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Nanocomposites coated with xyloglucan for drug delivery: *In vitro* studies

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ABSTRACT

Enalaprilate (Enal), an active pharmaceutical component, was intercalated into a layered double hydroxide (Mg/Al-LDH) by an ion exchange reaction. The use of a layered double hydroxide (LDH) to release active drugs is limited by the low pH of the stomach (pH ~1.2), in whose condition it is readily dissolved. To overcome this limitation, xyloglucan (XG) extracted from *Hymenaea courbaril* (jatobá) seeds, Brazilian species, was used to protect the LDH and allow the drug to pass through the gastrointestinal tract. All the materials were characterized by X-ray diffraction, Fourier transform infrared spectroscopy, elemental analyses, transmission electronic microscopy, thermal analyses, and a kinetic study of the *in vitro* release was monitored by ultraviolet spectroscopy. The resulting hybrid system containing HDL–Enal–XG(3) slowly released the Enal. In an 8-h of test, the system protected 40% (w/v) of the drug. The kinetic profile showed that the drug release was a co-effect behavior, involving dissolution of inorganic material and ion exchange between the intercalated anions in the lamella and those of phosphate in the buffer solution. The nanocomposite coated protection with XG was therefore efficient in obtaining a slow release of Enal.

1. Introduction

Layered double hydroxides (LDHs) or hydrotalcite-like compounds are a family of natural or synthetic materials with a formulation of $[M^{2+}_{1-x}M^{3+}_{x}(OH)_2][A^{n-}]_{x/n}\cdot zH_2O$, where M^{2+} and M^{3+} are, respectively divalent and trivalent metals, and A^{n-} is the intercalated hydrated counter-anion (Wypych and Satyanarayana, 2004). These materials form successive positively charged layers, compensated by intercalation of hydrated negatively charged species. LDH has a structure similar to that of brucite (the common name for magnesium hydroxide, with a basal distance of 4.8 Å) and their interlayer distance depends on the size of the intercalated hydrated anion.

A wide variety of LDHs can be obtained by varying the M^{2+} and M^{3+} cations and the intercalated A^{n-} anion. Owing to the intercalation property of LDHs, many intercalation compounds, with a variety of anions of pharmaceutical interest such as salicylate, citrate, glutamate and aspartate, have been produced successfully using two different synthetic methods. There are anion exchanges or reconstruction after calcination of certain LDHs at mild temperatures (Tronto et al., 2001). Other organic anions of biological interest have also been intercalated into LDHs, such as sorbic acid (Meng et al., 2005), biocatalysts (Rahman et al., 2004, 2005), porphyrins (Halma et al., 2002; Wypych et al., 2003, 2005a; Wypych and Arizaga, 2005b; Nakagaki et al., 2005; Barbosa et al., 2005), vitamins (Hwang et al., 2001), amino acids and peptides (Gerstel et al., 2006), among others. These incorporate the combination of the properties of the drugs and LDHs, resulting in another route for drug administration.

Some LDHs are biocompatible systems (Cavani et al., 1991; Choy et al., 2000, 2001; Constantino and Nocchetti, 2001) and can be used in pharmaceutical technologies as drug supports or matrices (Khan et al., 2001). Once encapsulated, the drug can be released at a rate determined by controlling the pH. Mg/Al-LDH has already found pharmaceutical applications as excipients (Tomohisa and Mitsuo, 1998; Woo and Yi, 2000), drug stabilizers (Ueno and Kubbota, 1987; Doi et al., 1989), and drug delivery systems, in which anionic drugs are intercalated into LDH, which can be deintercalated under specific conditions in the form of a controlled release formulation. From this point of view, for example, ibuprofen (Ambrogi et al., 2001) and diclofenac (Ambrogi et al., 2002; Dupin et al., 2004), non-steroidal anti-inflammatory drugs, are used to relieve symptoms of osteoarthritis and rheumatoid arthritis, but whose use is often limited by the side effects in the central nervous system and gastrointestinal tract (Hoyo, 2007). Ambrogi et al. (2001) showed that ibuprofen anions exchange all chloride counter ions of a LDH structure, producing an intercalation compound with a drug load of about 50% (wt).

However, given the basicity of LDHs, their use in drug delivery systems is questionable for the stomach, where the pH is 1.2. To

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overcome this problem, a core–shell material was proposed by Li et al. (2004), where fenbufen was intercalated into LDHs as the core, which was coated with enteric polymers, Eudragit® S 100 or Eudragit® L 100, as a shell. The composite material was used in a controlled release of the drug under *in vitro* conditions simulating its passage through the gastrointestinal tract.

Xyloglucan (XG) is a polysaccharide found in the primary cell walls of non-graminaceous (monocotyledons) and in the cotyledon of some dicotyledonous seeds, where they have function as storage polysaccharides. Their chemical structure is a (1 → 4)-linked β-D-glucan backbone, substituted at O-6 by α-D-xylose branches, partially substituted in turn at O-2 by β-D-galactose units (Hayashi, 1989). Coviello et al. (2007) reviewed applications of the xyloglucan and related a relevant number of publications and patents for its use as a food additive, although much less has been published on its use in the field of pharmaceutics. However, a few examples, reported below, indicate a wide variety of applications, with numerous advantages compared with other macromolecular systems.

The XG from *Tamarindus indica* (commercial source) has been proposed for the formulation of sustained release of indomethacin suppositories and the results showed that the drug was effective over a longer period of time (Miyazaki et al., 1998). Furthermore, XG was used for oral administration of cimetidine (Miyazaki et al., 2001) and as a vehicle for sustained release of a percutaneous formulation of non-steroidal anti-inflammatory drugs (Takahashi et al., 2002).

In the present work, an active pharmaceutical component known as enalaprilate (Enal) was intercalated into a layered double hydroxide (Mg/Al-LDH) by an ion exchange reaction. To protect the LDH and allow the drug to pass through the gastrointestinal tract, was employed a xyloglucan extracted from *Hymenaea courbaril* (jatobá) seeds, collected from a native Brazilian plant The advantage of using this XG for the enteric coating is that is not necessary to carry out a pre-enzymatic treatment, as in the case of *T. indica,* since that it is unable to form a gel, so that to produce one, tamarindo XG was partially degraded by β-galactosidase, making it suitable for studies on drug release (Miyazaki et al., 1998, 2001).

Enalaprilate is the pharmacologically active metabolite of enalapril maleate (1-[N-[(S)-1-carboxy-3-phenylpropryl]-L-anayl]-L-proline 1′-ethyl ester, maleate (1:1)), an antihypertensive agent, which is an active inhibitor of angiotensine-I converting enzyme (ACE). This drug was listed officially in USP 23 (US Pharmacopeia, 1995). Examination of the literature did not reveal an example of slow release of this drug, using a coating vehicle as protection.

2. Materials and methods

2.1. Materials

The reagents were of analytical grade and used without further purification. Enalapril maleate was purchased from a Manipulation Pharmacy in Curitiba, State of Paraná, Brazil (Gerbrás, 99.3%, wt). Ultra-pure water, decarbonated by boiling, was used in all preparations. *H. courbaril* seeds, obtained from the State of Rio Grande do Norte, Brazil, were supplied by Embrapa/Colombo-PR (Empresa Brasileira de Pesquisa Agropecuária).

2.2. Extraction of xyloglucan

Xyloglucan was extracted by an exhaustive aqueous process at 25 °C of pooled and milled seeds (40 g/L for each extraction process). The viscous extract was centrifuged at 7000 × *g* for 20 min and the purified polymer was obtained as a precipitate, following addition to two volumes of 96% (v/v) ethanol (Freitas et al., 2003).

2.3. Synthesis of NO_3-containing Mg/Al-LDHs

An appropriate volume of NH_4OH (37%, v/v) was added dropwise, under a nitrogen atmosphere, to a solution containing $Mg(NO_3)_2{\cdot}6H_2O$ (0.17 mol) and $Al(NO_3)_3{\cdot}9H_2O$ (0.082 mol) in 300 mL of ultra-pure water (Mg/Al = 2.0), reaching a pH of about 9.0. The resulting slurry was stirred vigorously, aged at 25 ± 3 °C for 3 or 6 days (3-LDH-NO_3 and 6-LDH-NO_3, respectively). The samples were then centrifuged for 10 min at 7000 × *g*, washed four times with ultra-pure water and dried at 60 °C in a vacuum oven.

2.4. Intercalation of enalaprilate

Enalaprilate intercalated into LDH (LDH–Enal) was prepared by an ion exchange reaction. The pH of 100 mL of an ethanolic solution of enalapril maleate (1.70 mmol) was adjusted dropwise with NH_4OH (37%, v/v) up to pH 9.0, and 1.1 g of the pristine 6-LDH-NO_3 was added. The reactions were kept at 25 ± 3 °C for 3 days, then centrifuged for 10 min at 7000 × *g*, washed four times with ethanol, and dried at 25 ± 3 °C.

2.5. Preparation of hybrid material for releasing enalaprilate

LDH–Enal (70 mg) was added to 3.1 mL of 0.5% (w/v) or 0.5 mL of 3% (w/v) aqueous solutions of xyloglucan. The mixture was stirred for 2 h at 25 ± 3 °C, yielding the hybrid products named as LDH–Enal–XG(0.5) and LDH–Enal–XG(3), respectively. These volumes of suspensions were placed in a dialysis membrane to minimize the interference of XG in the solution for the drug release tests. The test with the sample free of XG was done with 15 mg of LDH–Enal.

2.6. Characterization

Powder X-ray diffraction (XRD) patterns were collected in a SHIMADZU XRD-6000 difractometer using Cu Kα radiation (λ = 1.5418 Å), with a scan step of 1° and scan range between 5° and 45°. Fourier transform infrared spectra (FTIR) were recorded in an Excalibur FTS-4000 Bio-Rad spectrometer using the KBr pellet technique with an accumulation of 32 scans. Calculate differential thermal analyses (DTA) and thermogravimetric analyses (TG) were carried out using a Mettler Toledo TGA/SDTA851^e apparatus. The analyses were conducted in a dynamic flux of oxygen (50 mL/min) at a heating rate of 10 °C/min. Elemental microanalyses were obtained on an Elementar Vario elemental analyzer. The amounts of Enal were determined by UV-absorption, at 215 nm, using a UV–vis Biospectro spectrometer. TEM micrographs were obtained using a JEOL 1200EX-II transmission electron microscope.

2.7. Rheological measurements

For intrinsic viscosity determinations, the XG samples (0.8–0.1 g/L) were solubilized in potassium chloride (0.1 mol/L) for 19 h (Williams, 1971). The Huggins equation was applied to determine the intrinsic viscosity [η] by extrapolation of (reduced viscosity) η_{red} to the limit of zero concentration ($c \rightarrow 0$), where the linear coefficient is represented by [η] (Huggins, 1942).

Oscillatory analyses, in the linear viscoelastic region, were obtained for XG samples (0.5 and 3%, w/v) solubilized in ultra-pure water at frequencies of 0.05, 0.1, 1.0, 5.0 and 10.0 Hz (deformation of 1%).

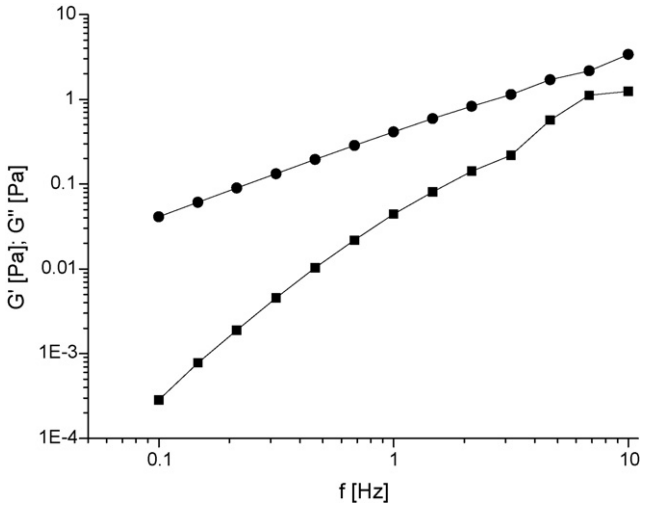

Fig. 1. Frequency sweeps of 0.5% (w/v) XG solution in ultra-pure water at 37 °C (●) G'' and (■) G'.

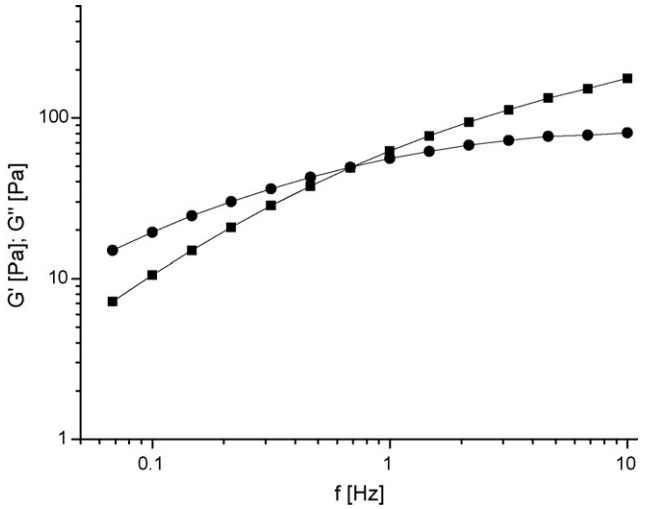

Fig. 2. Frequency sweeps of 3% (w/v) XG solution in ultra-pure water at 37 °C (●) G'' and (■) G'.

All the analyses were performed at 37 and 25 °C, using a Rheostress 600 rheometer, with a cone plate sensor C60/2°. A Haake DC 30 batch and a thermostatic Universal Temperature Control (UTC) were used to control the temperature.

2.8. Drug release measurements

The release rate of enalaprilate, for the systems LDH–Enal, LDH–Enal–XG(0.5) and LDH–Enal–XG(3), was measured at pH 5.0 (phosphate buffer), at 37 °C, over 120 min, as described in Section 2.5. The analyses were performed using membrane dialysis. Aliquots were removed at given intervals and replaced with fresh buffer solution. The drug concentration in the solution was determined by UV spectrometry at 215 nm. After these analyses, the best results were used to simulate the passage through the gastrointestinal tract, as previously indicated (Li et al., 2004).

3. Results and discussion

3.1. Characterization of the xyloglucan

The aqueous extraction of milled seeds from *H. courbaril* yielded 24% (w/w) of XG based on the whole seeds. The intrinsic viscosity [η] was calculated as 786.7 mL/g and *K*'s (Huggins' constant) as 0.6. The *K* value indicated that 0.1 mol/L aqueous KCl was a good solvent, increasing the interaction solute/solvent and decreasing intermolecular interactions (Rinaudo and Milas, 1991).

In Fig. 1 is possible to observe the rheological behavior of the 0.5% (w/v) XG solution. The result showed that the G'' (storage modulus) was higher than G' (elastic modulus) for all frequencies ranges, indicating that the system has a liquid behavior. On increasing the concentration to 3% (w/v), the result showed the formation of a viscoelastic system (Fig. 2); since that at lower frequencies the G'' was higher than G', and by increasing the frequency the difference between the two modulus became smaller, with a crossover after 0.8 Hz, when the G' was higher than G''. This behavior is typical for a concentrated polymer solution (Lapasin and Pricl, 1995). To confirm the formation of a viscoelastic system, a Coz–Merz analysis was performed (Fig. 3). It can be observed that XG, at a concentration of 3% (w/v), does not really form a gel, having only the aspect of a viscoelastic solution, since that dynamic viscosity was higher than the dynamic complex viscosity (Bot et al., 2001; Roberts and Cameron, 2002).

3.2. Characterization of the nanocomposite

The XRD pattern for LDH-NO_3 is shown in Fig. 4a, with diffraction peaks typical of layered structures (Hofmeister and Platen, 1992). The basal spacing, which was 8.9 Å for both 3-LDH-NO_3 and 6-LDH-NO_3 samples, corresponds to the sum of the ionic diameter of 4.1 Å of the nitrate anion accommodated in the interlayer space and the brucite-like layer thickness of 4.8 Å. The intensity and narrowness of the peaks for the 6-LDH-NO_3 after 6 days of aging was higher than that of the 3-LDH-NO_3 after 3 days, indicating a higher crystallinity, so that this sample was chosen for enalaprilate intercalation. An increase in the basal distance from 8.9 to 13.0 Å, as indicated in Fig. 4b, confirmed the intercalation of the enalaprilate between the layers. The presence of crystalline enalapril maleate is excluded, as it can be seen from the XRD pattern in Fig. 4c.

Fig. 5 shows the respective FTIR spectra of samples containing LDH–Enal, LDH-NO_3, LDH–Enal–XG(3), enalapril maleate and xyloglucan. Pure enalapril maleate (Fig. 5d) gave rise to many intense peaks and sharp absorption bands corresponding to the different functional groups existing in this molecule, i.e., the aromatic ring, carboxylic group, ester group, carbonyl of tertiary amide,

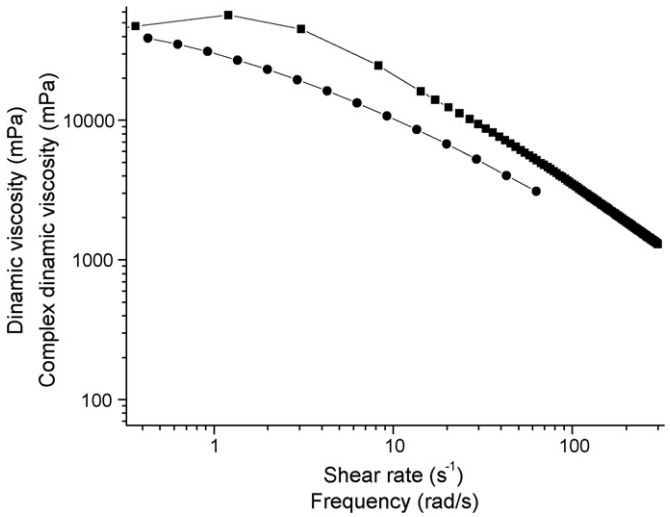

Fig. 3. Coz–Merz plot of 3% (w/v) XG solution in ultra-pure water at 37 °C, (■) dynamic viscosity and (●) complex dynamic viscosity.

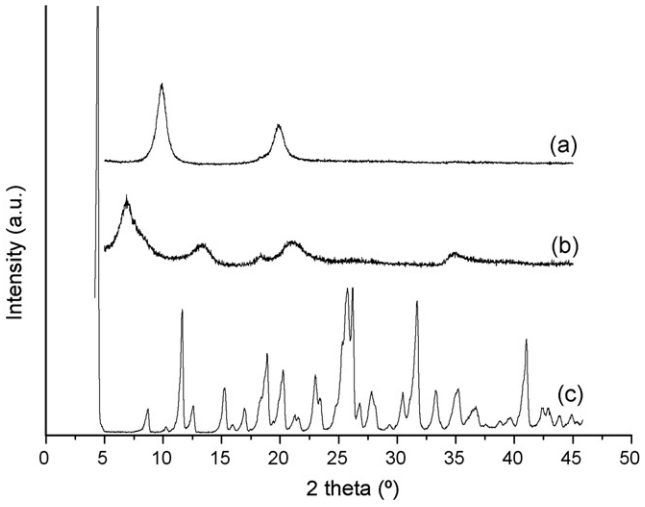

Fig. 4. X-ray diffraction patterns of (a) LDH-NO_3, (b) LDH–Enal, and (c) enalapril maleate.

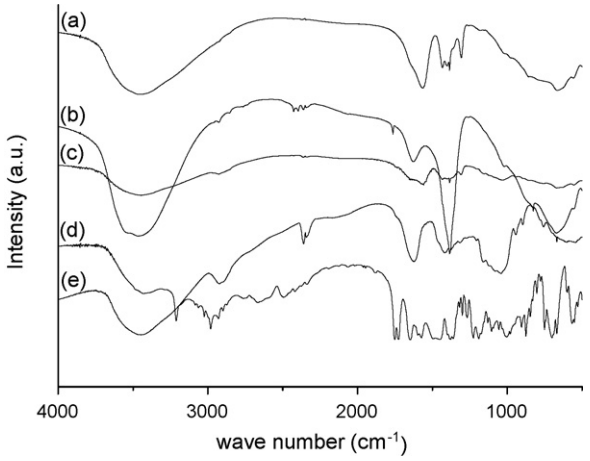

Fig. 5. FTIR spectra of (a) LDH–Enal, (b) LDH-NO_3, (c) LDH–Enal–XG, (d) enalapril maleate, and (e) XG.

amino and methyl group (Lin et al., 2002). The LDH–Enal spectrum (Fig. 5a) shows a wide band of about 3500 cm^{-1}, due to the stretching modes of the N–H, C–H and O–H groups. The intense bands and sharp peaks at 1566 and 1310 cm^{-1} were attributed to stretching modes of carboxylate groups (asymmetric ν and symmetric ν, respectively). The bands corresponding to the ν(C–C) stretching modes of the aromatic ring were between 1600 and 1450 cm^{-1}, while the bands corresponding to the deformation mode δ (N–H) of the amino groups were from 1650 to 1550 cm^{-1}, and those of the methyl group $\nu(CH_3)$ were between 1470 and 1430 cm^{-1}. This proximity of the positions of the bands from different groups made it very difficult to assign the bands more precisely. All the materials gave distinct peaks corresponding to the OH vibrations of about 3500 cm^{-1}, which was present in the LDH layer and the biopolymer chain. It was also found that the exchange reaction was incomplete since nitrate anions were still present, as indicated by the band at 1383 cm^{-1}. The xyloglucan (Fig. 5e) and LDH–Enal–XG (Fig. 5c) spectra show the C–O–H stretching mode, which is specific for carbohydrates.

Fig. 6 shows the TG/DTA curves of 6-LDH-NO_3 and LDH–Enal, respectively. The TG analysis of the 6-LDH-NO_3 reveals distinguishable weight loss steps and corresponding endothermic peaks (DTA analysis). The weight loss in LDH-NO_3 (Fig. 6a), that occurred between 25 and 295 °C, can be attributed to the removal of physisorbed surface water molecules and the loss of 19.17% (wt) to intercalated water, which was followed by three endothermic peaks at around 91, 150 and 255 °C, in the DTA profile. The second step (295–550 °C) was attributed mainly to the endothermic phenomena of dehydroxylation of the LDH layer and release of intercalated nitrate anions (loss of 36.99%, wt), and consequently, formation of oxides (residue of 43.84%, wt). The product obtained from the LDH-NO_3, based on the data from the thermal analysis, is consistent with the expected formula $Mg_{0.67}Al_{0.33}(OH)_2(NO_3)_{0.33}\cdot 1.07H_2O$.

The DTA curve of LDH–Enal (Fig. 6b) showed two endothermic peaks. The first at 90 °C, was attributed to the removal of adsorbed/absorbed water molecules in the crystallite surfaces, while the second at about 255 °C, was attributed mainly to the intercalated water molecules, which need more energy to be released from the interlayer space. The total mass loss of water, occurring up to 295 °C, was ascribed mostly to the endothermic peaks (25.09%, wt). The mass loss between 295 and 470 °C simultaneously to the exothermic peak at about 400 °C corresponds to combustion of the intercalated enalaprilate. In this range also occurred dehydroxylation of the layers and loss of nitrate anions (33.62%, wt). Above this temperature, formation of metal oxides (residue of 41.29%, wt) occurred.

The mass of Enal in the LDH–Enal cannot be calculated from the TG profile since it occurs near to the loss of hydroxyl and nitrate ions. However, quantification carried out by UV–vis spectroscopy and elemental analysis indicated contents of 13.7 and 14.6% (wt) of

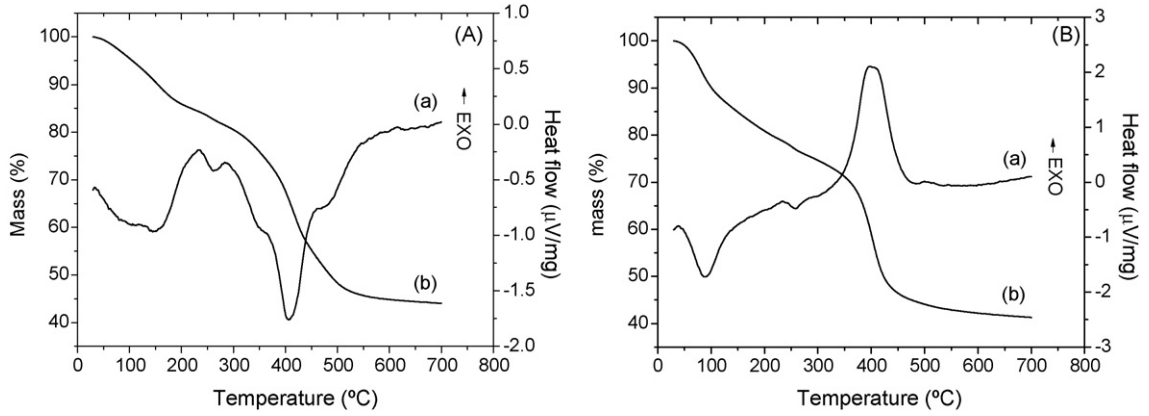

Fig. 6. DTA (a) and TG (b) analyses of LDH-NO_3 (A) and LDH–Enal (B).

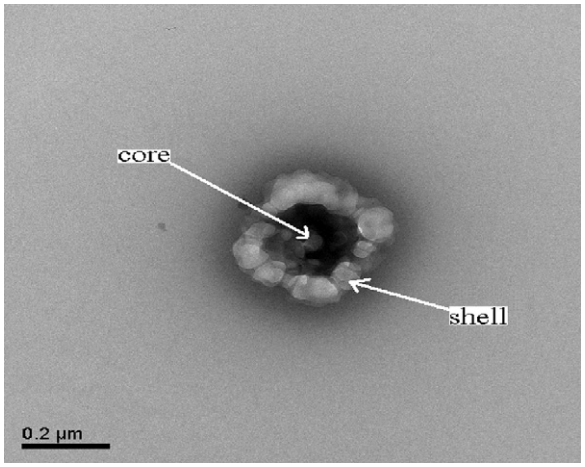

Fig. 7. TEM photograph of LDH–Enal–XG(0.5) microcomposite with inorganic material (core) and XG (shell).

Enal, respectively. Therefore, the average of these values was used to calculate the composition of the intercalation compounds. The general formula of LDH, based on the above data, is proposed to be $Mg_{0.67}Al_{0.33}(OH)_2(C_{18}H_{22}N_2O_5)_{0.047}(NO_3)_{0.236}\cdot 1.39H_2O$.

In the LDH–Enal, the negative charges of enalaprilate ion would be directed to the positive charges of the layers, defining the interlayer expansion. Since the charge density of layers must match those of the negative species positioned between the layers, it is reasonable to expect that nitrate ions are needed to compensate for the extra charges of the layers.

Figs. 7 and 8 illustrate the TEM micrograph of LDH–Enal–XG(0.5) and LDH–Enal–XG(3), respectively. The main difference between the two figures is that Fig. 7 corresponds to the composite with 0.5% XG, whose particles is in micrometer scale, whereas Fig. 8 is that of composite with 3% XG in nano-scale. In addition to the composition and size differences, the nanometric particles are heterogeneous, because besides the core–shell system, particles of pure XG are also found. However, in both the samples is possible to observe the dark LDH–Enal core coated with a lighter XG shell.

3.3. Release of enalaprilate from LDH–Enal

In Fig. 9, the results of *in vitro* studies of drug released from the LDH–Enal, LDH–Enal–XG(0.5) and LDH–Enal–XG(3) systems, at pH

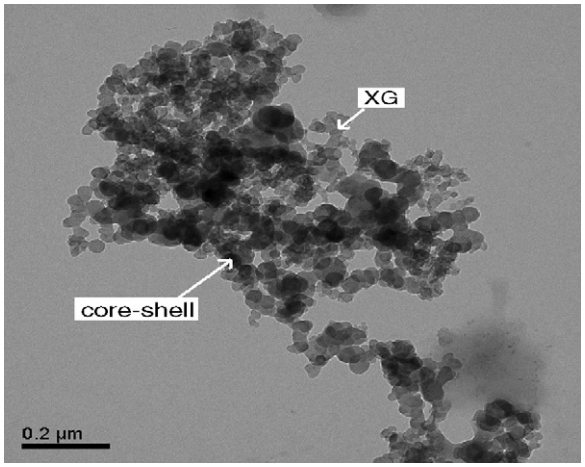

Fig. 8. TEM photograph of LDH–Enal–XG(3) nanocomposite with inorganic material (core) and XG (shell).

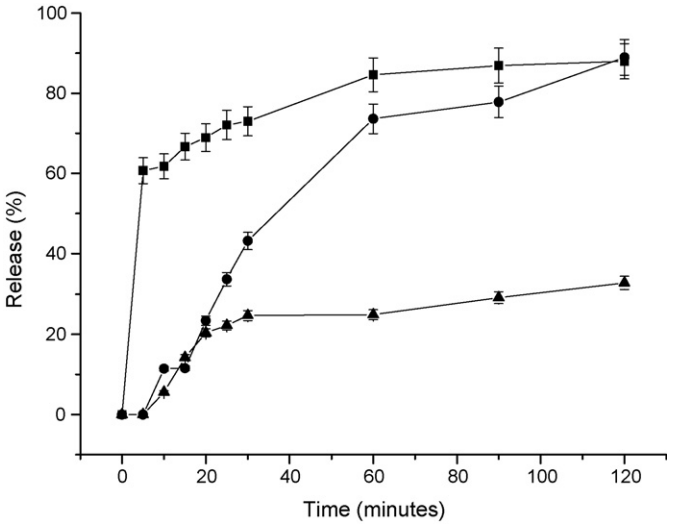

Fig. 9. Release profiles of enalaprilate at pH 5.0 (■) LDH–Enal, (●) LDH–Enal–XG(0.5), and (▲) LDH–Enal–XG(3).

5.0 during 120 min of analysis, can be compared. In the absence of xyloglucan the release of the drug was very rapid, in the first 5 min, which was attributed to the partial dissolution of the LDH layer in the weakly acidic solution (Zhang et al., 2006). Between 5 and 60 min, the Enal was slowly released up to a total of 80% (w/v). Afterwards no significant drug release was detected. The coating with 0.5% (w/v) XG (LDH–Enal–XG(0.5)) did not enhance the protection of Enal at pH 5, since up to 60 min 70% (w/v) of drug was released, similar to the non-coated system. This might be caused by the liquid behavior of the XG sample, as characterized by rheology. With the increase of XG concentration (3.0%, w/v), a viscoelastic system was obtained, and the coating with XG (LDH–Enal–XG(3)) enhanced the protection of Enal, since up to 2 h, only 30% (w/v) of drug was released. This formulation was selected to simulate the passage through the gastrointestinal tract.

In Fig. 10, whose pH was initially kept at 1.2 for 2 h, then 6.8 for 2 h, and finally 7.4 for 4 h, the total time of analysis was 8 h. It is possible to observe the fast dissolution of the LDH–Enal at pH 1.2 and the total release of the enalaprilate after 2 h. This behavior was expected, because the LDH layers would be destroyed in

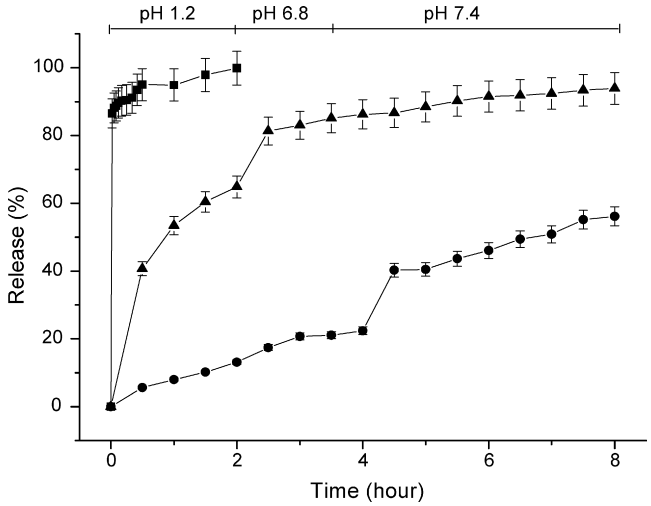

Fig. 10. Release profiles of enalaprilate from simulation of the gastrointestinal tract (■) LDH–Enal, (●) LDH–Enal–XG(3), and (▲) Enal–XG(3).

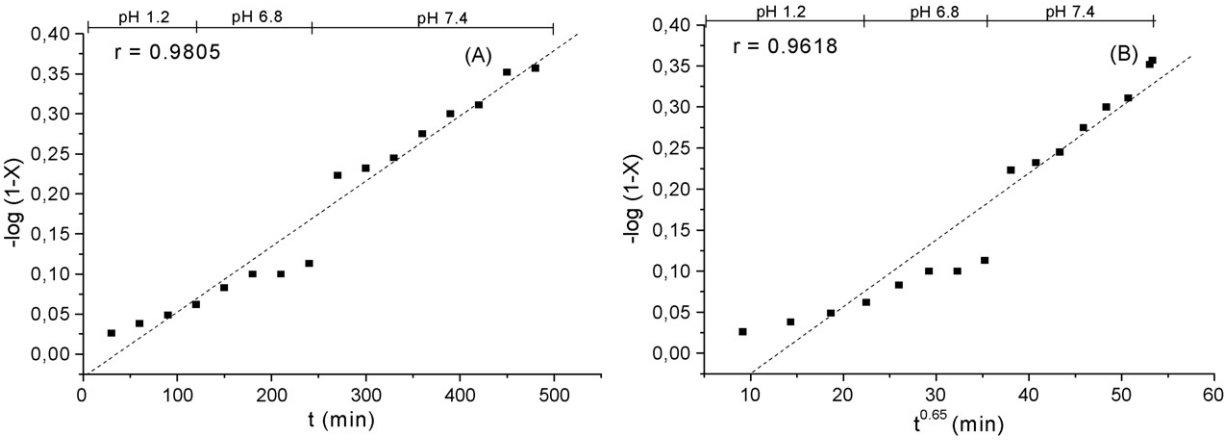

Fig. 11. Fitting the enalaprilate release data to different kinetic models (A) first-order model and (B) Bhaskar model, for the sample LDH–Enal–XG(3).

acidic media. When only the Enal–XG(3) system in the absence of HDL was used, after pH 1.2 (2 h) 80% (w/v) of the drug was released. However, for the LDH–Enal–XG(3) system, the release was slower (less than 60%, w/v, of enalaprilate in 8 h of analysis). This result suggests that the complete dissolution of the biopolymer and the deintercalation of Enal from LDH, decreased hydrogen bonding between the biopolymer and the surface of the LDH (Li et al., 2004). Between pH 6.8 and 7.4 the XG coating swelled and let the water go through, slowly, which was also favorable to ion exchange (hydroxyl by phosphate). Thus, the protection of the drug is enhanced by the core–shell structure formed by the XG coating the LDH–Enal nanocomposite.

The drug release in the LDH-drug system can be consistent with either with dissolution of LDH particles or by deintercalation of the interlayer species. When the drug release fraction is lower than 0.85, the Bhaskar equation (Eq. (1)) can be used to evaluate whether the diffusion through the particle is the rate-limiting step. The other equation used is the first-order (Eq. (2)), which is normally used to describe dissolution phenomena (Ambrogi, 2002)

$$-\log(1-X) \text{ versus } t^{0.65} \quad (1)$$

$$-\log(1-X) \text{ versus } t \quad (2)$$

Where X is the released fraction and the release time.

Fig. 11A and B shows results for LDH–Enal–XG(3). In the first-order model shown in Fig. 11A, the correlation factor of linear regression was 0.9805, and linear correlation in the Bhaskar model 0.9618 (Fig. 11B). It can be observed that the release of Enal conforms more with the first-order model than that of Bhaskar. These results can be explained based on those of Zhang et al. (2006), who discussed the possibility of drug release having a co-effect behavior, including dissolution of inorganic material and ion exchange between the intercalated anions in the lamella host and the phosphate anions in the buffer solutions.

4. Conclusions

The development of a hybrid system by intercalation of enalaprilate (Enal) between the layers of layered double hydroxide, and coating with 3% (w/v) xyloglucan protects throughout 40% (w/v) of drug at the end of the analysis (8 h), simulating its passage through the gastrointestinal tract. With this performance, the above-described formulation (LDH–Enal–XG(3)) could be used for slow drug release, especially when it is needed in other parts of the gastrointestinal tract. This is important when one considers hypertensive individuals and the amount of medicine that they ingest. In a system of slow release, individuals could reduce the amount of ingested drugs, reducing the stress factor and improving their quality of life.

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