Applied Clay Science 161 (2018) 395–403

Contents lists available at ScienceDirect

Applied Clay Science

journal homepage: www.elsevier.com/locate/clay

Research paper

Synthetic clay mineral as nanocarrier of sulfamethoxazole and trimethoprim

D. Hernández[a], L. Lazo[a], L. Valdés[b], L.C. de Ménorval[c], Z. Rozynek[d], A. Rivera[a,*]

[a] Zeolites Engineering Laboratory, Institute of Materials Science and Technology (IMRE), University of Havana, Cuba
[b] Department of Pharmacy, Institute of Pharmacy and Food (IFAL), University of Havana, Cuba
[c] Institut Charles Gerhardt Montpellier, Equipe Agrégats, Interface, et Matériaux pour l'Energie (AIME), Université Montpellier 2, France
[d] Faculty of Physics, Adam Mickiewicz University, Poland

ARTICLE INFO

Keywords:
Sulfamethoxazole
Trimethoprim
Antibiotics
Li-fluorohectorite
Synthetic clay mineral

ABSTRACT

In the present work the incorporation of two model drugs, sulfamethoxazole (SMX) and trimethoprim (TMP) on the Li-fluorohectorite (LiFHt), synthetic clay mineral was evaluated. Understanding the interactions established between these two antibiotics – which are complementary forms from the pharmaceutical point of view – and LiFHt, allows to develop new drug delivery formulations with both drugs in the same support. The quantification of both drugs was followed by ultraviolet (UV) spectroscopy. For the interaction clay mineral-drugs, different physical-chemical parameters – pH, drug initial concentration, temperature and interaction time – were studied. The results showed that, for both drugs, the best clay mineral-drug nanocomposites were obtained at acid pH, room temperature during 1 h, and initial drug concentration of 3 mg/mL. The resulting clay mineral-drug nanocomposites were characterized by X-ray diffraction (XRD), infrared (IR) spectroscopy and thermal gravimetry (TG). It was corroborated by XRD that the TMP was truly intercalated into the clay mineral. However, SMX seems to be adsorbed onto the clay mineral surface. For the LiFHt-TMP nanocomposite, IR suggested clay mineral-drug interactions via amine groups of the TMP. No significant changes in the IR spectrum for the LiFHt-SMX were observed. The drug release profiles showed to follow the pharmaceutical standards, and suggested the possibility to design formulations of drug delivery using LiFHt as carrier.

1. Introduction

It is well known that conventional release dosage forms provide an immediate drugs release, without much control of the release rate. In order to obtain therapeutically effective plasmatic concentrations, and to avoid significant fluctuations in the plasmatic drug levels, it is necessary to achieve dosage control. Failing to do so can lead to drug levels in the organism, by excess or defect, resulting in undesirable side effects, or in the lack of therapeutic benefits for the patient. Such disadvantages can be reverted through the use of materials to control the drugs release (Siegel and Rathbone, 2012; de Sousa et al., 2013).

Several reports about the use of clays and clay minerals in the pharmaceutical industry like active principles and/or excipients can be found (Aguzzi et al., 2007; de Sousa et al., 2013). Among the many benefits offered by clays, is their safety for the human health. The desirable physical and chemical properties of clay minerals – as adsorbents and ion exchangers – make them play a substantial role in pharmaceutical formulations (Aguzzi et al., 2007). For example, clays from the smectite family have been used as support materials in drug slow release systems. However, the use of synthetic clay minerals offers the possibility to optimize the conditions for the incorporation of model drugs, because this way the interference of spurious phases in the interpretation of the results is avoided. The Li-fluorohectorite, that belongs to the smectite group, is a 2:1 clay mineral with a negative charge net where a fraction of Mg^{2+} ions are substituted by Li^{+} in trioctahedral sites resulting in a negative structural charge of −1.2 electrons per unit cell (Kaviratna et al., 1996). It is compensated by exchangeable hydrated cations, i.e., Li located between clay layers allowing their stacking. The stacks can swell in the presence of water, which may enter the interlayer space, increasing the distance between layers. Based on the swelling property of this clay mineral, a few studies about its use as support system for pharmaceutical applications have been reported (Rivera et al., 2016; Valdés et al., 2016, 2017a, 2017b; dos Santos et al., 2017).

Trimethoprim (TMP) and sulfamethoxazole (SMX) are complementary pharmaceutical forms. The synergy between both drugs was first described in a series of in vitro and in vivo experiments published in the late 1960s (Maddileti et al., 2015). TMP or 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine is a broad spectrum, synthetic antibacterial agent, which acts as an inhibitor of bacterial dihydrofolate

* Corresponding author.
E-mail address: aramis@imre.uh.cu (A. Rivera).

https://doi.org/10.1016/j.clay.2018.03.016
Received 14 November 2017; Received in revised form 6 March 2018; Accepted 9 March 2018
Available online 26 May 2018

reductase, belonging to a group of compounds known as diaminopyrimidines (ElShaer et al., 2012). SMX or 4-amino-N-(5-methyl-3-isoxazolyl) benzenesulfonamide, is a bacteriostatic antibiotic belonging to the sulfonamides family. It is effective against most gram-negative and gram-positive bacteria and is frequently used for the treatment of urinary infections. Sulfonamides are structurally analogous to the natural substrate and competitive inhibitors of para-aminobenzoic acid (PABA) (Goodman-Gilman et al., 1991).

The aim of this study is to evaluate the potential of synthetic Li-fluorohectorite for the incorporation and release of the model drugs TMP and SMX and to understand the interactions between both materials using different characterization techniques (XRD, IR and TG). An in vitro drug release study from the clay mineral-drug nanocomposite tablets, simulating gastrointestinal tract conditions, was also performed. The main motivation of the study of these drugs is to develop new clay mineral-drug nanocomposite materials based on the combination of both drugs in the same support (LiFHt) with potential applications as a delivery system.

2. Experimental

2.1. Materials

The LiFHt used in the experiments was purchased from Corning Inc., New York. It contains about 80% by mass of LiFHt with nominal formula $Li_x(Mg_{6-x}Li_x)F_4Si_8O_{20}$ with $x = 1.2$, and about 20% of $Li_2O{\cdot}2SiO_2$ impurities (Rivera et al., 2016). In vivo acute toxicity assays performed on the LiFHt in Wistar albino rats indicated no clinical signs of toxicity in the organs, when the animal groups under study were examined (Valdés et al., 2017b). Based on that, it was possible to conclude that LiFHt can be used as raw material for medical applications, according to standard pharmaceutical requirements. Thus, it was demonstrated that the Li^+ amount present in the clay mineral-drug nanocomposite obtained does not represent any health problem. Trimethoprim ($C_{14}H_{18}N_4O_3$) and sulfamethoxazole ($C_{10}H_{11}N_3O_3S$)—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.

2.2. Sample preparation

For the interactions, the general procedure followed was: 10 mL of drug aqueous solutions was put in contact with 100 mg of LiFHt powder. After that, the mixture was centrifuged for 15 min at 300 rpm. The clay mineral-drug nanocomposites were dried at 65 °C. The drugs concentrations after the clay-drug interaction were analyzed and quantified by ultraviolet (UV) spectroscopy, using a spectrophotometer Rayleigh UV-2601 in the wavelength interval 200–400 nm.

The drugs uptake by the synthetic clay mineral (i.e., adsorbent loading) was calculated as:

$$q_e = \frac{(C_o - C_f) \times V}{m} \quad (1)$$

where q_e (mg/g) is the mass of drug adsorbed per unit mass of the adsorbent, C_o is the initial drug concentration in solution (mg/mL), C_f is the final concentration of drug solution (mg/mL), V is the volume of solution (mL) and m is the mass of the adsorbent (g) used in the experiments.

2.3. Drug incorporation and pre-formulation of the drug carrier system

In order to determine the best conditions to increase the drug load per gram of clay mineral, the influence of several physical-chemical parameters (pH, initial drug concentration, temperature and time of contact) was studied.

To evaluate the influence of pH on the incorporation process of TMP and SMX on the LiFHt, acid, neutral and basic pH values were considered. Taking into account the pKa values of both drugs, the pH studied for TMP were around 3.5, 7 and 12. For the case of SMX, four pH values (about 1, 3.5, 7 and 12) were evaluated. The pH was carefully adjusted using concentrated solutions of hydrochloric acid (HCl) and sodium hydroxide (NaOH). The drug amount in the supernatant solutions were determined by means of UV spectroscopy relative to calibration curves for the pure drugs solutions, taking into account the absorption maxima: for TMP, $\lambda_{max} = 271$ nm at acid pH, $\lambda_{max} = 285$ nm at neutral pH and $\lambda_{max} = 288$ nm at basic pH. For SMX, $\lambda_{max} = 265$ nm at acid pH and $\lambda_{max} = 256$ nm at basic pH. The dispersions were stirred during 2 h at room temperature at 3 mg/mL of initial drug concentration.

To evaluate the effect of the initial concentration for TMP and SMX, the interactions were performed in the range of 0.5–3 mg/mL–considering its solubility in aqueous medium (Li et al., 2005)–and 1–9 mg/mL (50 mg/100 mL at pH 8.54 and 1550 mg/100 mL at pH 5.5 (Dahlan et al., 1987)), respectively. The study was made at pH about 3.5 for 2 h and room temperature. The influence of temperature was also studied, performing the experiments at 27, 45 and 65 ± 1 °C, at pH about 3.5 for 2 h and 3 mg/mL of initial drug concentration. For kinetics studies the interactions were carried out during 30 min, 1, 2, 3, 4, 5, 6, 7, 8 and 24 h at pH around 3.5, room temperature, initial drug concentration of 3 mg/mL and constant stirring.

All the experiments were replicated three times in order to demonstrate their repeatability. The maximum difference between the outputs and their average was of 10 mg, which corresponds to a relative uncertainty of around of 3% in the mass of incorporated drug.

2.4. Structural, spectroscopic and thermal characterization

The solid samples in powder form before and after the interaction were analyzed with 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 angular scanning range 2θ from 2° to 40°at a scan rate of 1° min^{-1}.

Fourier transform infrared spectra (FTIR) were collected using a Nicolet AVATAR 330 Fourier–transform IR spectrometer in the wavenumber interval 400–4000 cm^{-1}. The samples were prepared using KBr pellet with 0.8% inclusion of the material to be analyzed.

Thermal gravimetric analysis (TGA) was performed with the aid of a NETZSCH STA 409 PC/PG and a STA6000 Perkin Elmer thermal analyzer, using a heating rate of 10 °C/min under dry air flow, from 25 up to 500 °C. The sensitivity of the thermobalance was ± 1 μg. A solid sample of about 0.03 g was used in each test.

2.5. Drug release assays

For the preliminary release studies different media, synthetic gastric juice (SGJ, i.e., 2 g of NaCl in 1 L of HCl 0.1 N), synthetic intestinal juice (SIJ, i.e., 6.8 g of K_2HPO_4, 0.2 L of NaOH 0.2 N and add water up to 1 L) and synthetic combined juice (SCJ, i.e., a mixture of SGJ and SIJ adjusting the pH to 4.5) were used, in order to simulate the conditions along the gastrointestinal tract (GIT). The sequential release was conducted in a buffer solution at pH 1.2 (synthetic gastric juice without pepsin) for 2 h (gastric emptying time). After that, the dissolution media was replaced with a buffer solution of pH 7.4 (synthetic intestinal juice) and analyzed for further 6 h.

The assays were carried out with the resulting materials in tablet form with about 30 mg of the clay mineral-drug nanocomposite (equivalent to 6.5 mg of TMP or 5.6 mg of SMX determined by UV as described before) and a compression agent in a Relation 1:1. The microcrystalline cellulose is a direct compressing agent accepted by the United States Pharmacopoeia (USP) for its use pharmaceutical formulations. The tablets were placed in dialysis membrane bags (Spectra/