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Ultrasonic degradation of aqueous dextran: Effect of initial molecular weight and concentration

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ABSTRACT

Seven dextrans with different initial molecular weight (IMW) were depolymerized by ultrasonic treatment. The effects of IMW in a wide range from 9.3×10^3 Da to 1.7×10^6 Da and solution concentration (1, 10 and 20 mg/mL) on dextran degradation were investigated. Changes in weight-average molecular weight (Mw) and polydispersity index (*D* value) were monitored as a function of ultrasonic time. Results showed that Mw and *D* value decreased with increasing time of ultrasonic treatment. Moreover, the degradation proceeded faster for higher IMW dextrans and more dilute solutions, yielding lower molecular weight dextrans and more homologous solutions. Percentage variation of dextran fragments at different molecular weight divisions showed that most of the degradation took place in larger molecular weight fragments. Ultrasonic treatment is a simple and controllable method for producing dextrans with low molecular weight, which are more suitable for clinical use.

1. Introduction

Dextran, a polysaccharide of D-glucose monomer, is composed of 95% α-(1 → 6) linkages in the main chain and 5% other linkages in the branch when produced by *Leuconostoc Mesenteroides* (Petronijevic, Ristic, Pesic, & Smelcerovic, 2007; Purama, Goswami, Khan, & Goyal, 2009; Santos, Rodrigues, & Teixeira, 2005). Varieties of the polymerization degree result in different molecular weights of dextrans. Low molecular weight dextrans (Mw = 10^4–10^5 Da), such as dextran 10, dextran 40 and dextran 70, are widely used as blood plasma extenders in pharmaceutical industry (Cote & Willet, 1999; Kardos & Luche, 2001). Even lower molecular weight dextrans (Mw < 10^4 Da) are usually used as the starting materials for iron-dextran and dextran sulfate (Belder, 2003). The properties of dextran depend critically on its molecular weight and chain microstructure, which need to be precisely controlled. Requirements for the molecular weight distribution (MWD) and weight-average molecular weight (Mw) have been detailedly described in the Chinese Pharmacopoeia and the United States Pharmacopoeia (Chinese Pharmacopoeia Commission, 2010; The United States Pharmacopieial Convention, 2010). The dextran produced by *Leuconostoc mesenteroides* has a wide molecular weight range from a few thousand to several million Daltons, resulting in poor homologous solution with large *D* value (*D* = Mw/Mn, polydispersity index of polymer). Incidences of anaphylactoid reactions induced by poor homogeneity of dextrans have been reported (Belder, 2003).

Three main approaches to depolymerize dextran into low molecular weight fragments are summarized herein: (1) chemical methods composed mainly of acid hydrolysis followed by organic solvent fractionation. A major disadvantage of this method is the large consumption of organic solvents (Chen et al., 2008); (2) enzymatic methods which use dextransucrase and dextranase to produce dextrans with desired molecular weight. However, the final products contain a lot of impurities (medium components and by-product of fructose) (Goulas, Fisher, Grimble, Grandison, & Rastall, 2004); (3) physical methods such as jet-cooking under high steam pressure, extrusion under harsh environmental conditions and ultrasonication. Cote and Willet (1999) found that of the three physical methods, the ultrasonic treatment caused the greatest degradation, yielding dextrans with much lower molecular weight and less viscous solutions than the other two methods. In addition, the final product produced by ultrasonic treatment is off-color.

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Ultrasonication is one of the most promising approaches for the degradation of polymer, leading to an irreversible lowering of the chain length caused by cleavage and not necessarily any chemical changes (Suslick & Price, 1999). A wide range of polymers (such as carboxymethyl cellulose, polyvinyl alcohol, pullulan, polyethylene oxide) depolymerized by ultrasonic treatment in aqueous solutions have been investigated (Koda, Taguchi, & Futamura, 2011; Mohod & Gogate, 2011). Most of these investigations focused on the effect of various processing parameters such as ultrasonic frequency, ultrasound power, temperature, concentration and viscosity of solution on the degradation of polymers (Antti, Pentti, & Hanna, 2008; Machová, Kvapilová, Kogan, & Sandula, 1999; Vijayalakshmi & Madras, 2006). Others described changes of molecular weight and MWD of polymers with ultrasonic time, and developed kinetic models to predict the degradation process (Akyuz, Catalgil-Giz, & Giz, 2008; Bose & Git, 2004; Popa-Nita, Lucas, Ladaviere, David, & Domard, 2009). For ultrasonic degradation of dextran, great efforts have been made to depolymerize dextrans into low molecular weight for clinical use. Earlier investigations have only examined the effects of operating conditions such as power, temperature and time of ultrasonic degradation (Lorimer, Mason, Cuthbert, & Brookfield, 1995; Zou et al., 2012). The present work focuses on the role of initial molecular weight and concentration in affecting the degradation process to obtain low molecular weight dextran, which has the potential for clinical use.

2. Experimental

2.1. Materials

A series of dextrans with different IMW were used for the degradation experiments. Dex-10, Dex-40, Dex-70, Dex-500 and Dex-1000 (Mw of those are 9.3×10^3, 4.5×10^4, 6.5×10^4, 5.4×10^5, 1.2×10^6 Da, respectively) were purchased from Pharmacia Fine Chemical Co., Ltd. (New Jersey, USA); Dextran High Fraction (Dex-HF, Mw = 2.8×10^5 Da) was obtained from Acros Organics (New Jersey, USA); Dextran fermentation sample (Dex-F, Mw = 1.7×10^6 Da) was produced by *Leuconostoc mesenteroides* 10074 (China Center of Industrial Culture Collection, CICC) on a sucrose substrate in our laboratory. All samples were dissolved in ultra pure water.

2.2. Methods

2.2.1. Ultrasonic degradation

An ultrasonic generator (Ningbo Scientz Biotechnology Co., Ltd, China) with a fixed frequency of 20 kHz was used in the study. 1, 10 and 20 mg/mL of dextran solutions were prepared to investigate the influence of concentration on dextran ultrasonic degradation. For ultrasonic treatment, 50 mL of dextran solution was poured into a glass vessel with a diameter of 40 mm, which was maintained at 10 ± 1 °C using an ice water bath. The depth of the ultrasonic horn was 15 mm below the surface of solution, and the output power of ultrasonic setup was set at 600 W; the conditions were optimized in a previous paper (Zou et al., 2012).

2.2.2. High performance gel permeation chromatography (HPGPC) analysis

After the commencement of ultrasonic treatment, samples of dextran were taken every 10 min and then analyzed in HPGPC (Agilent, USA). The HPGPC system was equipped with Agilent G1362A differential refraction detector and Shodex Sugar KS-801, KS-805 and KS-G columns. The temperature of columns was maintained at 50 ± 1 °C by a thermostatic container. Ultra pure water was used as the mobile phase at a flow rate of 1 mL/min. All samples were filtered using 0.45 μm membranes (Membrana, Germany) and 15 μL of filtered solution was analyzed in each run. The calibration curve was obtained using standard dextran, which was supplied by Polymer Laboratories Ltd. (USA). All the degradation experiments were conducted for 60 min until little change in the molecular weight was observed.

3. Results and discussion

3.1. Effect of initial molecular weight (IMW) on dextran degradation

Initial molecular weight plays an important role in the degradation kinetics and has received a great deal of attention in our recent study. Seven dextrans with different IMW were depolymerized by ultrasonic treatment at 20 kHz and 600 W. Changes in molecular weight as a function of ultrasonic time were shown in Fig. 1. Dextrans with low IMW (Mw < 70,000 Da) were insensitive to ultrasonic treatment under the experimental conditions. As shown in Fig. 1(a), the degradation proceeded slowly for the three samples, viz., Dex-10, 40 and 70. However, for relatively high IMW dextrans, significant degradation of dextran occurred, as shown in Fig. 1(b). Dextrans with high IMW (Mw > 28,000 Da) showed a remarkable degradation in the first 10 min and approached a limiting value of molecular weight (approximately 1.4×10^5 Da) after 60 min of

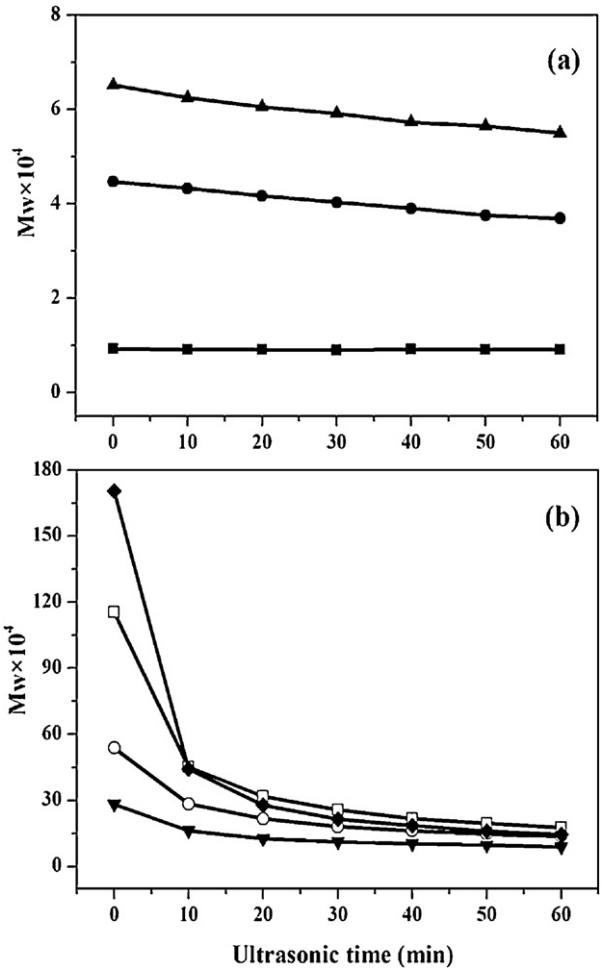

Fig. 1. Variations of weight-average molecular weight (Mw) as a function of ultrasonic time in seven dextrans (10 mg/mL). (a) ▲, Dex-70 (IMW = 6.5×10^4); ●, Dex-40 (IMW = 4.5×10^4); ■, Dex-10 (IMW = 9.3×10^3). (b) ♦, Dex-F (IMW = 1.7×10^6); □, Dex-1000 (IMW = 1.2×10^6); ○, Dex-500 (IMW = 5.4×10^5); ▼, Dex-HF (IMW = 2.8×10^5).

Table 1
Effect of ultrasonic degradation on *D* value of seven dextrans (10 mg/mL).

Samples	*D* value[a] after ultrasonic degradation for						
	0 min	10 min	20 min	30 min	40 min	50 min	60 min
Dex-40	2.2658	2.2087	2.1796	2.1180	2.0787	2.0515	2.0256
Dex-70	1.3544	1.3195	1.3099	1.2960	1.2851	1.2784	1.2713
Dex-HF	7.9327	5.0487	4.2169	3.9619	3.8268	3.7144	3.5607
Dex-500	7.4107	4.2737	3.5196	3.1130	2.9391	2.7794	2.6844
Dex-1000	7.7500	4.6720	4.2122	3.9734	3.8676	3.8076	3.7989
Dex-F	81.5100	14.2240	10.0050	8.6241	7.9129	7.2838	7.0944

[a] The ratio of Mw and Mn, which implies the polydispersity of dextran.

ultrasonic treatment. For example, the molecular weight of Dex-F with IMW of 1.7×10^6 Da was reduced to 4.4×10^5, 2.1×10^5 and 1.4×10^5 Da after 10, 30 and 60 min of ultrasonic treatment, respectively. Comparing the degradation kinetics of Dex-HF, Dex-500, Dex-1000 and Dex-F, it was found that the limiting molecular weight was independent of initial molecular weight. Dextrans with different IMW (Mw > 28,000 Da) showed a similar limit for the lowest molecular weight which can be achieved by ultrasonic treatment, indicating that longer chains are preferentially sheared.

Dextran narrows its molecular weight distribution after a given time of ultrasonic treatment, thus decreasing the polydispersity (*D* value) of dextran. Table 1 shows the variations of *D* value of seven dextrans investigated in the study. For Dex-10, 40 and 70, *D* value varied slightly due to the little change of molecular weight after the ultrasonic treatment. For Dex-HF, 500 and 1000, however, the homogeneity of molecular weight doubled after 60 min of degradation time. Moreover, the *D* value for Dex-F, which has a wide molecular weight range and poor homogeneity, decreased over 11-fold after 60 min of ultrasonic degradation (*D* value of 7.1 at 60 min in comparison to 81.5 at 0 min). The decrease of *D* value with ultrasonic time suggested that more homogeneous dextran solutions were obtained after ultrasonic treatment. This result agreed with reported literatures using ultrasonic treatment for dextran degradation (Wu, Sheth, & Johnson, 1977; Wu, Zivanovic, Hayes, & Weiss, 2008).

3.2. Effect of concentration on dextran degradation

1, 10 and 20 mg/mL solutions of all dextran samples were prepared to evaluate the effect of concentration on dextran degradation. The results of Dex-1000 were shown in Fig. 2. There were no notable differences in degradation kinetics along with ultrasonic time between 10 and 20 mg/mL solutions. However, the degradation proceeded faster in lower concentration solution such as 1 mg/mL. The experimental data in Fig. 2 illustrated that dextran depolymerized faster in dilute solutions, which was similar to other polymers reported elsewhere (Grönroos et al., 2001; Mason & Lorimer, 2002; Taghizadeh & Mehrdad, 2003). This is attributed to the less intense entanglement between chains as the concentration decreases (Kanwal, Liggat, & Pethrick, 2000; Tsaih, Tseng, & Chen, 2004). In more dilute solutions, the random coil structure of dextran extends freely so that dextran chains are not entangled and the cavitation bubbles become larger (Pu et al., 2012; Seto, Ohto, & Kawakita, 2011). As a result, the velocity gradients around the collapsing bubbles are higher at lower concentrations, which may benefit the ultrasonic degradation.

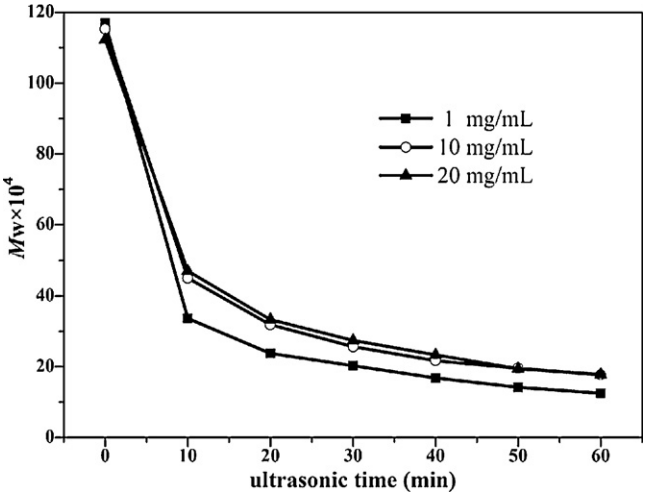

Fig. 2. Effect of concentration on ultrasonic degradation of Dex-1000.

3.3. Percentage variations of different molecular weight fragments in Dex-F with ultrasonic time

A number of studies have demonstrated that ultrasonic degradation narrows MWD of dextran in solution (Grönroos, Pirkonen, & Ruppert, 2004; Li, Li, Guo, & Li, 2005). Fig. 3 showed the MWD of Dex-F, which has a weight-average molecular weight of 1.7×10^6 Da but a comparatively high polydispersity (*D* = 81.5),

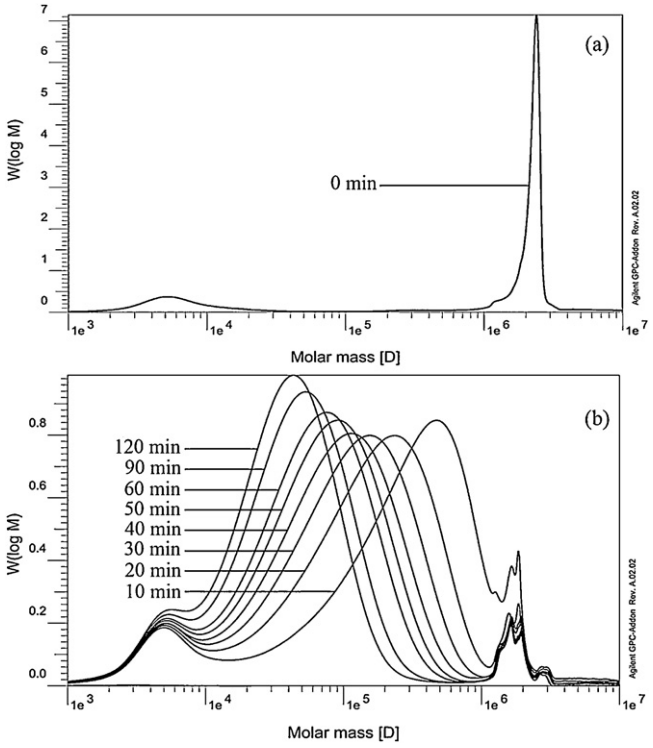

Fig. 3. Molecular weight distribution of Dex-F before and after ultrasonic degradation: (a) degraded for 0 min and (b) degraded for 10, 20, 30, 40, 50, 60, 90, 120 min, respectively.

Table 2
Molecular weight distribution of Dex-F before and after ultrasonic degradation.

Ultrasonic time	Molecular weight distribution (%)[a]						
	$<10^4$	10^4–10^5	10^5–5×10^5	5×10^5–10^6	10^6–2×10^6	2×10^6–3×10^6	$>3\times10^6$ Da[b]
0 min	13.21	5.23	2.50	1.78	15.91	56.54	4.83
10 min	9.40	15.28	43.43	20.59	9.86	1.16	0.28
20 min	9.88	27.21	49.65	7.86	4.45	0.83	0.12
30 min	10.18	36.29	45.11	3.11	3.59	1.04	0.68
40 min	10.71	43.69	37.93	1.45	3.53	1.22	1.47
50 min	11.30	51.05	32.33	0.71	3.10	0.92	0.59
60 min	11.98	56.80	26.44	0.50	2.95	0.80	0.53
90 min	12.52	66.92	14.96	0.38	3.27	1.02	0.93
120 min	13.63	71.75	9.22	0.34	3.30	0.88	0.88

[a] The percentage of dextran fragments in each molecular weight division.
[b] Molecular weight divided into seven divisions.

before and after ultrasonic treatment with a given time. The distribution of long chain fragments move from high molecular weight toward low molecular weight during the ultrasonic process, which was in good agreement with Szu's research (Szu, Zon, Schneerson, & Robbins, 1986), where Dex-2000 was used as a model to study the effect of ultrasonic treatment on the molecular weight of neutral polysaccharides.

Dextran is a long chain polymer of D-glucose, the molecular weight of Dex-F (dextran fermentation sample produced by *Leuconostoc Mesenteroides* in our laboratory) ranged from a few thousand to several million Daltons. The percentages of different fragments in each molecular weight division were obtained based on Agilent GPC data analysis software, as shown in Table 2. This table provided useful information about the role of ultrasonic treatment in decreasing the molecular weight of dextran by breaking the backbones of dextran chains. The initial Dex-F (0 min) concentrated its molecular weight mainly in 2×10^6–3×10^6 Da division; however, after 10 min ultrasonic treatment, a majority of the high molecular weight fragments were degraded into low molecular weight fragments (43.43% in the 10^5–5×10^5 Da divisions) and the percentage of 2×10^6–3×10^6 Da fragments decreased from 56.54% to 1.16%. The other dextran samples showed the similar results. These values provide a strong proof of the backbone breaking of long chains in dextran. A possible explanation for the results could be related to more chances of scission in longer dextran chains. The relatively high molecular weight fragments were gradually depolymerized into low molecular weight fragments as the ultrasonic time prolonged. It is noteworthy that the percentage of 10^4–10^5 Da fragment in Dex-F increased from 5.23% to 71.75% after 120 min ultrasonic treatment, indicating that the use of ultrasonic degradation may have a bright prospect in producing clinical dextran. The exact chain scission mechanism during ultrasonic process is still under debated, due to the lack of three-dimensional structure of polysaccharide; however, the midpoint chain scission model is generally accepted, with cleavage occurring preferentially near the middle of the chain (Bose & Git, 2004; Suslick & Price, 1999; Wu et al., 2008).

4. Conclusions

Ultrasonic treatment is capable of yielding dextran with lower molecular weight in aqueous solution, and improving the homogeniety of molecular weight distribution. The degradation was related to the IMW and concentration used in the experiments. Higher degree of degradation was observed for higher IMW dextran ($Mw > 2.8\times10^5$ Da) and more dilute solution (1 mg/mL).

Percentage variations of different molecular weight fragments in Dex-F before and after a given ultrasonic time were observed by GPC analysis, suggesting that high molecular weight fragments with long chain backbones are easily depolymerized, yielding dextran fragments with more uniform molecular weight. Additionally, the percentage of 10^4–10^5 Da fragment in Dex-F increased from 5.23% to 71.75% after 120 min ultrasonic treatment comparing with the control (0 min), indicating that the use of ultrasonic degradation is a simple, rapid and controllable method for preparing low molecular weight dextran, which are more desirable to obtain clinical dextran.

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