Layered zinc hydroxide–ibuprofen nanohybrids: synthesis and characterization

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Abstract. The nonsteroidal anti-inflammatory drug (NSAID), ibuprofen (IBU) anion, was intercalated into the layered zinc hydroxide (LZH) to form a new organic–inorganic nanohybrid. Then, IBU–LZH nanohybrid was dispersed into chitosan for the formation of the nanocomposite. The IBU–LZH nanohybrid was characterized by powder X-ray diffraction (PXRD) to study intercalation, scanning electron microscopy (SEM) for the investigation of surface morphology, Fourier transform infrared (FTIR) spectrophotometer to study the chemical interactions and thermal gravimetric analysis/derivative thermogravimetric analysis (TGA/DTG) for understanding the thermal stability. The PXRD patterns showed that the IBU was successfully intercalated into the interlayer space of LZHs as monolayers and the basal spacing of LZH increased from 9.57 to 19.54 Å. The FTIR analyses confirmed the formation of the host–guest nanohybrid. The DTG studies revealed that the thermal stability of IBU was increased after the intercalation into LZH. The *in vitro* release study of IBU from IBU–LZH and IBU–LZH/chitosan nanocomposite was investigated in phosphate buffer saline (PBS) solution of pH 4.8 and 7.4. The drug release from the LZH was studied by ultraviolet–visible (UV–vis) spectroscopy.

Keywords. Synthesis; ibuprofen; layered zinc hydroxide; nanohybrid.

1. Introduction

Organic–inorganic nanohybrids are formed by dispersing inorganic nanostructures in the organic matrices.¹ The nanohybrids have attracted considerable research interests, due to their unusual physicochemical properties, which cannot be otherwise achieved by any conventional solid state reactions.² This type of material offers a variety of applications in the industries and the environment such as optical and electronic materials, biomaterials, catalysis, sensing, coating, as well as in medical science and energy storage.^{3–5} Layered double hydroxides (LDHs) and layered metal hydroxides (LMHs) have been studied extensively and are recognized for their anion-exchangeable properties.^{6,7} LDHs compounds with inorganic brucite-like structures can be expressed by the general formula $[M(II)_{1-x}M(III)_x(OH)_2](A^{n-})_{x/n} \cdot yH_2O$, where M(II) is a divalent metal cation (Ca^{2+} , Mg^{2+} , Zn^{2+} , Co^{2+} , Ni^{2+} , Cu^{2+} and Mn^{2+}) and M(III) is a trivalent metal cation (Al^{3+} , Cr^{3+} , Fe^{3+} , Co^{3+} , Ni^{3+} and Mn^{3+}); n refers to the number of interlayer water molecules, x represents the layer charge density and A^{n-} refers to the exchangeable anion with a charge ($n-$).^{8,9} LZH is a type of LMH, having the empirical formula of $M(II)(OH)_{2-x}(A^{n-})_{x/n} \cdot nH_2O$, where M(II) is the metal cation, Zn^{2+} and A^{n-} are the counterions and the OH^- anions on the brucite hydroxide layer are substituted by water molecules and counter anions.^{10–12}

LZHs are currently being used as an additive for slow release herbicides and drugs.^{13–15} Some drugs have been intercalated into LZH, including diclofenac sodium,¹⁶ amoxicillin trihydrate,¹⁷ ciprofloxacin¹⁸ and cetirizine.¹⁹ There are many approaches that can be used to synthesize the LZH nanohybrid such as the co-precipitation method,²⁰ thermal decomposition method²¹ and ion-exchange method.^{22,23} From the aforementioned methods, ion-exchange method is frequently chosen for the preparation of LZH nanohybrid because it is an easy method of preparation with fewer steps and lesser involvement of chemicals.^{24,25}

NSAIDs are commonly used for the treatment of pain, inflammation, rheumatic disorders and osteoarthritis.^{26–28} Drugs in this category include diclofenac, naproxen, piroxicam, ketorolac, indomethacin, oxaprozin and meloxicam. α -Methyl-4-(2-methylpropyl) benzeneacetic acid (ibuprofen) is the oldest of all the innovative NSAIDs available and, in addition, possesses analgesic as well as antipyretic properties²⁹ (figure 1). The terminal half-life of ibuprofen is approximately 2 h. According to the Biopharmaceutical Classification System (BCS), IBU had been classified as a class II drug with low solubility at pH 1.2 and 4.5 and high solubility at pH 6.8, consequently, the drug dissolution may be a rate-limiting step in the drug absorption process.³⁰ Thus, the improvement of IBU dissolution for its immediate release is desirable for rapid IBU absorption.³¹ In this study, we highlighted the intercalation of IBU into LZH to form a nanohybrid. IBU–LZH was prepared by ion-exchange method under an aqueous condition with the purpose of

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forming a new organic–inorganic nanohybrid for a controlled release formulation. In addition, the effect of the IBU–LZH nanohybrid and IBU–LZH/chitosan nanocomposite on IBU release from LZH and LZH/chitosan was also studied.

2. Methods

2.1 Materials

Ibuprofen was purchased from the Alborz Drug Company in Iran. All other reagents were purchased from Merck Chemical Company and MP Company, and used without further purification.

2.1a Synthesis of LZH: LZH was prepared by the co-precipitation method. Briefly, 0.069 mol of zinc nitrate hexahydrate was dissolved in 20 ml of distilled water. Solutions of 50 ml sodium hydroxide with concentrations of 0.75 mol l^{-1} was added into zinc nitrate solution and suspension mixture was stirred for 2 h at room temperature. A white precipitate was obtained. It was then centrifuged, thoroughly washed with deionized water and dried in an oven for 24 h at 50°C .

2.1b Synthesis of IBU–LZH: IBU–LZH was prepared by the ion-exchange method. As described in the earlier works,¹⁶ about 0.2 g of LZH was dispersed in 50 ml of decarbonated water, whereas 0.56 g of IBU was dispersed in 20 ml of distilled water. The two solutions were simultaneously added to a beaker and stirred for 1 h. The pH of suspension was adjusted to 8 by dropwise addition of 1 mol l^{-1} sodium hydroxide solution. The mixture was stirred for 24 h at room temperature. The white precipitate was washed free of ions with decarbonated water at least three times, centrifuged at a speed of 1000 rpm for 15 min, and finally dried for 24 h at 60°C .

2.1c Synthesis of IBU/chitosan and IBU–LZH/chitosan nanocomposite: A 1% v/v solution of acetic acid was prepared by adding 1 ml of acetic acid to a 100 ml flask half filled with water, which was mixed and then diluted to 100 ml. Then, 0.15 g of chitosan was added to acetic acid solution and stirred for 30 min at 25°C to obtain a transparent liquid. Meanwhile, 0.05 g of IBU or IBU–LZH was mixed with 100 ml of chitosan dispersion and this suspension was stirred on a magnetic stirrer at room temperature for 24 h.

Figure 1. Ibuprofen molecule.

This mixture was added drop by drop into a 1% w/v tripolyphosphate (TPP) solution. The reaction mixture was stirred vigorously and aged for 12 h. Finally, the nanocomposites were washed twice with water and then dried in air.

2.1d Drug-release studies: *In-vitro* release of IBU from LZH and LZH/chitosan was studied at 37°C in phosphate buffer saline (PBS) at pH 7.4 and 4.8. Then, 20 mg of the IBU–LZH or IBU–LZH/chitosan was immersed in 10 ml of PBS at pH 7.4 and 4.8 and stirred at 500 rpm at 37°C up to 12 h. Every 10 min, 3 ml of solution was withdrawn and replaced with fresh phosphate buffer. The amount of IBU release was then measured at λ_{max} 265 nm by an UV–vis spectrophotometer.

The per cent of the drug release was evaluated by using the following definitions:

$$\text{Drug release (\%)} = \frac{\text{Amount of drug release (mg)}}{\text{Total weight of drug sample (mg)}} \times 100.$$

2.2 Characterization

The powder X-ray diffraction (PXRD) patterns of the samples were collected with a Bruker AXS model D8 advance diffractometer using $\text{CuK}\alpha$ source ($\lambda = 1.542 \text{ \AA}$) at 40 kV, 35 mA, and a scan range $2\text{--}70^\circ$. Infrared spectra were recorded with a Bruker Fourier transform infrared spectroscopy (FTIR), spectrometer model Bruker, using KBr pellets, scanned from 4000 to 400 cm^{-1} . Absorption spectra were recorded in the range 200–800 nm on a Shimadzu model 1601 PC UV–vis spectrophotometer. The thermal behaviour of the samples were determined by the thermogravimetric analyses (TGA) on a Mettler-Toledo TGA 851e apparatus in heating rate of $10^\circ\text{C min}^{-1}$ under the N_2 atmosphere. Scanning electron microscope (SEM) and micrographs were taken on a VEGA-TESCAN.

3. Results and discussion

3.1 PXRD and structural model

PXRD is now a common method to study the possibilities of alternations of the LMH structure, after the reaction with the IBU in aqueous solution, and verify the possible changes of the basal spacing after the ion-exchange reaction. PXRD patterns of the pristine LZH, the IBU–LZH nanohybrid and IBU are shown in figure 2. The IBU showed a crystalline structure as previously reported³² (figure 2a). Figure 2c exhibits the PXRD patterns of the LZH synthesized by the co-precipitation method. The PXRD patterns are in agreement with the previously published data (JPCDS file no. 01-72-0627, $\text{Zn}_5(\text{OH})_8(\text{NO}_3)_2 \cdot 2\text{H}_2\text{O}$) and showed high crystallinity of $9.57 \text{ \AA}$ with basal spacing, due to the 200 planes of the monoclinic structure.⁵ The XRD pattern of IBU intercalated into LZH is shown in figure 2b that exhibited the characteristic reflections of a layered nanohybrid which are

Figure 2. Powder X-ray diffraction patterns of (a) IBU, (b) IBU-LZH and (c) LZH.

sharp at lower theta angle and weaker at higher angles. The shifting of basal reflection towards low 2θ angle ($2\theta = 3.70^\circ$, due to a d -spacing of 19.54 Å) for the IBU-LZH confirms the intercalation of IBU into the interlayer galleries of the LZH.

The 3D molecular size, along with the x , y and z axes of IBU was estimated to be 9.54, 4.89 and 2.4 Å by ChemOffice software (Cambridge, MA, USA). Assuming a thickness of 4.8 Å for the LZH layer and 2.6 Å for each zinc tetrahedra, the gallery height for LZH nanohybrid was estimated to be 19.54 Å. Therefore, the gallery height of the LZH after the intercalation of IBU could be calculated by subtracting the thickness of the LZH layer plus the height of zinc cation moiety of the lattice from d -spacing, and found to be 9.54 Å ($19.54 - (4.8 + 2.6 + 2.6)$ Å). The obtained value (9.54 Å) was larger than the value of long and short axes of IBU molecule (figure 3a). Therefore, this suggests that IBU anions were arranged as monolayers in the interlayer of LZH.³³ Figure 3b shows IBU anions intercalated in the interlayer space.

3.2 FTIR

FTIR can be very helpful to show the successful intercalation of the anions into LZH. The FTIR for pristine IBU, IBU intercalated into the LZH interlayer and LZH are shown in figure 4. FTIR spectra of LZH showed two peaks at 438 and 468 cm^{-1} , respectively, due to the vibration of zinc-oxygen bonds. The absorption at 641 cm^{-1} can be assigned to the stretching vibration of oxygen-hydrogen. The weak absorption at 833 cm^{-1} is due to ν_2 mode of nitrate anions. The sharp absorption at 1373 cm^{-1} is due to ν_3 vibrational mode of nitrate ion with D_{3h} symmetry and ions intercalated in the interlayer spacing. An absorption band at 1640 cm^{-1} is attributed to δ -mode of oxygen-hydrogen groups. The 3486 cm^{-1} band due to hydroxyl groups of water molecules is placed in among the layers or is physisorbed onto the layer. An absorption band at around 3580 cm^{-1} is attributed to

Figure 3. Molecular structure of IBU and 3D molecular size of (a) IBU and (b) spatial orientation of IBU after intercalation.

stretching vibrations of hydroxyl groups on lattice¹⁷ (figure 4c). Figure 4b shows the FTIR spectra used to prove the intercalation of IBU into the LZH host. A very broad absorption band at about 3354 cm^{-1} is related to the $\nu(\text{OH})$ stretching vibration of the hydroxyl group of the host layers as well as interlayer and physically adsorbed water molecules. Typical $\nu(\text{CH})$ stretching vibrations of nanohybrid are observed at 2953, 2931 and 2868 cm^{-1} . The absorption bands at 1549 and 1366 cm^{-1} are related to the asymmetric and symmetric stretching of COO^- group, respectively. The $\text{C}=\text{O}$ stretching vibration of the $-\text{COO}^-$ group at 1721 cm^{-1} vanished in IBU. A band at 718 cm^{-1} may be attributed to the hydroxyl bending within the layers. The peaks and bonds at 422 and 480 cm^{-1} are due to the Zn-OH and Zn-O lattice vibrations. Figure 4a displays the FTIR spectra of IBU. The peak at 2956 and 2869 cm^{-1} is attributed to CH_3 asymmetric stretching and CH_2 asymmetric stretching vibration, respectively.

The band at 1721 cm^{-1} is due to asymmetrical stretching vibration of the $-\text{COOH}$ group. The sharp peaks at 1508 and 1420 cm^{-1} corresponded to C-C stretching vibration in the benzene ring. An absorption band at 1231 cm^{-1} is due to C-C

Figure 4. FTIR spectra of (a) IBU, (b) IBU-LZH and (c) LZH.

stretching vibration. Bands centred at 1460, 866, 407 and 522 cm^{-1} are assigned to CH_3 asymmetric deformation, C–H out of plane deformation, in plane ring deformation and CH_2 inplane rocking vibration, respectively.³⁴ The FTIR results confirmed the presence of IBU anions between the layers of LZH.

3.3 Thermal study

The curves of IBU and IBU-LZH are presented in figure 5. For IBU (figure 5a), thermal studies show that the temperature maxima is at 202.2°C with weight loss of 99.8% compared to 409.3°C for the IBU-LZH with weight loss of 78%. This indicates that IBU encapsulated into the inorganic interlamellae is thermally more stable than their counterpart in the anion form. DTG of IBU-LZH showed (figure 5b) a peak at 69.2°C with weight losses of 3.0% due to the removal of surface physisorbed and intercalated structure water molecules. The second weight loss at 409.3°C is due to dehydroxylation of the hydroxyl layer together with the decomposition of IBU. Increasing the decomposition temperature of IBU from 202.2°C for IBU pure to 409.3°C for IBU-LZH nanohybrid confirmed the greater thermal stability of IBU in nanohybrid than their counterpart in the unbound compound form.

3.4 Surface morphology study

The surface morphologies of LZH and IBU-LZH are shown in figure 6. The SEM micrograph of LZH in figure 6a

Figure 5. TGA/DTG thermograms of (a) IBU and (b) IBU-LZH nanohybrid.

Figure 6. SEM images of (a) LZH, (b) IBU-LZH and (c) IBU-LZH/chitosan.

displayed aggregated flake-like particles. The IBU-LZH nanohybrid showed compact irregular agglomerated structure with non-uniform size (figure 6b). These images exhibited that the transformation of LZH into an IBU-LZH nanohybrid produced surface morphology transformation and the particle size of IBU-LZH nanohybrid was reduced in comparison with the layered hydroxide.¹⁶ This indicated that the IBU anions intercalated into the interlayer space of LZH. Figure 6c shows a non-uniform structure for IBU-LZH/chitosan.

3.5 The release behaviour of IBU from nanohybrid and nanocomposite

The release profiles of IBU from chitosan, IBU-LZH and IBU-LZH/chitosan in PBS solution are displayed in figure 7. The release rate of IBU from chitosan, nanohybrid and nanocomposite is clearly dependant on the pH values; i.e., release of IBU at pH 7.4 is slower than that at pH 4.8, where the amount of drug released reaches 77% in 1200 min (figure 7a). The sustained release properties of IBU anions from

Figure 7. Release properties of IBU from (a) LZH, (b) chitosan and (c) LZH-chitosan nanocomposite at pH 4.8 and 7.4.

the nanohybrids were related to strong electrostatic interaction between the positively charged layered hydroxide and the negatively charged IBU anions in the interlayer. The increased release rate of IBU in pH 4.8 medium was noted. The difference in release rates may be due to the solubility of IBU in release media of different pH values. IBU is practically insoluble in acidic pH but is readily soluble in alkaline pH.³⁵ Figure 7b shows a release of IBU from IBU-chitosan nanohybrid at pH 7.4 and 4.8. The release rates of IBU from IBU-LZH at pH 7.4 is slower than the release rate of IBU at pH 4.8, where the release is >75% at pH 7.4 for 1200 min compared to the release of >60% at pH 4.8. This is due to the amine groups of chitosan that gets protonated, leading to the dissociation of the hydrogen bonds involving the chitosan amine groups with the carboxylic acid groups of the IBU molecules. The release behaviours at pH 4.8 in IBU-LZH/chitosan were very fast compared to pH 7.4, which can be attributed to the chitosan matrix. However, chitosan could not cap the openings of LZH. Consequently, the IBU anions can easily diffuse out from the LZH interlayer into the release medium.

4. Conclusion

The NSAID molecule IBU has been included within the galleries of the anionic clay, LZH by ion-exchange intercalation. PXRD, FTIR spectroscopy, SEM and DTA/DTG analysis have been used to characterize the confined IBU anions in the LZH drug nanohybrids.

PXRD suggested an expansion of interlayer spacing to 19.54 Å due to the monolayer arrangement of IBU anions. The FTIR analyses indicated a successful intercalation of IBU anions between the LZH layers. Surface area analysis displays the increase in surface area dramatically after intercalation and TGA/DTG analysis exhibits the obviously improved thermal stability of intercalated IBU anions after intercalating into LZH interlayer due to the host-guest interaction. The particle size of IBU anions intercalated LZHs was 50–100 nm. The strong electrostatic intercalations between the LZH layers and the organic species exhibited the controlled release of IBU anions in the interlayer. The results of *in vitro* drug release from the nanohybrid and nanocomposite indicated that the release rate from

nanocomposite is remarkably lower than that from the IBU–chitosan and nanohybrid at pH 7.4. These results show that layered zinc hydroxide may have application as the basis of a drug delivery system.

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