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Research paper

Clay-biosurfactant materials as functional drug delivery systems: Slowing down effect in the in vitro release of cinnamic acid

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ABSTRACT

The main objectives of the present paper were the preparation and characterization of new surfactant-modified clays and the evaluation of their potential applicability as drug delivery systems for the oral administration of the cinnamic acid (CA) drug. The organoclays (OC) were prepared by loading different amounts of the biocompatible nonionic polyoxyethylene sorbitan monolaurate surfactant (Tween20) onto K10 montmorillonite (Mt) clay and characterized through the construction of the adsorption isotherms by means of the spectrophotometric method. The performance of the prepared material was verified by gathering the adsorption isotherms of the cinnamic acid onto the Mt/Tween20 organoclay and by monitoring the release profiles in both simulated gastric (SGF) and intestinal fluids (SIF).

The quantitative analysis of the adsorption isotherms revealed that the uptake of the aromatic component onto both the blank and Tween20-loaded Mt was governed by positive cooperative processes and that the presence of the bio-surfactant enhanced the loading efficiency of the clay.

By relating the raw montmorillonite uptake capability with that of the OC it was assessed that the presence of the bio-surfactant enhanced about 2 times the loading efficiency of the clay. From the XRD characterization of the obtained complexes, the successful intercalation of the drug into the prepared organoclay was demonstrated.

Very useful information was obtained by the in vitro release studies, which showed that the release of the drug from both the clay and organoclay was prolonged in comparison with the pharmacokinetics of the free drug. Besides, the intercalation of the surfactant into the nano-carrier ensured the complete release of the CA after oral drug administration and the kinetics of the release process was strongly dependent on the type of drug formulation used, which means that the CA release can be modulated by properly functionalizing the clay surface.

1. Introduction

Nowadays, the topic of drug administration captures the interest of many scientists and engages them in solving the cogent problem of either over-dosing or under-dosing windows. Considerable efforts have therefore been devoted to the design of appropriate drug delivery systems (DDS) aimed at improving the efficiency and the safety of the product (Kulkarni et al., 2011). In this context clay minerals have been investigated as fundamental constituents of several DDS (Aguzzi et al., 2007; Ambrogi et al., 2012; Calabrese et al., 2013a ; Carretero, 2002; Choy et al., 2007; Iliescu et al., 2011; Nunes et al., 2007; Rodrigues et al., 2013; Viseras et al., 2010; Zheng et al., 2007).

Specifically, montmorillonite (Mt), whose structure consists of two silica tetrahedral sheets sandwiching an edge-shared octahedral sheet of aluminum (T-O-T sheets), attracted a great deal of attention in the research of drug administration (Ambrogi et al., 2012; Carretero, 2002; Cavallaro et al., 2015; Gereli et al., 2006; Lal and Datta, 2012; Lin et al., 2002; Massaro et al., 2015; Wang et al., 2008) because of its noteworthy

List of abbreviations and symbols: CA, Cinnamic acid (cis-3-phenylpropenoic acid); OC, Organoclays; Tween20, Nonionic polyoxyethylene sorbitan monolaurate surfactant; Mt, montmorillonite clay; SGF, simulated gastric fluid; SIF, simulated intestinal fluid; DDS, drug delivery system; FWHM, full width at half-maximum; E(kj m^{-1}), free energy of absorption $E = -(2k)^{-0.5}$; DR equation, Dubinin–Radushkevich equation $\ln C_s = \ln X_m - k\varepsilon^2$; K_F, Freundlich adsorption coefficient; K_L, Langmuir adsorption coefficient; q^m, maximum absorption capacity; K_H, Hill adsorption coefficient; χ^2, Chi square test; *ESS*, sum of squared errors; R^2, coefficient of multiple determination; n, parameter related to the cooperative process; DEM model, Double Exponential Model; $\varepsilon = RT \ln(1 + 1/C_e)$, Polanyi Potentiali; R (kJ mol^{-1} K^{-1}), gas constant; T (K), temperature; C_s (mol g^{-1}), amount of adsorbate per unit weight of adsorbent; X_m (mol g^{-1}), adsorption capacity; C_e (mol dm^{-3}), equilibrium concentration of adsorbate in solution; k (mol^2 k^{-1} J^{-2}), constant related to adsorption energy; $A = \varepsilon$ l C, Lambert-Beer law; pV, Pseudo-Voigt function; η, Pseudo-Voigt function mixing parameter; U, V, W, Coefficients of caglioti formula $(FMHM)^2 = (U \tan^2\theta + V\tan\theta + W)^{1/2}$.

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properties including large specific surface area, good adsorption ability, cations exchange capacity, adhesive ability, and drug-carrying and releasing capability.

The already promising features of the clay can be further improved by intercalation with surfactants (Iliescu et al., 2011). The obtained organoclays (OC) exhibit higher organophilic character in comparison with the unmodified clay, i.e., higher uptake ability toward organic substances (Lee and Tiwari, 2012; Shah et al., 2013; Shen, 2004). Moreover, the surfactant functionalization enhances the dispersion stability in aqueous media, which has important implications in adsorption and bioavailability of the drug molecules (Calabrese et al., 2013b; Cavallaro et al., 2014).

In the light of the above considerations, the major objective of the present work lies in the design of an organoclay-based delivery system for the oral administration of the cinnamic acid (cis-3-phenylpropenoic acid) (CA) drug.

This compound was selected because of the very well assessed pharmacologic properties including anti-inflammatory antimicrobial, antimalarial, antioxidant, antidiabetic and anti-cancer activities (Akao et al., 2003; Foti et al., 2004;Wiesner et al., 2001; Zhang and Ji, 1992).

Pharmacokinetics and bioavailability study of CA after oral administration have shown that CA is quickly absorbed, with peak concentrations occurring at 3–10 min after the administration (Chen et al., 2009). This short acting drug requires the use of repeated treatments, which causes the unwanted typical pulsed trend of the plasma concentration of the drug.

The employment of clay and organoclays as nano-carriers for CA delivery system, is here proposed as an efficient alternative to conventional formulations, in order to obtain a slower release of the drug, thus decreasing the number of daily administrations, minimizing the temporal variation of the drug concentration and reducing the side effects.

On the other hand, it should also be taken into account that CA and its phenolic derivatives represent dangerous contaminating agents in wastewaters of agricultural origin (Isidori et al., 2005; Poerschmann et al., 2013). Therefore, the investigation of the adsorption properties of the prepared OC toward this compound, could serve the additional purpose of providing useful information to be exploited in the remediation field.

In the present paper, the organoclays were prepared by loading the biocompatible nonionic polyoxyethylene surfactant (Tween20) onto the K10 montmorillonite (Mt) clay.

The choice of the Tween20 surfactant was prompted by its attested non-toxicity which allows it to be applied in drug delivery systems. The results of some preliminary experiments (Calabrese et al., 2013b) further support this choice because the successful intercalation of the Tween20 onto the clay and the stabilization effect brought about the adsorption of the surfactant on the Mt dispersion, have been demonstrated.

In the first step of the work, the organoclays were prepared and characterized through the construction of the adsorption isotherms. In a second step the adsorption isotherms of the CA compound in both the pristine Mt and the organoclay were studied and the sites of interactions of the clay surface were proposed on the basis of the XRD results. Finally, the release profiles of the CA compound from the prepared hybrids in both simulated gastric (SGF) and intestinal fluids (SIF) pH were investigated.

2. Materials and methods

2.1. Materials

All the reactants, i.e. montmorillonite-K10 (Mt), polyoxyethylene sorbitan monolaurate (Tween20), cinnamic acid (CA), hydrochloric acid (HCl) and sodium hydroxide (NaOH) standard solutions, were purchased from Sigma Aldrich and used as received. Montmorillonite-K10, possesses BET surface area of 220 m^2/g and the following structural formula:

$$(K_{0.25}Na_{0.118}Ca_{0.022})(Al_{1.06}Fe_{0.206}Mg_{0.166})(Si_{7.39}Al_{0.61})O_{20}(OH)_4$$

Although it is known from the literature (Golubeva et al., 2016; Jiang and Zeng, 2003) that Mt of grade K10 contain different impurities (in particular, muscovite and quartz), the choice of this clay mineral was dictated by the extensive literature dealing with the investigation and exploitation for industrial and biomedical applications of K10 Mt/biomolecules complexes. .

Deionized water from reverse osmosis (Elga, model Option 3), having a specific resistance higher than 1 MΩ cm, was used to prepare all solutions.

2.2. Organoclay preparation

Tween20 aqueous stock solutions were prepared by dissolving weighted amounts of the surfactant in an aqueous HCl solution at pH 4.0, previously prepared by proper dilution of the standard 1 M HCl solution.

Mt aqueous dispersion was prepared, according to a procedure previously reported (Sciascia et al., 2011), by crushing the clay mineral in an agate mortar and then mixing 1 g of the powder with 25 mL aqueous HCl solution. The obtained dispersion was stirred for about 2 h before use.

The pH of the aqueous solution/dispersion was measured and, when necessary, the pH was adjusted to pH = 4 by adding microvolumes of HCl or NaOH standard solutions.

The organo-clays were prepared by adding appropriate aliquots of the surfactant solutions to the Mt dispersion at room temperature. The surfactant concentration was changed in the range $1.0–5.0\cdot10^{-3}$ mol dm^{-3} while the amount of Mt was kept constant at 25 mg mL^{-1}. The mixture was stirred for 24 h, then centrifuged 10 min at 8000 rpm by means of a Centra MP4R IEC centrifuge. This way, the supernatant was separated from the solid, which was air dried for 2 days at room temperature and, then, crushed in an agate mortar and employed for XRD characterization. The gathered supernatants were spectrophotometrically analyzed in order to construct the adsorption isotherms. In particular the spectra of the aqueous surfactant solutions were registered in the wavelength range 200–400 nm with a diode-array Analytic Jena S600 spectrophotometer equipped with thermostated compartments for $1 \times 1 \times 5$ cm cuvettes and an appropriate magnetic stirring apparatus.

The Tween 20 aqueous solutions follow the Lambert-Beer law in the concentration range 0.1–6.0 mmol dm^{-3} with a molar absorption coefficients ε of 334 ± 2 dm^3 mol^{-1} cm^{-1} (at λ_{max} = 231.0 nm, R^2 = 0.9998).

Triplicate experiments were performed and the results are reported as the average value of each single measurements.

2.3. Adsorption of the CA into Mt Mt/Tween20 organoclay

The adsorption of the cinnamic acid onto the organoclay prepared by loading the higher surfactant concentration (0.22 mmol g^{-1}), was performed by following the same procedure as for the surfactant adsorption. Adsorption onto the unmodified Mt was also carried out.

Appropriate amounts of stock solution of CA were added to the clay/organoclay aqueous dispersion in order to obtain a CA concentration ranging from $1.0\cdot10^{-5}$ to $9.0\cdot10^{-5}$ mol dm^{-3}.

The mixtures were stirred for 24 h and the resulting products were separated by centrifugation.

The obtained powder was employed for the XRD characterization and for the release tests, while the supernatant was used for the construction of the adsorption isotherm by means of the spectrophotometric method by registering the whole spectrum in the wavelength range 200–400 nm.

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