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Drug release behavior of chitosan–montmorillonite nanocomposite hydrogels following electrostimulation

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Abstract

Nanocomposites hydrogel (nanohydrogel) composed of chitosan (CS) and montmorillonite (MMT) were prepared and systematically studied for drug release behavior following electrostimulation. The deterioration of the responsiveness and reversibility of CS upon repeated on–off electrostimulation switching operations are major limitations for clinical applications, as it suffers from too much structural instability for the precise control of the release of drug upon cyclic electrostimulation. To overcome these limitations, an inorganic phase, MMT, was incorporated in the CS matrix to enhance the anti-fatigue property and corresponding long-term stable release kinetics. X-ray diffraction analysis and time-dependent optical absorbance showed that the MMT incorporated into the nanohydrogel exhibited an exfoliated nanostructure. The exfoliated silica nanosheets are able to act as cross-linkers to form a network structure between the CS and MMT, and this difference in the cross-linking density strongly affects the release of vitamin B_{12} under electrostimulation. With a lower MMT concentration (1 wt.%), the release kinetics of vitamin B_{12} from the nanohydrogel shows a pseudo-zero-order release, and the release mechanism was changed from a diffusion-controlled mode to a swelling-controlled mode under electrostimulation. Further increasing the MMT content reduced both the diffusion exponent n and the responsiveness of the nanohydrogel to electrostimulation. In addition, a consecutively repeated "on" and "off" operation shows that the electroresponsiveness of the nanohydrogel with higher MMT concentrations was reduced, but its anti-fatigue behavior was considerably improved. In this work, the nanohydrogel with 2 wt.% MMT achieved a mechanically reliable and practically desirable pulsatile release profile and excellent anti-fatigue behavior, compared with that of the pure CS.

Keywords: Chitosan; Montmorillonite; Nanocomposite hydogel; Electrostimulation controlled release; Anti-fatigue

1. Introduction

Smart polymer hydrogels have been studied with particular emphasis on their reversible volume changes in response to external stimuli, such as pH, solvent composition, temperature, ionic concentration and electric field [1–3]. These hydrogels have been developed and studied with regard to their application in several biomedical fields, e.g. separation techniques, soft-actuators and controlled drug delivery systems [4,5]. Of these, their use in electrically controlled drug delivery may offer unique advantages for providing on-demand release of drug molecules from implantable reservoirs. In addition, electrical control is advantageous for coupling to sensors and microelectronics in feedback controlled systems [6].

For electrosensitive hydrogels used as controlled drug delivery systems, the drug release rate can be easily controlled simply by modulating the electric field. Generally, the extent of drug release increases with the magnitude of electric field and time, but is not linearly proportional to them [7]. Hence, it becomes more difficult to precisely control the release of drug by electrostimulation. In particular, an important goal of drug delivery is to obtain a constant release rate for a prolonged time. However, one problem

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common to all hydrogels is that the responsiveness and reversibility will decrease after several on–off switching operations. For commercial applications, this fatigue property must be improved to achieve a stable pulsatile release under repeatedly operations. Unfortunately, few studies have addressed this important issue, so this is one of the research objectives of this investigation. In order to overcome the fatigue problem of conventional hydrogels to some extent, the incorporation of an inorganic nanophase is an attractive alternative, i.e. production of an inorganic–organic nanocomposite hydrogel (nanohydrogel), where the properties of polymer matrix could be improved and have a significant effect on the electrical deformation and relaxation behaviors [8]. For example, Gong et al. [9] reported that organically modified clay can enhance the temperature response of clay–poly(*N*-isopropylacrylamide) (PNIPAAm) nanocomposites. Based on hydration theory, the organically modified clay introduces a hydrophobic environment at the interface that can enhance the efficiency of the thermal transition, narrow the transition range and increase the transition rate. However, to the best of our knowledge, little research work had been reported on the drug release behavior of polymer–(nano)clay nanohydrogel following electrostimulation.

Polymer–clay nanohydrogels are expected to have novel properties because of the nanometric scale on which the nanoclay particles, with their plate-like shape, would alter the physical and chemical properties of the polymeric materials and improve their mechanical properties and thermal stability [10]. Chitosan (CS), which is used as polymeric matrix in this study, is a cationic biopolymer and has been proposed for electrically modulated drug delivery [11]. In our previous study [12], we demonstrated that the addition of clay to the CS matrix could strongly affect the cross-linking density as well as the mechanical property, swelling–deswelling behavior and fatigue property of the nanohybrids. Hence, the incorporation of negatively charged delaminated (exfoliated) montmorillonite (MMT) is expected to electrostatically interact with the positively charged $-NH^{3+}$ group of CS, to generate a strong cross-linking structure in the nanohydrogel [13] and, thus, strongly affect the macroscopic property of the nanohydrogel and the drug diffusion through the bulk entity. In present work, variations in the release kinetics and the mechanism of vitamin B_{12} action with respect to MMT content were investigated under a given electric-field stimulus. Furthermore, the anti-fatigue behavior with respect to the repeated field stimuli of the resulting nanohydrogel in terms of the MMT addition was also elucidated.

2. Materials and methods

2.1. Materials

The chitosan used in this study to prepare the CS–MMT nanohydrogels was supplied by Aldrich–Sigma and used without purification. The same type of chitosan was used by Darder et al., who reported that it has an average molecular weight of 342,500 g mol^{-1} and a deacetylation degree (DD) of ca. 75% [14]. Acetic acid and sodium phosphate for the preparation of buffers were purchased from Aldrich Chemicals. Vitamin B_{12} (Sigma–Aldrich Co.) was chosen as a model molecule to characterize the release behavior from the nanohydrogel. Na^+-montmorillonite, supplied by Nanocor Co., is an Na^+ form of layered smectite clay with a cationic exchange capacity (CEC) of 120 meq. $(100\ g)^{-1}$. The MMT platelet shows a surface dimension of about 200–500 nm in length and several tens of nanometers in width.

2.2. Preparation of CS–MMT nanohydrogels

To prepare the CS–MMT nanohydrogels, the preparation procedure is separated into two stages. The first stage is to prepare a suspension containing MMT and CS with a weight ratio of 1:2 (where the CS solution was prepared by dissolving predetermined amounts of CS in 1 wt.% acetic acid solution and stirring for about 4 h until the CS was completely dissolved). The CS–MMT suspensions were obtained by adding CS to an aqueous solution containing 2 wt.% MMT (i.e. 0.5 g of Na^+-MMT dispersed in 25 ml of double-distilled water), followed by stirring at 50 °C for 24 h. To enhance the formation of exfoliation of the MMT in the final nanohydrogel, the suspension with a CS to MMT ratio of 2:1 was then subjected to ball-milling for 24 h, after which the as-prepared final CS–MMT suspension was used to form nanohydrogel.

In the second stage of the CS–MMT nanohydrogel preparation, 2 wt.% CS solution was obtained by dissolving CS in 1 wt.% acetic acid solution. A small amount of the ball-milled CS–MMT suspension was then added to the prepared CS solution to form a CS-rich suspension, with the MMT content controlled in the range of 1, 2, 3 and 4 wt.%, relative to the total weight of CS in the suspensions, under continuous stirring at 60 °C for 1 h. This final suspension was then cast onto Petri dishes and dried at 30 °C for 24 h, to form final dried nanohydrogels. The dried nanohydrogels were then rinsed with an aqueous solution of 1 M NaOH to remove any residual acetic acid, followed by washing with distilled water and drying for 1 week at 40 °C in vacuum until use. The compositions of the nanohydrogels are expressed using the value of n to define the content of MMT in CS–MMTn, where $n = C_{MMT}$, the content of the MMT incorporated in the nanohydrogels, which ranged from 1% to 4%.

2.3. Characterization

The crystallographical structures of CS–MMT nanohydrogels were determined using an X-ray diffractometer (XRD; M18XHF, Mac Science, Tokyo, Japan). The diffraction data were collected from $2\theta = 1$–$30°$ at a scanning rate of $2°\ min^{-1}$. The nanohydrogel was a circular plate with a radius of about 1.5 cm. The average thickness and

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