Textural Properties of Amoxicillin -Anionic Clays Composites for Possible Oral Diseases Uses

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Hybrid nanostructures based on amoxicilin – hydrotalcite type anionic clays were synthesized by using coprecipitation and reconstruction of initial structure as synthesis methods. Scanning electron microscopy (SEM) technique and nitrogen adsorption-desorption isotherms was used to describe textural characteristics of the obtained hybrids. The plate - let morphology defines the texture of the iron containing clay but these features changed to nonporous solid structures for the drug-clay hybrid materials. Results showed that these aggregated nanoparticles of layered double hydroxides or substituted ones could be good candidates as host for drug delivery systems with potential applications in dentistry. Texture of LDHs and intercalated compounds was studied to determine the way the guest molecules of amoxicillin were intercalated between hydrotalcite sheets.

Keywords: layered double hydroxides, amoxicillin, delivery systems, dentistry

Specific textural characteristics of layered double hydroxides refer to porous properties and morphological features of these materials. Layered double hydroxides represent a class of layered materials with chemical composition expressed by the general formula $[M^{II}_{1-x}M^{III}_{x}(OH)_2]^{x+}(A^{n-})_{x/n}\cdot yH_2O$, where M^{II} is a divalent metal ion, such as Mg^{2+}, Ca^{2+}, Zn^{2+} etc, M^{III} is a trivalent metal ion, such as Al^{3+}, Cr^{3+}, Fe^{3+}, Co^{3+} etc and A^{n-} is an anion, such as Cl^-, CO_3^{2-}, NO_3^- etc. The basic layered structure of LDHs is based on that of brucite [$Mg(OH)_2$] which consist of a hexagonal close packing of hydroxyl ions with alternate octahedral sites occupied by Mg^{2+} ions. In case of LDHs, some of divalent cations of these brucite like sheets are isomorphously substituted by a trivalent cation and the mixed metal hydroxide layers thus acquire a net positive charge. This excess charge on the metal hydroxide is counterbalanced by the anions accumulated in the interlayer region which also contain some water molecules for the stabilization of the crystal structure [1]. A schematic representation of LDHs structure is shown in figure 1.

The simplest and most commonly used synthesis method is *coprecipitation*. In this method, aqueous solutions of M^{2+} and M^{3+} containing the anion that is to be incorporated into the LDHs are used as precursors. In order to ensure simultaneous precipitation of two or more cations, it is necessary to carry out the synthesis under conditions of supersaturation. After precipitation at low and high supersaturation, a thermal treatment process is performed to increase the yields and crystallinity of the materials. This is followed by an aging process conducted for a period ranging from a few hours to several days [2, 3].

Many LDH materials show unique phenomenon called "memory effect" which involves the regeneration of the LDH initial structure from their calcined form, when the later is dispersed in an aqueous solutions containing suitable anion [4]. This property is extensively reported in numerous papers [2, 5, 6,]. There is the possibility of varying the identity and proportions of divalent and trivalent cations which belong to the LDH family.

Layered double hydroxides (LDH), also known as hydrotalcite like compounds are well known for their peculiar characteristics like good biocompatibility, anion exchange capacity, high chemical stability and *p*H-dependent solubility which aid for the design of smart drug delivery systems [7].

There are studies suggesting that the composites based on drugs – LDHs could form the basis for a well defined drug – release system. Controling the point of drug release it is possible to establish pharmokinetic profile by selection of the metals ions in the host layers of the drug – LDH composite and improve drugs long-term stability and storage [8, 9].

The most commonly used antibiotic in dental practice, penicillins in general, were found to be the most commonly prescribed antibiotics by dentists, [10-12] the most popular one being amoxicillin,[13, 14] followed by penicillin V, [15-17] metronidazole,[13, 14] and amoxicillin and clavulanate [18]. Antibiotic therapy requires that antibiotics have certain characteristics, such as: rapid onset of action, bactericidal activity, lack of propensity to induce resistant mutants, easy penetrability into tissues, activity against non-dividing bacteria, not being affected by adverse infection conditions (low *p*H, anaerobiasis, presence of pus, etc.), administration at an optimal dose, and optimal dosing regimen [19]. Empirical antibiotic therapy and drainage are recommended for more severe infections such as facial cellulitis, pericoronitis, lateral periodontal abscess, and necrotizing ulcerative gingivitis. Amoxicillin is

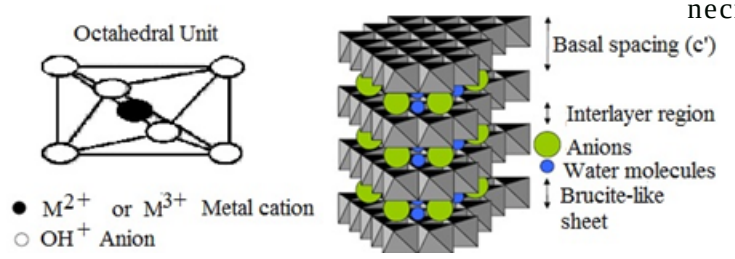

Fig. 1. Structure of layered double hydroxides

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recommended for dental infections in doses ranging from 250 mg to 500 mg, every 8 h [20, 21]. The use of 3 g amoxicillin repeated after 8 h is also mentioned, as a short course of oral therapy. Furthermore, some researchers observed that amoxicillin/clavulannic acid are the only orally administered antimicrobials with adequate pharmacokinetic/ pharmacodynamic properties to be effective against the most commonly isolated oral pathogens for the treatment of orofacial infections [22-24].

In order to obtain information about textural characteristics of these materials we used Scanning electron microscopy (SEM) as an advanced technique for morphological features and N_2 adsorption-desorption isotherms for porosity determination.

This work aims to reveal new results about the textural properties of the composites based on amoxicilin-anionic clays, type LDH for possible applications in dental medicine.

Experimental part

Materials and methods

Synthesis of layered double hydroxides and iron substituted layered double hydroxides by the direct coprecipitation method

Anionic clays were obtained by coprecipitation method using as precursors metal salts with different molar ratio and NaOH / Na_2CO_3 as precipitants. The precipitants and the metal salts used were added dropwise together in such a way to mentain the *p*H constant value of 9.5. The resulting white precipitate was aged at 60°C for 24 h under stirring to achieve the aging step. The obtained precipitates were separated by centrifugation, washed extensively with deionized water until sodium free and dried under vacuum at 60°C. These samples are denoted as LDHs and FeLDHs.

Synthesis of amoxicillin-LDHs and amoxicillin-FeLDHs by the reconstruction method

Composite materials type amoxicilin-LDHs and amoxicillin – FeLDHs were prepared by using the reconstruction method; the amount of antibiotic was optimized to overcome 2 times the anionic exchange capacity of the clay.

LDHs and FeLDHs anionic clay was calcined at 550°C for 5 h, under continuous air flow. 2 g of freshly calcined hydrotalcite – like sample was added in an aqueous solution containing 0.1 mol of amoxicillin, under bobbling a constant flow of N_2 in the medium; the obtained precipitate was aged for 18 h at 40°C, separated by centrifugation, washed with deionised water until sodium free and dried under vacuum at 30°C. These samples are denoted as Amox-LDHs and Amox-FeLDHs.

In order to obtain information about textural characteristics of these materials we used Scanning electron microscopy (SEM) as an advanced technique for morphological features and N_2 adsorption-desorption isotherms for porosity determination.

Results and discussions

SEM images presented in figure 2 and figure 3 show that hydrotalcites and iron substituted samples consist in highly interconnected particles, typical thin platelet morphology of LDHs particles with approximately hexagonal shape. Differences are due mostly to the different interconnect way and rate of agglomeration in layered double hydroxides but also to the changes in particles sizes. FeLDHs sample revealed wide cavities between particles. Mean value of particles size was found to be 130 nm for MgAlLDHs and 100 nm for FeLDHs.

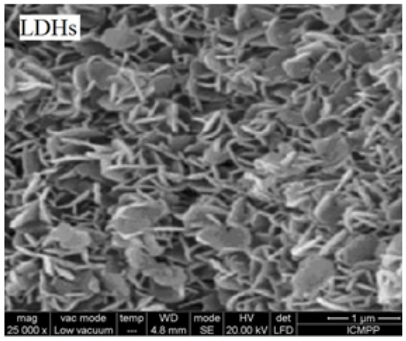

Fig. 2. Image of LDHs by SEM technique

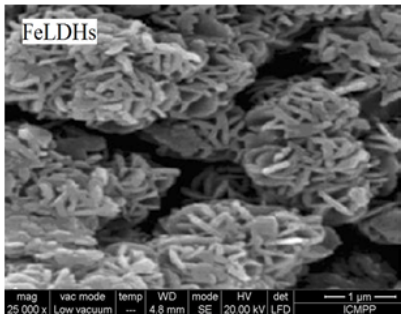

Fig. 3. Image of FeLDHs by SEM technique

The SEM analysis points out the alteration of the textural characteristics of the samples containing amoxicilin.

When the drug is introduced in the porous matrix of the iron substituted clay the morphological characteristics of AmoxLDH and AmoxFeLDH (shown in fig.4 and fig.5) indicate that the incorporation of antibiotic in the inorganic clay matrixes gives rise to an intricate morphology defined by a compact, nonporous solid structure. This image is typical for intercalated LDHs nanocomposites, different from the *sandrose* morphology of layered double hydroxides.

Adsorption - desorption isotherms were used to determine samples porosity. Contribution of pores, as a function of their size range in total volume of pores was obtained by using pore size distribution results. In figure 6 and figure 7 it can be observed that pores belonging to 5 - 20 nm area contribute with almost sixty percent to total pores volume for LDHs sample, while contribution related to 3-40 nm pore size area is almost twenty percent for iron substituted sample.

Pore size distribution is used to verify and to complete the SEM results. For FeLDH sample it can be observe that a sharp and high peak with a 3.5 nm maximum. This fact shoes that small pores like microspores and very small mesopores establish the porous characteristics of this clay.

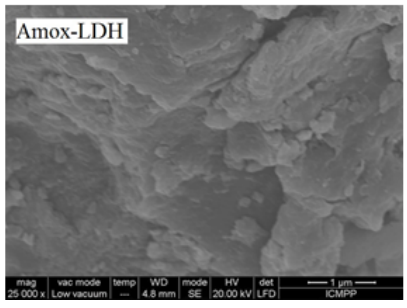

Fig. 4. Image of Amox LDHs by SEM technique

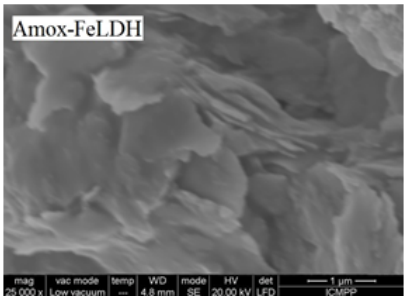

Fig. 5. Image of Amox-FeLDHs by SEM technique

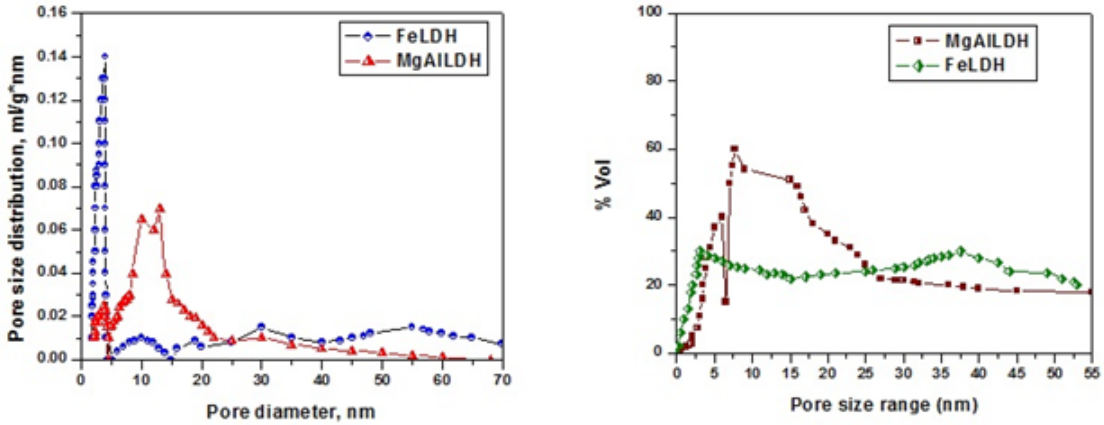

Fig. 6. Pore size distribution of FeLDH and LDHs (MgAlLDH) samples

Wide mesopores and macropores arised and FeLDH porous structure presents an accentuate ununiformity.

Pore size distribution curve of LDHs (MgAlLDH) is larger aand modified to a bigger dimension with 2 maximum of 9.1 and 12.4 nm. In this case pores belonging to a hole area of mesopores characteristics arised.

Mesoporous structure of simple LDHs sample can occur due to the space between particles, mesoporous features being well defined by the particle shape and size and by the particle interconnect ways.

Conclusions

Hybrid materials based on amoxicillin-hydrotalcites were synthesised by using the reconstruction method. The scanning electron microscopy results show that the typical thin platelet morphology of LDHs is characteristic for the parent clay while a compact, nonporous solid structure is formed in the case of the amoxicillin- LDHs composites. It can be observed that both the structural and textural properties of the clay alter for the drug composites.

Nowadays researchers concern is to develop non-toxic, biocompatible drug delivery systems that could improve the efficacy of drugs in order to control drug release profile. Anionic clays type layered double hydroxides fit well to these demands due to their high capacity to incorporate in their layers many components like anions, polymers, drugs, enzymes etc. The distinct nature and electro-negativities of the ions present in the synthesis medium, and the different molar ratio of the starting solutions could be important factors to control the morphology and to determine the changes of the textural properties.

An important issue of nanotechnology is to obtain new textural properties of biocompatible composites systems like LDHs-drug for efficient uses in medicine, especially dentistry treatments. Some possible directions of using these composites are for brackets applications in orthodontics, caries treatment on six years old molars or permanent molars sealing at six and twelve years old.

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