



Self-assembly of acetylated dextran with various acetylation degrees in aqueous solutions: Studied by light scattering

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ABSTRACT

Self-assembly of acetylated dextran (Ac-DEXs) was investigated with a modified dextran with acetic anhydride in the presence of pyridine. The effect of acetylation degree on solution properties has been investigated by static and dynamic light scattering (DLS). Molecular weight (M_w) and the radius of gyration (R_g) of dextran significantly increased with acetylation degree due to the aggregates formation. However, those aggregates noticeably reduced with further increase of acetylation degree. It suggested that the aggregates have shrinkage. The aggregate formation is clearly confirmed by DLS analysis in the presence of the bimodal relaxation distribution for Ac-DEXs. The hydrodynamic radius (R_h) of fast and slow mode is distinctly corresponded with single dextran macromolecules and aggregates, respectively. The R_h of aggregates varied slightly with increasing acetylation degree. The aggregates of Ac-DEXs represent hard spherical nanoparticles whereas the random coil structure is found in dextran. Formation of gel nanoparticles was monitored at the highest acetylated substitution.

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1. Introduction

Recently, polysaccharides based nanoparticles have been broadly investigated in drug delivery applications due to their biodegradability, non-toxicity, and controllable hydrophilicity properties. Different methods were available to prepare nanoparticles based on the nature of the polymers and its drug encapsulation efficiency. Self-assembled nanoparticles of polysaccharides have been presented by a block copolymerization with another polymers (Abul-Haija & Ulijn, 2015; Houga et al., 2009; Zepon et al., 2015). Moreover, the outstanding properties of polysaccharides are expected with the presence of various derivable groups on molecular chains (e.g. hydroxyl groups), which can be easily modified chemically, resulting in many kinds of polysaccharide derivatives. Many studies have demonstrated that polysaccharides show self-assemble phenomena in different solution conditions to form nanoparticles in variety of hydrophobic modification such as xylinan (Berth, Dautzenberg, Christensen, & Smidsrød, 1999), pullulan (Jung, Jeong, & Kim, 2003; Kuroda, Fujimoto, Sunamoto, & Akiyoshi, 2002), chitosan (Korchagina & Philippova, 2010; Shelma,

Paul, & Sharma, 2010), hyaluronan (Chytil & Pekar, 2009), mannan (Akiyama et al., 2007) and dextran (Filippov et al., 2008; Nichifor, Stanciu, & Zhu, 2004; Zhang et al., 2015). The presence of hydrophilic and hydrophobic groups in the structure of modified polysaccharides lead tendency to self-assemble through various interactions. Self-assemble nanoparticles of polysaccharide derivatives composed of inner hydrophobic core and an outer hydrophilic shell. Inner hydrophobic core offers a drug incorporation site (use to solubilize and encapsulate active ingredients with low solubility in aqueous media). Outer hydrophilic shell can be used to prevent attack by biologic entities, such as microphages and plasma proteins (would adsorb hydrophilic molecule through non-covalent interaction) (Jung et al., 2003).

Dextran, a polysaccharide consisting predominantly of α -1,6-glucosidic linkages with a few percent of α -1,3-linked side chains has a long history in clinical applications as a polymeric drug carriers (Broaders et al., 2009; Filippov et al., 2008; Kauffman, Do et al., 2012; Kauffman, Kanthamneni et al., 2012; Nichifor et al., 2004; Zhang et al., 2015). The intra- and/or intermolecular aggregation can be formed in water by hydrophobically modified dextran with bile acids (Zhang et al., 2015) and sterically-hindered phenol (Filippov et al., 2008). In this work, dextran was modified by replacing the hydroxyl groups of glucose unit with acetate groups to produce hydrophobically modified dextran (Ac-DEXs). Ac-DEXs have been widely used as particle-based carriers for vaccine appli-

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cation, to overcome the drawback in completely non-degradation of iron oxide and the slow degradation rate of the polyesters, and derivatives. The degradation rate of Ac-DEXs can be controlled through the adjustment of acetylation degree by releasing of acetone, an alcohol, and water-soluble dextran as the degradation products, which do not change the pH of the local microenvironment (Broaders et al., 2009; Kauffman, Do et al., 2012; Kauffman, Kanthamneni et al., 2012; Lin et al., 2015). Moreover, the pH-sensitive Ac-DEXs can lead to slow release of drug in extracellular conditions (pH 7.4) whereas faster in more acidic environment (pH 5.0) (Broaders et al., 2009; Kauffman, Do et al., 2012; Kauffman, Kanthamneni et al., 2012).

Solution properties are dominated by various parameters such as polymer concentration, temperature, solvent quality, pH and ionic strength, which play a crucial role in self-assembly (Qun & Ajun, 2006). The dissolution process is another key parameter that has impact on morphological aspects of the nanoparticles formation (Zhang et al., 2004). Therefore, the self-assembly phenomenon in solution is extremely complex; numerous theoretical and experimental studies have been devoted to this subject (De Gennes, 1978; Wu & Gao, 2000). Solution properties and information of aggregation process can be studied by light scattering method simultaneously. Static and dynamic light scattering (SLS and DLS) allow the determination of weight average molecular weight, radius of gyration and shape information of the solute. Both SLS and DLS give complementary pieces of information and for this reason many authors have generally used concurrently for characterization of polymer solutions (Bosmans et al., 2014; Chakraborty, Sahoo, Teraoka, & Gross, 2005; Ghareeb, Malz, Kilz, & Radke, 2012; Houga et al., 2009; Hugiin, 1972; Kita, & Dobashi, 2015; Li et al., 2010; Maki, Sasaki, & Nakata, 2004; Philippova et al., 2012).

Thus, the purpose of this work is to investigate the self-assembly with respect to solution properties of modified dextran along with varying degree of acetylation by light scattering method, which will help to understand more deeply about the self-assembly process and the way to generate stable morphologies to apply in drug delivery system.

2. Materials and methods

2.1. Materials

Dextran ($M_w = 40,000$ g/mol), acetic anhydride, and pyridine were purchased from the Sigma Aldrich, Japan. Dimethyl sulfoxide (DMSO) and ethanol were obtained from the Wako Pure Chemical Industries, Ltd., Japan.

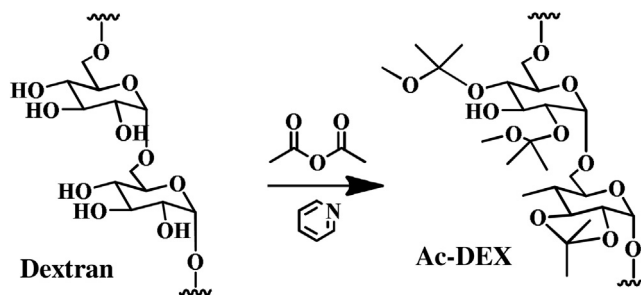
2.2. Synthesis of acetylated dextran (Ac-DEXs)

Ac-DEXs synthesis process was as follows: At first, dextran was dissolved in DMSO and

reacted with various amounts of acetic anhydride to change the acetylation degree with the presence of pyridine. The mixed solutions were stirred at 50 °C for 24 h. The obtained product was precipitated in ethanol. The solid material was vacuum-dried for 3 days and finally white powder was obtained. The Ac-DEXs are designated as Ac-DEX1, Ac-DEX2, Ac-DEX3, Ac-DEX4, and Ac-DEX5 for acetylation degree of 4.62%, 9.62%, 17.11%, 20.85, and 26.43%, respectively. The acetylation degree was characterized by ^1H NMR (Fig. S1). The chemical reaction leading to the formation of Ac-DEX chains is given in Scheme 1.

2.3. Determination of refractive index increment

The refractive index increment (dn/dc) value was determined for aqueous solutions of dextran and Ac-DEXs. The measurements



Scheme 1. Formation of Ac-DEX chains.

were made with a differential interferometer with the operating wavelength of 632.8 nm. The samples were dissolved in milli-Q water with different concentration (0–20 g L⁻¹). The dn/dc values of 0.1280 ± 0.0005 and 0.1313 ± 0.0005 cm³/g were obtained for dextran and Ac-DEXs, respectively. The dn/dc of dextran has been reported to be 0.1340 cm³/g for molecular weight of 86.7 kg/mol (Sugaya, Wolf, & Kita, 2006). The dn/dc is independent on the acetylation degree in this studied range. The independence of dn/dc on the content of hydrophobic groups has been also reported in previous study (Akiyama et al., 2007; Kuroda et al., 2002).

2.4. Analysis of gel permeation chromatographic (GPC)

Weight average molecular weight ($M_{w,GPC}$) and molecular weight distribution were determined via GPC (TOSOH HLC-8220GPC) at 30 °C on TSK gel Super Multipore HZ-M column a with a RI detector. Poly(ethylene glycol) and poly(ethylene oxide) are used as standards. The standard and samples were dissolved in the 0.1 M NaCl aqueous solutions at concentration of 1.0 g/L and operated at flow rate of 1.0 ml/min. The results were shown in Fig. S2 and collected in Table 1.

2.5. Measurement of light scattering

Light scattering measurements were performed on dextran and Ac-DEXs to determine the

weight average molecular weight (M_w), radius of gyration (R_g), second virial coefficient (A_2), the hydrodynamic radius (R_h) and the diffusion coefficient (D) of solutions. The experiments were carried out in an angular range of 25° < θ < 150° by a step size of 5°. A He-Ne laser with a wavelength of 632.8 nm was used as light source. The correlation function of scattered light was obtained with an ALV-6000E correlator. The temperature of sample cell was controlled by a circulating water bath at 25.0 °C with an uncertainty of 0.1 °C. All samples were kept at the measured temperature for at least one hour to ensure thermal equilibrium before starting the data acquisition. The samples were dissolved in the milli-Q water in the concentration range of 2–10 g L⁻¹. The angular dependence of the excess scattered intensity with respect to the solvent, that is, reduced Rayleigh ratio $R_\theta(q)$, was measured.

For a dilute polymer solution at a relatively small scattering angle θ , Rayleigh ratio $R_\theta(q)$ is related to the weight-average molecular weight M_w , the second virial coefficient A_2 , and the z-average R_g via the following expression (Zimm, 1948),

$$\frac{Kc}{R_\theta} \approx \frac{1}{M_w} \left(1 + \frac{1}{3} R_g^2 q^2 \right) + 2A_2c, \quad (1)$$

where c is the polymer concentration, $K = 4\pi^2 n^2 (dn/dc)^2 / (N_A \lambda^4)$ is the optical constant, and

$q = (4\pi n/\lambda) \sin(\theta/2)$ is the scattering vector. Here, N_A is Avogadro's number, λ is the wavelength of light, n is the refractive index of solvent, and dn/dc is the refractive index increment. For convenience, the abbreviation $R_g \equiv (\langle R_g^2 \rangle_z)^{1/2}$ is used.

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