



Original Research Article

Nanohybrid based on layered zinc hydroxide with salicylic acid drug: Investigation of the structure and controlled release properties

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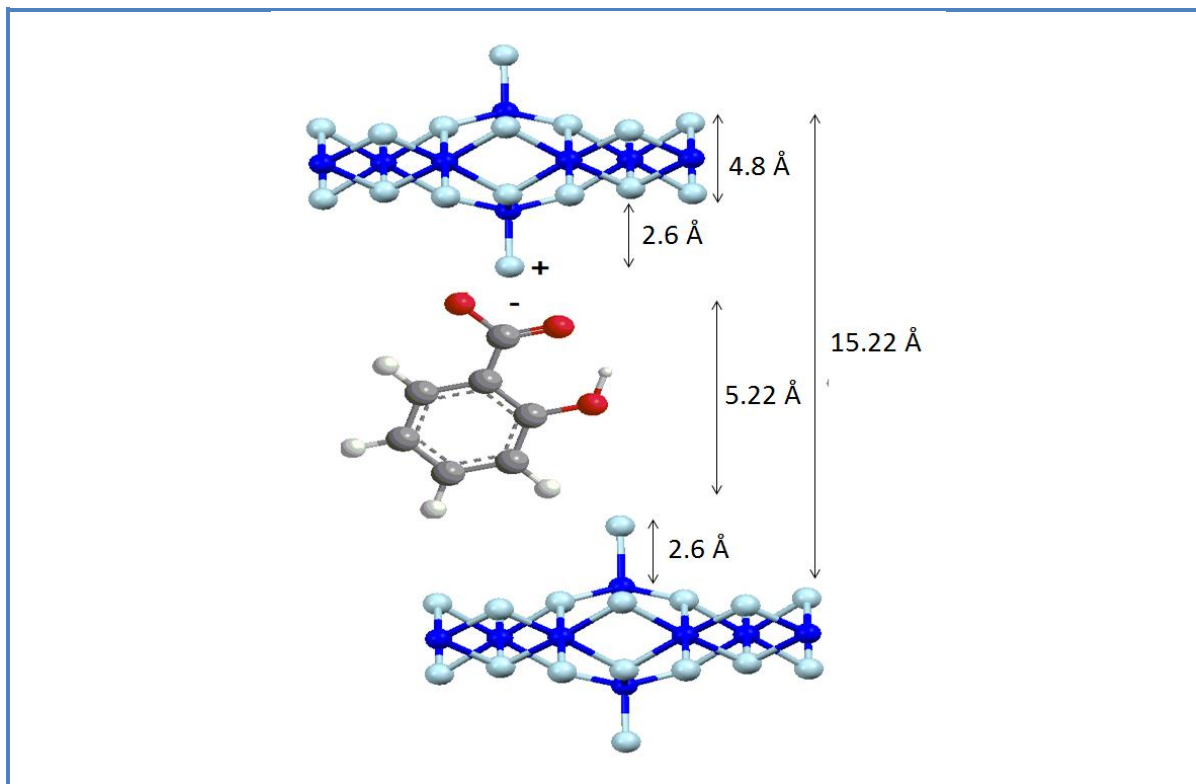
ABSTRACT

Recently, nanoparticles have attracted much attention owing to their potential in biomedical applications, such as drug delivery systems, sustained release and controlled release. Various nanocarriers have been employed to ameliorate the efficacy and cytotoxicity of drugs, reducing their side effects through changing their pharmacokinetic properties. A simple and well-known model of pharmaceutical carriers is the layered zinc hydroxide (LZH) compound. In the present research, salicylic acid (Sal)-loaded LZH was synthesized using the ion-exchange method. The resulted nanohybrid (Sal-LZH) was characterized using the PXRD, FT-IR spectroscopy, STA analysis, BET, and SEM. Sal anions were intercalated into the interlayer gallery space of LZH, leading to different drug releases at pH 4.8 and 7.4. It was found that, the release of Sal anions from the synthetic nanohybrid occurred in a controlled manner, and the resulting material is suitable for use as a controlled-release formulation for various kinds of anti-inflammatory agent.

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Graphical Abstract



Introduction

In the traditional methods of drug delivery, concentration of the drug in the blood increases suddenly, causing the kidneys to repel a certain amount of the drug. In this regard, a gradual release of the drug in a controlled and purposeful method can increase the duration of the drug release process and prevent drug waste. Under the acidic conditions of the stomach, there is a possibility that a part of the drug is destroyed [1-3]. It is, therefore, very useful to encapsulate drugs in a hydroxide layer so as to protect the drug [4, 5]. Layered hydroxide salts (LHSs), $M^{2+}(OH)_{2-x}(A^{m-})_{x/m} \cdot nH_2O$, are the derivative compounds of brucite-like structures in which bivalent cations are in the center and their surfaces are composed of hydroxyl groups. In the mentioned formula, M^{2+} (e. g. Mg^{2+} , Ni^{2+}

Zn^{2+} , Ca^{2+} , Cd^{2+} , Co^{2+} , Cu^{2+}) can be a bivalent cation, and A represents the number of ions with m^- charge. Hydroxyl groups can be replaced with small anions such as chlorine, nitrate, acetate or oxyanions; there is even the possibility of substitution with water molecules. Following the discovery of hydroxide salts, LHSs were divided into two types: Copper hydroxide nitrate $Cu_2(OH)_3NO_3$ and zinc nitrate hydroxide (ZNH). The layered structure in copper nitrate hydroxide is octahedral where the center is occupied by copper cations coordinated to hydroxyl groups, and nitrate ions are located at hydroxyl sites [6, 7]. ZNHs were divided into I and II formulas. Form I, $Zn_2(OH)_2(NO_3)_2 \cdot 2H_2O$, is a compound where zinc atoms are coordinated octahedrally with six hydroxide groups, and the nitrate groups are directly coordinated with the zinc cations. Form II is classified into II_a and II_b types. Type

II_a, Zn₅(OH)₈(NO₃)₂·2H₂O, is named Layered Zinc Hydroxide, a layer in which 1/4 of octahedrally coordinated zinc cations are empty. On either side of the empty octahedra are found tetrahedrally coordinated zinc cations with three hydroxylated groups of brucite-like layer and water molecules. The nitrate ion is not coordinated with the zinc cations and located in the interlayer space of LZH. Type II_b, Zn₅(OH)₈(NO₃)₂, arranges the cations and anions in a way similar to type II_a [8, 9].

LZH synthesis is facile and widely performed in different laboratories and industries. This compound is applicable in various fields such as drug delivery due to its positive charge, ability to absorb, maintain, release ions, high specific surface, memory effect, chemical stability, ion exchange, pH dependent solubility, structural variation and easy and low-cost synthesis. Drugs such as ibuprofen [10], nalidixic acid [11], gemifloxacin [12] diclofenac sodium [13] amoxicillin trihydrate [14] have been located between the layers by coprecipitation and ion-exchange methods; furthermore, drug release has been studied through LZH [15-16]. LZH is unstable in acidic conditions, dissolving in lysozymes, creating zinc anions that enter the food cycle [11, 17]. In this research, by use of Sal, we fabricated and studied nanohybrid based on LZH for a controlled release of drugs. In order to synthesize Sal-LZH nanohybrid, ion exchange method was used. Techniques such as PXRD, FTIR, BET, and STA were used to characterize Sal-LZH. The controlled release of the drug was performed via synthesized nanohybrid compounds in a buffer environment of phosphate at pH 7.4 and 4.8.

Experimental

Materials and methods

Zinc nitrate hexahydrate (Zn(NO₃)₂·6H₂O), sodium hydroxide (NaOH), salicylic acid (Sal), hydrochloric acid (HCl), ethanol, buffer solutions were purchased from Merck chemical company and used without further purification.

Preparation of LZH

13.25 g of Zn(NO₃)₂·6H₂O was dissolved in 20 mL of deionized water. After adjusting the pH to 7.0 using an aqueous solution of NaOH (0.75 mol/L), the resulting suspension was magnetically stirred for 18 hours at room temperature until the final pH of 8. The precipitate was washed with deionized water and dried in a vacuum oven for 24 h.

Preparation of Sal-LZH

0.5 g of Sal was dispersed in 50 mL of ethanol. The solution was added to a suspension containing 0.2 g LZH in 50 mL distilled water. The mixture was stirred using a magnetic stirrer at room temperature for 2 days, following which time, it was centrifuged and then washed three times with distilled water and ultimately dried at 60 °C for 24 h.

Drug-Release studies

To determine the amount of the intercalated drug in LZH, a certain amount of drug was dissolved in 6 mol/L HCl. Sal release from LZH was studied via the dynamic diffusion of membrane dialysis. In this regard, 0.01 gr of Sal loaded LZH was transferred to a dialysis bag. It was immersed in 100 mL solution of phosphate buffered with pH 7.4 and 4.8 in a shaking water bath at 37 °C to acquire sink conditions. At different intervals (each 1 h), 2 mL was removed from the buffer around the bag and replaced with the same amount of fresh buffer; after that, the optical absorption of the drug was measured at a 237 nm; the amount of drug

release was further determined at different times by help of the standard curve.

Characterizations

Powder X-ray diffraction patterns (PXRD) were recorded on Bruker AXS model D8 advance diffractometer using Cu-K α source ($\lambda=1.542 \text{ \AA}$) at 40 KV, 35 mA, and a scan range of 2°–70°. Fourier Transform Infrared (FTIR) spectra of the materials were recorded using a Bruker spectrometer on self-supported samples over the range of 4000–400 cm⁻¹. The thermal behavior of the samples was specified via Simultaneous Thermal Analysis (STA) on a Mettler-Toledo 851e apparatus at a heating rate of 10 °C/min under N₂ atmosphere. Scanning electron microscope (SEM) and micrographs were taken on a VEGA-TESCAN. The nitrogen adsorption–desorption isotherms of the samples were measured at 77 K using a micromeritics ASAP 2020 analyzer. The absorption values were measured with an UV/Vis spectrometer, JASCO model 7850. The specific surface area was obtained using the Brunauer-Emmett-Teller (BET) method; further evaluated was the pore size distribution through the use of Barrett-Joyner-Halenda (BJH) method.

Results and Discussions

Figure 1 illustrates the PXRD patterns for LZH, nanohybrid and Sal. PXRD pattern for LZH

at a range of $2\theta=2-74^\circ$ confirms the formation of brucite-like structure with the basal spacing value around 9.57 \AA , in agreement with literature [17-19]. The Sal-LZH nanohybrid material, obtained after ion-exchange with Sal, showed a peak at 5.80° in 2θ , which assigned to a basal spacing of 15.22 \AA , indicating that the Sal anion was successfully intercalated into LZH, thus displacing the original Zn-OH-NO₃ nitrate ions in the interlayer region (Figure 1b). High crystallinity of pristine Sal was observed, as demonstrated in Figure 1c. The length and width of Sal molecule were obtained employing Chemoffice Ultra 2008 software (Cambridge, MA), 8.4 \AA along the y axis and 6.9 \AA along the x-axis, respectively. Intercalation of Sal anions into the interlayer spaces between the LZH resulted in an increase of basal spacing related to the dimension and spatial arrangement of the anions in the intergallery space of host material, LZH. Subtracting the thickness of the LZH basal layer (4.8 \AA) [11] and the zinc tetrahedra (2.6 \AA each) from the d-spacing of Sal-LZH nanohybrid obtained from the PXRD (15.22 \AA), the gallery heights was estimated to be 5.22 \AA . As this value was smaller than the dimension of Sal molecule along the y-axis and x-axis, the anions were arranged as a monolayer with an angle from the X-axis between the LZH interlayers, with the -COO⁻ groups positioned towards the LZH inorganic layers (Figure 2).

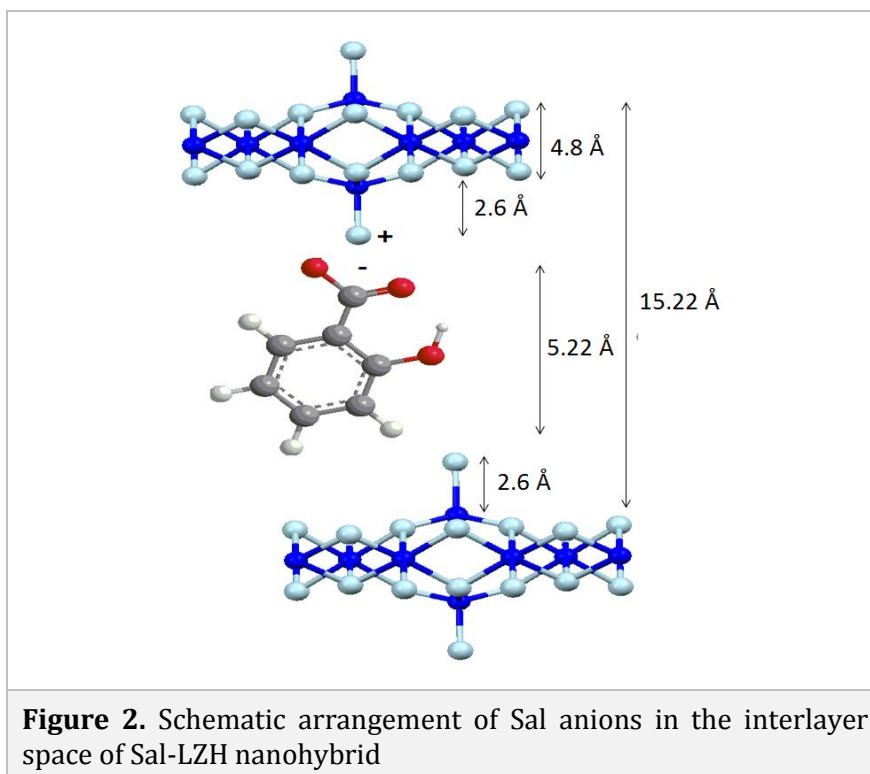
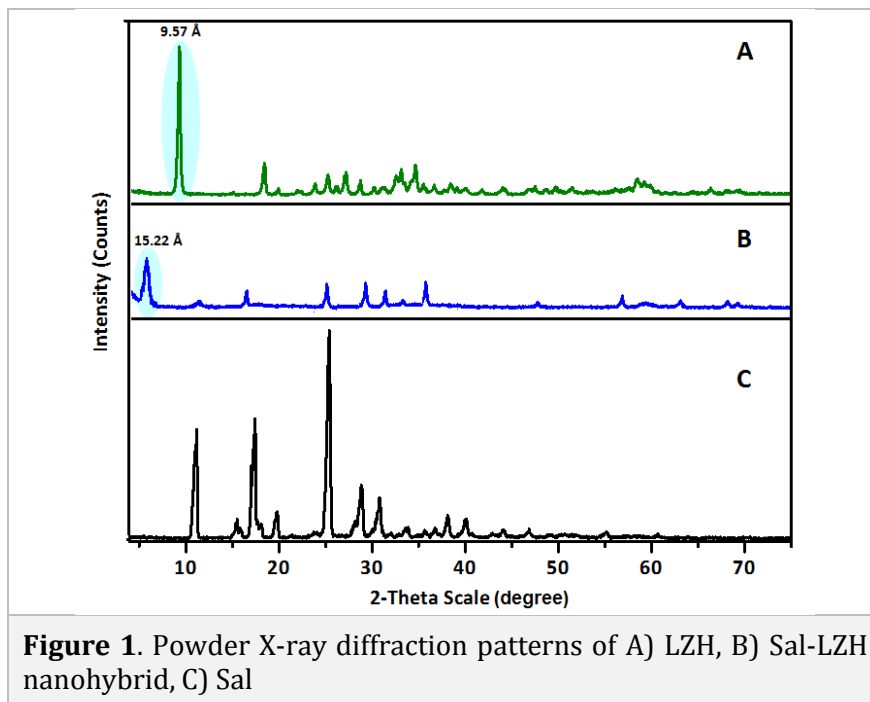
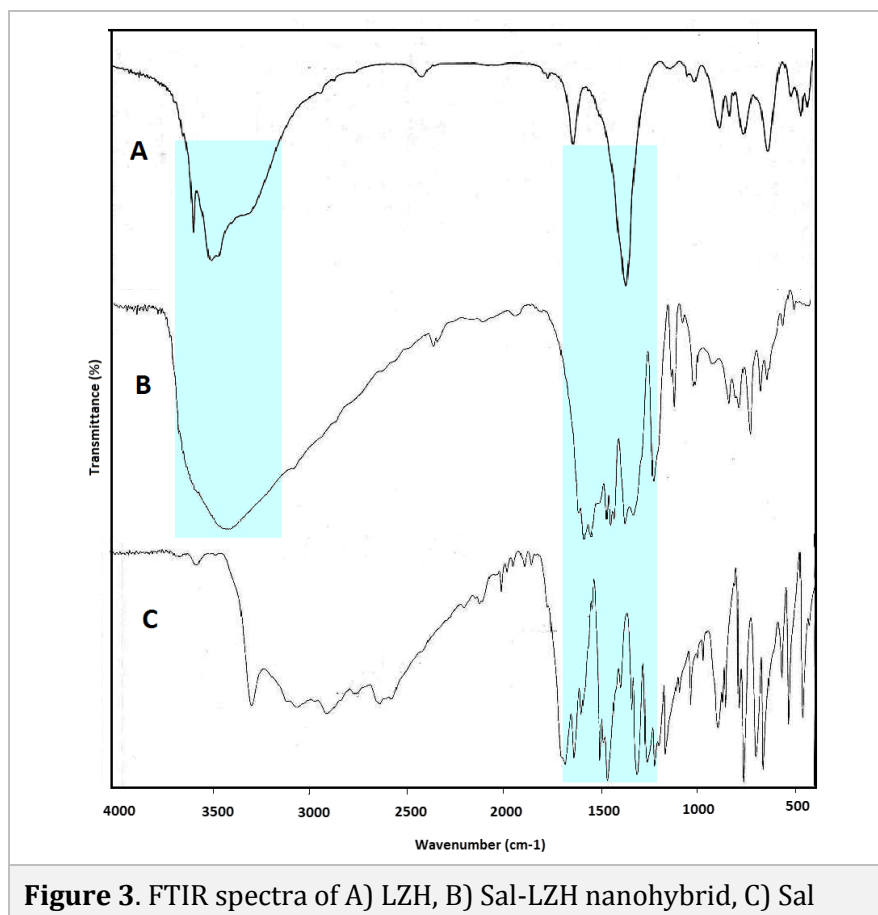


Figure 3 demonstrate the FTIR for LZH, Sal-LZH nanohybrid and pristine Sal. The FTIR spectrum of LZH (Figure 3a) presented two

peaks at 833 and 1373 cm^{-1} , which are characteristic of nitrate ions intercalated in the interlayer spacing. The band at 1630 cm^{-1} are

attributed to the angular deformation of the OH groups of water molecules. The peaks at 438 and 468 cm^{-1} due to the stretching vibration of zinc-oxygen bonds. The vibrations appearing at 641 cm^{-1} can be attributed to the stretching vibration of oxygen-hydrogen. A strong broad vibration band centered at 3486 cm^{-1} can be observed, which can be ascribed to the typical stretching vibrations of physisorbed water molecules and hydroxyl groups that belong to brucite-like layers [20]. FT-IR spectrum of crystalline Sal in acid form (Figure 3c) shows a broad absorption band that spreads from 3235 cm^{-1} to 2592 cm^{-1} , assigned to the O-H stretching vibration; at 1656 cm^{-1} a band assigned to asymmetric stretching vibration of -COOH group; 1621 cm^{-1} and 1443 cm^{-1} bands due to the C-C stretching of the aromatic ring; 1295 cm^{-1} and 1247 cm^{-1} bands are assigned to

the stretching vibration of C-O and O-H, respectively [21]. The disappearance of a C=O stretching band in the -COOH group for pure Sal after intercalation confirms that the guest anions that were intercalated into the LZH interlayers. The most important observation in the FTIR spectrum of the Sal-LZH nanohybrid was the reduction of the nitrate anion band intensity at 1373 cm^{-1} , indicating that the nitrate anions were totally replaced by the guest anions. A band at 1566 cm^{-1} is due to the asymmetric vibration, and another band at 1349 cm^{-1} is due to the symmetric vibration of carboxylate group. In addition to that, bands recorded at 1249 cm^{-1} and 1142 cm^{-1} are assigned to the stretching modes of C-C in the aromatic ring, while a band corresponding to zinc-oxygen absorption is detected at 460 cm^{-1} (Figure 3b).



In Figure 4a, the Sal thermogram curve shows a weight loss of 99% at a temperature range of 100-220 °C, which can be related to complete combustion of the pure Sal. The TGA profiles of Sal-LZH nanohybrid are reported in Figure 4b where three weight loss peaks are present in the nanohybrid thermogram curve. As seen, the first weight loss (10.05%) occurs at 25-175 °C due to the loss of interlayer water molecules and water molecules that are physically adsorbed. The second peak pertains

to the weight loss of 30.52% and the temperature range of 175-250 °C associated with Sal decomposition. The third weight loss (8%) between 275 and 345 °C is assigned to dehydroxylation of the hydroxide layers and decomposition of the organic moieties. It is worth noting that the increase in the temperature of Sal degradation in the nanohybrid indicates that the Sal has been intercalated between the layers and its thermal stability has increased [21].

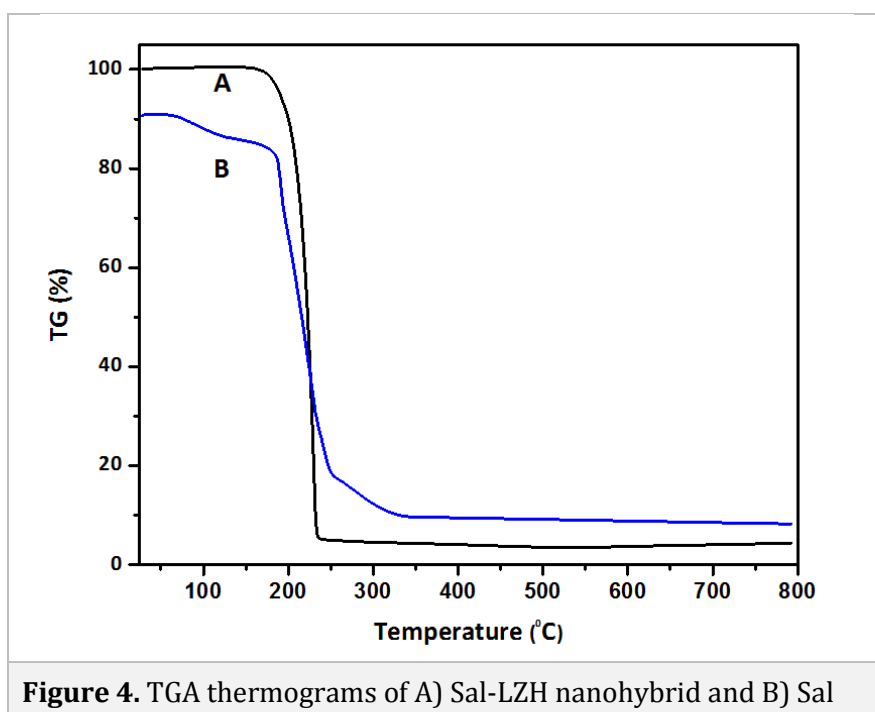


Figure 4. TGA thermograms of A) Sal-LZH nanohybrid and B) Sal

Figure 5 depict type IV adsorption-desorption isotherm following the IUPAC classification which indicates the mesoporous nature of LZH and Sal-LZH nanohybrid. The uptake of adsorbate for both materials occurred slowly at low relative pressure in the range of 0.0-0.8, followed by rapid adsorption at a relative pressure more than 0.8. For the nanohybrid material, the optimum uptake is slightly lower than LZH. The desorption branch

of the hysteresis loop for nanohybrid material is narrower than LZH, indicating different pore texture of the materials. The intercalation process and formation of the new nanohybrid leads to modification of the pores [22]. The surface area of the nanohybrid material is generally higher than LZH. The surface area of LZH increased from 22.56 m²/g to 26.54 m²/g in nanohybrid.

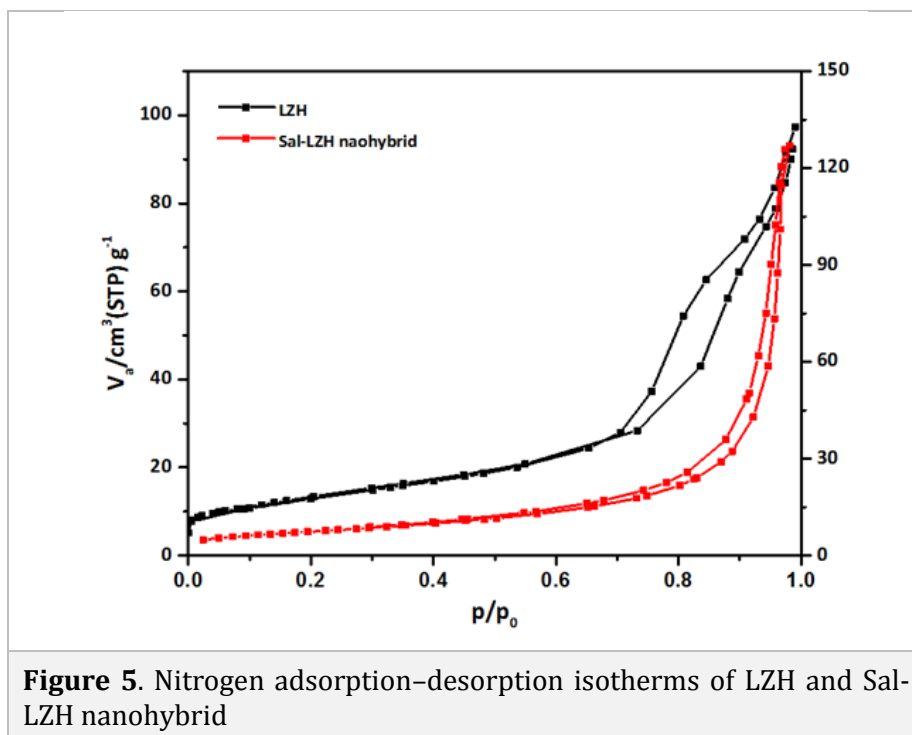


Figure 5. Nitrogen adsorption-desorption isotherms of LZH and Sal-LZH nanohybrid

The morphology of the LZH and Sal-LZH nanohybrid were assessed using the SEM analysis, as shown in Figure 6a and 6b, respectively. The morphology of LZH shows plate-like structure. This structure is transformed into a non-uniform granular structure when the nanohybrid material is

formed by ion-exchange method under aqueous environment. This illustrates that the intercalation of Sal into the interlayer space of LZH have resulted in the change of the surface morphology from plate-like structure to an irregular granular structure.

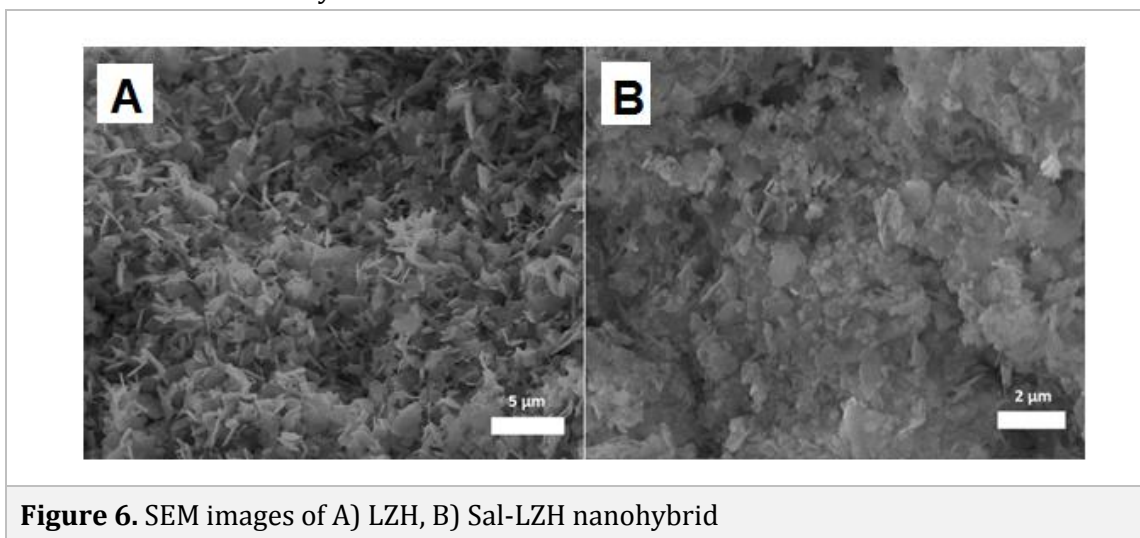


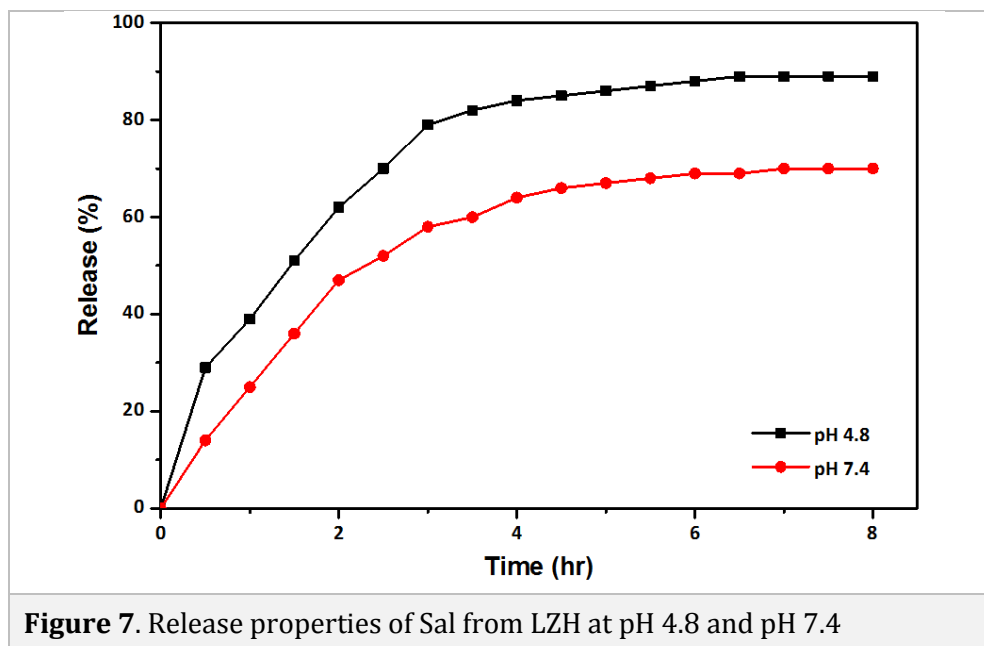
Figure 6. SEM images of A) LZH, B) Sal-LZH nanohybrid

To investigate the release behavior of Sal and Sal-LZH nanohybrids, they were separately

dispersed into PBS at pH 7.4 and pH 4.8. Figure 7 demonstrate the release profile of Sal into PBS

at pH 4.8 is remarkably faster than that at pH 7.4. At pH 7.4, the release percentage of Sal from Sal-LZH was 25% after 1 h, 64% after 4 h and 70% after 8 hr. The first relatively rapid drug release can be explained with the release of Sal anions taken up on the surface of the LZH and those

intercalated in the external surface of the layered hydroxide. The slower release corresponds to the exchange of Sal anions that are in the internal surface of the layer and have to diffuse through the LZH particles. The loading amount of Sal is 21 (w/w) %.



Conclusion

A new anti-inflammatory agent nanohybrid compound in which Sal is into the interlamellar space of the host LZH was synthesized by ion exchange route of LZH with Sal under aqueous environment. On intercalating the Sal agent, the gallery height of the LZH was expanded. The strong electrostatic interaction between layers and guest anions showed the controlled release of Sal anions in the interlayer. TG analyses revealed the improved thermal stability of Sal in hybrid, which implies their improved ability to store and release drugs. *In vitro* drug release the Sal-LZH nanohybrids at pH 7.4 exhibited that the release rate Sal-LZH nanohybrids was significantly lower than pH 4.8. All of these results suggested that Sal-LZH nanohybrids

were appropriate material to be utilized for drug delivery and pharmacological application.

Acknowledgments

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Conflict of interest

We have no conflicts of interest to disclose.

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