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Smart composite materials based on chitosan microspheres embedded in thermosensitive hydrogel for controlled delivery of drugs

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ABSTRACT

Smart composite hydrogels (SCHs) consisting of chitosan (CS) microspheres physically embedded within a thermoresponsive hydrogel are synthesized and tested for their capacity of loading and long-term release of a small molecule drug. CS microspheres were used since they display pH-sensitive properties and have the capacity to bind electrostatically the opposite charged salicylic acid (SA), taken as model drug. These microspheres are ulterior physically entrapped within a thermoresponsive hydrogel based on poly(*N*-isopropylacrylamide-*co*-hydroxyethylacrylamide) copolymer, cross-linked with *N,N'*-methylenebisacrylamide. The morphology, swelling behavior, temperature and pH sensitivity, degradability and drug release behavior of the new smart drug delivery system were investigated. Swelling ratios as well as the sharpness of the phase transition, largely depended on the cross-linking degree. The thermoresponsive network slightly protected the CS microspheres from the in vitro degradation. *In vitro* studies showed that the SA followed a prolonged release profile from SCHs in accordance with pH and temperature.

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1. Introduction

Controlled drug delivery systems have been used to defeat the drawbacks of conventional drug formulations (Bajpai & Sonkusley, 2002; Graham & Mc-Neil, 1984). Even if large progress has been made in the controlled drug delivery area, in some cases (i.e. diabetes and rhythmic heart disorders) the drug has to be delivered in response to signals caused by disease and the necessary amount of drug could be adjusted upon the stimulation of such a signal.

Hydrogels have been used extensively in the development of the smart drug delivery systems (Hoffman, 1997). They are composed of three-dimensional network of hydrophilic polymer chains that could be cross-linked by covalent bonds, hydrogen bonding, van der Walls interactions or physical entanglements (Kamath & Park, 1993; Park, Skalaby, & Park, 1993). Hydrogels can entrap and protect the drug from hostile environments for the subsequent slow release by diffusion or erosion depending on their state of hydratation. They can also control drug release rate by changing the structure in response to environmental stimuli such as temperature, pH, electric and magnetic fields, solvent composition, light, ions, etc (Amin, Rajabnezhad, & Kohli, 2009; Bae, 1997; Hoffman, 1997). These stimuli-sensitive materials are also called "intelligent" or "smart" hydrogels (Park & Park, 1999).

Temperature-sensitive hydrogels have been studied more extensively since the triggering agents for controlled drug release are the changes in temperature (Bromberg & Ron, 1998; Fundueanu et al., 2005). The most popular thermosensitive hydrogel is that based on poly(*N*-isopropylacrylamide) (PNIPAAm). This hydrogel possess a transition temperature at about 33 °C (Bae, Okano, & Kim, 1990; Grinberg et al., 2000; Inomata, Wada, Yagi, Goto, & Saito, 1995) accompanied by a rapid decrease in the volume of the gel resulting in a fast release of entrapped drug and solvent (Gandhi, Paul, Sen, & Sen, 2015). However, it was found that the drug loaded within the PNIPAAm-based hydrogels is quickly released due to the swollen and porous PNIPAAm network (Bae, Okano, Hsu, & Kim, 1987; Hoffman, Afrassiabi, & Dong, 1986; Zhang, Wu, & Chu, 2004; Zhang, Zhuo, Cui, & Zhang, 2002).

Recently, smart drug delivery systems obtained by the incorporation of drug-loaded microspheres within the sensitive hydrogel have proved to accomplish the long-term drug delivery. The literature presents several reports concerning smart composite materials such as those based on PLGA microspheres or nanoparticles dispersed in chitosan/PVA hydrogel (Tang, Zhao, Li, & Du, 2010), thermoresponsive chitosan/β-glycerophosphate hydrogel (Joung,

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Choi, Park, & Park, 2007), thermoresponsive methylcellulose hydrogel (Lin, Sun, Jiang, Zan, & Ding, 2007), *etc*. In addition, drugs, peptides or growth factors-loaded CS microspheres were incorporated in poly(lactic acid) scaffolds (Niu, Feng, Wang, Guo, & Zheng, 2009), mucoadhesive hydrogel (El-Leithy, Shaker, Ghorab, & Abdel-Rashid, 2010), or in biodegradable CS scaffolds (Cai et al., 2007; Liu et al., 2012) for the same purpose. Of note, CS is frequently used for the construction of smart composite materials, both as continuous polymeric matrix for the incorporation of different kinds of particles and as microspheres to be embedded in various polymeric matrix. Indeed, CS with excellent biodegradable and biocompatible characteristics, is a naturally occurring polysaccharide which has been extensively applied in the pharmaceutical industry for its potential in the development of drug delivery systems (Illum, 1998; Morris, Kök, Harding, & Adams, 2010). In addition, due to the primary amino groups with a pKa of around 6.5, CS is recognized as a natural polymer with pH-sensitive properties.

In this work, we designed and synthesized a temperature- and pH-sensitive drug delivery system by incorporation of CS-based microspheres into poly(*N*-isopropylacrylamide-*co*-hydroxyethylacrylamide) (P(NIPAAm-co-HEAAm)) hydrogel. CS microspheres were obtained by suspension crosslinking technique. Salicylic acid, taken as model anionic drug, was loaded into CS microspheres after their physically incorporation into hydrogels. The smart properties of the new drug delivery system were investigated by analyzing the swelling ratio and response kinetics upon cooling and heating. The protective effect of the thermoresponsive network on the *in vitro* degradation of incorporated CS microspheres was studied. The release profiles showed a pattern according to pH and temperature.

2. Materials and methods

2.1. Materials

Low molecular weight chitosan (Mw = 104 KDa, DD = 83.5%) (CS), hydroxyethylacrylamide (HEAAm), and salicylic acid (SA) were purchased from Sigma-Aldrich Chemical Co. (St. Louis, USA). *N*-Isopropylacrylamide (NIPAAm), supplied from Sigma-Aldrich Chemical Co. (Milwaukee, WI, USA), was re-crystallized from hexane. Ammonium persulfate (APS), *N,N′*-methylenebisacrylamide (BisAAm), *N,N,N′,N′*-tetramethylethylenediamine (TEMED) were supplied from Fluka AG (Buchs, Switzerland).

Glutaraldehyde (GA) (aqueous solution 25%, w/v) was supplied by Fluka AG (Seelze, Germany).

Cellulose acetate butyrate (CAB) was purchased from Eastman Inc. (Kingsport, Tennesse, USA).

Dichloroethane (DCE) supplied from Chemical Company SA (Iasi, Romania) was used as received.

2.2. Methods

2.2.1. Preparation of chitosan microspheres

CS microspheres were prepared by the suspension cross-linking procedure. In a 500 mL reactor fitted with a mechanical stirrer, condenser, and thermometer, CS (1 g) was dissolved in 50 mL of an aqueous acetic acid solution (1%, v/v) and then dispersed in 100 mL of DCE containing 2.4 g CAB (as a stabilizer for suspension). This mixture was stirred at 1000 rpm for 1 h at 50 °C, then 1 mL of GA was added, afterwards the cross-linking reaction continued for another 2 h. Finally, the chitosan microspheres were recovered by filtration, successively washed with DCE, acetone, water, and acetone and dried in vacuum at 50 °C.

2.2.2. Preparation of smart composite material

0.85 g of a mixture of NIPAAm and HEAAm (9.5:2 molar ratio) were dissolved in 10 mL distilled water. After complete dissolution of monomers, various amounts of cross-linker (BisAAm) and CS microspheres were added and the mixture was left at room temperature for 2 days for a complete swelling of microspheres in the above solution. Dried nitrogen was bubbled through the solution for 50 min. Then, the initiator (APS) (3%, w/w, relative to monomers) and the accelerator (50 μL of TEMED) were added and the mixture was quickly transferred into a syringe (i.d. × h = 15 × 70 mm). After 24 h of polymerization, smart composite hydrogels (SCH_x; x means the percentage of BisAAm relative to monomers) were obtained. The resulting material was removed from the syringe and kept for 2 days in a large amount of water, frequently refreshed to remove the soluble fraction of polymer and initiator residues. All SCH samples were cut into cylinder-like pieces approximately 15 mm in diameter and 10 mm in thickness for the following studies. Finally, the hydrogel was recovered by drying at room temperature or by lyophilization for further investigations.

Similar preparation conditions were used for the smart hydrogels SH_x, without CS microspheres.

2.2.3. Morphological and dimensional analysis

The optical images of the SH and SCH samples were recorded by a Cannon digital camera. CS microsphere size was determined by measuring the diameters of at least 100 microspheres on scanning electron micrographs. The SHs and SCHs swollen in deionized water at room temperature (23 °C) were quickly frozen in liquid nitrogen and then freeze-dried (−57 °C, 5.5×10^{-4} mbar) for at least 24 h until all the solvent was sublimed. The freeze-dried hydrogel was carefully fractured and the interior morphology was observed by an Environmental Scanning Electron Microscope (ESEM), type Quanta 200, operating with secondary electrons in Low Vacuum, at 20 kV.

2.2.4. Temperature and pH responsive properties

2.2.4.1. The equilibrium swelling ratios. SHs and SCHs swelling ratio was measured at different temperatures ranging from 23 to 60 °C, controlled up to 0.2 °C, using a thermostated water bath. Preweighed samples were equilibrated in simulated physiological fluids (standard acidic solution (pH 1.2, 64 mM HCl + 50 mM KCl), standard phosphate buffer (pH 7.4, 50 mM Na_2HPO_4 + NaOH)) for at least 24 h at each predetermined temperature. Then, the samples were taken out from the water bath, excess liquid was wiped off from the surface with moistened filter paper, and were weighed. The swelling ratio was determined according to the following Eq. (1) (Ngah, Endud, & Mayanar, 2002).

$$\text{Swelling ratio} = \frac{W_s - W_d}{W_d} \quad (1)$$

Where W_s is the weight of the swollen hydrogel at equilibrium at each temperature and W_d is the weight of the dry weight sample.

The volume phase transition temperature (VPTT) of the hydrogel was determined as the inflexion point of the curve swelling ratio *vs* temperature by Boltzman fitting of the experimental data.

2.2.4.2. Swelling kinetics. The swelling kinetics of SCHs were studied by immersing dried samples in buffer solutions of pH 1.2 or 7.4, at 23 °C or 37 °C. The hydrogels were removed from medium at regular time intervals, wiped off with moistened filter paper and then weighed.

2.2.4.3. Swelling/deswelling kinetics. The oscillatory swelling behavior of SCHs was measured in buffer solutions of pH 1.2 or 7.4 maintained for 2 h at alternate temperatures of 23 and 42 °C. The SCHs were first equilibrated in buffer solutions at 23 °C, and

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