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Research paper

Smectite as ciprofloxacin delivery system: Intercalation and temperature-controlled release properties

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ABSTRACT

Clays have shown to be good candidates as drug delivery carriers. In the present paper, the temperature-dependent swelling of smectites was exploited to obtain composites able to release a drug in a controlled way. More specifically, synthetic fluorohectorite-ciprofloxacin composites were prepared, in which the drug molecules were intercalated between the clay layers. The drug-release systems were characterized by X-ray diffraction (XRD), infrared spectroscopy (IR), thermal gravimetric analysis (TGA), ultraviolet spectroscopy (UV) and atomic absorption spectrometry (AAS). The results from the X-ray diffraction allowed confirming the ciprofloxacin incorporation into the interlayer space, and the results from UV spectroscopy indicated that more than 90% of the initial drug was uptaken by the clay. The thermally activated drug release from a colloidal dispersion of nanosized composite particles in both pure water and synthetic gastric juice was evaluated at temperatures from 37 °C (body temperature) to 85 °C. The studies indicated that the clay promotes the slow release of ciprofloxacin, and that the release of drug increases with both time and temperature. The profiles of drug-release from the clay fulfilled the pharmaceutical standards for these systems. As a result, a clay-based Temperature-Controlled Release System (TCRS) with potential biomedical applications has been obtained.

1. Introduction

Clays and clay minerals have been widely used for medical purposes. For example, they can be found in pharmaceutical formulations, both as inactive (excipients) and active agents (drugs) (Carretero, 2002; López-Galindo and Viseras, 2004; López-Galindo et al., 2007; USP30-NF25, 2007; Viseras et al., 2007). The therapeutic uses of these materials (López-Galindo and Viseras, 2004) are associated to their chemical and physical properties, which depend ultimately on their structure.

Temperature–controlled drug release is desirable in many scenarios: for example, when the local body temperature varies during different stages of a disease, or in response to external stimuli. To date, just a few materials able to release an active principle as a function of temperature have been investigated. Recently, hydrogel-based composites have been created to release proteins (Wu et al., 2005; Kang and Song, 2008), as well as microscale polymers able to release small molecules and nanoparticles within a certain temperature range (Hyun et al., 2013).

In recent years, different porous materials have been used as drug hosts (Rivera and Farías, 2005; Joshi et al., 2011). In particular, clay minerals and their modified forms have been employed in the development of new drug delivery systems (Viseras et al., 2010). Among them, montmorillonite has been the most commonly used for drug delivery applications (Park et al., 2008; Joshi et al., 2009), although kaolinite and laponite have also been investigated (Hamilton et al., 2014). Most of them have been typically used as hosts for pH-controlled release.

Synthetic hectorites show a number of advantages as drug hosts, like controllable pore-size distribution, as well as purity and composition, which result in higher reproducibility. In addition, these materials have shown to be non-toxic for trans-dermal application and oral administration (Takahashi et al., 2005; Joshi et al., 2011). Their swelling transition (Hansen et al., 2012), on the other hand, suggests their

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potential as hosts of large molecules of pharmaceutical interest and their temperature–controlled release. However, few reports about the use of fluorohectorite, a commercially available synthetic smectite, as a drug-hosting material, can be found in the literature (Jung et al., 2008; Park et al., 2008; Joshi et al., 2011). From a structural point of view, in their dry form, fluorohectorite layers assemble to form stack-of-card-like particles. The stacks are held together by van der Waals forces, and by electrostatic forces in the case of clays with negative layer charges. In the interlayer space of these clays, there are positive counter-ions, leading to an attractive interaction similar to a salt bridge (Franchi et al., 2003; Bosshard et al., 2004); water can be also located between lamellae (da Silva et al., 2003; Anderson et al., 2010).

Ciprofloxacin (1-cyclopropyl-6-fluoro-4-oxo-7-(*l*-piperazinyl)-1,4dihydroquinoline-3-carboxylic acid) belongs to the quinolone class of semisynthetic antibiotics and is orally administrated to patients in its hydrochloride salt form. Ciprofloxacin is a potent and broad-spectrum antibiotic with high antibacterial activity against most gram-negative bacteria and gram-positive cocci (Wolfson and Hooper, 1985; Hoogkamp-Korstanje, 1997). Although the incorporation of ciprofloxacin (Cipro) into clays has been reported, the use of a temperature–dependent swelling clay as host for Cipro has not been investigated. The present work focuses on the intercalation of Cipro into the interlayer space of a Li-fluorohectorite (LiFh) to sustain the controlled release of the drug. The molecular structure of Cipro is shown in Fig. 1. The drug-loaded LiFh was characterized using several experimental techniques. The in vitro drug release study from the colloidal composite dispersion was investigated in diverse media and at different temperatures. The obtained composites will be called *Temperature–Controlled Release Systems* (TCRS).

2. Experimental

2.1. Starting materials

The chemical composition of synthetic fluorohectorite is $M_x(Mg_{6-x}Li_x)F_4Si_8O_{20}$, where the exchangeable cations are denoted by M. These clay particles are polydisperse with lateral dimensions of the order of μm, and they possess a net negative surface charge (x e^- per unit cell), which is balanced by counter-ions localized between clay lamellar sheets. Ideally x = 1.2 (Kaviratna et al., 1996).

Li-fluorohectorite (LiFh) was purchased from Corning Inc., New York, and characterized by X-ray diffraction (XRD) and atomic absorption spectrometry (AAS) using the procedures described later on. From those studies, it was concluded that the purchased material contained about 80% by mass of LiFh clay described by the nominal formula $Li_x(Mg_{6-x}Li_x)Si_8O_{20}F_4$ with x = 1.2, and about 20% of $Li_2O{\cdot}2SiO_2$ impurities.

Cipro in the form of ciprofloxacin hydrochloride ($C_{17}H_{19}ClFN_3O_3$), acetaminophen ($C_8H_9NO_2$) and ibuprofen ($C_{13}H_{18}O_2$)—pharmaceutical grade according to the United States Pharmacopoeia (USP30-NF25, 2007)—were the model drugs studied; they were used as received from the Cuban pharmaceutical industry. All other chemicals used in the study were analytical grade.

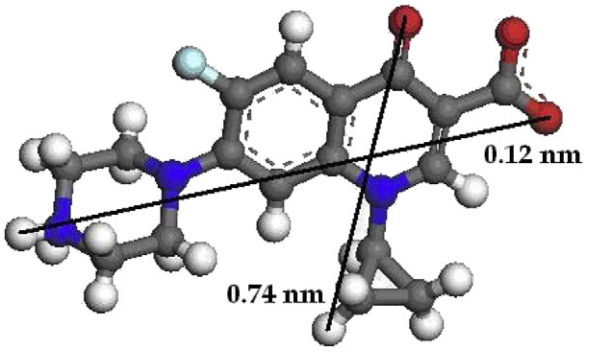

Fig. 1. Molecular structure of the ciprofloxacin drug molecule.

2.2. Sample preparation

For the interactions, 50 ml of drug solutions at 3 mg/ml (pH near 4.5) was put in contact with 0.5 g of each clay. The experiments were carried out at room temperature and at 65 °C ± 5 °C during 4 h and 24 h, in order to study the influence of temperature and time on the amount of drug captured by the clays. All these studies took place under agitation with a magnetic stirrer. By the end of the interactions, the pH of the Cipro-clay dispersions was around 8. In the case of drug adsorption in the dispersions, the drug's concentrations before and after the contact with the clays were analyzed and quantified by ultraviolet spectroscopy (UV), according to standard procedures (USP30-NF25, 2007) (the drug-clay dispersions were centrifuged, and the drug contents in the supernatant was determined by UV relative to calibration curves for the pure drug solutions). The UV spectra were collected by means of a Rayleígh UV-2601 spectrophotometer in the wavelength interval 200–400 nm (including the adsorption maxima at 276, 245 and 273 nm for the Cipro, acetaminophen and ibuprofen, respectively). Each composite LiFh-Cipro was prepared in five batches and the analysis was replicated three times for each one, in order to check repeatability. The maximum difference between the outputs and their average was of 10 mg, corresponding to a relative uncertainty of approximately 3% in the mass of incorporated drug. As demonstrated below, the UV studies showed that, among the drugs investigated, only Cipro is significantly captured by the clay, so further characterization was performed only on Cipro-clay composites.

2.3. Chemical and physical characterization

For atomic absorption spectrometry (AAS) measurements, 0.1 g of LiFh was digested overnight using HCl, HF and $HClO_4$ in 100 ml of water. After that, the dissolutions were analyzed by means of standard AAS (PYE UNICAM SP9). The whole process was replicated five times.

X-ray diffraction (XRD) for the different clays before and after the drug adsorption, was conducted on a Philips Xpert diffractometer, using Cu Kα radiation (λ = 1.54 Å) at room temperature, operating at a voltage of 45 kV and working current 25 mA. The experiments were done at a scan rate of 1° min^{-1} for a 2θ range spanned from 2 to 40°.

The solid clay samples were analyzed by thermal gravimetric analysis (TGA) and infrared spectroscopy (IR) before and after interaction with the Cipro. TGA was performed on a NETZSCH STA 409 PC/PG thermal analyzer under dry air flow (50 ml/min), and a heating rate of 10 °C/min, from 20 up to 800 °C. The sensitivity of the thermobalance was ± 1 μg. To perform IR analysis, the solids were dried overnight in an oven at 100 °C and 65 °C for the native clay and the clay-drug composite, respectively (the lower temperature used in the case of the composite avoids Cipro decomposition). A Nicolet AVATAR 330 Fourier-transform IR spectrometer, in the wavenumber interval 400–4000 cm^{-1} with a resolution of 2 cm^{-1}, was used. The samples were prepared using the KBr pressed-disk technique, with 0.8% inclusion of the material to be analyzed.

2.4. Drug release assays

The studies of Cipro release from the composites were carried out for the LiFh clay. About 30 mg of the powdered composite (equivalent to 8.3 mg of Cipro determined by UV as described before) was put in contact with 50 ml of synthetic gastric juice without pepsin at 37 ± 1 °C—according to the method reported in the Pharmacopoeia for this kind of system (USP30-NF25, 2007), and 100 rpm stirring. Release studies under identical conditions but at 65 ± 5 °C were also carried out in order to evaluate the temperature dependence of the Cipro release from