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Synthesis, characterization of biodegradable dextran–allyl isocyanate–ethylamine/polyethylene glycol–diacrylate hydrogels and their in vitro release of albumin

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Abstract

Based on dextran–allyl isocyanate–ethylamine (Dex-AE) and polyethylene glycol–diacrylate (PEGDA), a pH sensitive biodegradable hydrogel with improved protein release was prepared through UV photo-crosslinking. The Dex-AE precursor was prepared through a two-step chemical modification and characterized by FT-IR and ^{1}H NMR. The effects of reaction conditions on the synthesis of Dex-AE were studied. The interior morphology data by scanning electron microscopy (SEM) revealed that an increase in Dex-AE content led to an initial decrease in pore size of the microstructure of the Dex-AE/PEGDA hydrogels, but a further increase in Dex-AE content resulted in a relatively looser network structure. The swelling data indicated that the swelling ratio depended on the precursor feed ratio and was correlated to the morphology of the microporous network structure. The pH sensitive property of the Dex-AE/PEGDA hydrogels was studied in different pH buffer solutions and was found that these hydrogels were pH sensitive due to the presence of ample pendant amino groups. The ionic strength data demonstrated that the Dex-AE/PEGDA hydrogels exhibit the highest swelling ratio in pure water, but the swelling ratio became lower as the ionic strength of the media increased. The in vitro albumin release from these hydrogels was examined in different pH (3.0, 7.4) buffer solutions. Both the protein loading and release data indicated that the Dex-AE/PEGDA hydrogels had more protein loading and sustained release capability than pure PEGDA hydrogel, and this ability increased as the Dex-AE composition increased; the Dex-AE/PEGDA hydrogel also showed a faster BSA release in a lower pH than a higher pH medium.

Keywords: Dextran; Polyethylene glycol; Hydrogel; Biodegradable; Albumin

1. Introduction

Polyethylene glycol (PEG) is a unique amphiphilic polymer, which has been explored for many biomedical applications because of its well-known hydrophilicity, biocompatibility, and nonbiodegradability. PEG has been employed to improve biocompatibility (Chung, Kim, Kim, & Rhee, 2003; Zhang, Li, Dong, Zhao, & Zhang, 2002), promote peptide immobilization (Hern & Hubbell, 1998; Wang, Tan, Kang, & Neoh, 2002), prolong protein drug circulating time (Greenwald, Choe, McGuire, & Conover, 2003; Koumenis et al., 2000), increase bioactivity (Muslim et al., 2001), and reduce immunogenicity (Hu, Zhai, He, Mei, & Liu, 2002). Interestingly, PEG is not biodegradable but it can be readily excreted from the body via kidney and liver, and forms nontoxic metabolites, which makes it more suitable for drug delivery. Some PEG-based hydrogels are already used as drug carriers and wound care products. Due to the above properties, PEG-based products have been approved by FDA for human intravenous (i.v.), oral and dermal applications (Greenwald et al., 2003).

The potential value of proteins as therapeutics has long been recognized. A wide range of protein-based drugs have become commercially available as therapeutic agents.

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However, many therapeutic proteins suffer from short circulating half time and low stability in vivo, and therefore sustained release of proteins has been difficult. In order to reduce protein loss through kidney filtration, Abuchowski, McCoy, Palczuk, Vanes, and Davis (1977) increased the molecular weight of proteins by conjugating PEG onto proteins, which was later termed as PEGylation. PEGylation can increase the molecular weight of proteins up to 70 kDa, and has significantly increased the circulating half time of proteins in vivo, reduced immunogenicity and antigenicity, and retention of a large portion of proteins' bioactivity. It has been postulated that these effects are due to a shell of PEG macromolecules around the proteins (Greenwald et al., 2003). Such a sheltering could sterically hinder the reaction of immune cells and protects sheltered proteins from proteolytic inactivation.

For years, hydrogels have been proved to be another effective way for protein controlled release (Wu, Zhang, & Chu, 2003; Zhang & Chu, 2002a, 2002b, 2002c, 2002d; Zhang & Chu, 2001). Hydrogels are three-dimensional crosslinked network that can swell dramatically in the presence of water/biological fluids and retain the absorbed liquid while maintaining their structure. Due to their structural similarity to natural living tissues (Ratner & Hoffman, 1976), hydrogels have found various applications in the fields of cell culture, tissue engineering, and controlled drug release. Most hydrogels are not limited to work only as the carriers for controlled release; they can also protect proteins from their hostile environment. In addition, hydrogels also have a good compatibility with proteins (Chen, Jo, & Park, 1995; Molina, Li, Martinez, & Vert, 2001), which makes hydrogels more suitable for protein delivery. Recently, physically crosslinked hydrogels have shown some promising applications in the biomedical fields (Ikada, Jamshidi, Tsuji, & Hyon, 1987; Inoue, Chen, Hoffman, & Nakamae, 1998; Jeong, Kim, & Bae, 2002; Nakamae, Miyata, & Hoffman, 1994). However, the more general approach based on chemical crosslinking for designing biodegradable hydrogels continues to be highly desirable because of their easy manipulation by controlling the crosslinking agents, initiator concentrations, ratio, and concentration of precursors.

Intelligent hydrogels have received more attention than other hydrogels. These types of hydrogels are capable of responding to external stimuli, such as temperature (Chen & Hoffman, 1995; Hoffman, 1987; Peppas & Klier, 1991; Zhang & Chu, 2003, 2004a, 2004b; Zhang, Lewis, & Chu, 2005; Zhang, Sun, Chu, 2004; Zhang, Sun, Wu, & Chu, 2004), pH (Chen et al., 1995; Peppas & Klier, 1991; Zhang, Wu, & Chu, 2004), electric field (Kim, Yoon, Lee, & Kim, 2003; Liu & Calvert, 2000), and photo field (Mamada, Tanaka, Kungwatchakun, & Irie, 1990). Generally, an ideal controlled release mechanism for a drug carrier is the zero-order drug release; namely, the release rate is independent of time. However, it is more desirable if drugs could be administered under temporal modulations, such as temperature, pH, light, and so on to meet some physiological need (Li & D'Emanuele, 2001). It is known that all pH sensitive hydrogels have either acidic or basic groups, which can respond to pH environment by gaining or losing protons. The stomach has a low pH (<3), which is quite different from the neutral intestinal environment, and this has drawn more attention to pH sensitive hydrogels.

Dextran is a biodegradable polysaccharide and composed of linear α-l,6-linked D-glucopyranose residues with a low percentage of α-1,2, α-1,3, and α-l,4 linked side chains (Stenekes, Talsma, & Hennink, 2000). Dextran is a colloidal, hydrophilic, biocompatible, and nontoxic polymer, and can be biodegraded by dextranase (Franssen, Vandervennet, Roders, & Hennink, 1999). From the structure point of view, dextran has chemically active functional groups (i.e., –OH group) that can be chemically modified to form hydrogels via crosslinking. Because of these properties, dextran and their hybrids have been intensively investigated as drug carriers. For examples, dextran-based biomaterials have been employed in cell immobilization (Massia, Stark, & Letbetter, 2000) and gene transfection (Azzam, Eliyahu, Makovitzki, & Domb, 2003) and as carriers for a variety of pharmaceutically active drugs (Chu, 2003; Kim, Jeong, Kim, Lee, & Kim, 2001; Kim & Chu, 2000a, 2000b; Won & Chu, 1998, 2000; Zhang & Chu, 2002a, 2002b, 2002c, 2002d).

In this study, the PEG derivative (PEG–diacrylate, PEGDA) was chemically incorporated into dextran derivative (dextran–allylisocyanate–ethylamine, Dex-AE) via photo-crosslinking to form hybrid biodegradable hydrogels having pH sensitivity. The chemical structure and morphology of the resulting hybrid hydrogels and the effects of reaction time and temperature, the molar ratio of reactants and catalyst on the degree of substitution were examined. The swelling property and protein release profiles of these hybrid hydrogels were studied as a function of the feed ratio of PEGDA to Dex-AE precursors and pH. Bovine serum albumin (BSA) was chosen as the model protein for the controlled release study.

2. Experimental section

2.1. Materials

Dextran (Dex) of MW 43,000, allyl isocyanate (AI), magnesium chloride, and sodium chloride were purchased from Sigma Chemical Company (St. Louis, MO). Dextran was dried in a vacuum oven for 24 h at 50 °C before use. Dimethyl sulfoxide (DMSO), dibutyltin dilaurate (DBTDL), 2-bromoethylamine hydrobromide (BEAHB), triethylamine, acryloyl chloride, and polyethylene glycol (PEG) of MW 8000 and other chemicals were purchased from Aldrich Chemical Company (Milwaukee, WI), and dried in a vacuum oven for 24 h at room temperature before use. 2-Hydroxy-l-[4-(hydroxyethoxy)phenyl]-2-methyl-l-propanone (HHPMP) was donated by Ciba Specialty Chemicals Corporation. Bovine serum albumin (BSA) of MW 69,000 was purchased from Sigma Chemical