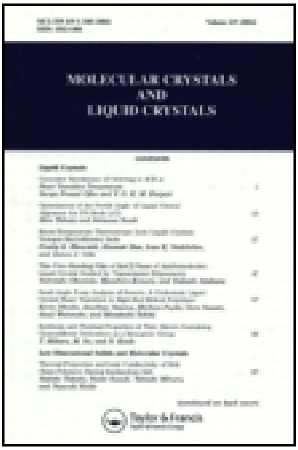

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Jairo Tronto [a], Eduardo Luis Crepaldi [a], Paulo César Pavan [a], Cleberson Cipriano De Paula [a] & João Barros Valim [a]

[a] Department of Chemistry, Faculdade de Filosofia, Ciências e Letras de Ribeirão Preto, University of São Paulo, Av. Bandeirantes, 3900, 14040-901, Ribeirão Preto, SP, Brazil

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# Organic Anions of Pharmaceutical Interest Intercalated in Magnesium Aluminum LDHs by Two Different Methods

JAIRO TRONTO, EDUARDO LUIS CREPALDI, PAULO CÉSAR PAVAN, CLEBERSON CIPRIANO DE PAULA and JOÃO BARROS VALIM

*Department of Chemistry, Faculdade de Filosofia, Ciências e Letras de Ribeirão Preto, University of São Paulo, Av. Bandeirantes, 3900, 14040–901, Ribeirão Preto, SP, Brazil*

Layered double hydroxides (LDHs) are a class of materials with increasing interest due to their singular properties, which make possible their application in a wide variety of fields. Because LDHs can intercalate anions within their interlayer region, they can be used in medicine as drug supports or matrices. Once encapsulated, the drug could be released at a rate dependent on the pH value.

The aim of the present work was to intercalate a variety of anions of pharmaceutical interest, such as salicylate, citrate, glutamate and aspartate, using two different synthesis methods, a direct one (coprecipitation) and an indirect one (anion exchange of dodecylsulfate). The materials obtained were characterised by PXRD, simultaneous TG-DTA, chemical analysis and FT-IR spectroscopy. Furthermore, the buffer effect of the intercalated LDHs was evaluated.

*Keywords:* Layered Double Hydroxides; Anionic Clays; Hydrotalcite; Salicylic Acid; Citric Acid; Amino Acids

## INTRODUCTION

Layered double hydroxides can be structurally described as the stacking of positively charged layers with hydrated anions in the interlamellar domain. The positively charged layers result from the isomorphous substitution of bivalente cations by trivalent ones in a brucite structure, which consists of Mg(II) cations in the center of octahedra, sharing edges, with hydroxyl groups in the vertices, resulting in a planar structure. To neutralise the positive charge, anions must be intercalated between the layers, resulting in the hydrotalcite-like structure. The general formula that can represent this class of materials is: $\left[M^{II}_{1-x}M^{III}_{x}(OH)_2\right]A^{m-}_{x/m} \cdot nH_2O$, where $M^{II}$ is a bivalent cation, $M^{III}$ is a trivalent cation, and A is an anion with charge m- [1].

These compounds can be synthesised by direct or indirect methods. Among the direct methods, the most frequently used is the coprecipitation one [1]. Indirect methods, based on the exchange of a pre-intercalated anion of a precursor synthesised by a direct method, may also be used. Among the indirect exchange methods the anion exchange from a precursor intercalated with a sulfated or sulfonated surfactant, promoted by the addition of a quaternary ammonium cationic surfactant, has been recently reported by us [2].

These compounds can be used for different applications such as adsorbents, ion exchangers, catalysts and catalyst support, etc... Because LDHs can intercalate anions into their interlayer region, they can be used in medicine as drug supports or matrices. Once encapsulated, the drug can be released at a rate dependent on the pH [3].The commercial use of hydrotalcite compounds in medicinal applications was recently reviewed by Carlino [3]. The most common application of LDHs in the medicinal field is in the treatment of dyspepsia and related stomach disorders [4].

The aim of this work was to study the intercalation of some anions of pharmaceutical interest, such as salicylate, citrate, glutamate and aspartate, using two different synthesis methods, i.e. coprecipitation and dodecylsulfate anion exchange methods. A set of methods was used in order to characterise the obtained materials with respect to their chemical composition, crystallinity and thermal stability. Furthermore, the buffer effect of LDHs was evaluated.

## EXPERIMENTAL

### Direct Synthesis by the Coprecipitation Method

The following procedure was used for synthesis by coprecipitation: a solution containing 0.050 mol of $Mg(NO_3)_2.6H_2O$ and 0.0167 (0.025 for citrate containing LDHs) mol of $Al(NO_3)_3.9H_2O$ in 35 $cm^3$ of water was added in a solution containing 0.0333/m (where m is the anion total charge) mol of the desired anion in 140 $cm^3$ of water. During the addition, a 2 mol $dm^{-3}$ NaOH solution was added in order to keep a constant pH ( $\pm$ 0.2 units). The obtained materials were separated and washed by centrifugation and dried under vacuum in the presence of activated silica gel at room temperature.

### Anion Exchange from a Dodecylsulfate-LDH precursor

Anion exchange was performed according to a method previously described [2]. Thus, 20 $cm^3$ of a 0.15 mol $dm^{-3}$ CTAB (N-cetyl-N,N,N-trimethyl-ammonium bromide) solution was added to a mixture containing: 20 g of a precursor suspension (1.3 g of LDH per g of suspension); a solution containing 0.015/m mol of the desired anion in 60 $cm^3$ of water; and 30 $cm^3$ of chloroform. After a contact time of 30 minutes at room temperature, the solid material was separated by centrifugation, washed with chloroform (twice), acetone (once) and water (twice), and dried under vacuum as described before.

### Hydrothermal Treatment

In some cases a hydrothermal treatment was applied in order to improve the material's crystallinity, using a stainless steel vessel with a total capacity of 400 $cm^3$, with magnetic stirring. The medium used was a solution containing 0.0333/m mol of the anion in 140 $cm^3$ of water. The pressure was adjusted to 3 bar with nitrogen and the temperature set at 70 °C. The time of aging ranged from 18 to 192 hours. After the thermal treatment the materials obtained were separated, washed and dried as described before.

### Characterization of the Obtained Materials

PXRD measurements were performed using a Siemens D5005 equipment, with a graphite monochromator selecting the Cu K$\alpha$ radiation ($\lambda$ = 1.5406 Å). The step used was 0.02° $s^{-1}$, continuous method, in a $2\theta$ range from 2 to 70°. Simultaneous TG-DTA analysis was performed with a TA Instruments SDT 2960 Simultaneous DTA-TGA equipment. The conditions of analysis were: synthetic atmospheric air in a flux of 100 $cm^3$ $min^{-1}$, heating rate of 10 °C $min^{-1}$, from room temperature to 1000 °C. FT-IR spectroscopy were carried out in the range from 4000 to 400 $cm^{-1}$, at 60 scans per sample in a Nicolet 5ZDX instrument, using pressed KBr pellets containing 2% of the sample. The C, N and H contents were determined using a Perkin-Elmer 2400 CHN instrument. Mg was determined by atomic absorption and Al by potentiometric titration.

### Buffer Potential Evaluation

To evaluate the buffer effect of the LDH containing the intercalated anions of interest, we added 0.5 $cm^3$ aliquots of HCl solution (1 mol $dm^{-3}$) to a suspension containing 200 mg of the LDH in 20 $cm^3$ of water. Thirty minutes after the addition of each acid aliquot (to permit equilibration) the pH of the mixture was measured.

## RESULTS AND DISCUSSION

### Synthesis of the Dodecylsulfate-LDH (DS-LDH) Precursor

Dodecylsulfate-LDH precursor was synthesised by the coprecipitation method at pH 11. The PXRD data for these materials are shown in figure 1. The basal spacing obtained, 25.1 Å for dodecylsulfate-LDH, was very close to the data reported for hydrotalcite-like compounds[2]. Chemical analysis indicated an Mg:Al ratio very close to 3 for both samples, and an anion:Al ratio very close to 1. The nitrogen content in the dodecylsulfate-LDH was very low (less than 0.1%). This result indicated a low level of contamination by nitrate in the DS-LDH.

### Citrate Containing LDHs

Citrate containing LDHs were prepared by the two different methods. In the preparation by coprecipitation, precipitation did not start until the addition of about 30% of the nitrate cations solution for all pH values tested (8.5, 9.5 and 11.5). This fact may indicate that the anion was forming complex ions with the metal cations. The material obtained at pH 11.5 was the most structurally organised. So, using the material precipitated at this pH value, the effect of hydrothermal treatment on the structural organisation of the materials was investigated. The results are shown in figure 2 for the hydrothermal treatment at 70 °C for different periods of time. The crystallinity of the obtained materials increased up to 72 hours of hydrothermal treatment, decreasing thereafter. Complementing this data, chemical analysis for the sample precipitated at pH 11.5 and not treated showed an Mg/Al ratio of 1.93, very close to the expected one, 2. This ratio increased with aging time until 72 hours, when it reached 2.49, decreasing to 2.14 after 192 hours. The carbon content of the samples was around 9.5%, decreasing with aging time up to 72 hours, and increasing again thereafter. This behaviour is exactly the opposite of the one observed for the Mg:Al ratio with aging time.

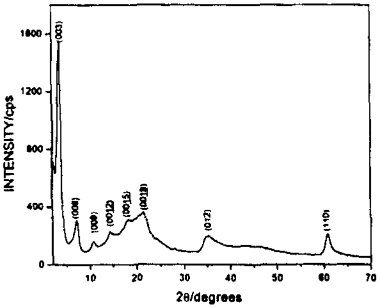

FIGURE 1 PXRD pattern for dodecylsulfate-LDH.

Based on these results, it was possible to formulate a hypothesis to explain the variation in the structural organisation observed. The process can be schematised as follows:

$$Mg^{2+} + Al^{3+} + n\,C_6H_5O_7^{3-} \rightarrow Mg(C_6H_5O_7^{3-})_n^{(3n-2)-} + Al(C_6H_5O_7^{3-})_n^{(3n-3)-} \quad (1)$$

$$Mg^{2+} + Al^{3+} + n\,C_6H_5O_7^{3-} + OH^- \xrightarrow{\text{LDH formation}} LDH \cdot C_6H_5O_7^{3-} \quad (2)$$

$$Mg(C_6H_5O_7^{3-})_n^{(3n-2)-} + Al(C_6H_5O_7^{3-})_n^{(3n-3)-} \xrightarrow{\text{LDH formation}} Mg^{2+} + Al^{3+} + n\,C_6H_5O_7^{3-} \quad (3)$$

Firstly, based on the fact that a large amount of the cations solution was added before the precipitation starts (30%), we infer that the citrate anions were forming complex ions with the metal cations (Eq. 1), reducing the concentration of free citrate in solution. When the precipitation starts (probably due to the reduction of citrate anions in solution), with the formation of an LDH (Eq. 2), citrate anions were intercalated, reducing their concentration in the solution. So, the equilibrium was displaced, and both the metal cations and citrate anions were released to the solution (Eq. 3).

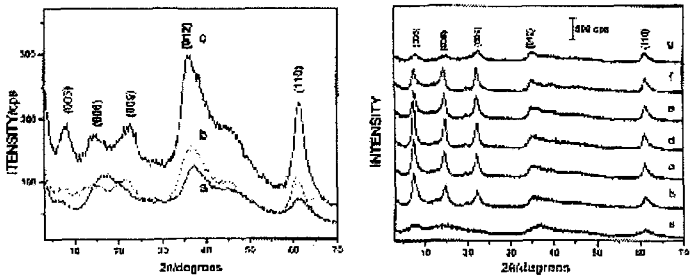

FIGURE 2 Left – PXRD diagrams for materials obtained at different pH values during coprecipitation: (a) 8.5, (b) 9.5 and (c) 11.5. Right – Effect of the hydrothermal treatment period at 70 °C and 3 bar in an $N_2$ atmosphere, for the sample obtained at pH 11: (a) without treatment; (b) 18; (c) 42; (d) 72; (e) 100; (f) 192 hours; and (g) intercalation by anion exchange of dodecylsulfate without hydrothermal treatment.

The existence of this process can explain the Mg:Al ratio very close to the one added, even though the precipitation did not begin until the addition of 30% of the cations solution. Moreover, it can explain the very low structural organisation obtained after the addition, since this process implies a competition between the complex and LDH formation. During the hydrothermal treatment (or ageing), it seems that a preferential solubilization of the aluminium cations occurred, increasing the Mg:Al ratio, probably caused by the abstraction of aluminium cations from the layers by the citrate anions.

The basal spacing of the obtained materials did not vary significantly with the hydrothermal treatment, keeping around 12 Å (12.08 Å for the sample hydrothermally treated for 72 hours). The elemental analysis of nitrogen showed very low amounts of this element (less than 0.1%), indicating that the materials are practically nitrate free. In agreement, the FT-IR spectra for the obtained materials (data not shown) did not present any bands related to the nitrate anion.

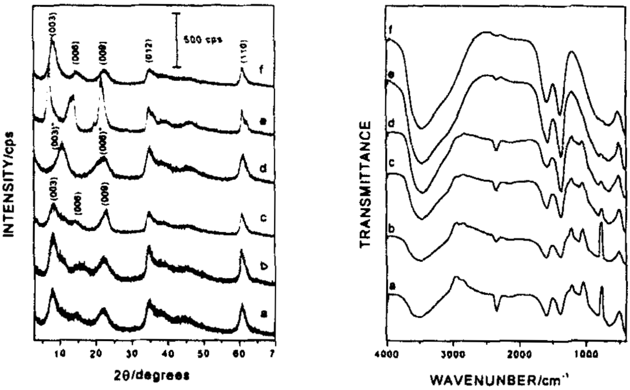

FIGURE 3 Left - PXRD patterns; and Right - FT-IR spectra for (a) aspartate-LDH by coprecipitation, (b) aspartate-LDH by coprecipitation after a hydrothermal treatment, (c) aspartate-LDH by dodecylsulfate anion exchange, (d) glutamate-LDH by coprecipitation, (e) glutamate-LDH by coprecipitation after a hydrothermal treatment, and (f) glutamate-LDH by dodecylsulfate anion exchange. * indicates the nitrate containing LDH phase.

The intercalation of citrate anions by anion exchange of dodecylsulfate (figure 2g, right) yielded a better ordered LDH than the one obtained by direct coprecipitation, without a hydrothermal treatment, but less organised than any sample coprecipitated and hydrothermally treated. This result indicates that the use of hydrothermal treatment is very important in the intercalation of citrate anions.

## Aspartate and Glutamate Containing LDHs

Aspartate and glutamate containing LDHs were prepared by both synthesis methods. The PXRD patterns for the materials obtained are shown in figure 3. The coprecipitation and anion exchange methods, as well as the hydrothermal treatment, were conducted at pH 11.

For aspartate containing LDHs, a basal spacing was around 11 Å, close to the one reported in the literature [5]. The hydrothermal treatment practically did not affect their structural organisation. Moreover, the compounds obtained by coprecipitation showed higher crystallinity than those obtained by anion exchange. The IR spectra were very similar and did not show the presence of nitrate, for coprecipitated materials, or the presence of dodecylsulfate, for anion-exchanged materials. These results indicate that the best way to obtain aspartate-LDHs is by the coprecipitation method, and that the hydrothermal treatment is not necessary.

For glutamate containing LDHs, the coprecipitation method yielded an LDH with basal spacing of 8.2 Å. After hydrothermal treatment the basal spacing was 12.3 Å. When the anion exchange method was applied, the basal spacing was 12.1 Å. The IR-spectra for these materials showed two bands related to the carboxylic group, at about 1580 and 1370 $cm^{-1}$. The relative intensity of the band near 1370 $cm^{-1}$ was greater than that around 1580 $cm^{-1}$. However, for the sample prepared by coprecipitation, without any hydrothermal treatment, the relative intensity of the band at 1370 $cm^{-1}$ was higher than that at 1580 $cm^{-1}$. Nitrate anions present a characteristic band at about 1340 $cm^{-1}$ [6], and nitrate containing LDHs present a basal spacing close to 8 Å [6]. Therefore, these results indicate that nitrate anions were co-intercalated during coprecipitation. Hence, hydrothermal treatment in the presence of glutamate and in the absence of nitrate anions led to the anion exchange of the co-intercalated nitrate, resulting in a basal spacing close to that previously reported for the glutamate-LDH, 12.2 Å [5]. The best structural organization for glutamate-LDHs was obtained by coprecipitation followed by hydrothermal treatment, which was considered here the best method to obtain this intercalated compound.

### Salicylate Containing LDHs

Salicylate containing LDHs were synthesised by the two cited methods. The PXRD patterns obtained for the prepared materials are shown in figure 4. When a salicylate-LDH was coprecipitated at pH 8.5, 10 and 12, the results showed that salicylate anion was not intercalated at pH 10 and 12 (data not shown), and the basal spacing observed in these cases was about 8 Å, close to the one expected for nitrate or hydroxyl anions [6]. At pH 8.5, two phases were observed in the PXRD diagram: one with basal spacing about 8 Å, and the other, evidenced by only one peak, with basal spacing around 15 Å, indicating the possible co-intercalation of salicylate and nitrate anions. The FT-IR spectrum for this sample showed an intense band at around 1360 $cm^{-1}$, characteristic of nitrate anions, as well as two bands characteristic of the carboxylic group (see figure 4). This result confirmed the co-intercalation of nitrate and salicylate anions. After hydrothermal treatment, the basal spacing observed was around 15 Å, and peaks not related to the lamellar structure were observed. Furthermore, the FT-IR for the hydrothermally treated sample showed a weak, but identifiable band at 1360 $cm^{-1}$, indicating that nitrate anions remained intercalated. So, the low crystallinity observed can be attributed to the presence of two different anions in the interlamellar domain, as well as to the observed low tendency of the salicylate anions to be intercalated.

The anion exchange of dodecylsulfate anions resulted in a lamellar material with a basal spacing around 30 Å, as well as a large amount of unidentified impurities (see figure 4c, left). The FT-IR spectrum for this sample showed characteristic bands of the carboxylate (salicylate) and dodecylsulfate anion, indicating that the anion exchange was not complete. Moreover, this spectrum did not show bands related to the quaternary ammonium group of the CTAB. This result indicated that the surfactants' salt was completely eliminated, therefore, leading us to conclude that the basal spacing of 30 Å was originated by an interlamellar arrangement of dodecylsulfate and salicylate anions. Probably, this distribution occurred due to an interaction between the hydrophobic portions of each molecule (benzene group for salicylate and carbonic chain for dodecylsulfate), keeping the charged groups (carboxylic group for salicylate and sulfate group for dodecylsulfate) near successive layers.

The results obtained so far show that coprecipitation followed by hydrothermal treatment is the best method tested for preparing a salicylate-LDH.

## Thermal Behavior

Although the intercalated materials prepared here were very different from each other, their thermal behaviour was almost similar. All the materials, independently of the anion, showed a loss of mass c.a. 10 to 15% from room temperature to about 200 °C. Decomposition of the layers hydroxyl groups occurred thereafter from 250 to 550 °C, with a loss of mass dependent on the anions, but always in the 30 to 40% range. After 600 °C no mass loss occurred in any case, indicating that the material was converted to the mixed oxide. In general, this resulting oxide consisted of $MgO$ and $MgAl_2O_4$ [7].

## Buffer Potential

The results for the titration of the citrate-LDH prepared by coprecipitation are shown in figure 5. It is possible to observe that the buffer effect of the citrate containing LDH occurred in the 3-4 pH range. The buffer effect ended with the complete destruction of the LDH.

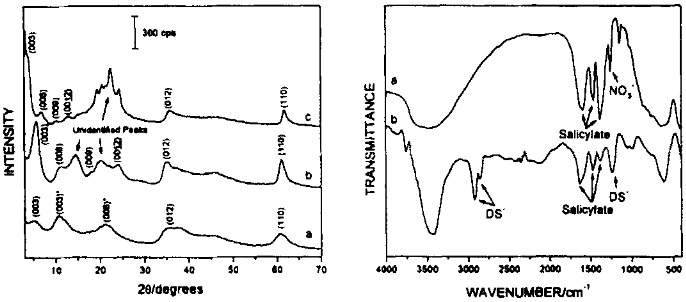

FIGURE 4 Left – PXRD data for salicylate-LDH prepared by (a) coprecipitation, (b) coprecipitation followed by hydrothermal treatment, and (c) dodecylsulfate anion exchange. Right – FT-IR spectra for salicylate-LDH prepared by (a) coprecipitation, and (b) dodecylsulfate anion exchange.

## CONCLUSION

On the basis of the results obtained, we conclude that all of the anions intercalated have a small tendency to be intercalated in Mg-Al-LDHs, since low-ordered hydrotalcite-like compounds were obtained in all cases. Citrate anions complex with $Mg^{2+}$ and/or $Al^{3+}$ cations, making intercalation difficult. For the intercalation of glutamate and salicylate we observed the co-intercalation of nitrate anions, even though nitrate presented a very small tendency to be intercalated.

On the other hand, the use of a hydrothermal treatment permitted intercalation, resulting in hydrotalcite-like compounds with the anions of interest in the interlayer. The amount of nitrate in the hydrothermally treated material was still high only for salicylate-LDHs, and it is a problem to be solved for the application of these compounds in the medicinal area.

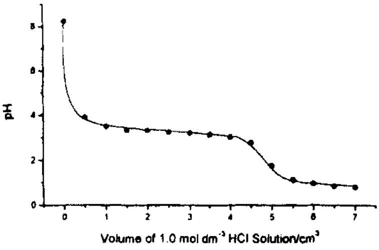

FIGURE 5 Titration of the citrate-LDH prepared by coprecipitation and hydrothermally treated for 72 hours.

The buffer effect of citrate-LDHs in 3-4 pH range seems to be ideal for the application, using the antacid property. This buffer effect may be very useful for the administration of drugs that can irritate the human stomach, such as salicylic acid.

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