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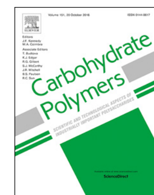
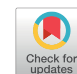


Controlling the degradation of an oxidized dextran-based hydrogel independent of the mechanical properties



Punnida Nonsuwan[a,b], Akimasa Matsugami[c], Fumiaki Hayashi[c], Suong-Hyu Hyon[d], Kazuaki Matsumura[a,*]

[a] School of Materials Science, Japan Advanced Institute of Science and Technology, 1-1 Asahidai, Nomi, Ishikawa 923-1292, Japan
[b] Department of Chemistry, Faculty of Science, Chulalongkorn University, 254 Phayathai Road, Pathumwan, Bangkok 10330, Thailand
[c] Advanced NMR Application and Platform Team, NMR Research and Collaboration Group, NMR Science and Development Division, RIKEN SPring-8 Center, 1-7-22 Suehiro-cho, Tsurumi-ku, Yokohama, Kanagawa 230-0045, Japan
[d] Joint Faculty of Veterinary Medicine, Kagoshima University, 1-21-24, Korimoto, Kagoshima 890-8580, Japan

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ABSTRACT

The objective of this study is to control and elucidate the mechanism of molecular degradation in a polysaccharide hydrogel. Glycidyl methacrylate (GMA) immobilized dextran (Dex-GMA) was oxidized by periodate to introduce aldehyde groups (oxidized Dex-GMA). The hydrogel was formed by the addition of dithiothreitol to the oxidized Dex-GMA solution through thiol Michael addition with the preservation of the aldehyde group for degradation points. It was experimentally determined that the degradation of this hydrogel can be controlled by the addition of amino groups and the speed of degradation can be controlled independently of mechanical properties because crosslinking and degradation points are different. In addition, the molecular mechanism of the crosslinking between the thiol and aldehyde groups was found to control the degradation of dextran derivatives. It is expected that these results will be beneficial in the design of polymer materials in which the speed of degradation can be precisely controlled. In addition, the cytotoxicity of oxidized Dex-GMA was approximately 3000 times lower than that of glutaraldehyde. The low cytotoxicity of the aldehyde in oxidized Dex-GMA was the likely reason for the harmless functionalized polysaccharide material. Possible future clinical applications include cell scaffolds in regenerative medicine and carriers for drug delivery systems.

1. Introduction

Hydrogels are crosslinked polymer networks with a large number of hydrophilic domains. They can expand in numerous solvents and aqueous environments without dissolving owing to the chemical or physical bonds formed between polymer chains (Bhattarai, Gunn, & Zhang, 2010; Hoare & Kohane, 2008). Natural polymers, specifically polysaccharides, are frequently used for hydrogel preparation because of their biocompatibility and chemical structure; this facilitates the development of desirable functionalized materials (Maia, Ferreira, Carvalho, Ramos, & Gil, 2005). Until now, low-toxicity, biocompatible, and degradable hydrogels have been designed using polysaccharides and functionalized polysaccharides for biomedical applications such as tissue engineering scaffolds, wound dressings, and controlled drug delivery systems (Chen et al., 2017; Ferreira et al., 2007; Jukes et al., 2010; Mehvar, 2000; Möller, Weisser, Bischoff, & Schnabelrauch, 2007; Van Tomme & Hennink, 2007; Zhao et al., 2015). For example, alginate and its derivative hydrogels are compatible with a variety of techniques for controlling gelling and possess desirable physical and chemical properties that can be used to facilitate cell adhesion and control the speed of degradation, all of which can be combined to promote cell transplantation (Augst, Kong, & Mooney, 2006). The periodate oxidation of alginate, which can be crosslinked with multivalent cations (Ca^{2+}) to produce hydrogels, was observed to degrade in vitro in a phosphate buffer saline solution (PBS) (pH 7.4, 37 °C) within nine days (Bouhadir et al., 2001). These hydrogels can potentially be used in cartilage-like tissue formation. In addition, self-healing polysaccharide hydrogels were developed (Zhao et al., 2015). Hydrogel networks are attributed to two sensitive crosslinked bonds, i.e., imine bonds and acylhydrazone bonds, which impart the self-healing capability of hydrogels. The same group explored the integration of carboxymethyl cellulose-based hydrogels with photoluminescent performance to provide the dual function of self-healing and photoluminescence under ultraviolet light (Chen et al., 2017). Such a hydrogel can be developed

* Corresponding author.
E-mail address: mkazuaki@jaist.ac.jp (K. Matsumura).

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as a sealant for vessels and stomach mucosa perforation. The position of an adhesive hydrogel can be easily detected using a photoluminescent emitter; this provides high potential for application in the tissue engineering field. Focusing on hydrogel drug delivery systems, an active therapeutic agent was integrated with a polymeric network structure that could control its release rate by allowing a hydrogel to safely degrade in the body when it was no longer required (Jogani, Jinturkar, Vyas, & Misra, 2008). Biodegradable polysaccharides, such as chitosan, alginate, xanthan gum, and dextran, have been widely researched for potential applications in drug carriers (Debele, Mekuria, & Tsai, 2016; Liu, Jiao, Wang, Zhou, & Zhang, 2008; Morris, Kok, Harding, & Adams, 2010; Togo et al., 2013). Among these, dextran has received significant attention.

Dextran is a bacterial polysaccharide that is broadly applicable in the biomedical field owing to its biocompatibility (Cadee et al., 2000; Ferreira et al., 2004), low toxicity (Hyon, Nakajima, Sugai, & Matsumura, 2014), high natural abundance, and ability to degrade via enzymes in various parts of the human body such as the spleen, liver, and colon. In addition, it is available in a wide range of molecular weights (Khalikova, Susi, & Korpela, 2005; Mehvar, 2000) Furthermore, dextran contains a large number of hydroxyl groups, which provide it with high hydrophilicity and enable it to be used in chemical functionalization (Levesque & Shoichet, 2007; Maia et al., 2005; Massia & Stark, 2001; Mehvar, 2000). Hyon et al. (2014) prepared hydrogels via the reaction between the aldehyde groups in periodate oxidized dextran and the amino groups in poly-L-lysine. In this case, the hydrogels exhibited degradation in PBS. Degradation time could be controlled by the rate of aldehyde introduction and amine concentration. The mechanism of the degradation was reported as follows: The main chain of the oxidized dextran was degraded by the Maillard reaction, which was triggered by Schiff base formation between the aldehyde and amino groups. A two-dimensional (2D) nuclear magnetic resonance (NMR) scan revealed that the partial hemiacetal structures produced by the periodate oxidation reacted with the amino groups and underwent an Amadori rearrangement, which led to the scission of the glucose unit ring (Chimpibul et al., 2016) (Fig. S1). This study is based on this reaction, which is utilized to overcome the following drawback: In previous works, degradation speed depended on the number of chemical crosslink points during gelation because the crosslink points formed by the reaction between the aldehyde groups in the oxidized dextran and the amino groups in poly-L-lysine triggered the degradation of the hydrogel (Kirchhof et al., 2015; Togo et al., 2013). However, as the formation and degradation of this hydrogel occurred simultaneously after the Schiff base formation reaction between the aldehyde and amino groups, it was difficult to control the timing of the degradation. In addition, as the mechanical properties of the hydrogel were determined by the number of crosslinking points, degradation time also depended on mechanical properties, much like stiff hydrogels exhibit longer degradation times while soft hydrogels exhibit shorter degradation times. If degradation control that is independent of mechanical properties, such as hard/fast or soft/slow combinations, can be identified with respect to time and space, these hydrogels could prove to be valuable platform materials for the fabrication of biodegradable scaffolds and drug carriers.

In this study, glycidyl methacrylate (GMA) was immobilized into dextran (Dex-GMA) and oxidized by sodium periodate to introduce aldehyde groups, thereby creating oxidized Dex-GMA. Oxidized Dex-GMA was crosslinked with dithiothreitol (DTT) by a thiol Michael addition reaction to form a hydrogel with the remaining aldehyde groups. Then, a posteriori degradation was controlled by the addition of an amine source so that the degradation was independent of the mechanical properties of the hydrogels. It is considered that this novel strategy may open new avenues of approach to create tissue engineering and drug delivery system materials via unique chemical stimuli (amino group) responsive degradation control.

2. Experimental procedure

2.1. Materials

Dextran (molecular weight (Mw) = 70 kDa) was acquired from Meito Sangyo (Nagoya, Japan), GMA and DTT were purchased from TCI (Tokyo, Japan), and 4-Dimethylaminopyridine (DMAP) was obtained from Sigma Aldrich (St. Louis, MO, USA). Acetyl cysteine (Ac-Cys-OH) was obtained from Watanabe Chemical Ind., Ltd. (Hiroshima, Japan), and sodium periodate ($NaIO_4$), disodium hydrogen phosphate (Na_2HPO_4), sodium dihydrogen phosphate (NaH_2PO_4), glycine, and other chemicals were purchased from Nacalai Tesque, Inc. (Kyoto, Japan). All chemicals were used without purification.

2.2. Synthesis of oxidized Dex-GMA

Dex-GMA was synthesized by applying the method reported by Liu et al. (2015). 5 g of dextran was combined with 20 mL of dimethyl sulfoxide (DMSO), and the solution was stirred until dextran was completely dissolved. Then, the transparent solution was stirred for 30 min under nitrogen gas. Next, 0.8 g (6.5 mmol) of DMAP and 2.2 g (15.5 mmol) of GMA were added to the solution under nitrogen gas for 30 min. The solution was stirred at 50 °C for 12 h, followed by the addition of 6.5 mmol of hydrochloric acid (HCl) to the solution mixture to neutralize DMAP. The mixture was dialyzed against distilled water for one week using a dialysis membrane (MWCO = 3.5 kD). The resulting product was air dried for 48 h at 47 °C and vacuum dried for 48 h at 25 °C to obtain the Dex-GMA derivative as a pale yellow-brown flake product.

Oxidized Dex-GMA was synthesized by the oxidation of Dex-GMA with sodium periodate (Hyon et al., 2014). Here, 2.5 g of Dex-GMA was dissolved in 10 mL of distilled water, and various amounts of sodium periodate (0.375, 0.75, and 1.25 g) were dissolved in 5 mL water. The solutions of Dex-GMA and sodium periodate were mixed, and the reaction was allowed to continue at 50 °C for 1 h. The mixture was dialyzed against distilled water for 32 h using a dialysis membrane (MWCO = 3.5 kD). The resulting product was processed by air drying for 48 h at 47 °C and freeze drying for 48 h to obtain oxidized Dex-GMA. In addition, oxidized dextran without GMA was synthesized by following the same method, except that dextran was employed as the starting material.

2.3. Characterization of oxidized Dex-GMA

2.3.1. Characterization of oxidized Dex-GMA with nuclear magnetic resonance (NMR) spectroscopy

The synthesized products were characterized by ^{1}H NMR (600, 700, and 900 MHz equipped with a cryogenic probe, Bruker). Two-dimensional NMR techniques were used to analyze oxidized Dex-GMA, including ^{1}H–^{13}C heteronuclear single quantum correlation spectroscopy (HSQC), ^{1}H–^{13}C heteronuclear multiple-bond correlation spectroscopy (HMBC), total correlation spectroscopy (TOCSY), and double quantum filtered-correlation spectroscopy (DQF-COSY). The results of the ^{1}H NMR spectroscopy were used to investigate the degree of substitution (% DS) by comparing the ratio of the area under the proton peaks at 2.0 ppm (methyl protons in GMA) to the peak at 3.3–4.2 ppm (dextran sugar unit protons).

2.3.2. Determination of aldehyde content

The amount of aldehyde content in functionalized dextran was determined using the fluorometry method (Li, Sritharathikhun, & Motomizu, 2007). To prepare the mixture solution, 2.5 ml of 4.0 M ammonium acetate, 1.0 ml of 0.2 M acetoacetanilide (AAA), 1.0 ml of ethanol, and a series of standard glutaraldehyde solutions or samples were combined. Then, the mixtures were diluted to 5 mL with purified water and left for 10 min. The relative fluorescence intensities of the

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