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# Preparation and characterization of cetirizine intercalated layered double hydroxide and chitosan nanocomposites

Kamellia Nejati[a,*], Hassan Keypour[b], Parvaneh Delir Kheirollahi Nezhad[a], Zolfaghar Rezvani[c], Karim Asadpour-Zeynali[d]

[a] Department of Chemistry, Payam-e-Noor University, P.O. BOX 19395-3697 Tehran, Iran
[b] Faculty of Chemistry, Bu-Ali Sina University, Hamedan, Iran
[c] Department of Chemistry, Faculty of Basic Sciences, Azarbaijan Shahid Madani University, Tabriz, Iran
[d] Department of Analytical Chemistry, Faculty of Chemistry, University of Tabriz, Tabriz 51666 16471, Iran

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ABSTRACT

The syntheses and characterization of Zn–Al layered double hydroxide (LDH) and chitosan nanocomposits are reported in the present paper. By increasing chitosan concentration, the crystallite growth is inhibited in both directions a and c. Afterward, cetirizine-intercalated LDH was synthesized. According to XRD patterns, increase in basal spacing indicated that cetirizine anions were intercalated into LDH. *In-vitro* drug release experiments have been investigated. On the basis of the release profiles, it was found that increase in chitosan concentration causes in decrease in drug release rate. Therefore, chitosan concentration can be adjusted to control the rate of the drug release.



## 1. Introduction

Layered compounds are a class of materials in which strong bonding, *i.e.*, ionic or covalent, is limited to two dimensions, or one. In the third dimension, only weak Vander Waals interactions are present [1]. Layered double hydroxides (LDHs), also known as hydrotalcite-like compounds, are a class of host–guest layered solids with the general formula of $[M_{1-x}^{2+}M_x^{3+}(OH)_2]^{x+}[A^{n-}]_{x/n}\cdot yH_2O$. In this formula, $M^{2+}$ and $M^{3+}$ are di- and trivalent cations respectively, $x$ is equal to the molar ratio of $M^{3+}/(M^{2+}+M^{3+})$ in the range 0.2–0.33, and $A^{n-}$ is an organic or inorganic anion [2–6]. These materials form successive positively charged layers that are compensated by intercalation of hydrated negatively charged species and their interlayer distance depends on the size of the intercalated hydrated anion [7–10].

In recent years, LDHs have received considerable attention because of their application as catalysts [11,12], ion exchangers [13,14], absorbents [15,16], ceramic precursors, and organic–inorganic nanocomposites [17,18]. Owing to the intercalation property of LDHs, many LDH compounds with intercalated beneficial organic anions, such as amino acid [19], pesticide [20], and drugs [21–24] have been prepared. Because the release of drugs in drug-intercalated layered materials is potentially controllable, these new materials have great potential as delivery hosts in the pharmaceutical field. Cetirizine dihydrochloride, chemically known as (±)[2-[2-[4-[(4-chlorophenyl)-phenylmethyl]piperazin-1-yl]ethoxy]acetic acid dihydrochloride, is a non-drowsy antihistamine (Scheme 1) that reduces the natural chemical histamine in the body. Histamine is released from histamine-storing cells (mast cells) and then attaches to other cells that have receptors for histamine. The attachment of histamine to the receptors causes the cells to be "activated," releasing other chemicals that produce effects associated with allergy, for example, sneezing [25–28].

Chitosan (CS) is a cationic polysaccharide that can be obtained by deacetylation of chitin, which is produced from shells of crustaceans, insects, and some other sources [29–30]. Chitosan, an unbranched cationic biopolymer, has amounts of hydroxyl and amido groups, which can form strong coordinate bond with metal ions. The strong interaction between chitosan molecules and LDHs particles is supposed to occur during the growth of LDHs crystal, which can lead to special size and morphology [31,32].

In this paper, we report the synthesis and characterization of Zn–Al–$NO_3$-LDH and chitosan nanocomposites and also intercalation of cetirizine into Zn–Al–$NO_3$-LDH by the coprecipitation method in the presence of chitosan. Also release characteristics of cetirizine from intercalations have been investigated.

* Corresponding author. Tel.: +98 411 5412117; fax: +98 411 5412108.
*E-mail addresses:* nejati_k@yahoo.com, k_nejati@pnu.ac.ir (K. Nejati), haskey1@yahoo.com (H. Keypour), parvanehdalir@yahoo.com (P.D.K. Nezhad), z_rezvani@yahoo.com (Z. Rezvani), k.zeynali@gmail.com (K. Asadpour-Zeynali).

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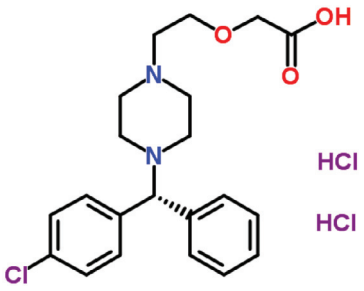


**Scheme 1.** Chemical structure of cetirizine dihydrochloride.

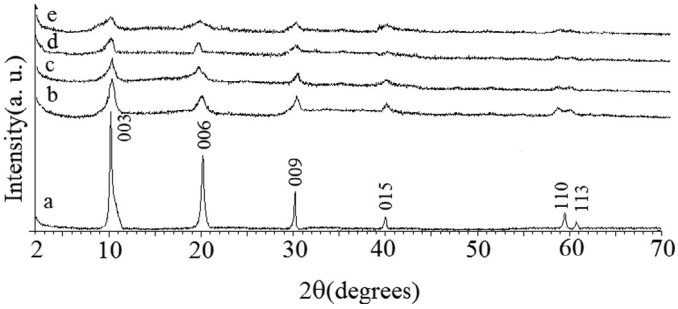


**Fig. 1.** The XRD patterns of LDH precursor (a), chitosan–LDH nanocomposites (chitosan, 0.25 g/L (b), 0.5 g/L (c), 0.75 g/L (d), 1 g/L (e)).

## 2. Materials and methods

### 2.1. Materials

Cetirizine hydrochloric acid ($C_{21}H_{25}ClN_2O_3 \cdot 2HCl$, abbreviated as CT) was purchased from Upha Pharmaceutical Manufacturing (Malaysia) with 99.9% purity and used as received. Chitosan with low molecular mass of $1.5 \times 10^5$ and degree of deacetylation of 85% was purchased from Sigma–Aldrich. $Zn(NO_3)_2 \cdot 6H_2O$, $Al(NO_3)_3 \cdot 9H_2O$, and other reagents were all of analytical grade (A.R.) and were used as received without further purification (all chemical reagents were purchased from Merck). Deionized water, from which carbon dioxide was removed by boiling under nitrogen, was used in all of the preparations.

### 2.2. Zn–Al–$NO_3$-LDH preparation

Pristine Zn–Al–$NO_3$-LDH was prepared as described in the literature [33], with slight modification at pH 7.5 by the co-precipitation method under $N_2$ atmosphere to avoid or at least to minimize contamination by atmospheric $CO_2$ in mixed distilled water and 1-propanol solvent system. First, 35 mL solution containing $Zn(NO_3)_2 \cdot 6H_2O$ (0.36 g, 0.0012 mol) and $Al(NO_3)_3 \cdot 9H_2O$ (0.15 g, 0.0004 mol) in a mixture of distilled water (25 mL) and 1-propanol (10 mL) was prepared under nitrogen atmosphere with vigorous magnetic stirring. Then NaOH solution (0.5 M) was added dropwise into it until the final pH adjusted to 7.5. It was then transferred into a Teflon-lined autoclave and hydrothermally treated at 120 °C for 18 h. The obtained precipitates were recuperated by filtration, washed several times with distilled water to remove any ions possibly remaining in the final products, and then dried at 80 °C in vacuum. This reaction was repeated in the presence of 30 mL of various concentrations of chitosan (0.25, 0.5, 0.75 and 1.0 g/L), while the concentration of $\beta$-alanine (used to accelerate the dissolution of chitosan) was 0.005 M. The solids were extensively washed with deionized water to remove superfluous chitosan and other inorganic ions. The products were labeled as Chitosan–LDH.

### 2.3. Cetirizine–LDH preparation

The cetirizine-intercalated Zn–Al–$NO_3$-LDH was synthesized by the coprecipitation method, as described in the literature [18,34], with slight modification. The intercalation was typically carried out as follows.

A solution was prepared by adding 35 mL of a mixture of distilled water (25 mL) and ethanol (10 mL) to $Zn(NO_3)_2 \cdot 6H_2O$ (0.0012 mol) and $Al(NO_3)_3 \cdot 9H_2O$ (0.0004 mol). The pH of the solution was adjusted to 9 with a solution of 0.75 M NaOH. The solution thus formed was slowly added into a solution of the drug prepared by dissolving 0.36 g (0.0008 mol) of cetirizine in 20 mL water under nitrogen atmosphere with vigorous magnetic stirring. The required amount of 0.75 M NaOH and the salts solution were added simultaneously in order to maintain pH at 9. The resulting slurry was transferred into a Teflon-lined autoclave and hydrothermally treated at 100 °C for 24 h. The resulting precipitate was then centrifuged and washed with distilled water and then dried at 60 °C in vacuum. The product was labeled as CT–LDH. This reaction was repeated in the presence of 30 mL of various concentrations of chitosan (0.25, 0.5, 0.75 and 1.0 g/L) while the concentration of $\beta$-alanine (used to accelerate the dissolution of chitosan) was 0.005 M. The solids were extensively washed with deionized water to remove superfluous chitosan and other inorganic ions. The products were labeled as CT–chitosan–LDH.

### 2.4. Characterization

The PXRD patterns were recorded with a Bruker AXS model D8 advance diffractometer using Cu-$K_\alpha$ radiation ($\lambda = 1.542$ Å), with the Bragg angle of 2–70°. The FT-IR spectra were collected using KBr disk method at room temperature with a Shimadzu 8400s spectrophotometer in the range of 4000–400 $cm^{-1}$. Zn and Al contents of the samples were determined using an atomic absorption (Varian AA 220, including Zeeman) instrument after dissolving the samples in nitric acid. C, H, and N contents were determined using a Perkin-Elmer model 240B elemental analyzer. TGA curves were recorded with a Mettler-Toledo TGA 851e at the heating rate of 10 °C $min^{-1}$ in nitrogen atmosphere. The morphology of the samples was observed by using the scanning electron microscopy (SEM; HITACHI S-4160).

### 2.5. Drug release studies

A known amount of sample (0.2 g of CT–LDH or CT–chitosan–LDH) was poured in a porous dialysis membrane and then immersed in 150 mL phosphate buffer solution (PBS) (0.2 M) at pH of 7.4 while it was stirring (speed of 150 rpm) at 37 ± 0.1 °C (according to USP) [35]. At specific time intervals, a certain volume of the solution (2.0 mL) was removed, separated through a 0.2 μm syringe filter and immediately replaced with an equal volume of fresh buffer to keep the volume constant. The absorbance of the removed solution at 231 nm was measured with a UV–vis spectrophotometer. The runs were performed three times. For comparison, the release test of the physical mixtures of LDH with CT was also performed.

## 3. Result and discussion

### 3.1. X-ray diffraction analysis (XRD)

The XRD patterns of the LDH and chitosan–LDH nanocomposites are shown in Fig. 1.

The XRD pattern of the LDH precursor (Fig. 1a) shows the characteristic sharp and symmetrical peaks at lower $2\theta$ values, which are ascribed to diffractions by planes (0 0 3) and (0 0 6), corresponding to the basal spacing and its higher order diffractions [36]. The (0 0 3) reflection is typical of the hydrotalcite-type materials, the intensity of which is related to the crystallinity degree of the material