Carbohydrate Polymers 106 (2014) 84–93

Contents lists available at ScienceDirect

Carbohydrate Polymers

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

Characterization and properties of carboxymethyl cellulose hydrogels crosslinked by polyethylene glycol

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ARTICLE INFO

Article history:
Received 19 December 2013
Received in revised form 31 January 2014
Accepted 5 February 2014
Available online 14 February 2014

Keywords:
Biodegradable hydrogel
Carboxymethyl cellulose
Polyethylene glycol
Protein adsorption
Protein release.

ABSTRACT

Novel hydrogels were prepared from carboxymethyl cellulose (CMC) sodium salt by crosslinking with polyethylene glycol diglycidyl ether (PEGDE). The detailed structures of the hydrogels were determined via FTIR and solid-state NMR spectroscopic analyses. Increasing the feed ratio of PEGDE to CMC in the reaction mixture led to an increase in the crosslinking degree, which enhanced the physical strength of the hydrogels. The hydrogels exhibited enzyme degradability, and after 3 days of incubation with cellulase, 62–28 wt% of the CMC in the hydrogel was degraded under the conditions employed in this study. In addition, the hydrogels exhibited protein adsorption and release abilities, and the amounts of proteins adsorbed on the hydrogels and the release profile of the proteins depended on the protein sizes and crosslinking degree of the hydrogels. These unique properties might enable the use of CMC-based hydrogels as drug delivery system carriers for protein-based drugs if the biological safety of the hydrogel can be verified.

1. Introduction

Carboxymethylcellulose sodium salt (CMC), obtained from the reaction of the hydroxyl groups of the anhydroglucose units (AGUs) of cellulose with chloroacetic acid, is an important water-soluble cellulose ether used in food, cosmetics, and paints as a viscosity modifier, thickener, emulsion stabilizer, and water-retention agent. CMC also has tremendous potential for use in pharmaceutical products including site-specific or controlled-release drug delivery system carrier matrices due to its high biocompatibility, biodegradability, and low immunogenicity (Colombo, Bettini, Sabti, & Peppas, 2000; Ugwoke, Kaufmann, Verbeke, & Kinget, 2000). Crosslinked CMC has also been accomplished with the use of bifunctional crosslinking agents such as epichlorohydrin (Chang, Duan, Cai, & Zhang, 2010), diepoxy (Lin, Kumar, Rozman, & Noor, 2005; Rodŕiguez, Alvarez-Lorenzo, & Concheiro, 2003; Kono, Onishi, & Nakamura, 2013), and dicarboxylic acid compounds (Akar, Antinişk, & Seki, 2012). Crosslinked CMC generally absorbs large amounts of water, and swells to form hydrogels with excellent physical properties and dynamic viscoelasticities (Nerurkar, Elliott, & Mauck, 2010). These CMC-based hydrogels were recently investigated for their use in wound dressing, drug delivery, agriculture, and sanitary pads, as well as for trans-dermal systems, dental materials, implants, injectable polymeric systems, ophthalmic applications, and hybrid-type organs (Sannino, Demitri, & Madaghiele, 2009; Saha, Saarai, Roy, Kitano, & Saha, 2011).

Among the various chemical crosslinking agents for CMC, epichlorohydrin (ECH) is the most popular and extensively used reagent to produce hydrogel materials because ECH is a strong etherification agent toward the hydroxyl group (Chang, Duan, Cai, & Zhang, 2010). The reaction of CMC with ECH in concentrated solutions of aqueous sodium hydroxide (NaOH) results in the formation of diether crosslinks between the hydroxyl groups of CMC and ECH to form a hydrogel (Ali Hebeish, Hashem, Abd El-Hady, & Sharaf, 2013; Yang, Fu, Liu, Zhou, & Li, 2011). However, ECH produces a large amount of poisonous and carcinogenic byproducts under strong alkaline conditions (Wester, van der Heijden, Bwiisschop, & van Esch, 1985). Other groups obtained similar CMC-based hydrogels with the use of ethylene glycol diglycidyl ether (EGDE) as a crosslinker (Lin et al., 2005; Rodŕiguez et al., 2003). It

Abbreviations: AGU, anhydroglucose unit; BPA, bisphenol A; BSA, bovine serum albumin; CMC, carboxymethyl cellulose; CD, cyclodextrin; DP, degree of polymerization; DD/MAS, dipolar-decoupled/magic angle spinning; DOSY, diffusion-ordered spectroscopy; DSS, 4,4-dimethyl-4-silapentane-1-sulfonic acid; ECH, epichlorohydrin; EGDE, ethylene glycol diglycidyl ether; FTIR, Fourier transform infrared spectroscopy; pI, isoelectric point; Mw, molecular weights; NMR, nuclear magnetic resonance; PBS, phosphate-buffered saline; PEG, polyethylene glycol; PEGDE, polyethylene glycol diglycidyl ether; SEM, scanning electron microscopy; SPINAL64, small phase incremental alternation with 64 steps; NaOH, sodium hydroxide.

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http://dx.doi.org/10.1016/j.carbpol.2014.02.020
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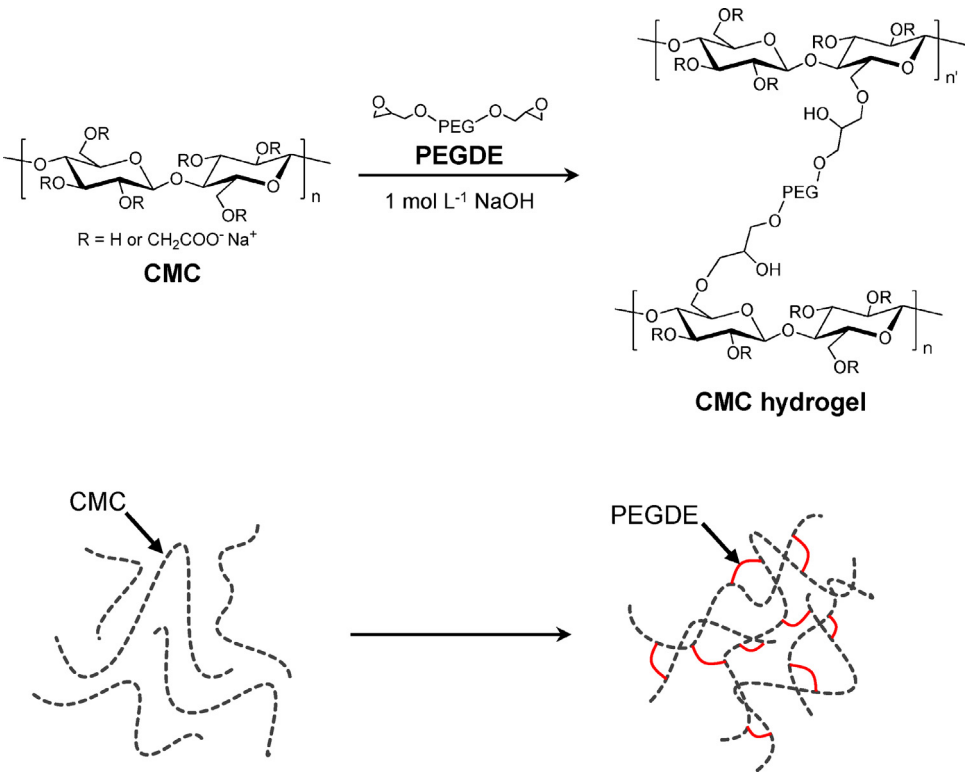

Fig. 1. Scheme for CMC hydrogel synthesis via crosslinking of CMC with PEGDE (top), and schematic illustration of the formation of the CMC hydrogel from CMC and PEGDE (bottom). In the top figure, the linkage positions of CMC and PEGDE are shown at C6 of AGU in CMC. PEGDE can also react with the hydroxyl groups of the other position of CMC and PEGDE to form cross-linked linkages. This possibility was omitted in this figure.

was recently reported that cyclodextrin (CD)-grafted CMC hydrogel beads were prepared from a mixture of CMC and β-cyclodextrin (β-CD) by the crosslinking reaction with ethylene glycol diglycidyl ether (Kono et al., 2013c). The CD-CMC hydrogels showed excellent water absorption as well as a high adsorption capacity toward bisphenol A (BPA) in water.

Polyethylene glycol (PEG) is a synthetic polyether that is readily available in a range of molecular weights. The polymer is amphiphilic and soluble in water as well in many organic solvents including ethanol, acetone, toluene, and chloroform (Bailey & Koleske, 1991; Bailey & Koleske, 1976). This polymer has been found to be nontoxic and is approved by the U.S. Food and Drug Administration for use as an excipient or as a carrier in different pharmaceutical formulations, foods, and cosmetics (Fuertges & Abuchowski, 1990). In addition, most PEGs with molecular weights (Mw) < 1,000 are known to be rapidly removed from the human body (Working, Newman, Johnson, & Cornacoff, 1997), which contributes to their wide use in biomedical research, drug delivery, tissue engineering scaffolds, surface functionalization, and so forth (Torchilin, 2002; Craig, 2002).The wide range of available end-groups, e.g., azide, biotin, thiol, carboxyl acid, hydroxyl, and epoxy-functionalized PEGs, also enhances the wide spread use of PEGs in biomedical and biomaterial research (Zalipsky, 1995).

Therefore, the preparation of a novel biodegradable hydrogel from CMC with polyethylene glycol diglycidyl ether (PEGDE) as a crosslinking agent, as shown in Fig. 1, is described here. By changing the feed ratio of PEGDE to CMC, we prepared a series of CMC-based hydrogels, and characterized the structure of the hydrogels using FTIR, solid-state NMR, and scanning electron microscopy (SEM). The viscoelasticities of the swelled hydrogels were characterized by using a rheometer. In addition, we also evaluated the protein adsorption and release properties of the CMC hydrogels using lysozyme and bovine serum albumin (BSA) as model proteins.

2. Experimental

2.1. Materials

Pharmaceutical grade CMC was kindly supplied by CP Kelco Co., Ltd. (Finland). PEGDE was purchased from Sigma–Aldrich Co. (USA). The weight-average molecular weight (Mw) and degree of substitution of the starting material CMC, and average degree of polymerization (DP) of PEGDE were estimated by solution-state NMR spectroscopic analysis before use, and the procedure is described below (see Section 2.3). Deuterium oxide (D_2O; 99.9% isotopic purity) containing 4,4-dimethyl-4-silapentane-1-sulfonic acid (DSS) as an internal standard was purchased from Sigma-Aldrich Co. (USA). *Trichoderma viride* Cellulase (ONOZUKA R-10) was purchased from Yakult Pharmaceutical Co. Ltd. (Japan). Protein assay kit II was purchased from Bio-Rad Laboratories Co. (USA). BSA and egg white lysozyme were purchased from Wako Pure Chemicals Co. (Japan). All other chemicals were purchased from Kanto Chemicals (Japan) and Wako Pure Chemicals (Japan), were of reagent grade, and were used as received.

2.2. Preparation of hydrogels

A series of five CMC hydrogels (entries **1**–**5**) were prepared from CMC with PEGDE. A typical procedure to prepare the CMC hydrogel was performed as follows: 5.0 g of CMC (23 mmol for monomeric unit) was completely dissolved in 100 mL of 1.5 mol L^{-1} aqueous NaOH solution, and 0.50 g of PEGDE (1.1 mmol) was subsequently added to the solution with stirring at 300 rpm using a Teflon impeller at 25 °C. After 10 min, the crosslinking reaction was performed at 60 °C with stirring at 300 rpm for 3 h. The reaction mixture was washed twice with a solution of 1:1 (v/v) deionized water and ethanol, and the resultant reaction mixture was dialyzed