

Preparation and characterization of ketoprofen-layered double hydroxide compounds

M. SILION, D. HRITCU^a, M. I. POPA^{*}

Department of Chemical Engineering, Faculty of Chemical Engineering and Environmental Protection, Technical University Iasi, Bd. D. Mangeron 71A, 700050, Iasi, Romania

^a“P. Poni” Institute of Macromolecular Chemistry, 41A, Aleea Grigore Ghica Voda, 700487, Iasi, Romania

Organo-mineral nanohybrid materials in which the organic moiety is intercalated inside the inorganic lamella were prepared by an ion exchange method. Ketoprofen (KET) anions were used as guest molecules, while ZnAl and MgAl layered double hydroxides (ZnAILDH and MgAILDH) were used as inorganic hosts. The intercalated compounds were examined by X-ray diffraction (XRD), FTIR spectroscopy, thermo gravimetric and scanning electron microscopy analysis techniques. The XRD patterns of the samples were found to be typical to those of well crystallized solids with the hydrotalcite structure. The basal spacing of the ZnAILDH with nitrate as intergallery anion expanded from 8.74 Å to 22.36 Å upon drug intercalation. In the case of MgAILDH the basal spacing expanded from 8.50 Å to 22.54 Å. The FTIR spectroscopy results prove the presence of the organic compound in the network structure of the synthesized hydrotalcites. The thermal stability of the intercalated KET was enhanced compared with the pure drug before intercalation. Elemental and chemical analysis of the intercalated compounds showed a good intercalation percentage, i.e. 45% for ZnAILDH_KET and 50% for MgAILDH_KET respectively (by weight).

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1. Introduction

Ketoprofen (chemical name [2-3(benzoylphenyl) propionic acid]) is an analgesic, antipyretic and a nonsteroidal anti-inflammatory drug. It is widely used in the treatment of rheumatoid arthritis, osteoarthritis, ankylosis spondylitis and also for non-rheumatoid diseases [1, 2]. The half-life of ketoprofen in blood plasma was found to be 2 to 3 h and order to maintain therapeutic plasma levels the drug needs to be administered at least twice daily [3]. The oral administration of ketoprofen has side effects such as peptic ulceration or bleeding and anorexia [4, 5], these disadvantages added to the very short half-life render ketoprofen as a very good candidate for the production of controlled release formulations. Natural polymeric or inorganic supports are currently used for designing controlled release drug systems [6, 7].

Layered double hydroxides are currently used in a variety of applications in fields such as catalysis, electronics, photo-chemistry, medicinal chemistry, as inorganic supports for the intercalation of anti-inflammatory drugs such as ibuprofen, indometacin, diclofenac, fenbufen, salicylic acid, ciprofloxacin, [8-14], dyes, enzymes, pesticides [15-19] or polymers [20,21]. Layered double hydroxides (LDHs) are a large class of layered materials, with interlayer spaces containing exchangeable anions. Their general formula can be expressed as $[M_{(1-x)}^{II}M_x^{III}(\text{OH})_2]^{x+}A_{x/z}^{z-} \cdot n\text{H}_2\text{O}$, where M^{II} and M^{III} are divalent and trivalent cations, and A^{z-} is the gallery anion. In this work M^{II} is Zn^{2+} or Mg^{2+} , M^{III} is Al^{3+} and A^{z-} is NO_3^- respectively.

The *in vivo* pharmacological studies show that intercalation of the drugs in the LDH has a synergic effect. On one hand the presence of the layered double hydroxides ensures a buffered environment and on the other hand it reduces the ulcerating side effects of the intercalated drug [22-25].

This paper reports on the synthesis by the ion exchange method and the characterization of layered double hydroxides with Mg^{2+} (Zn^{2+}) and Al^{3+} cations in the brucite-like layer and ketoprofen anions in the interlayer.

The incorporation of KET anions into the LDH is achieved by mixing the LDH with a concentrated KET solution. The solution is then crystallized using the same method as employed in the preparation of the LDH host material [26].

Layered double hydroxides were used because of their capability to prevent taurocholate induced gastric injury in rat was earlier demonstrated and reported in the literature [27] and this is the reason for choosing them as hosts in the present study.

The obtained composites were characterized by powder X-ray diffraction, FTIR spectroscopy, thermal analysis and scanning electron microscopy (SEM).

2. Experimental

2.1 Materials

All chemicals including $\text{Zn}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$, $\text{Al}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$, $\text{Mg}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$, NaOH were analytical grade. Ketoprofen was purchased from Aldrich.

2.2 Synthesis of precursor hydrotalcites

The parent ZnAILDH and MgAILDH were prepared under nitrogen atmosphere, by pH controlled coprecipitation of zinc or magnesium and aluminium nitrates. An aqueous solution of 0.2 mol $\text{Zn}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ or 0.2 mol $\text{Mg}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ and 0.1 mol $\text{Al}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ and an aqueous solution of 1M NaOH, were mixed by dropwise at room temperature, under vigorous stirring. The pH of the reaction mixture was kept constant at 8.5 ± 0.3 using of TitraLab TIM 854 apparatus. The resulting slurry was aged at constant temperature (40°C) for 24h under stirring and nitrogen flow. The crystalline material was then recovered by centrifugation, washed extensively with deionised and decarbonated water and finally dried under vacuum at 45°C .

2.3 Synthesis of ketoprofen intercalated hydrotalcites

ZnAILDH_KET and MgAILDH_KET were prepared by anionic exchange method. 1 g ZnAILDH or MgAILDH was dispersed in 150 ml H_2O and was placed in a three-neck round bottom flask and degassed with nitrogen for 20 min. 1M NaOH solution was then added until $\text{pH} = 8.5$. 150 ml hydroalcoholic solution (50/50 v/v) containing 1.25 g dissolved Ketoprofen was added to the previous mixture and stirred vigorously at 60°C for 16 h under nitrogen atmosphere in order to avoid atmospheric carbonate contamination. The resulting solids were washed, vacuum-dried and used for subsequent investigation.

2.4 Determination of intercalated ketoprofen content

Two methods were used for estimating Ketoprofen content of the composite samples: elemental analysis and spectrophotometric technique. In the spectrophotometric analysis a known amount of LDH_KET was dissolved 6 M HCl and diluted successively with pH 7.2 phosphate buffer. The absorbance was determined at $\lambda = 255 \text{ nm}$ and the amount of intercalated ketoprofen was calculated using a calibration curve.

2.5 Characterization techniques

X-ray powder diffraction (XRD) patterns were recorded 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. FTIR spectra were recorded on a FT-IR Bomem MB 104 spectrometer under the following experimental conditions: 200 scans in the mid-IR range ($400\text{--}4000 \text{ cm}^{-1}$) using KBr (ratio 5 / 95 wt %) pellets, and a resolution of 4.0 cm^{-1} .

TG-DTA thermograms were recorded on Mettler-Toledo TGA/SDTA instrument in the temperature range from 25 to 850°C , at a heating rate of $5^\circ\text{C}/\text{min}$ in nitrogen atmosphere. The molecular modeling studies were carried out using the Hyperchem software package. A Vega TESCAN scanning electron microscope was used for scanning electron microscopy (SEM).

3. Results and discussion

3.1 Elemental analysis and spectrophotometric results

Both methods used for determining intercalated Ket yielded the same results. The intercalated KET percentage was 45% for ZnAILDH_KET and 50% for MgAILDH_KET, respectively (by sample weight).

3.2 Powder X-ray diffraction (XRD)

The powder XRD patterns of the precursor ZnAILDH, MgAILDH and its organo-mineral nanohybrid ZnAILDH_KET and MgAILDH_KET are shown in Fig. 1. The diffractograms of LDH precursors have a typical layered structure similar to those reported in the literature for these materials [28, 29]. The basal spacing of ZnAILDH and MgAILDH with nitrate as interlamella anion is 8.74 \AA and 8.50 \AA , respectively. These values correspond to the basal spacing of anion nitrate incorporated in hydroxide layer.

The magnitude of the basal spacing found in hydrotalcites samples increases upon the inclusion of KET into the lamella of the LDH. This trend is shown in Fig. 1 b and d, where the basal spacing of ZnAILDH_KET and MgAILDH_KET is 22.36 \AA and 22.54 \AA , respectively. This expanded interlayer separation is due to molecular size and geometrical arrangement of KET in the interlayer space. These results are in good agreement with those reported in the literature regarding intercalation of organic anions of similar size to ketoprofen. For example upon intercalation of diclofenac, 4-biphenylacetic acid, mefenamic acid, meclofenamic acid and ibuprofen anions the expanded interlayer spacing was in the range of 20.4 to 23.2 \AA [8-11].

In each case, the reflections can be indexed to a hexagonal lattice with R-3m rhombohedral symmetry, commonly used for the description of the LDH structures. The unit cell parameter, a , is the average distance between two metal ions in the layers and c is three times the distance from the center of one layer to the next. The value of a ($=2d_{110}$) is a function of the average radii of the metal cations whilst the value of c ($=3d_{003}$) is a function of their average charge, the nature of the interlayer anion and the water content.

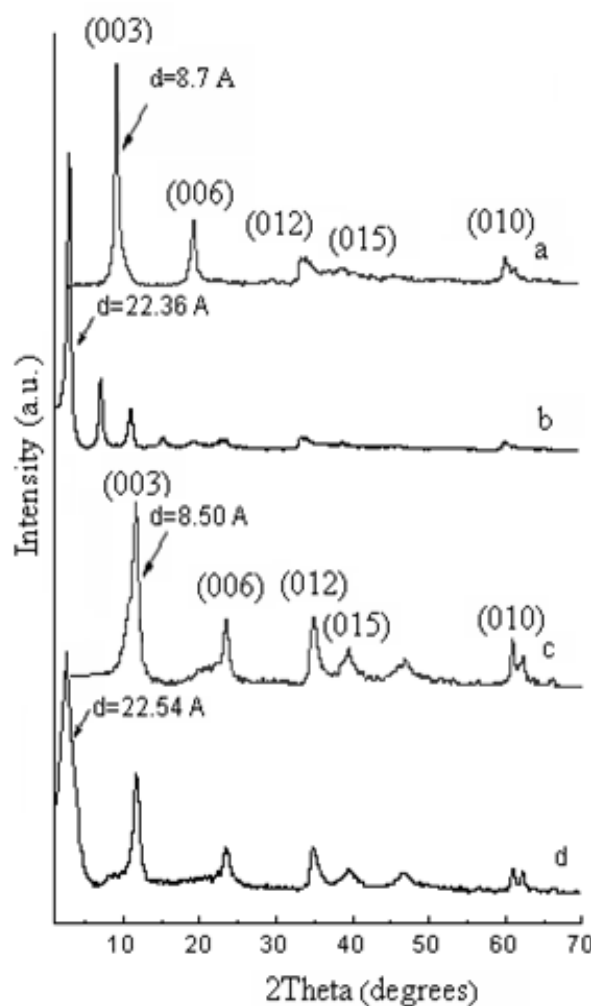


Fig. 1. Powder XRD patterns for (a) ZnAILDH, (b) ZnAILDH_KET, (c) MgAILDH, (d) MgAILDH_KET

After the intercalation of KET, the value of parameter c increases due the replacement of nitrate anions with KET anions. Table 1 lists the gallery height and lattice parameters.

Table1. Lattice parameters and gallery height.

Pillared compound	d_{003} (Å)	c (Å)	a (Å)	Gallery height (Å)
ZnAILDH	8.74	26.22	3.06	3.94
MgAILDH	8.50	25.50	3.04	3.70
ZnAILDH KET	23.36	67.08	3.05	17.56
MgAILDH KET	22.54	67.62	3.03	17.74

3.3 Structural modeling

The length of ketoprofen anion is 11.89 Å, calculated by the method of molecular mechanics (using Hyperchem software). A gallery height of 17.56 Å and 17.74 Å suggests that the KET ions are accommodated in the interlayer region as a monolayer of species partially superimposed with their aromatic ring perpendicular to the layer plane and with the carboxyl of individual anions attaching alternately to the upper and lower hydroxide layers. The model also takes into account the length of the hydrogen bonds established between the anions and the LDH hydroxyl groups. Based on these data, a schematic representation of the probable arrangement for LDH and LDH_KET is shown in Fig. 2.

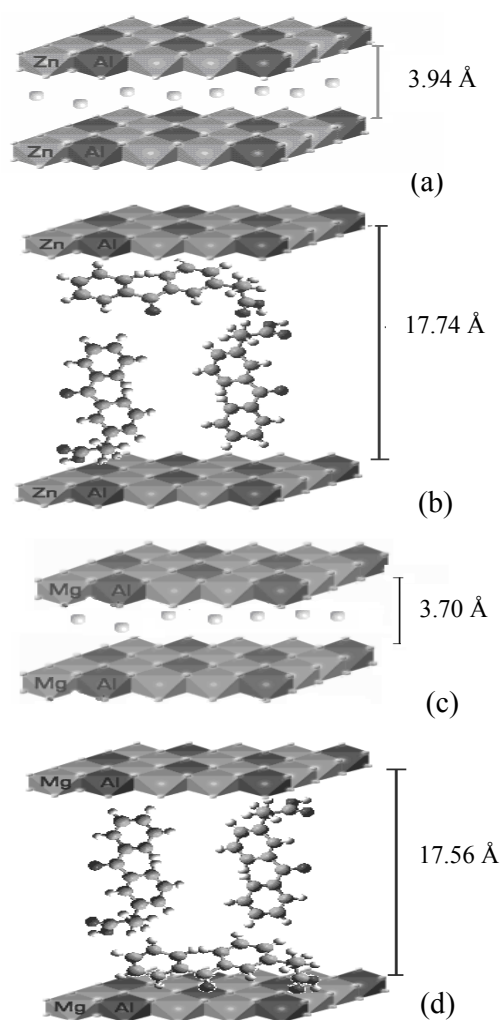


Fig. 2. Schematic models of the intercalation of KET into various LDHs. (a) ZnAILDH, (b) ZnAILDH_KET, (c) MgAILDH (d) MgAILDH_KET.

3.4 FTIR spectroscopy

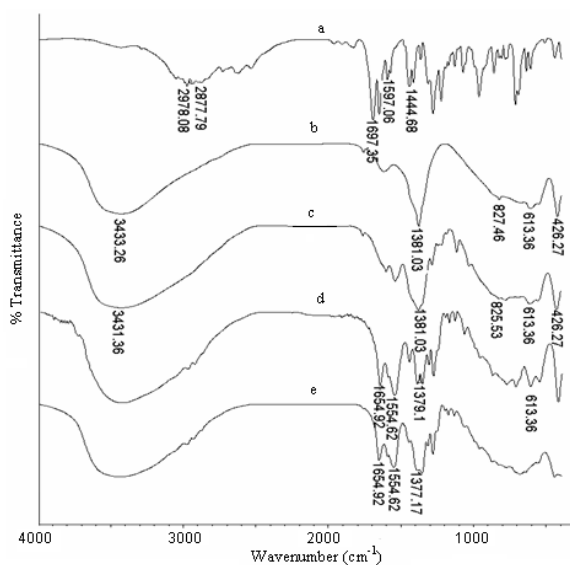


Fig. 3. FTIR spectra for (a) KET, (b) ZnAILDH, (c) MgAILDH, (d) ZnAILDH_KET, (e) MgAILDH-KET

FT-IR spectra of ketoprofen, layered double hydroxides and LDH_KET samples are presented in Fig. 3.

The results confirm the intercalation of ketoprofen in the MgAILDH and ZnAILDH lamella. FT-IR spectrum of pure ketoprofen (Fig. 3 (a)), shows characteristic vibration bands associated with this compound. The main peaks correspond to the following frequencies: 2990-2878 cm^{-1} (methyl ν -CH), above 3018 cm^{-1} (aromatic ring ν -CH), 1697 cm^{-1} (carbonyl ν C=O), 1655 cm^{-1} (ν -C=O, stretching of the ketone), 1597 cm^{-1} , 1585 cm^{-1} and 1445 cm^{-1} (aromatic ring ν C=C) [2].

In Fig. 3 (b), (c) the FTIR spectra of ZnAILDH and MgAILDH are shown. The broad and strong band in the frequency range of 3600-3200 cm^{-1} , centered at 3431 cm^{-1} , is a common feature for all the hydrotalcite-type materials corresponding to the OH stretching vibration due to the presence of water molecules [30]. The bands observed in the low-frequency region of the spectrum are associated to the lattice vibration modes and can be attributed to M-O from 850 to 600 cm^{-1} and M-O-M near 426 cm^{-1} (M = Al, Zn, Mg) in the LDH sheets [31]. The appearance of a strong band at 1381 cm^{-1} is due to the symmetric vibration of the interlayer nitrate anion from MgAILDH and ZnAILDH.

All the vibration bands associated with the organic anion are present in the spectra of the samples containing intercalated ketoprofen, as well as the absorption bands characteristic for LDHs (Fig. 3 (d), (e)).

The characteristic band of the C=O group is located at 1655 cm^{-1} and the band assigned to the C=C bond in the ketoprofen aromatic ring is located at 1554 cm^{-1} . The absence of the band at 1381 cm^{-1} in the spectrum of MgAILDH_KET and ZnAILDH_KET, confirms the fact that the interlayer nitrate anions have been displaced.

3.5 Thermal stability

The TG and DTG curves for all samples are depicted in Fig. 4 and 5 respectively. The thermogravimetric curves show a number of degradation stages, depending upon the nature of the layer cations and on the nature of the interlayer anion.

The analysis of the data presented in Fig. 4 and Fig. 5 leads to the conclusion that the thermal decomposition of raw clays (ZnAILDH and MgAILDH) takes place in various stages resulting in various weight loss percentages, similar to previous reports in the literature [32]. The first two stages, which take place in the temperature range of 25 to 260 $^{\circ}$ C, correspond to elimination of the physically adsorbed water located either on the surface or between the layers. The amount of water eliminated during these stages is about 23% by weight of the ZnAILDH sample and 18% of the MgAILDH sample respectively. In the next stages, at temperatures higher than 260 $^{\circ}$ C, the main process that takes place is the dehydroxylation of the brucite-like layers as well as the decomposition of nitrate ions, which gives a weight loss of approximately 35% of the ZnAILDH sample and about 43% of the MgAILDH sample, respectively.

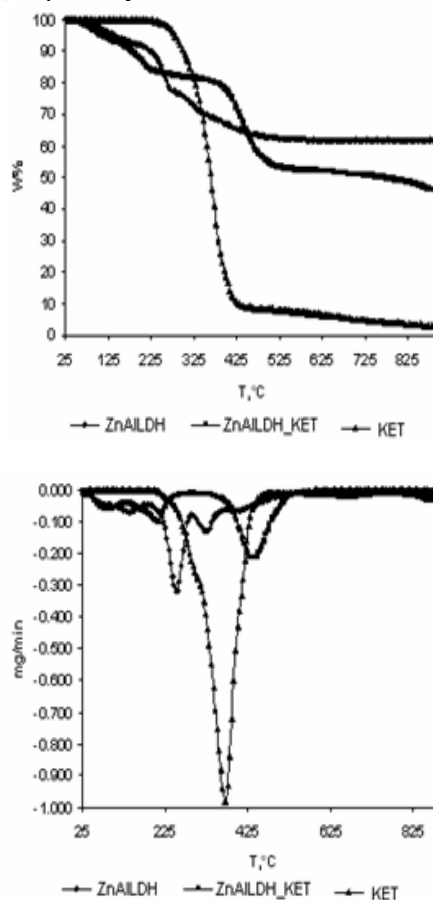


Fig. 4. TG and DTG curves for ZnAILDH, ZnAILDH_KET and KET samples (a) TG curves (b) DTG curves.

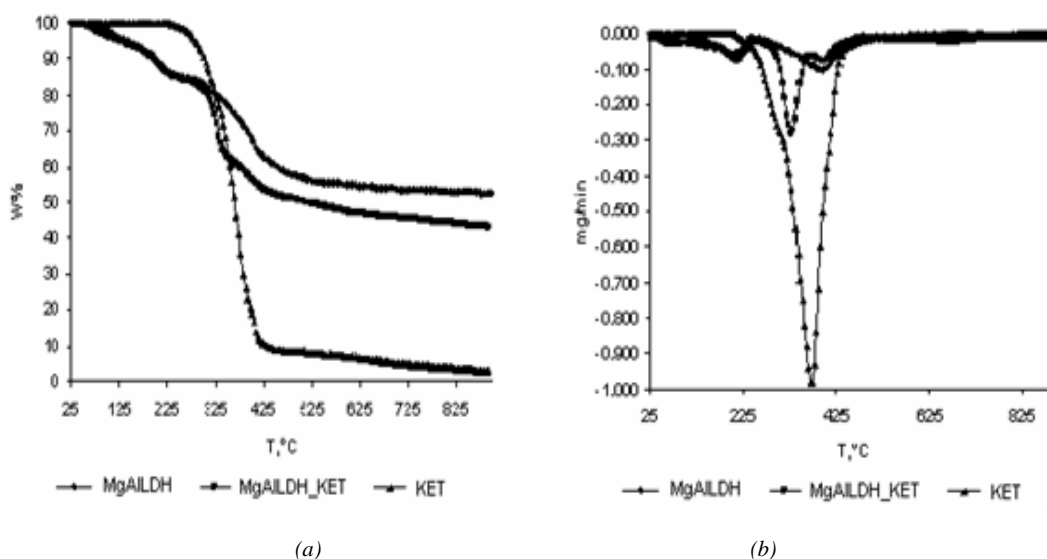


Fig. 5. TG and DTG curves for MgAILDH, MgAILDH_KET and KET samples (a) TG curves (b) DTG curves.

The thermal degradation process takes place in a single stage in the case of KET. The weight loss is about 98% and the degradation rate reaches its maximum at 373°C.

The DTG curves (Figs. 4 (b) and 5 (b)) are characteristic for a complex degradation mechanism. After the intercalation of ketoprofen into LDH host, a modified thermal degradation process is observed, as well as a

different number of degradation stages. The thermostability range was determined to be between 222 and 396°C for the ZnAILDH_KET and MgAILDH_KET composites.

The thermogravimetric parameters T_{onset} , T_{peak} and T_{endset} , in addition to the percentage weight losses are presented in Table 2.

Table 2. The thermogravimetric parameters.

Sample	Stage	T_{onset}	T_{peak}	T_{endset}	W%	Residue
Ket	I	273	373	430	98.03	1.97
MgAILDH	I	50	209	261	14.69	52.38
	II	261	386	542	32.93	
MgAILDH_KET	I	50	80	122	7.30	39.92
	II	122	230	242	8.92	
	III	242	330	345	27.36	
	IV	345	414	620	16.50	
ZnAILDH	I	50	142	162	7.44	61.54
	II	162	254	266	16.11	
	III	266	324	334	6.85	
	IV	334	406	541	8.06	
ZnAILDH_KET	I	50	86	162	7.71	51.36
	II	162	225	239	13.32	
	III	400	440	520	27.61	

T_{onset} - initial temperature of a decomposition process, T_{endset} - final temperature of a decomposition process, T_{peak} - the maximum degradation rate, W% - weight loss of the compounds after the end of a decomposition process.

The temperature T_{peak} corresponding to the maximum degradation rate is shifted by 70°C towards a higher value in the case of the ZnAILDH_KET compound compared to the pure ketoprofen. The same parameter is shifted by 45°C towards a lower value in the case of the MgAILDH_KET compound. If one ignores the water

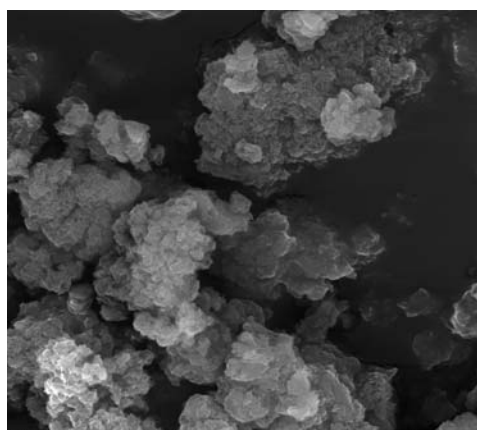
elimination stages, the results lead to the conclusion that the ZnAILDH_KET product is thermally more stable than the MgAILDH_KET product. Compared to the raw clay, the process has one less degradation stage for ZnAILDH and one extra stage for MgAILDH. Different hydrotalcite

degradation mechanisms take place at temperatures higher than 300°C depending on their precursor used.

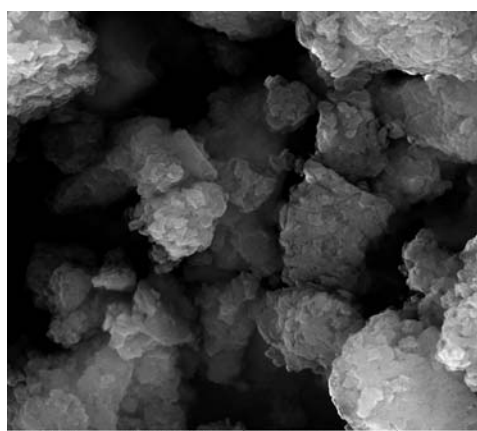
The amount of sample residue leftover after degradation at temperatures higher than 900°C is 10 to 20% lower for the layered double hydroxides containing KET than for the precursor, which is further proof on the presence of the organic compound intercalated within the LDH layers.

3.6 Surface morphology

The morphology of precursor and its derivatives obtained by SEM are shown in Fig. 6 and 7. The comparison of the scanning electron micrographs of ZnAl LDH and MgAlLDH shows that the former well-formed and regular hexagonal-shaped particles in the size range of 1-1.5 μm . The SEM image relative to the intercalated products revealed microcrystals in a nearly hexagonal form, in comparison to LDH in nitrate form.

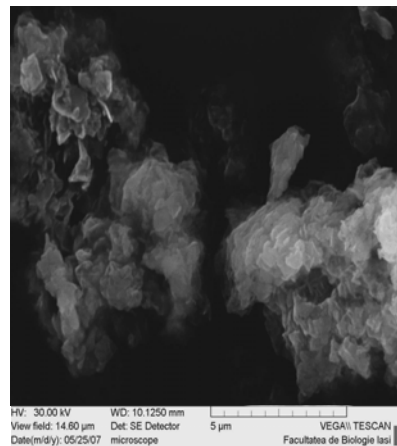


(a)

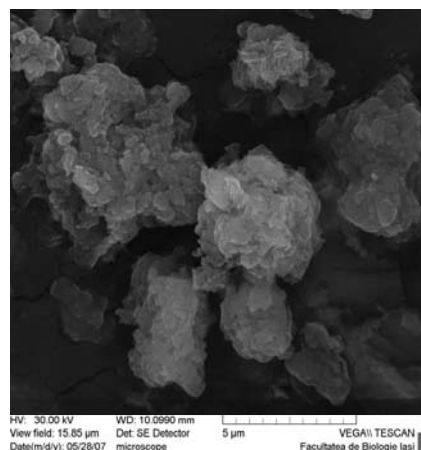


(b)

Fig. 6. SEM micrograph for (a) ZnAlLDH, (b) ZnAlLDH_KET.



(a)



(b)

Fig. 7. SEM micrograph for (a) MgAlLDH, (b) MgAlLDH_KET.

The results are consistent with SEM images presented in the literature for the hydrotalcites and its nanohybrids [11, 33, 34].

3. Conclusions

LDHs_KET were obtained by intercalation of KET anions into ZnAl and MgAl layered double hydroxide by ion exchange reaction. XRD diffractometry, FTIR spectroscopy, and thermo gravimetric analysis were used to confirm that the intercalation process of the drug took place. The XRD patterns of the precursors are typical to this class of well crystallized solids with the layered double hydroxides structure. The basal spacing of nanohybrids is expanded due to drug intercalation. A structural model for intercalates has been proposed based on optimized geometry of KET. The anions are accommodated in the interlayer region as a bilayer with the carboxylate groups interacting simultaneously with

both upper and lower hydroxide layers belonging to LDHs.

In the FTIR spectra, the band characteristic for nitrate group disappeared due to its replacement with KET anions. The thermal stability and the degradation mechanism of KET were modified upon intercalation.

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*Corresponding author: mipopa@ch.tuiasi.ro