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Synthesis and characterization of Schiff base contained dextran microgels in water-in-oil inverse microemulsion

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ABSTRACT

Polysaccharide-based microgels with high water content, excellent biocompatibility and controllable particle size have been widely studied as ideal candidates for drug release and delivery. In this study, microgels based on dextran were developed *via* the Schiff base formation between aldehyded dextran and ethylenediamine in a water-in-oil (W/O) microemulsion. Particle size of the resulted microgel was controllable between 800 and 1100 nm by modulating the amount of the employed co-surfactants (Span 80/Tween 80). Furthermore, fluoresceins (*e.g.*, aminofluorescein) and drugs (*e.g.*, doxorubicin) with free amino groups can be conjugated onto the network of the dextran-based microgel *via* Schiff base linkages. Since the Schiff base linkages are degradable *via* hydrolysis and their stability decreases with the environmental pH decreases, the resulted Schiff bases contained microgel showed a pH dependent degradation profile. These results indicated that the pH-sensitive microgel based on dextran could be used as promising drug delivery systems for biomedical applications.

1. Introduction

Hydrogels are there-dimensional polymeric networks that capable of imbibing large amount of water or biological fluids while remaining insoluble in aqueous solutions (Peppas, Bures, Leobandung, & Ichikawa, 2000). Since the pioneer work of Wichterle & Lim (1960) on a type of hydrophilic gel and its biological applications in the early 1960s, lots efforts and studies have been devoted to exploring the potentials of hydrogels, especially for their applications as biomaterials (Hoare & Kohane, 2008; Lee & Mooney, 2001; Lin & Metters, 2006). Generally, hydrogels can be formulated into a variety of physical forms, such as micro/nanosized particles, coatings or membranes, depending on their applications. Micro/nanosized hydrogel particles (also known as micro/nanogels) are particulate networks composed of hydrophilic or amphiphilic polymers, which have unique properties by combining the characteristics of hydrogel (extremely high water content) with micro/nanoparticles (small size, large surface area). Due to their excellent biocompatibility, high loading capacity, and responsiveness to environmental factors (pH, temperature, and ionic strength), hydrogel particles are considered as promising delivery systems for drug, biomacromolecules and imaging agents (Hamidi, Azadi, & Rafiei, 2008; Kabanov & Vinogradov, 2009; Li et al., 2013, 2015; Satarkar, Biswal, & Hilt, 2010; Smith & Lyon, 2012).

Hydrogels can be prepared from synthetic or natural polymers, and natural polymer-based hydrogels have recently attracted many researchers' interests owning to their intrinsic good biocompatibility, low toxicity and biodegradability (Bhattarai, Gunn, & Zhang, 2010; Coviello, Matricardi, Marianecci, & Alhaique, 2007; Giri et al., 2012; Peppas et al., 2000; Xu, Jha, Harrington, Farach-Carson, & Jia, 2012). Polysaccharides are natural polymers consisting of repeat monosaccharide units. As natural biomaterials, polysaccharides do not suffer from some of the disadvantages of other natural polymer, such as immunogenicity and the potential risk of transmitting animal-originated pathogens (Liu, Jiao, Wang, Zhou, & Zhang, 2008). In addition, there are a large number of reactive groups on their molecular chains, such as hydroxyl (—OH), carboxyl (—COOH) and amino groups ($—NH_2$), which make polysaccharides can be easily modified chemically and biochemically. Amongst those widely used polysaccharides, dextran is a highly hydrophilic and biocompatible polymer consisting mainly of linear chains of α-1,6 linked glucopyranose residues, and has long been investigated as a blood plasma substitute since the early 1940s. Recently, dextran and its derivatives with good biocompatibility have become of interest as carrier materials for drug, gene, protein and imaging probe delivery (Lin et al., 2015; Pacelli, Paolicelli, & Casadei,

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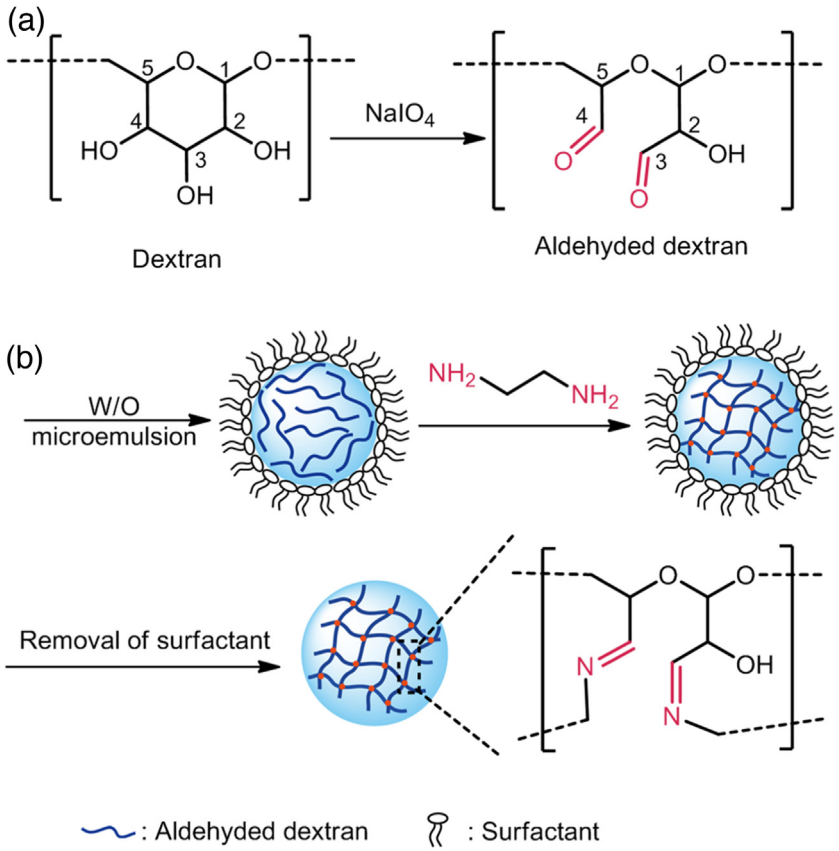

Scheme 1. Schematic illustration of the synthesis of dextran-based microgels in W/O inverse microemulsion. (a) Periodate oxidation of dextran, (b) Chemical cross-linking of aldehyded dextran in W/O inverse microemulsions.

2015; Peng, Tomatsu, Korobko, & Kros, 2010; Su et al., 2013; Wang et al., 2009). In previous studies (Su et al., 2013; Wang et al., 2009), we have developed a series of micelle nanoparticles self-assembled from amphiphilic dextran, and their functions as imaging probe and drug carrier were investigated. *In vitro* and *in vivo* tests demonstrated that these dextran micelles were highly biocompatible and can be used as promising carrier systems. These attractive properties make dextran-based hydrogel particles ideal candidates as particulate drug delivery systems.

In order to prepare hydrogel particles with controllable size and morphology, microemulsion polymerization and cross-linking techniques have been widely used (Oh, Lee, & Park, 2009; Raemdonck, Demeester, & De Smedt, 2009; Sasaki & Akiyoshi, 2010). Cross-linking method in water-in-oil (W/O) inverse microemulsion involves a heterogeneous gelation process of preformed polymers. Usually, water-soluble polymer was firstly dispersed into microsized aqueous droplets in continuous organic phase, and then cross-linked with water-soluble cross-linkers inside the droplets stabilized with surfactants, leading to microgel particles. Recently, polysaccharides-based microgels, such as hyaluronan (HA), chitosan and alginate microgels, with controllable size were prepared *via* the W/O microemulsion techniques, and their applications as carrier systems were evaluated (Jameela, Kumary, Lal, & Jayakrishnan, 1998; Ramesh Babu et al., 2006; Yun, Goetz, Yellen, & Chen, 2004). Water-soluble drugs (*e.g.*, doxorubicin) and bioactive macromolecules (*e.g.*, DNA and proteins) can be easily incorporated into hydrogel particles prepared using this method.

Here in this study, microgels based on natural dextran were designed and prepared *via* the W/O inverse microemulsion technique. As shown in Scheme 1, the dextran hydrogel particle was formed by Schiff base formation between aldehyded dextran (Dex-CHO) and ethylenediamine in a W/O inverse microemulsion stabilized by the Span 80/Tween 80 co-surfactants. The resulted dextran microgel can be labeled effectively with aminofluorescein before or after the gelation reaction. Finally, pH dependant degradation profile of the Schiff base contained microgel was preliminarily investigated.

2. Materials and methods

2.1. Materials and reagents

Dextran T40 (Mw = 40 000 Da), sodium periodate ($NaIO_4$), ethylenediamine, 5-aminofluorescein, glycerol and cyclohexane (AR, 99.5%) were purchased from Aladdin CO. Ltd. (Shanghai, China) and used as received. Span 80 (Sorbitan monooleate) and Tween 80 were purchased from Sigma Aldrich Chemical Co. Ltd. (Shanghai, China) and used as received.

2.2. Synthesis of aldehyded dextran

Aldehyded dextran (Dex-CHO) was synthesized by the periodate oxidation of dextran in aqueous solution of sodium periodate, as shown in Scheme 1a, which yields a purified product with a simple dialysis step. Briefly, an aqueous solution of dextran T40 (5.0 g, 12.5% w/v) was oxidized by the addition of 6.6 g $NaIO_4$ in a light-protected container. After stirring for 6 h at room temperature, an equimolar amount of glycerol was added to stop the oxidation reaction. The resulted mixture was dialyzed against distilled water (MWCO 14 kDa membrane) for 3 days and then lyophilized. FT-IR spectra of pure dextran and Dex-CHO were recorded using a Bruker