Antibiotic-anionic Clay Matrix Used for Drug Controlled Release

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Anionic clay matrix acting as drug controlled release system have shown in last years a great potential for delivery of bioactive molecules and chemical therapeutics. This organic-inorganic nanohybrid system is high efficient offering an excellent protection of intercalated compounds from degradation. Compared to other nanoparticles used in medical area, anionic clays type layered double hydroxides have found to be biocompatible according to toxicological studies. Ampicillin containing MgAlLDHs and ZnAlLDH samples have been prepared following two routes: anion-exchange procedure and reconstruction from calcined layered double hydroxides. Solid samples have been characterized by FTIR and SEM-EDX highlighting the alteration of pristine LDHs structure when the antibiotic is introduced in the interlayer gallery.

Keywords: anionic clay, drug release, SEM-EDX, FTIR, orthodontics, public health dentistry

It is well known that clay minerals have been used as therapeutics due to their special properties at nanometric scale. Selecting the suitable anionic clay as matrix for different pharmaceutical formulations facilitates the administration of an active principle, improves their efficacy and assures a better stability. Furthermore, because of their biocompatibility, anionic clays type hydrotalcites or layered double hydroxides are used as active principles in various formulations requiring sterilizers, adsorbent products, anti-inflammatory or antimicrobial agents. In addition, most of layered double hydroxides used in pharmaceutical field can be good host for active molecules intercalated in the interlayer space acting as drug delivery carriers thus improving the drug release profile. These nano-sized materials exhibit unique physicochemical properties due to the ease of tailoring the synthesis conditions [1-5]. Layered double hydroxides (LDHs) are represented by general formula $[M^{II}_{1-x}M^{III}_{x}(OH)_2^{x+}(A^{m-})_{x/m}\cdot nH_2O]$ (x = 0.2–0.4; n = 0.5–1),where $M^{II}$is a divalent metal cation, M^{III} a trivalent metal cation and A^{m-} represents anions located between two layers that can counterbalance the positive charge of layers by electrostatic interactions [6-8]. Figure 1 present a structural model of anionic clay type layered double hydroxide.

Biologically active molecules intercalated into interlayer space include antibiotic anions with antibacterial activity.

The intercalation of antimicrobial drugs as ampicillin can be performed as long as the new formulation can maintain its pharmacological action for a longer period, to delivery and to release the drug in a controlled manner while avoiding adverse effects of drug administration. Ampicillin is one of the largest broad spectrum antimicrobial agents used for years because of its irreversible bactericidal effect [9-11]. This drug is clinically useful although its action fights with bacterial resistance thus motivating the researchers to design new stable modified formulations. The increased bacterial resistance determines us to develop new effective compounds consisting in broad-spectrum antibacterial agents [12-22].

Therefore, our work focused on synthesis and characterization of nanomaterials type antibiotic-anionic clay matrix used for ampicillin controlled release improving thus oral health by limiting bacteria colonization or treating microbial infections in oral cavity.

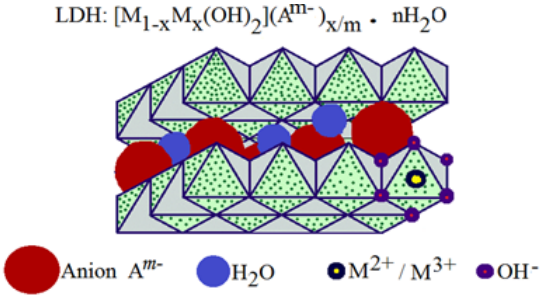

Fig. 1. Structural model of layered double hydroxides

Experimental part

Materials and methods

MgAlLDHs and ZnAlLDH samples using magnesium nitrate, aluminum nitrate and zinc nitrate precursor salts in a 3:1 and 2:1 molar ratio were prepared by coprecipitation route. Metal salts dissolved in 700 mL deionized water were added drop wise to a $NaOH/Na_2CO_3$ solution under stirring to a *p*H value of 9.5-10. The resulting gel was aged for 24h at 60°C, separated by filtration and dried at 60°C for 12h. An amount of these samples were calcined at 550°C for 5 h in order to be used for ampicillin intercalation by rehydration.

Drug intercalation into anionic clay gallery was carried out by anion exchange method using MgAlLDHs and ZnAlLDHs parent samples and by reconstruction using calcined samples.

Thereby 1 g ofMgAlLDHs and ZnAlLDHs respectively and 1 g of each calcined ones was added to a 100 mL solution containing 0.5 g ampicillin dissolved in deionized water. The obtained samples type antibiotic-anionic clay matrix denoted as ampicillin - MgAlLDHs and ampicillin - ZnAlLDHs were stirred for 24 h at room temperature, separated by filtration and dried at 40°C for 24h.

Structure and morphology of final products were analyzed using FTIR and SEM-EDX characterization techniques.

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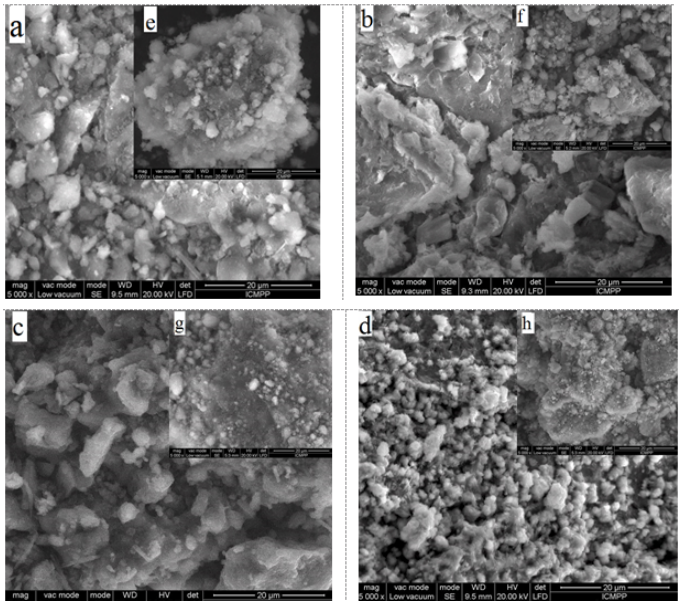

Fig. 2. SEM images of samples: a) MgAl-anionic clay; b) ZnAl-anionic clay; c) calcined MgAl-anionic clay; d) calcined ZnAl-anionic clay; e) Ampicillin-MgAl by anion exchange route; f) Ampicillin-ZnAl by anion exchange route; g) Ampicillin-MgAl by reconstruction method; h) Ampicillin-ZnAl by reconstruction method

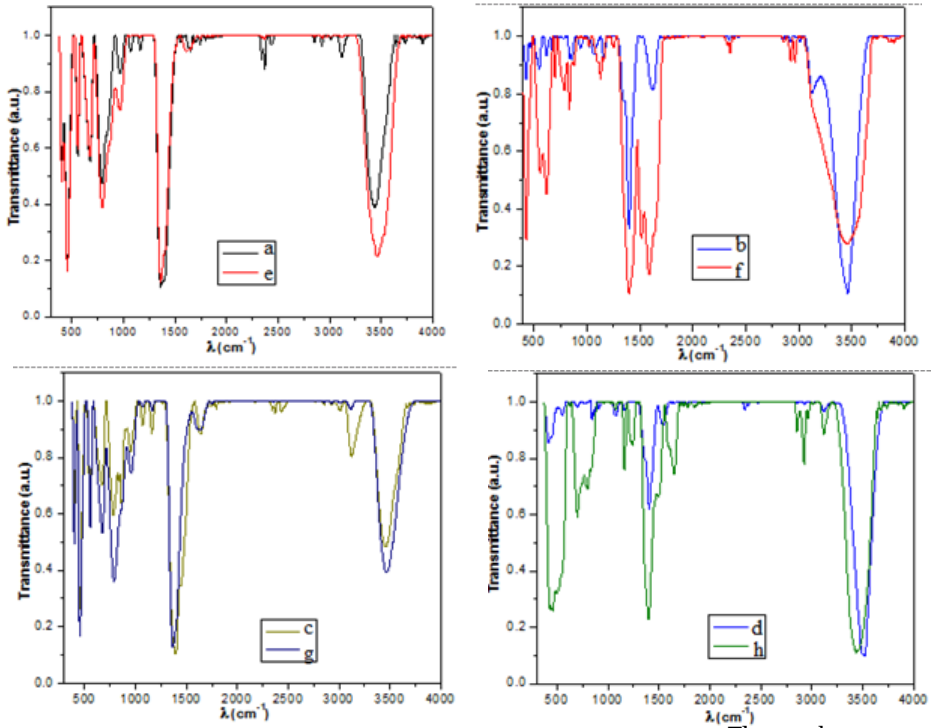

Fig. 3. FTIR spectra of samples: a) MgAl-anionic clay; b) ZnAl-anionic clay; c) calcined MgAl-anionic clay; d) calcined ZnAl-anionic clay; e) Ampicillin-MgAl by anion exchange route; f) Ampicillin-ZnAl by anion exchange route; g) Ampicillin-MgAl by reconstruction method; h) Ampicillin-ZnAl by reconstruction method.

Results and discussions

All samples shape and sizes were performed through scanning electron microscopy (SEM). Nanoparticles with hexagonal platelet shape were noticed for Mg(Zn)Al anionic clays (fig. 2a, 2b) while aggregates shapes were found for corresponding antibiotic- anionic clays (fig. 2e, 2f). Morphologies of pristine samples are specific to anionic clays structures type layered double hydroxides containing Mg(Zn)Al as well as for thermally treated ones and their sizes are around 90 nm (fig. 2c, 2d). It can also be observed that their shape and agglomeration degree modifies when ampicillin is present in the interlayer gallery (fig. 2g, 2h).

Intercalation of ampicillin into anionic clay interlayers was also confirmed by comparing FTIR spectra (figure 3) of drug intercalated samples with pristine anionic clays nanoparticles.

Pristine anionic clays spectrum shows intense broad band around 3445 cm^{-1} assigned to stretching vibration of –OH groups and interlayer water molecules. The band at 1630 cm^{-1} is associated with bending vibration of water molecules present into interlayer space of anionic clay. Stretching vibration of anionic nitrate groups can be observed at around 1385 cm^{-1}.

The peak at around 550 cm^{-1} is attributed to M-O and M-O-H stretching vibration in the hydrotalcite layers. MgAl anionic clay has a characteristic band at around 445 cm-1 (fig. 3a, 3b, 3c, 3d) .

FTIR spectra of ampicillin intercalated samples (fig. 3e, 3f, 3g, 3h) present an absorption peak at around 1750 cm^{-1} attributed to C=C stretching, at 1665 cm^{-1} is the result of C=O amide stretching and 1560 cm^{-1} belong to N-H amide groups. Carboxylate groups present stretching vibration at around 1590 cm^{-1} and 1390 cm^{-1} respectively.

Conclusions

Nanomedicine offers many opportunities to enhance the efficacy of currently used antibiotics in order to destroy pathogen resistance mechanism. Nanotechnology facilitated the advanced design of new nanomaterials type antibiotic-anionic clay matrix having uses in pharmaceutical area thus improving public health dentistry by limiting and successfully treating bacterial infections. Drug intercalated anionic clays having specific properties as drug carriers have revolutionized nanodentistry particularly in drug controlled release systems. Due to their

special ability to penetrate biofilms and pathogen bacteria, nanoparticles type layered double hydroxides intercalated with antibiotic molecules acting as antimicrobial agents have gained a high reputation for controlling infectious diseases. Ampicillin loaded MgAlLDHs and ZnAlLDHs exhibiting antibacterial properties can be successfully used in medical applications especially in dentistry.

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