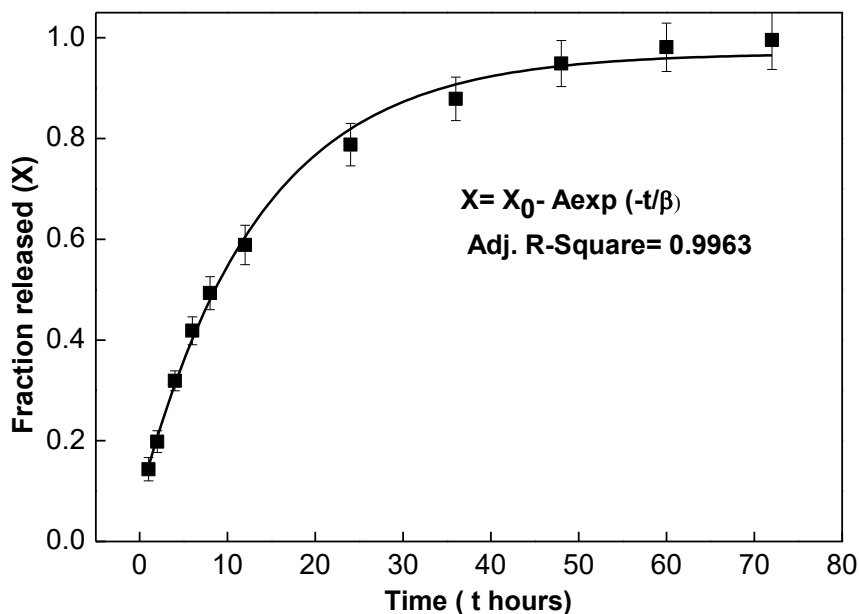


Fig 5: Cumulative percent release of drug molecule in PBS buffer solution (pH 7.4) vs. time.

The release of ibuprofen from LDH- IBU nano hybrid showed a little faster kinetics up to 16 hours without any apparent burst release. This faster kinetic was primarily attributed to the release of loosely bound IBU molecules from the edges of interlayer spaces and free surfaces of LDH. After 16 hours, a little slower release of ibuprofen was primarily because of de-intercalation of IBU molecules from the interlayer space of LDH. The later stage of slower release of ibuprofen after 26 hours governed by a combination of drug diffusion and LDH dissolution. The release profile shows that ~45% of the loaded ibuprofen was released in 16 hours, that increased nonlinearly to ~75% in 30 hours. The entire amount almost ~99% of ibuprofen was released within the time frame of 72 hours that clearly demonstrated the ability of LDH as carrier for controlled and sustained release of ibuprofen. The non-linear release behaviour of ibuprofen from LDH- IBU nano hybrid with respect to incubation time in PPS solution could be best explained by an exponential release rate as given in Figure 5.

$$X = M_t / M_\infty = X_0 - A \exp(-t/\beta) \dots\dots\dots(1)$$

Where $X_0 = 1.0802$, $A = 0.5605$ and $\beta = 35.457$ in this case.

It is evident that the ibuprofen drug release from LDH followed first order release kinetics with a satisfactory coefficient of 0.9891 and could be best fitted in equation (2).

$$X = 1 - \exp[-k(t - \alpha)] \dots\dots\dots(2)$$

where X , t , k , and α are the fraction of drug release, release time, kinetics constant, modified parameter respectively.

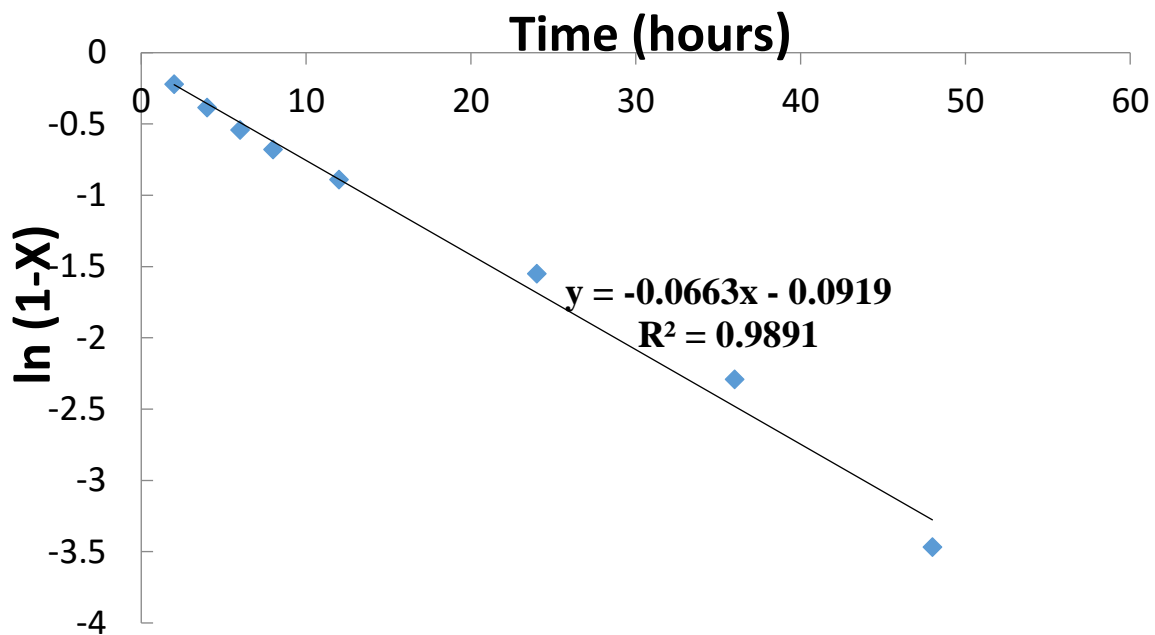


Fig 6: Fit of first order release kinetic data to observed release rate

It is evident that the ibuprofen drug release from LDH followed first order release kinetics with a satisfactory coefficient of 0.9891 as in Fig 6. The ibuprofen release rate was primarily governed by a combination of drug diffusion and LDH dissolution in physiological solution [15], that is closely relevant to first order release kinetics.

5. Conclusions

Non-steroid anti-inflammatory drug(NSAID) ibuprofen intercalated Mg-Al layered double hydroxide was synthesized through coprecipitation method. The synthesised nanohybrids showed an average particle size of 55 nm with spherical morphology that is ideal for exhibiting its efficacy as a carrier of anti-inflammatory drug. The left shift of peaks in the basal planes like (003) and (006) to lower 2θ value in the XRD plot of intercalated sample confirmed the increase in basal spacing in LDH, which is because of intercalation of ibuprofen drug into the interlayer space of LDH. FTIR analysis indicated ibuprofen molecules were intercalated into the hydroxide interlayer space and were stabilized by electrostatic forces, intermolecular bonds and Vanderwall's interaction. The cumulative release profile of ibuprofen in PBS (pH =7.4) medium revealed an exponential and sustained release upto 72 hours of incubation time and fitted very well with First order release kinetics model.

6. References

- [1]. J.-H. Choy, J.-S. Jung, J.-M. Oh, M. Park, J. Jeong, Y.-K. Kang and O.-J. Han, "Layered double hydroxide as an efficient drug reservoir for folate derivatives" *Biomaterials*, **25**, 3059-64 (2004).
- [2]. J.-M. Oh, M. Park, S.-T. Kim, J.-Y. Jung, Y.-G. Kang and J.-H. Choy, "Efficient delivery of anticancer drug MTX through MTX-LDH nanohybrid system," *J. Phys. Chem. Solids*, **67**, 1024-27 (2006).

- [3]. S.-J. Choi, J.-M. Oh and J.-H. Choy, "Anticancer drug-layered hydroxide nanohybrids as potent cancer chemotherapy agents", *J. Phys. Chem. Solids*, **69**, 1528-32 (2008).
- [4]. Vanessa R.R. Cunha, Viviane A. Guilherme "Delivery system for mefenamic acid based on the Nano carrier layered double hydroxide: physiochemical characterization and evaluation of anti-inflammatory and antinociceptive material", *Material science and engineering C* 58(2016) 629-638.
- [5]. Aamir I. Khan, Lixu Lei, Alexander J. Norquist and Dermot O'Hare "Intercalation and controlled release of pharmaceutically active compounds from a layered double hydroxide." *Chem. Commun.* 22 (2001): 2342-2343
- [6]. Cao F, Wang Y, Ping Q, Liao Z, "Zn-Al-NO(3)-layered double hydroxides with intercalated diclofenac for ocular delivery", *Int J Pharm.* 2011 Feb 14;404(1-2):250-6.
- [7] Gordijo CR, Barbosa CA, Da Costa Ferreira AM, Constantino VR, de Oliveira Silva D. "Immobilization of ibuprofen and copper-ibuprofen drugs on layered double hydroxides", *J. Pharm. Sci.*, **94**, 1135-48 (2005)
- [8]. Xu ZP, Zeng QH, Lu GQ, et al. Inorganic nanoparticles as carriers for efficient cellular delivery. *Chem Eng Sci.* 2006a;61:1027–1040.
- [9]. Zhi Ping Xu, Tara L Walker , Kerh-lin Liu, Helen M Cooper, GQ Max Lu, and Perry F Bartlett "Layered double hydroxide nanoparticles as cellular delivery vectors of supercoiled plasmid DNA", *Int J Nanomedicine.* 2007 Jun; 2(2): 163–174.
- [10]. Katharina Ladewig, Marcus Niebert, Zhi P. Xu, Peter P. Gray, Gao Q.M. Lu "Efficient siRNA delivery to mammalian cells using layered double hydroxide nanoparticles" *Biomaterials*, Volume 31, Issue 7, March 2010, Pages 1821–1829
- [11] Elkordy AA, Essa EA "Dissolution of ibuprofen from spray dried and spray chilled particles", *Pak J Pharm Sci.* 2010 Jul;23(3):284-90.
- [12]. Manjusha Chakraborty *et al.*, "Layered double hydroxide: Inorganic organic conjugate nanocarrier for methotrexate", *Journal of Physics and Chemistry of Solids* 72(2011)779–783.
- [13]. Z Wang, E Wang, L Gao, L Xu, Synthesis and properties of Mg₂Al layered double hydroxides containing 5-fluorouracil. *J. Solid State Chem.* **2005**, 178, 736-741.
- [14]. Soumini Mondal, Sudip Dasgupta , Kanchan Maji "MgAl- Layered Double Hydroxide Nanoparticles for controlled release of Salicylate", *Materials Science and Engineering: C*, Volume 68, 1 November 2016, Pages 557–564
- [15] L. Zhang, Y. Lin, Z. Tuo, D.G. Evans, D. Li "Synthesis and UV absorption properties of 5-sulfosalicylate-intercalated Zn–Al layered double hydroxides" *J. Solid State Chem.*, 180 (4) (2007), pp. 1230–1235