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Incorporation of *tramadol* drug into Li-fluorohectorite clay: A preliminary study of a medical nanofluid

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Abstract. During the last years, clays have been increasingly explored as hosts for drugs. In the present paper, we have been able to host the non-steroidal anti-inflammatory drug, *Tramadol*, into the clay Li-fluorohectorite (Li-Fh). We preliminary evaluate its incorporation by means of UV spectroscopy and X ray diffraction. Our results indicate that the clay hosts the drug molecule in its interlayer space. We suggest a set of parameters to guarantee an efficient incorporation process. Future studies will concentrate on the release of the drug from the clay nanofluid.

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1 Introduction

The non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of minor pain and for the management of edema and tissue damage resulting from inflammatory joint disease [1]. A number of these drugs possess antipyretic activity in addition to having analgesic and anti-inflammatory actions. In general, NSAIDs structurally consist of an acidic moiety (carboxylic acid, enols) attached to a planar, aromatic functional group, as illustrated for *tramadol* (TM) in Fig. 1. As for many other drugs, the controlled release of NSAIDs from physiologically-friendly hosts is highly desirable [2]. Our group has re-

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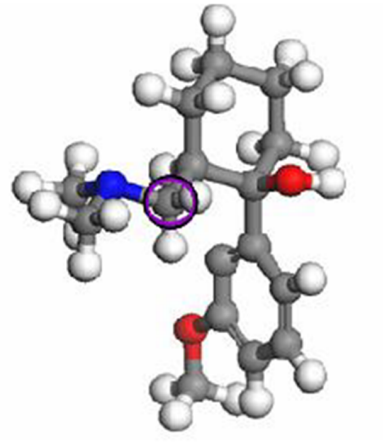

Fig. 1. Chemical structure of pure tramadol. Gray, white, blue and red spheres represent carbon, hydrogen, nitrogen and oxygen, respectively. A free-rotation carbon is encircled. The dimensions of the molecule are approximately 1.0 nm × 0.8 nm.

cently demonstrated that the synthetic clay Li-fluorohectorite (LiFh) has a temperature-controlled layered structure able to contain organic molecules, so it constitutes a good candidate to be used as drug host [3].

In this work we test the ability of the synthetic clay Li-fluorohectorite (LiFh) nanoparticles to host a widely used NSAID drug: *tramadol*.

2 Experimental

The tramadol hydrochloride (pharmaceutical-grade according to Pharmacopoeia [4]) was used as received from the Cuban pharmaceutical industry. The Li-fluorohectorite (LiFh) clay was purchased in powder from Corning Inc., New York. It contains about 80 percent by mass of LiFh clay with nominal formula $Li_x(Mg_{6-x}Li_x)Si_8O_{20}F_4$ with x = 1.2, and about 20 percent of $Li_2O.2SiO_2$ impurities [3].

For the drug incorporation process, 10 ml of TM aqueous solutions were put in contact with 0.1 g of LiFh powder with continuous stirring. After the interaction, the mixture was centrifuged for 15 min at 300 rpm. The resulting LiFh-TM suspensions after interaction (i.e., drug solutions) were analyzed and quantified by UV-vis spectroscopy, according to standard procedures [4]. The UV spectra were collected by means of a Raylegh UV-2601 spectrophotometer in the wavelength interval 200-400 nm (adsorption maxima at 271nm).

Influence of pH in the drug incorporation Experiments at different pH values of clay-drug suspensions were performed to determine the optimum pH for intercalation of the drug molecule into the LiFh interlayer nanospace (i.e., those pH values at which the TM amount into the LiFh was maximum). For this purpose, the suspensions were treated at pH values around 4, 7 and 10 at room temperature (25±1^{o}C), for two hours of interaction. The initial concentration of drug was 2mg/ml.

Influence of initial drug concentration These experiments were performed to determine the maximum amount of drug incorporated into the LiFh as a function of the initial concentration of TM. The interaction process TM-LiFh took place at initial concentrations of the drug between 3 mg/ml and 8 mg/ml at acid pH, at 25±1^{o}C and 2h of interaction.

Effect of temperature This study allowed to determine the optimum temperature of TM incorporation into

LiFh. The suspensions drug-clay were evaluated at different temperatures (between 25±1^{o}C and 65±1^{o}C), at acid pH, TM concentration of 2 mg/ml for 2 h, and permanent agitation.

All the interaction experiments were performed in triplicate and the average values were used for data analysis.

The true incorporation of the drug into the inter-layer space of the clay was evaluated using XRD analysis of the solid samples. Diffraction patterns of samples in powder form were obtained by means of a *Philips Xpert* diffractometer, using CuK$_\alpha$ radiation (λ = 0.154 nm) in the angular range $2^o \leq 2\theta \leq 40^o$.

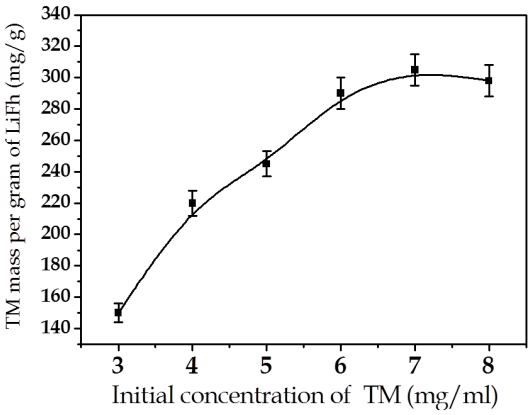

Fig. 2. Dependence of the incorporation of tramadol into LiFh on the initial concentration of the drug.

3 Results and discussion

Tramadol hydrochloride (TM) showed a sizable incorporation into the clay for certain pH values, as seen in Table 1: neutral and acid pH implied an incorporation of roughly 50 percent of the initial mass of TM. Based on that results, we decided to further explore experimental parameters always working at acid pH. It is worth noting that low pH values allows the "protonation" of the drug, which facilitates the interaction with the negatively charged clay layers (- 1.2 electron charges per unit cell).

Figure 2 shows the dependence between the initial concentration of TM and the amount of TM incorporated into the LiFh. In the graph it is observed that at concentrations bigger than 6mg/ml the amount of TM incorporated remains almost constant. So, taking into account the efficiency of the process we decide to work at initial concentration of 6mg/ml.

In Figure 3, X-ray diffractograms for LiFh and for the drug-clay composite (LiFh-TM) are shown (the composite was prepared at at acid pH of about 4, initial TM concentration of 6 mg/ml, and 25±1^{o}C). In the XRD diffraction pattern of the Li-Fh, the peak at $2\theta = 7.30\ ^o$ corresponds to the 001 plane. The interlayer distance corresponding to this angle, calculated according to Bragg's Law, is 1.2 nm (see peak labeled (a) in Figure 3). This value agrees with that reported in the literature for LiFh with one layer of water intercalated in the stacks in ambient conditions [5]. The XRD pattern for LiFh-TM, shows an intense, well defined peak labeled as (c) which we assign to one tramadol molecule incorporated into the interlayer space of the Li-Fh: it's size much bigger than the water molecule implies a shift of peak (a) towards smaller diffraction angles. The small "shoulders" identified as (b) and (d) may be assigned to two water molecules, and to one tramadol

Table 1. Effect of pH in the incorporation of tramadol into Li-Fh

pH	∼4 (acid)	∼7(neutral)	∼10(basic)
TM incorporation (mg TM/g Li-Fh)	140±5	150±5	75±5

molecule plus two water molecules intercalated between the clay layers, respectively [3]. We thus believe that LiFh hosts tramadol by true intercalation in the interlayer space of the clay.

Finally, we discuss the temperature dependence of the drug incorporation. The mass of drug incorporated into the clay does not evidence a significant temperature dependence: the number of mg of TM incorporated per gram of LiFh at 25^{o}C and 65^{o}C are around 285±8 mg/g. This result is somewhat unexpected if we take into account that LiFh is "thermally activated" near 65^{o}C: recently Hansen *et al.* have reported novel observations of the transition from a "passive", or not swell able clay, to "active" or swell able induced by temperature [6]. Previous work by our group demonstrated that the incorporation of the molecule model ciprofloxacin (Cipro) in an"active" LiFh is temperature-dependent [3]. Based on this, one might think that the addition of any drug could depend on the temperature, which appears not to be the case of tramadol. However, while the dimensions of the Ciprofloxacin molecule are slightly bigger than the interlayer spacing of LiFh at room temperature, the dimensions of the tramadol molecule are not (see Fig. 1). This means that a "temperature activated opening" of the layered structure of the

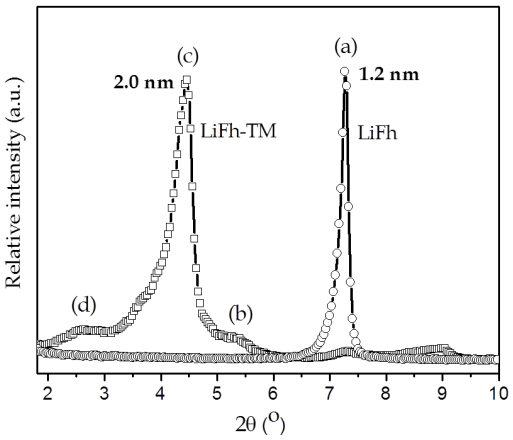

Fig. 3. Relevant peaks in the X-ray diffractograms of pure LiFh (circles) and tramadol-LiFh composite (squares).

LiFh is not crucial to the incorporation of tramadol. In addition, due to the existence of "free-rotation" carbon atoms in the tramadol structure (Fig. 1) suggests that, when in solution, the molecule may adopt conformations that easy the entrance into the LiFh interlayer spacing, without the need of thermally activated increase of the interlayer spacing.

4 Conclusions

We have shown that the non-steroidal anti-inflammatory drug, tramadol, can be incorporated into the interlayer space of lithium fluorohectorite clay nanopoarticles, in nanofluidic conditions. After optimization of the basic parameters for the obtention of the clay-drug nanocomposite, we recommend to put in contact the LiFh clay with a TM solution of 6 mg/ml at acid pH for 2 h at room tem-

perature (25 $\pm 1^{o}$C). The study of drug release from the composite in conditions similar to the fluids of the human stomach are now in progress.

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