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Research paper

Drug release material hosted by natural montmorillonite with proper modification

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ABSTRACT

In developing new generations of coatings for drug and drug controlled release, there is a need for self-assembled materials that provide controlled sequential release of multiple therapeutics, while provide a tunable approach to time dependence and the potential for sequential or staged release. Herein, we demonstrated the ability to develop a self-assembled, in ciprofloxacin intercalated montmorillonite (CIP-Mt), the release rate and amount of interlayer ciprofloxacin (CIP) could be controlled by modifying the layer charge of montmorillonite (Mt). Compared with common sustained release materials, this composite had better effect on antibacterial and disinfection. The CIP-Mt system effectively blocked diffusion-based release, leading to approximately 50% reduction in bolus doses and 10-fold increase in the release timescale. Mt was a non-toxic and non-polluting sustained release material, could be applied to drug release research, and the release rate and time of its interlayer CIP can be controlled by modifying layer charge.

1. Introduction

Nowadays, microorganism threat on human health and environmental safety has become a serious public concern (Carey et al., 2011; Touré et al., 2014). Pathogenic bacteria, fungi and viruses, etc., are responsible for the transmission of most of the serious diseases (Ghosh et al., 2012; Harimawan et al., 2013). It is thus quite essential to conduct studies with aspects of sterilization, prevention, disinfection, etc., to control microbial pollution. Antibacterial agents offer a solution to this microbial problem (Sahiner and Yasar, 2013). However, the overuse and misuse of antibiotics has led to the emergence of antibiotic-resistant bacteria, compromising the effectiveness of antimicrobial therapy because the infectious organisms are becoming resistant to most antibiotics (Pruneau et al., 2011; Marti and Balc-azar, 2013). Since a high local concentration of antibiotics is provided through sustained release, bacteria are killed before they grow into biofilm (Diaz-Rodriguez et al., 2011; Deacon et al., 2015). In fact, the emergence and spread of antibiotic resistant bacteria has been classified by the World Health Organization (WHO) as one of the three biggest threats to public health in the 21st century.

These antibiotics have good efficacy, while excessive intake would cause some side effects (Li and Chauhan, 2006), and especially for long-time excessive intake would decline antibiotic effect and human immunity. For example, a rapid rise of drug concentration after intake is considered to cause poisoning, allergies and other symptoms (Schwartz and Calvert, 1990; Akahane et al., 1993; Lomaestro, 2000). A short half-life drug leads to rapid loss of metabolism, reducing the duration and concentration of the antibiotics in the human body and weakening the efficacy. The preparation of sustained release of antibiotic composite is significant for improving the efficacy. The sustained release of drug can be realized by a combination of active ingredient and molecule host, where a slow released drug agent with strong efficacy can be obtained by controlling release rate of drug by diffusion and penetration (Cheow et al., 2010; Ochs et al., 2010; Mayol et al., 2014). Sustained release of drug not only prolongs the action, thus reducing the frequency of drug administration, but also attempts to maintain drug levels within the therapeutic window to avoid potentially hazardous reflections in drug concentration.

In recent years, clays, such as Mt, intercalated by drug molecules have attracted much interest from researchers due to their novel physical and chemical properties (Lin et al., 2002; Park et al., 2008; Joshi et al., 2009, 2010). Moreover, it has also been reported that intercalation of some drugs onto Mt can overcome the problem of oral administration in clinical application (Lin et al., 2002; Donga and Feng, 2005). As one of the smectite groups, Mt is composed of silica tetrahedral sheets layered between alumina octahedral sheets. The imperfection of the crystal lattice and the

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isomorphous substitution induces a net negative charge that leads to the adsorption of alkaline earth metal ions in the interlayer spaces. Such imperfection is responsible for the activity and exchange reactions with organic compounds. Mt is a natural mineral exhibiting good adjustability among common inorganic layered materials, as well as non-toxic, non-irritating and without side effect. Thus, Mt can be applied to drug release research, and the release rate and time of its interlayer CIP can also be controlled by modifying layer charge.

In the research, a ciprofloxacin-montmorillonite (CIP-Mt) composite was prepared as a sustained release drug system, and the sustained ability can be controlled by adjustment of layer charge. The improved sustained ability indicates potential applications in retard drugs. When CIP enters Mt interlayer space, the releases of CIP is affected by the distribution of CIP in the interlayer spaces and its interaction with the Mt layers. Changes in charge density of Mt (AMt) lead to variations in electric strength in the interlayer space region. This affects amount of intercalated CIP to Mt and electrostatic attraction between CIP and Mt layers. After adjustment of layer charge, release time of CIP-AMt is 700 min longer than that of CIP-Mt, and release amount is also stable and controllable, whose characteristics are applicable to practical retard drug system.

2. Experiment and methods

2.1. Materials

The montmorillonite used was SWy-2 obtained from the Clay Mineral Repositories in Purdue University (West Lafayette, IN) without further purification. It had a chemical formula of $(Ca_{0.12}\ Na_{0.32}\ K_{0.05})[Al_{3.01}\ Fe(III)_{0.41}\ Mg_{0.54}][Si_{7.98}\ Al_{0.02}]O_{20}(OH)_4$, a CEC of 85 ± 3 $mmol_c$/100 g (Borden and Giese, 2001), a layer charge of 0.32 eq/mol per $(Si,Al)_4O_{10}$ (Chipera and Bish, 2001), an external surface area (ESA) of 23 m^2/g, respectively (Mermut and Lagaly, 2001), and a mean particle size of 3.2 μm with a d_{25} to d_{75} in the range of 3–10 μm.

Ciprofloxacin (CIP) was used as received without further purification. CIP hydrochloride (purity > 99.6%) was purchased from Beijing Solarbio life sciences Co., Ltd., (China). Its pKa_1 and pKa_2 values were 6.1 and 8.7, respectively (Chang et al., 2016).

2.2. Experiment

Natural Mt was treated by HCl at concentrations of 0, 0.05, 0.1, 0.5, and 1.0 mol/L to adjust its structure and charge density (AMt). After the acid treatments, the Mt was washed with two portions of distilled water to remove the residual Cl. The samples (denoted as AMt) were dried naturally before interaction of CIP into Mt.

The initial CIP concentrations varied from 5 to 10,000 mg/L for the intercalation isotherm study. The mass of Mt was 0.5 g and the volume of solution was 10 mL for all studies, except for the kinetic study (for which 50 mL of solution was used). The solid and solution were combined in each 50 mL centrifuge tube and shaken for 4 h at 150 rpm at room temperature for all studies, except for the kinetic study. The mixtures were centrifuged at 10000 rpm for 20 min, then dried at 60 °C and ground before characterizations. A mixture, composed of 0.5 g and 50 mL NaCl (the concentration was 10 mol/L), was shaken at 150 rpm for 5–1440 min at room temperature.

P. aeruginosa, a strain isolated from the institute of microbiology Chinese academy of sciences, was preserved in our laboratory, and was identified to have excellent algicidal activity on *M. aeruginosa*. Briefly a nutrient agar (pH 7.0–7.2) was prepared by dissolving 10 g peptone, 3 g beef extract, 5 g NaCl, 20 g agar in 1 L distilled water. After sterilization in an autoclave (100 kPa, 120 °C, 20 min), the nutrient agar was casted on Petri dishes and cooled to the room temperature. Then, 100 μl diluted degrading medium containing microorganisms was coated on the nutrient agar surface. After being incubated at 37 °C for 24 h, the number of microorganism colonies, representing the living microorganisms, was counted.

2.3. Materials characterization

The equilibrium CIP concentrations were analyzed by a UV–Vis spectrophotometer (Model T6 New Century 1650, made by General Instrument, Inc. LLT, Beijing China) at the wavelength of 275 nm, corresponding to its maximal absorbance. Calibrations were made following standards of 10, 20, 30, 40, 50, and 60 mg/L with a regression coefficient of 0.9998. The amount of CIP adsorbed was calculated as the difference between the initial and final concentrations.

Powder XRD analyses were performed on a Rigaku D/max-III a diffractometer (Tokyo, Japan) with a Ni-filtered $Cu_{K\alpha}$ radiation at 30 kV and 20 mA. Orientated samples were scanned from 3° to 10° or 3° to 70° with a scanning step of 0.01°. Powder samples were packed in horizontally held trays. The changes in the XRD reflection positions reflected the intercalation of the dye into layered silicates. The Bragg equation was applied to calculate the basal spacing of Mt layers. The interlayer space sizes of intercalated hybrids were deduced from XRD reflection positions of (001) of the hybrids.

Elemental compositions of Mt were determined by X-Ray Fluorescence spectrometry (XRF) to confirm the dissolution of Si after acid treatment. It was carried out by using a portable XRF spectrometer (Oxford Instruments) with a molybdenum anode, at 25 kV and 0.1 mA. A Si-PIN detector from AMPTEK was employed and characterized by an energy resolution of about 200 eV at 5.9 keV.

Thermogravimetric analyses were carried out on TGA Q-500 (TA Instruments, New Castle, USA) from room temperature to 800 °C with a heating rate of 10 °C/min under a nitrogen flow of 60 mL/min. TG curves were used to determine the percentage of mass loss. Differential scanning calorimetry (DSC) was performed using a differential scanning calorimeter (TA Instruments Q100) fitted with a cooling system using liquid nitrogen. It was calibrated with an indium standard. Samples of 6 mg Mt were accurately weighed into aluminum pans, sealed and then heated from 30 to 800 °C at 10 °C/min under a nitrogen flow of 60 mL/min.

Molecular simulation was performed under the module 'CASTEP' of Materials Studio 6.1 software to investigate the sorption sites of CIP on Mt. The primitive unit cell of Mt was optimized with the generalized gradient approximation (GGA) for the exchange-correlation potential (PW91) that was appropriate for the relatively weak interactions present in the models studied. The resulting primitive unit cell was characterized by the parameters a = 15.540 Å, b = 17.940 Å, c = 12.56 Å, and $\alpha = \gamma = 90°$, $\beta = 99°$. Based on the primitive unit cell, a series of (3 × 2 × 1) supercells were built with the spacing of layers set to15.24 and 15.04 Å, respectively. The number of cycles was 3 and the steps of one cycle were 10^6, a representative part of the interface devoid of any arbitrary boundary effects.

3. Results and discussions

3.1. The modification of Mt and preparation of CIP-Mt

The structure modification of Mt and the preparation process of CIP-Mt are shown in Fig. 1. Over the course of fabrication, Mt was treated by HCl firstly at concentrations of 0.05, 0.1, 0.5 and 1.0 M (mol/L) to adjust its structure. The acid treatment would result in Mt with different charge densities. However, the crystal structure of Mt after acid treatment was intact as observed by XRD analyses (Fig. 1a). Meanwhile, the intensity of the reflection at 27.8° reduced gradually until disappeared, and the main phase was feldspar. The small changes in d_{001} value could be attributed to the changes in layer charge (Wu et al., 2016).

This study was done to mimic the behavior of Mt with CIP. In contrast to many drug projects that have used completely purified and modified Mt, the experiment was done on pure and modified Mt as it has CIP for cation exchange processes (Majzik and Tombacz, 2007). Initial concentration of CIP solution had a profound influence on the amount of Mt intercalation. The removal of CIP by Mt and AMt