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Title:

**A STUDY ON THE INTERCALATION PROCESS OF TRAMADOL
HYDROCHLORIDE IN ZnAl - NITRATE LAYERED DOUBLE
HYDROXIDES**

By

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In this paper we report the preparation and characterization of new hybrid composites based on ZnAl-nitrate layered double hydroxides (ZnAlLDHs) and tramadol hydrochloride (TrH) via anionic exchange method. LDHs and their hybrid composites were studied by X-ray diffraction (XRD), FT-IR, RAMAN and energy dispersive x-ray (EDX) spectroscopy and scanning electron microscopy (SEM). The obtained results point out the presence of the Tramadol hydrochloride in the network structure of the new synthesized materials, when used for the ion exchange 0.8 g TrH for each 2g ZnAlLDH. In the other cases, was observed the partial drug intercalation and a significant absorption on the surface of LDH. Considering together the analgesic

activity of TrH and the biocompatibility of the LDHs, the new hybrid materials could open interesting perspectives for obtaining the drug reservoirs and controlled release systems.

INTRODUCTION

Layered double hydroxides (LDHs) also called anionic clays or synthetic hydrotalcite-like¹ compounds represent a class of materials characterized by layered structure, in which the lamellae are positively charged and stability of the structure is ensured by the anions which connects adjacent layers in an electrostatic way.² Their structure is similar with the $\text{Mg}(\text{OH})_2$ (brucite) in which some of Mg^{2+} are replaced by trivalent cations like M^{3+} .^{3,4} LDHs composition can be expressed by the following general formula: $[\text{M}^{2+}_{1-x}\text{M}^{3+}_x(\text{OH})_2]^{x+} [(\text{A}^{n-})_{x/n} \cdot m\text{H}_2\text{O}]^{x-}$, where M^{2+} and M^{3+} are divalent or trivalent cations, A^{n-} is the interlayer anion and x is the molar fraction of the trivalent cation ($\text{M}^{3+}/[\text{M}^{2+}+\text{M}^{3+}]$).⁵ A great variety of interlayer anions can be intercalated in their structure giving rise to a class of materials which can have a broad range of applications such as catalytical,^{6,7} pharmaceutical,⁸ environmental protection,⁹ polymer industry.^{10,11} Also, LDHs are biocompatible materials, and can be explored as matrix for biomolecules/drugs storage and controlled release systems.¹²⁻¹⁶ It was reported that the intercalation of the drug molecules in the layered double hydroxides matrix do not only reduces the negative effects of the drug, but in some cases, there is an increase in drug solubility.^{17,18} Among the first representative pharmaceutical applications of LDHs, synthetic hydrotalcite, we can mention the antacid formulations,¹⁹ stabilization and controlled release of nifedipine²⁰ and antipyretic drugs, analgesics and non-steroidal anti-inflammatory (ibuprofen,²¹ ketoprofen,^{22,23} salicylic acid,²⁴ ciprofloxacin,²⁵ naproxen²⁶ and diclofenac²⁷ etc).

Tramadol hydrochloride (TrH) (2-[dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride) is an opioid pain medication used to treat moderate to moderately severe pain,^{28,29} it can weakly inhibits norepinephrine and serotonin reuptake.³⁰ It has central analgesic properties with effects similar to morphine and codeine, acting on specific opioid receptors. This presents less intense and frequent sides effects than other opioids, leading to an increase of TrH prescriptions in the last few years.³¹ However, TrH is fast processed by the human body and therapeutic effect is lost in only four to approximately six hours and for maintain its effect must be administered five daily doses. Therefore, several systems for

controlled release of TrH have been developed using montmorillonite composites,³² ethyl cellulose microparticles,³³ ion-exchange fiber³⁴ etc.

ZnAILDH have been extensively studied in recent years due to their easy accessibility, less toxicity and simple synthesis method.³⁵ For this reason, in this paper ZnAl-nitrate LDHs are intercalated with TrH by anionic exchange method, in order to obtain the drug reservoirs and controlled release systems. The precursors and hybrid materials based on ZnAILDH and TrH were characterized by XRD, FT-IR, RAMAN, EDX and SEM.

EXPERIMENTAL

All chemicals including $\text{Zn}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$, $\text{Al}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ and NaOH were purchased from Sigma-Aldrich. Tramadol hydrochloride ($\text{C}_{16}\text{H}_{13}\text{NO}_2\text{HCl}$) was purchased from KRKA, Smarjeska, Novo mesto, Sloven. The chemicals were used without further purification. Deionized water was used for the preparation of all aqueous solutions.

1. Characterization of ZnAILDH and ZnAILDH_TrH hybrid composites

X-ray powder diffraction (XRD) patterns were obtained on a Bruker AXS D8 diffractometer using monochromatic $\text{CuK } \alpha$ radiation ($\lambda = 0.154 \text{ nm}$), operating at 40 kV and 50 mA over a 2θ range from 4 to 70 degree. The FT-IR spectra were recorded on a FT-IR Bomem MB 104 spectrometer under the following experimental conditions: 200 scans in the mid-IR range (400-4000 cm^{-1}) using KBr (ratio 5 / 95 wt %) pellets, and a resolution of 4.0 cm^{-1} . The SEM micrographs were obtained with a Quanta 200 scanning probe microscope, the specimens being fixed with adhesive past on cylindrical-shaped Al conducting supports and then sputtered-coated with gold. The microscope was equipped with an Oxford Inca Energy Dispersive X-ray (EDX) system for chemical analysis, elemental analysis mapping and linescans. For the Raman spectroscopy was used a NT-MDT NTEGRA Spectra AFM coupled with Renishaw Raman confocal microscope.

2. Preparation of ZnAILDH and ZnAILDH_TrH hybrid composites

The matrix ZnAILDH was prepared by coprecipitation method, at constant pH value of 8.5 and a temperature of 50°C, under nitrogen atmosphere. 100 mL aqueous solution of 0.04 mol $\text{Zn}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ and 0.02 mol $\text{Al}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ ($\text{Zn}/\text{Al}=2$) was delivered with 0.5 mL/min flow rate into a round bottom flask containing 60 mL deionized water that was previously bubbled with nitrogen for half an hour in order to remove carbonate

anion contamination. The pH was maintained constant by simultaneous addition of a 1.0 M NaOH solution, using a TitraLab TIM 854 apparatus. The resulting white precipitate was aged at constant temperature (50°C) for 24 h under stirring. After the ageing step, the precipitate was separated by centrifugation, washed extensively several times with deionized water until reaching a pH value of 7, then dried overnight under vacuum at 70°C.

ZnAILDH_TrH was prepared by anionic exchange method. ZnAILDH was dispersed in a round bottom flask containing 60 mL deionised water which was adjusted at pH 8 by adding 1 M NaOH solution, under nitrogen atmosphere in order to avoid atmospheric carbonate contamination. Tramadol hydrochloride was used in different amounts 0.1, 0.4 and 0.8 g for each 2 g ZnAILDH. It was added to the previous mixture and stirred vigorously at 50°C for 24 h. The resulting material was separated by centrifugation, washed extensively several times with deionized water until reaching a pH value of 7, then dried overnight under vacuum at 70°C.

RESULTS AND DISCUSSION

X-ray powder diffraction

The XRD diffractograms (fig. 1) shows symmetric reflections of the basal (003), (006), (009) and (110) planes, characteristic to layered materials. ZnAILDH containing nitrate and the obtained materials after intercalation exhibits similar features with those reported in the literature.³⁶ In addition, specific parameter d_{003} peaks shifts to lower values of 2θ angle, and its value increases with molecular size and geometrical arrangement of the interlamellar space. According to the XRD data, the intercalation of the TrH molecule it was carried out only in the case of ZnAILDH_TrH 0.4 and ZnAILDH_TrH 0.8 samples, when occurs an increase of the interlayer distance from 8.74 Å for ZnAILDH to 9.29 Å and 11.55 Å for the hybrid compounds. In the case of ZnAILDH_TrH 0.1 intercalation has not been performed (there is no shifting in XRD diffractogram), but occurred the TrH adsorption only on the LDHs surface.

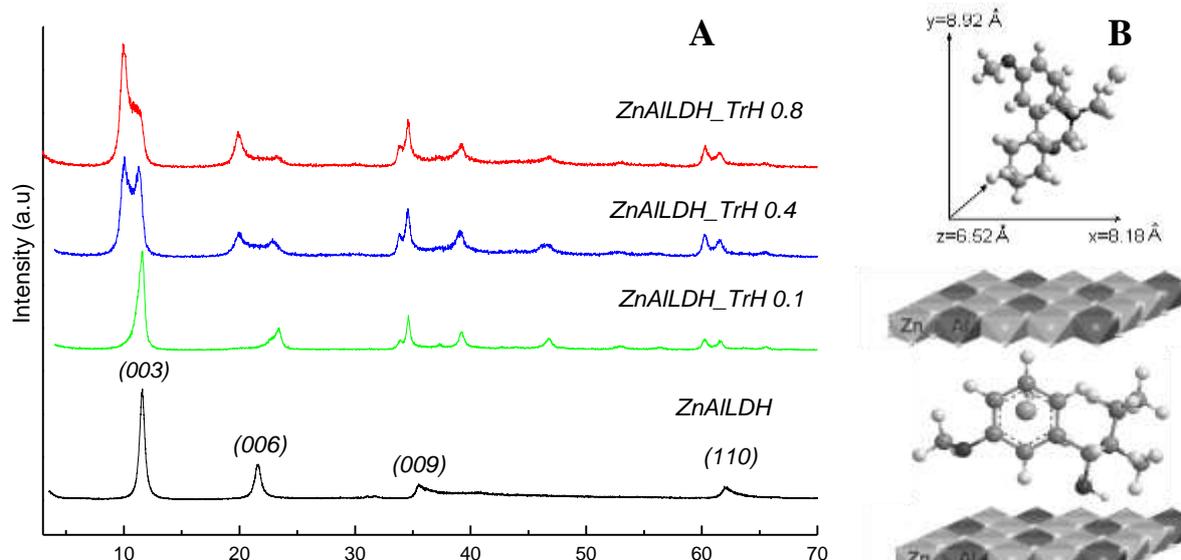


Fig. 1 - (A) XRD patterns of ZnAILDH, ZnAILDH_TrH 0.1, ZnAILDH_TrH 0.4 and ZnAILDH_TrH 0.8; (B) Three-dimensional size of TrH and proposed model for the orientation of the TrH in the interlayer space.

The cell parameter a is a function of the metal-metal distance within the layers pointing out the cations stacking in the 003 planes while the c parameter is related to the distance from the centre of one layer to the centre of another. The basal space value is given by the sum between the thickness of the layer 4.8 \AA and interlamellar space occupied by the anions, whose ionic diameter depends on the orientation of the existing anions. The calculated main cell parameters a and c and the interlamellar distances are presented in Table 1.

Table 1

Lattice parameters and interlayer distances

Compound	$d_{003}(\text{\AA})$	$c=3 d_{003}(\text{\AA})$	$a=2 d_{110}(\text{\AA})$	Interlayer distance (\AA)
<i>ZnAILDH</i>	8.74	26.22	3.048	3.94
<i>ZnAILDH_TrH 0.1</i>	8.83	26.49	3.045	4.03
<i>ZnAILDH_TrH 0.4</i>	9.29	27.87	3.050	4.49
<i>ZnAILDH_TrH 0.8</i>	11.55	34.65	3.042	6.75

The molecular dimensions of TrH, calculated using the chemical bond lengths and atomic angles, using Hyperchem software is shown in fig.1. Considering the size of TrH molecules intercalated, the length of the hydrogen bonds established between the anions and the hydroxyl group from LDH layers may be proposed the model of the TrH anions orientation.

Infrared and Raman spectroscopy

FT-IR and Raman spectroscopy (fig. 2) gives us information about the nature of the ions present between layers. The FT-IR spectrum of ZnAILDH presents adsorption bands at 3543 cm^{-1} due to the OH bond may be associated with the presence of the hydroxyl group of the LDHs and physically adsorbed water

molecules. The appearance of strong bands at 1385 cm^{-1} and a band less strong 825 cm^{-1} is associated to ν_3 vibration of nitrate anion.^{37,38} Also, it has been observed that the bands recorded under 600 cm^{-1} corresponding to the region of low frequencies vibration and are attributed to the translations links of Zn / Al-OH from the layers. The spectrum of the pure TrH show many intense, sharp absorption bands, due to the different functional groups existing in these molecules: those due to the aromatic ring, the amine group and the methyl group. Intense bands that appear in the spectrum are assigned to the following groups: $3545\text{-}3418\text{ cm}^{-1}$ ($\nu\text{H-OH}$) $1638\text{-}1603\text{ cm}^{-1}$ (carbonyl group $\nu\text{C}=\text{O}$), 1583 cm^{-1} , 1483 cm^{-1} and 1464 cm^{-1} ($\nu\text{C}=\text{C}$ aromatic ring), $1252\text{-}1286\text{ cm}^{-1}$ ($\nu\text{C-N}$), 785 cm^{-1} , 704 cm^{-1} (deformation vibration of the benzene ring, $\delta\text{-CH}$). In the FT-IR spectra of hybrid materials can be observed characteristic absorption bands to LDH matrix with a number of characteristic vibration bands of TrH.^{39,40} Also, in the case of ZnAILDH_TrH 0.8, the disappearance or overlapping band at 1381 cm^{-1} (assigned to structural vibration of nitrate ion) suggests that the nitrate ions from LDH layers were replaced with the molecules of TrH. Moreover, this technique is very useful for detecting the presence of unwanted carbonate anions at characteristic vibration band around 1360 cm^{-1} .

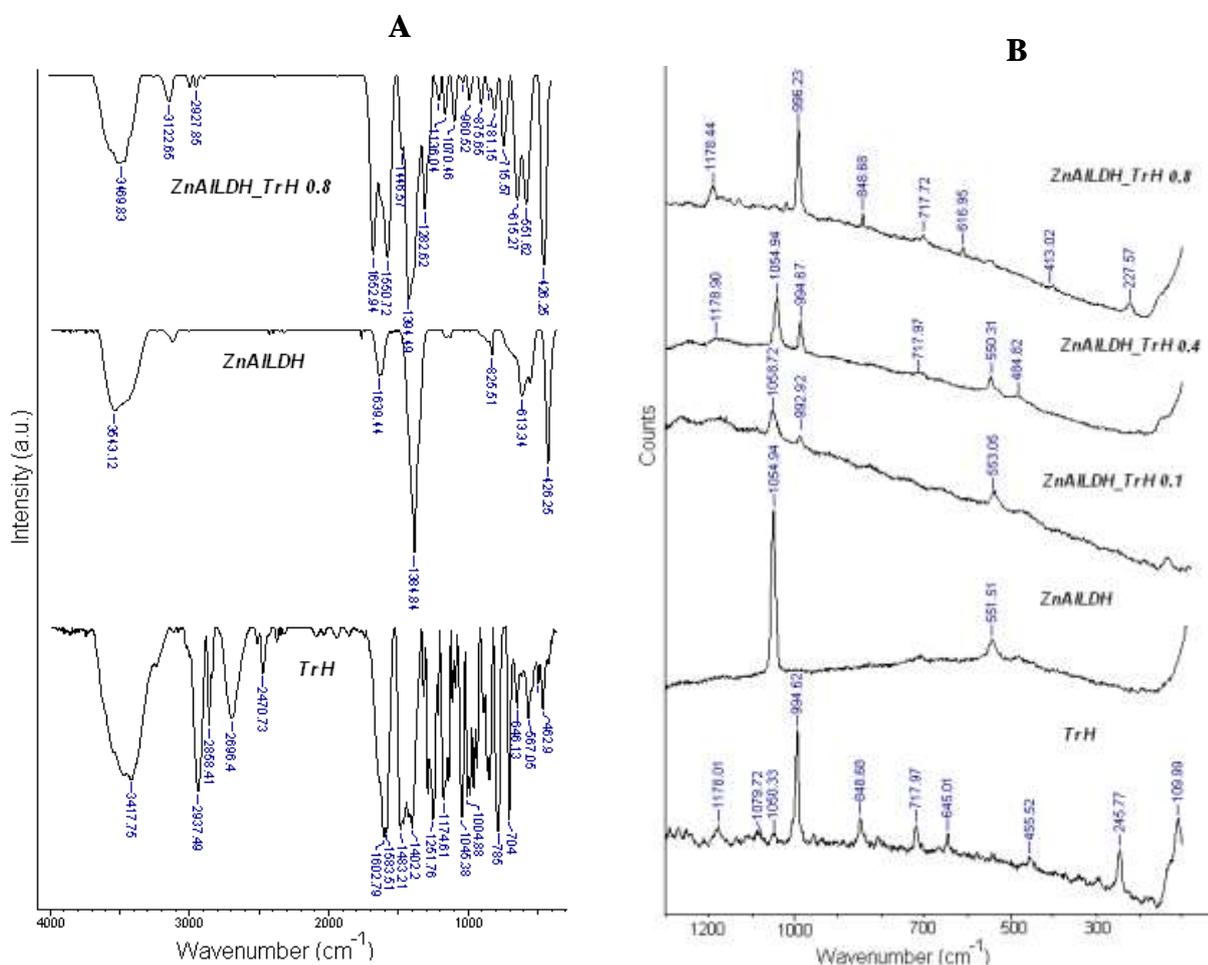


Fig. 2 - (A) FT-IR and (B) RAMAN spectra recorded for indicated samples

In addition to FT-IR spectroscopy the obtained results from Raman spectroscopy claim that were obtained specific structures corresponding to the studied materials. In the Raman spectrum of LDH the broad and strong band at 1054 cm^{-1} is assigned to vibration of the nitrate ions found in the interlamellar space.⁴¹ Strong band at 551 cm^{-1} is due to stretching vibration of the links of Al-O-Zn from the layers. Intense bands that appear in the Raman spectrum of pure TrH at 995 cm^{-1} and 848 cm^{-1} are assigned to the deformation vibration of the CN group.⁴² For the hybrid system, a higher amounts of TrH (ZnAILDH_TrH 0.1>ZnAILDH_TrH 0.4>ZnAILDH_TrH 0.8) increases the peaks intensity due to the drug-intercalated material, while for the nitrate-LDH decreases, which also confirms their replacement with TrH anions.

SEM and EDX analysis

EDX analysis confirms the presence in the hybrid compound of TrH molecules, by increasing the carbon percentage and by the chlorine presence from TrH molecules.

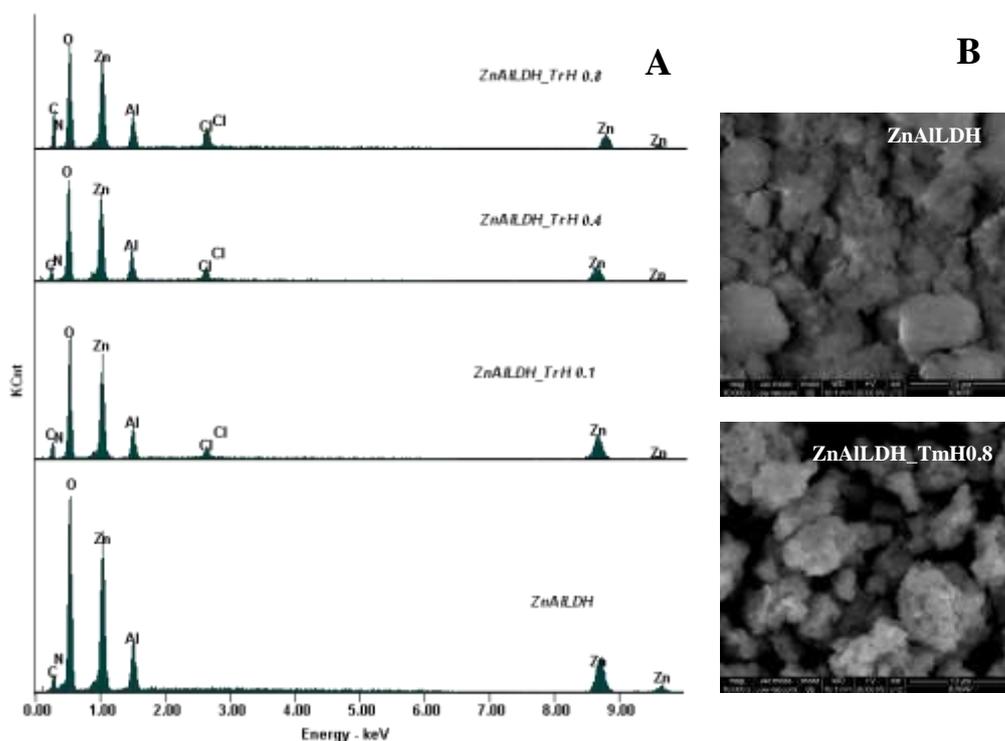


Fig. 3 - (A) EDX spectra of ZnAILDH, ZnAILDH_TrH 0.1, ZnAILDH_TrH0.4 and ZnAILDH_TrH0.8; (B) SEM micrograph for ZnAILDH and ZnAILDH_TrH0.8

The SEM micrograph of the ZnAILDH shows a porous structure with particles of regular hexagonal shape in the size range of 1-1.5 μ m.

CONCLUSIONS

In the present paper the intercalation process of TrH in ZnAILDH was investigated. The precursors and hybrid materials were characterized by XRD, FT-IR, RAMAN, EDX and SEM. The obtained results point out the presence of the TmH in the interlamellar space in the case of ZnAILDH_TrH 0.4 and ZnAILDH_TrH 0.8 when a larger amount of TrH was used for the ion exchange. The FTIR and RAMAN spectra points out the absence of vibration bands characteristic to nitrate ions, which also confirms their replacement with TrH anions. In the other cases was observed the partial TmH intercalation and a significant absorption on the surface of ZnAILDH. This study suggests that TmH can be intercalated into ZnAILDH, and the new hybrid materials could open interesting perspectives for obtaining the drug reservoirs and controlled release systems.

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