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Porous clay heterostructures: A new inorganic host for 5-fluorouracil encapsulation

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ABSTRACT

This study proposed a new inorganic host for drug encapsulation. Porous clay heterostructure (PCH), synthesized using modified montmorillonite with dodecylamine, was used as host material and 5-fluorouracil (5-FU) as guest drug.

Drug encapsulation within PCH in different conditions (soaking time, temperature and pH value) was investigated. Possible interactions of 5-FU with PCH were pointed out using different characterization methods like spectroscopic techniques (FT-IR, UV–vis, XPS), thermogravimetrical and BET analysis. The obtained results suggested that PCH host exhibits a high drug encapsulation efficiency which was influenced by factors like soaking time and pH value.

PCH zeta potential value was strongly influenced by pH value. The PCH zeta potential significantly varies at acid pH, while a pH value higher than 7 provides a less variation.

UV–vis analysis showed that after 30 min PCH host registered a maximum encapsulation efficiency value (44%) at room temperature using an incubation solution with a pH of 11. The soaking temperature does not substantially affect the loading of drug in PCH host.

Thermogravimetrical analysis highlighted that drug encapsulation efficiency of PCH was mainly influenced by pH values.

BET results confirmed the PCH synthesis and drug loading capacity.

1. Introduction

Porous clay heterostructures (PCH) are porous materials characterized by attractive properties of micro- and mesoporous structures (Galarneau et al., 1995; Kooli et al., 2006).

PCH can be classified between layered silicates (montmorillonite), pillared clays and mesoporous silica. PCH possess a layered structure (smectites), like montmorillonite, pillars between adjacent layers, like pillared clays, and a high surface area, porosity and tunable pore diameters like mesoporous silica.

In comparison with classical montmorillonite, characterized by a lower surface area (40–70 m^2/g) and porosity (0.006–0.010 cm^3/g), PCH show higher value for these two features (Kooli, 2014). In addition, PCH are characterized by the presence of micropores specific for zeolites and mesopores like mesoporous silica (Pires et al., 2008).

Similar to pillared clays, the PCH are synthesized by a cationic exchange and subsequent intercalation which involves the silica precursors polymerization between layers of clay pretreated with organic cation and neutral amines as co-surfactants (Chmielarz et al., 2009a,b,c; Cecilia et al., 2013; Manova et al., 2010).

Like in case of synthetic clays (pillared clays, mesoporous silica), the PCH properties (pores dimension, BET surface area, adsorption capacity) depend on the synthesis conditions (surfactant type, surfactant concentration, co-surfactant type, ratio between starting layered silicate: silica precursor: co-surfactant) (Santos et al., 2010; Zapata et al., 2013; Nunes et al., 2008; Chmielarz et al., 2009a,b,c; Betega de Paiva et al., 2008; Čapková et al., 2006; Hedley et al., 2007; Zhou et al., 2004).

The advantageous properties of natural and synthetic clays recommend these materials in a wide range of applications, like heterogeneous catalysts, molecular sieves, adsorbents, decontamination agents and drug delivery systems (Qu et al., 2009; Chmielarz et al., 2009a,b,c; Arellano-Cárdenas et al., 2010; Pires et al., 2008; Kuźniarska-Biernacka et al., 2011; Nguyen-Thanh et al., 2006; Apps et al., 2014).

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The classical pharmaceutical formulations based on antitumor drug used in cancer therapy have many disadvantages like low light stability, low water solubility, modest stability to pH variation, high toxicity (haematological, gastrointestinal and neurological toxicity), fast release of active pharmaceutical ingredients. (Plumb et al., 2012; Specenier et al., 2009). For example, in case of platinum-based anticancer drug (cisplatin), the highest drug concentration after administration was achieved in a very short time period (shorter than 5 min).

For these reasons, a new concept of pharmaceutically formulations based on host–guest systems was introduced. Hybrid materials based on natural and synthetic clays were proposed as hosts for drug encapsulation. These host–guest systems were characterized by advantageous features such as high drug encapsulation efficiency, controlled/slow release of active pharmaceutical ingredient, high drug protection against pH variations, etc. (Joshi et al., 2009; Ha and Xanthos, 2011; Kong et al., 2010; Szegedi et al., 2011).

The most used natural or synthetic clays as drug delivery vehicles include cationic (montmorillonite, halloysite) and anionic (layered double hydroxide (LDH)) layered silicates, zeolites and mesoporous silica (Datt, 2012; Rimoli et al., 2008; Khodaverdi et al., 2014; Amorim et al., 2012; Vilaça et al., 2013).

In the present work, we proposed and investigated a new host–guest system based on PCH (as host) and 5-fluorouracil (a chemotherapeutic drug characterized by high toxicity). Factors, including soaking time, pH value and temperature, which affect the PCH capacity for drug loading, were studied using various characterization methods like BET, FTIR, UV–vis, TGA, XPS and zeta potential measurement.

2. Experimental

2.1. Raw materials

Nanofil 116 (a natural montmorillonite (MMT)), with a cationic exchange capacity (CEC) of 116 mEq/100 g clay, was provided from Southern Clay Products. Hexadecyltrimethylammonium bromide (HDTMA), tetraethyl orthosilicate (TEOS), dodecylamine (DDA) and 5-fluorouracil (5-FU) drug were supplied from Sigma and used as received. The chemical structures of the raw materials are shown in Fig. 1.

2.2. Synthesis of porous clay heterostructures (PCH)

PCH host was synthesized using a method described in our previous paper (Gârea et al., 2014). The PCH synthesis involved three main steps: (1) HDTMA intercalation between montmorillonite layers, (2) TEOS polymerization between montmorillonite layers, in the presence of HDTMA as surfactant and DDA as co-surfactant and finally (3) thermal treatment of PCH to remove the organic templates.

Following these steps, MMT (10 g) was swelled in deionized water (900 ml) for 1 h at 50 °C under mechanically stirring. After the MMT swelling step, a cation exchange reaction occurred due to the presence of HDTMA (6 g). The obtained suspension was maintained for 5 h at 50 °C and finally the modified clay was filtered and washed with water. The modified MMT (HDTMA–MMT) was air dried for 24 h and then was treated with a precise amount of DDA and TEOS in the presence of water. For PCH synthesis, an organoclay/amine/TEOS molar ratio of 1:20:120 was used. The PCH precursor was calcined at 650 °C, for 6 h.

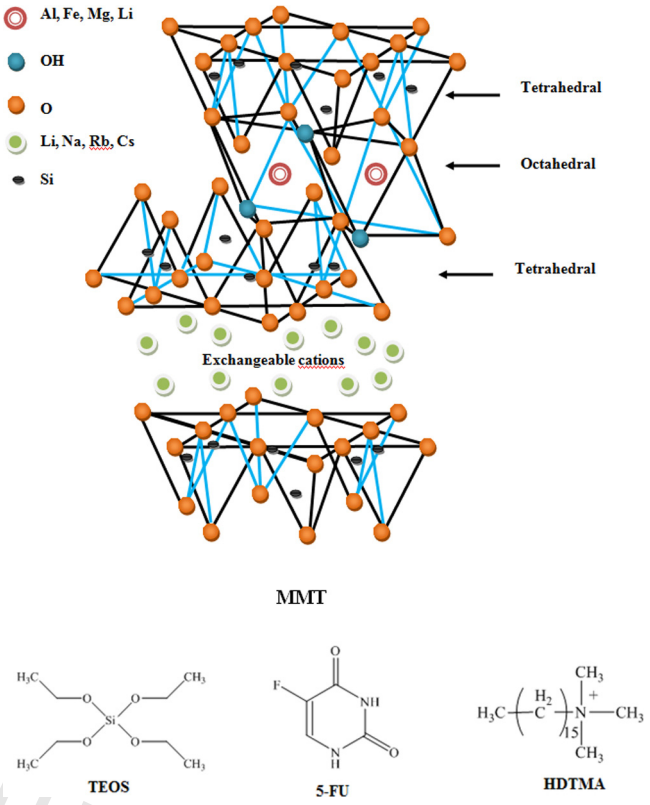

Fig. 1. Chemical structure of raw materials.

2.3. The influence of soaking parameters (time, temperature and pH value) on drug encapsulation

The adsorption experiments were performed at different soaking times, temperature and pH values, in order to reach the optimum parameters for a maximum drug loading into PCH.

pH effect on drug loading within PCH was studied by maintaining 0.05 g of PCH with 0.01 g of 5-FU for 1 h, at room temperature, in incubation solutions with different pH value (2, 3, 4, 5, 6, 7, 8, 9, 10, 11). The samples were abbreviated as follow: PCH-5-FU-pH 2, PCH-5-FU-pH 3, PCH-5-FU-pH 4, PCH-5-FU-pH 5, PCH-5-FU-pH 6, PCH-5-FU-pH 7, PCH-5-FU-pH 8, PCH-5-FU-pH 9, PCH-5-FU-pH 10 and PCH-5-FU-pH 11.

The influence of soaking time was performed by mixing 0.01 g of 5-FU with 0.05 g PCH at pH 9 and 11 for 5, 10, 30, 60, 120, 180, 240 and 360 min. The samples were abbreviated as follow: PCH-5-FU-5 min, PCH-5-FU-10 min, PCH-5-FU-30 min, PCH-5-FU-60 min, PCH-5-FU-120 min, PCH-5-FU-180 min, PCH-5-FU-240 min, PCH-5-FU-360 min.

The same quantities of drug and PCH were used to study the influence of temperature on the drug encapsulation. In this case, the mixtures based PCH and drug dissolved in 10 ml of incubation solution were stirred for 1 h at different temperature (20 °C, 40 °C and 60 °C). The samples were abbreviated as follow: PCH-5-FU-20 °C, PCH-5-FU-40 °C and PCH-5-FU-60 °C. The final samples were centrifuged and freeze dried at -50°C for 3 h.

2.4. Characterization techniques

UV–vis spectra were recorded on UV 3600 Shimadzu equipment provided with a quartz cell having a light path of 10 mm. The UV spectra were measured at $\lambda = 266$ nm.

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