Colloids and Surfaces B: Biointerfaces 123 (2014) 657–663

Contents lists available at ScienceDirect

Colloids and Surfaces B: Biointerfaces

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

A study of chitosan hydrogel with embedded mesoporous silica nanoparticles loaded by ibuprofen as a dual stimuli-responsive drug release system for surface coating of titanium implants

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ARTICLE INFO

Article history:
Received 20 June 2014
Received in revised form 3 October 2014
Accepted 4 October 2014
Available online 13 October 2014

Keywords:
Chitosan hydrogel
Electrodeposition
Ibuprofen
Controlled drug release
Mesoporous silica nanoparticles
Titanium implants

ABSTRACT

In this study, the complex pH and electro responsive system made of chitosan hydrogel with embedded mesoporous silica nanoparticles (MSNs) was evaluated as a tunable drug release system. As a model drug, ibuprofen (IB) was used; its adsorption in MSNs was evidenced by Fourier transform infrared spectroscopy (FT-IR), scanning electron microscopy (SEM) and thermogravimetric analysis (TG). In order to prepare the complex drug release system, the loaded particles IB-MSNs were dispersed in chitosan solution and then the complex IB-MSNs/chitosan film of 2 mm thickness was deposited as a hydrogel on the titanium electrode. The codeposition of components was performed under a negative biasing of the titanium electrode at −0.75 mA/cm^2 current density during 30 min. The IB release from the IB-MSNs/chitosan hydrogel film was studied as dependent on pH of the release media and electrical conditions applied to the titanium plate. When incubating the complex hydrogel film in buffers with different pH, the IB release followed a near zero-order profile, though its kinetics varied. Compared to the spontaneous IB release from the hydrogel in 0.9% NaCl solution (at 0 V), the application of negative biases to the coated titanium plate had profound effluences on the release behavior. The release was retarded when −1.0 V was applied, but a faster kinetics was observed at −5.0 V. These results imply that a rapid, mild and facile electrical process for covering titanium implants by complex IB-MSNs/chitosan hydrogel films can be used for controlled drug delivery applications.

1. Introduction

Mesoporous silica nanoparticles (MSNs), firstly described in 1990s, are considered as one of the potential carriers for drug delivery [1–3]. MSNs possess several competing advantages including large surface area, high pore volume, tunable pore size and nontoxicity. The tailorable and ordered mesoporous structure of MSNs facilitates the loading of target drugs and their subsequent controlled release [4]. Surface functionalization and capping are common strategies to increase the targeting, stabilize the carried cargo and modify the release behavior [5]. The surface of MSNs can be functionalized with targeting ligands, tracking markers and biocompatible molecules. Coating of MSNs with chitosan enables pH responsive drug release and demonstrates great potential for targeted drug delivery [6–8]. Chitosan is an amino-polysaccharide, which is the deacetylation product of chitin, with well-documented properties as biocompatibility, biodegradability, pH-responsive and gel-forming. The presence of amino groups facilities the connection of chitosan to the surface of MSNs and the pH-responsive property of chitosan adjusts the drug release behavior to external stimuli. Moreover, chitosan coating on MSNs increases the endocytosis of target cells. For instance, Chung and Gulfam [9] reported that a cancer drug doxorubicin released slowly from chitosan-coated MSNs at pH 7.4 but released rapidly at pH 4.4 due to the pH-sensitivity of chitosan. Xu et al. [10] conjugated antibody to chitosan modified MSNs and the nanoparticles showed good performance in delivering TNF-α to breast cancer cells both *in vitro* and *in vivo*.

Recently, stimuli responsive drug delivery from MSNs causes considerable interests since it enables the on demand drug release at specific time and location. External stimuli such as pH, light, magnetic, temperature and chemical reagent have been demonstrated

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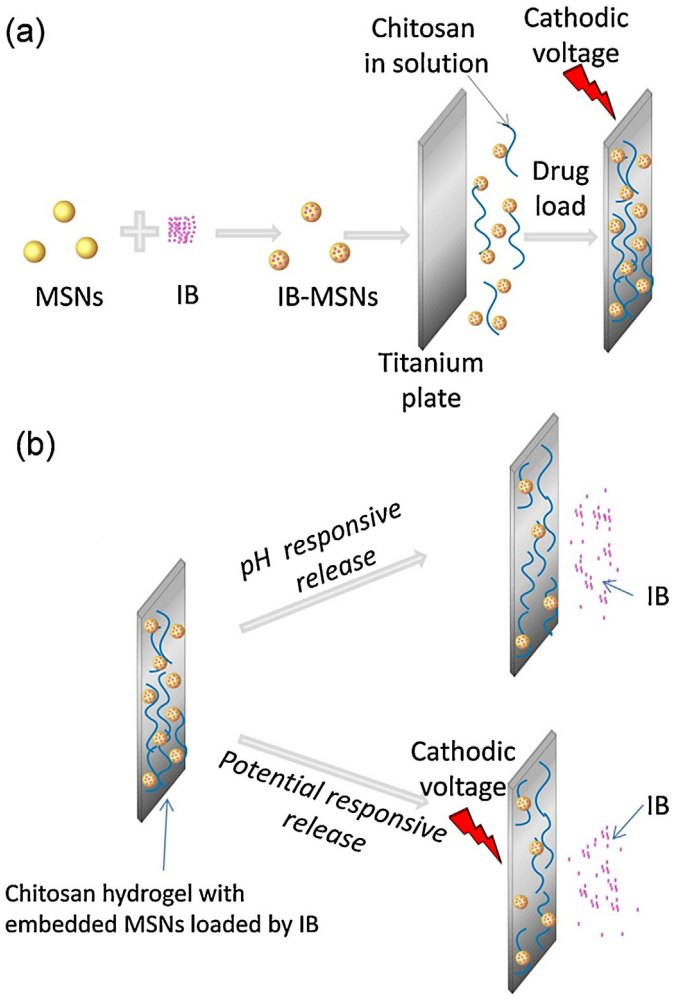
http://dx.doi.org/10.1016/j.colsurfb.2014.10.013
0927-7765/



Scheme 1. Illustration of the ibuprofen load (a) and release (b) from chitosan/IB-MSNs hydrogel.

to control the drug release efficiently [11–14]. However, there are few reports that utilize electrical potentials to trigger the drug release from MSNs. Electrical potential guided drug release poses the advantages of simplicity, accurate dosage control as well as easy coupling to bioelectronics. In our previous work, pH responsive chitosan hydrogel was electrodeposited on the surface of electrode and the drug release from the hydrogel was controlled by using electrical potentials [15,16]. However, the quick diffusion of the drug in chitosan hydrogel might cause large spontaneous drug release and compromise the electrical controllability.

The introduction of MSNs in chitosan hydrogel could substantially sustain the release of encapsulated drug [17]. In addition, the composite hydrogel exhibited good cell biocompatibility and pH responsive drug release [18,19]. Herein, we studied the stimuli-controlled ibuprofen (IB) release from chitosan/MSNs complex hydrogel formed on the titanium plate by electrocodeposition. The experimental procedure was illustrated in Scheme 1. IB was loaded in MSNs by immersing MSNs in hexane solution containing IB. The IB loaded MSNs (IB-MSNs) were dispersed in chitosan solution and codeposited with chitosan hydrogel on a titanium plate. The codeposition was performed by immersing a titanium plate (as a cathode) and a platinum wire to the chitosan solution (pH ~ 5) containing IB-MSNs. A cathodic voltage was applied to the titanium plate and the increased pH change induced the gelation of chitosan solution. During the codeposition process, IB-MSNs were entrapped in chitosan hydrogel. After removal of the titanium plate from the chitosan solution, an opaque chitosan hydrogel with IB-MSNs could be observed on the titanium plate. The release of ibuprofen from the hydrogel on titanium plate is responsive to pH, remarkably slower than that from bare MSNs and demonstrates a near linear release. Further, the ibuprofen release profile could be modified by applying external electrical potentials. The release accelerated when a high negative voltage was applied. The results demonstrated in this study suggest the possibilities of the dual responsive chitosan/MSNs hydrogel for controlled drug release.

2. Experimental

2.1. Materials

Chitosan provided as a coarse powder was purchased from Sigma with a deacetylation degree of 85% and a molecular weight of 200 kDa. Tetraethoxysilane (TEOS), cetyltrimethylammonium bromide (CTAB), anhydrous ethanol, ammonium hydroxide (30%) were purchased from Shanghai Reagent Co., Ltd (China). All other reagents were of analytical grade and were used without further purification.

2.2. Preparation of mesoporous silica nanoparticles

MSNs were synthesized by a sol–gel/emulsion method according to previously reported work [20]. Typically, TEOS (2 ml) and CTAB (0.32 g) were added in a mixture of water (110 ml) and anhydrous ethanol (52 ml) under a stirring speed of 700 rpm for 15 min, then 2 ml of ammonium hydroxide was added. The mixture was allowed to react for 3 h to produce a white precipitate. The white precipitate was collected by centrifugation (9000 rpm for 10 min) and washed with a large amount of water, then the particles were dried overnight at 60 °C and milled to fine power in a mortal. The particles were calcined at 550 °C for 5 h to remove the residual surfactant and 0.6 g MSNs were obtained for characterization and drug loading.

2.3. Ibuprofen loading on MSNs

A typical procedure for the load of IB was as follows [21]: MSNs (0.285 g) were added to 40 ml ibuprofen hexane solution (7 mg/ml) and stirred for 2 days at room temperature. Then the IB loaded MSNs (IB-MSNs) were collected by centrifugation (9000 rpm for 10 min) and washed with hexane, dried overnight at 60 °C. To measure the amount of IB loaded in MSNs, IB-MSNs (50 mg) was dissolved in 50 ml boiling sodium hydroxide solution (0.25 M) for complete IB release. The absorbance of the sodium hydroxide solution was measured at 264 nm and its concentration was calculated by referring to the standard curve. The standard curve was plotted by correlation known concentrations of IB in sodium hydroxide and their absorbances.

The IB loading capacity (LC) of IB-MSNs was defined as follow:

$$\mathrm{LC} = \frac{M_1}{M_2} \times 100\%$$

where M_1 is the mass of IB loaded in MSNs, M_2 is the mass of IB-MSNs.

2.4. Eletrocodeposition of chitosan and IB-MSNs as a complex hydrogel on a titanium plate

Chitosan solution was prepared by dissolving chitosan flakes in HCl solution (pH 3) under vigorous stirring and the undissolved flakes were removed by filtration. The pH was adjusted to ~5 by 1 M NaOH and NaCl was added to 50 ml chitosan solution to a final concentration of 0.25% (w/v). IB-MSNs (0.15 g) were dispersed in