Synthesis and Characterization of Dextran Hydrogels Prepared with Chlor- and Nitrogen-Containing Crosslinkers

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ABSTRACT: In this study, we have synthesized dextran hydrogels by the crosslinking reactions of dextran with some selective Cl-, and N-containing functional monomers, such as epichlorohydrin (ECH), *N*,*N*′-methylenebisacrylamide (MBAm), and glutaraldehyde (GA). Crosslinking reactions were carried out in the basic aqueous solutions (2.8*N* NaOH) at 25–50°C. The optimum conditions for effective crosslinking, i.e., temperature, crosslinking time, and amount of crosslinker, were determined for each system. The hydrogel discs of 3 mm diameter and 1.5 mm thickness were subjected to a number of Tris-buffer solutions of desired pH (2.0–9.0) at 37°C. Swelling kinetics of the hydrogels were evaluated with second–order swelling model. The pH-dependent swelling of hydrogels was strongly influenced by the functional group of crosslinker and crosslinker content. While the hydrogels prepared with ECH and MBAm shows higher swelling ability at basic medium than that of acidic medium, GA-containing hydrogels exhibited just the opposite behavior. Mesh sizes (ξ) and average molecular weights between crosslinks (M_c) were estimated from swelling data using the Flory-Rehner theory. Characterization studies were completed by Fourier transform infrared spectroscopy and thermal gravimetric analysis. © 2006 Wiley Periodicals, Inc. J Appl Polym Sci 102: 4213–4221, 2006

Key words: dextran; hydrogel; crosslinking; swelling

INTRODUCTION

Hydrogels have been extensively used in medical implants, diagnostics, biosensors, bioreactors, bioseparators, and drug delivery matrices since they have high water contents like body tissues and are highly biocompatible.[1,2] Many synthetic and naturally derived materials have been reported to form well-characterized hydrogels. One such material is dextran, a linear, bacterial polysaccharide. Dextran consists mainly of (1,6) α-D-glucoside linkages with about 5–10% (1,3) α-linked branching, on average, three hydroxyl groups per glucose residue in the structure. Dextrans are colloidal, hydrophilic, and water-soluble substances, inert in biological systems and do not affect cell viability.[3] Because of these properties, dextrans have been used for many years as blood expanders to maintain or replace blood volume, and studied for use as a carrier system for a variety of therapeutic agents including antibiotics, anticancer drugs, peptides, proteins, and enzymes.[4–6] Dextrans can be degraded by the dextranase which is found to be present in the colon. Taking advantage of these enzymes, polymeric prodrugs for colonic drug delivery based on dextran were previously designed.[7–9]

Several approaches have been adopted to prepare dextran hydrogels. It is known that dextran is easily crosslinked with various functional organic and inorganic compounds with formation of swollen aqueous gels.[10] Edman et al. synthesized dextran hydrogels by sequential reactions of dextran with glycidyl acrylate, followed by free radical polymerization of the functionalized dextran in the presence of *N*,*N*′-methylenebisacrylamide (MBAm) as an additional crosslinker.[11] Hovgaard and Brøndsted obtained hydrogels directly by crosslinking dextran with 1,6-hexanediisocyanate in DMSO[12] or crosslinking with glutaraldehyde (GA).[13] Kim et al. prepared dextran hydrogels by photocrosslinking of vinyl group carrying functional dextrans.[14] Van Dijk-Wolthuis et al.[15] firstly prepared methacrylate-derivatized dextran and they obtained hydrogels by free radical polymerization of this functional dextran in aqueous solution using inititiator system, consisting of ammonium peroxydisulfate and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine. Güner et al. synthesized dextran hydrogels from the self-crosslink-

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able dextran/epichlorohydrin (ECH), dextran/MBAm, and dextran/phosphorus oxychloride.[16] Recently, pH-sensitive dextran hydrogels were prepared from carboxylate-containing dextran.[17]

Regulation of swelling by pH change enables hydrogels to protect peptide or protein drugs from enzymatic hydrolysis in the upper gastrointestinal tract and enhance drug release at colon by means of extensive gel swelling and degradation. For this reason, we studied the synthesis of dextran hydrogels by direct crosslinking with organic functional monomers, such as ECH, MBAm, and GA, to obtain suitable pH-sensitive hydrogels at rather drastic conditions which allow loading of drugs during the crosslinking reactions.

EXPERIMENTAL

Materials

The medical grade Dextran (T-70) was purchased from Sigma (Germany). Its molecular weight characteristics were determined by the manufacturer as the weight average and number average molecular weights of 70,000 and 46,800 g mol^{-1}, respectively. The crosslinking agents, *N*,*N*′-methylenebisacrylamide (MBAm), epichlorohydrin (ECH), and glutaraldehyde (GA) were supplied by Aldrich (Germany). Sodium hydroxide was used in the preparation of alkaline medium for the crosslinking reactions and it was supplied by Sigma (Germany). Hydrochloric acid (37%) and 2-amino-2-hydroxymethyl-1,3-propanediol (Tris) used in the swelling studies were obtained from Sigma (Germany). All chemicals were of analytical grade and were used as received.

Synthesis of the dextran hydrogels

Synthesis of the dextran hydrogels from dextran-crosslinker mixtures was carried out by intermolecular side-chain reaction of dextran hydroxyl groups with monomeric crosslinking agents, MBAm, ECH, or GA, in alkaline solutions at 25–50°C. In a typical experiment, dextran was dissolved in distilled water containing 2.8*M* NaOH at a concentration of 20% (w/v). The crosslinking agent was added to the dextran solution in varied ratios from 40 to 80 wt %, and stirred magnetically for 10 min. The polymer mixture was then poured into glass molds of 6 mm diameter and 3 mm depth and placed into an incubator (ES 500, Nüve, Turkey) with appropriate temperature program. Temperature and time period of crosslinking reaction were changed according to the type of crosslinking agent. Resulting disc-shaped hydrogels of 3 mm diameter and 1.5 mm thickness were removed from the molds and placed in distilled water for 3 days to get rid of the impurities (uncrosslinked dextran and/or crosslinker). Washed hydrogels were dried in vacuum at 25°C until no weight loss could be detected.

Swelling measurements

Dried hydrogels were immersed in buffered solutions of different pH at 37°C, and their swelling ratios (S) were determined gravimetrically. The buffered solutions (Tris, Sigma) ranged from pH 2.0–9.0. The swelling was followed by measuring the weight gain with the time of immersion in 25 mL of the corresponding buffered solution. The gel was weighed every 30 min after drying the surface. Measurements were taken until the equilibrium was reached (S_{eq}), which was considered to be when three consecutive determinations gave the same weight.

The swelling of the hydrogels was expressed as swelling ratio by the following equation:

$$S = [(M_t - M_0)/M_0] \quad (1)$$

where M_0 is the dry weight of hydrogel (initial weight) and M_t is the weight of swollen gel at given time (t).

All swelling measurements were repeated in an incubator at least three times and the results were reported as averages.

Determination of average molecular weight between crosslinks (M_c) and mesh size of (ξ) the hydrogels

The molecular weight between the crosslinks (M_c) can be determined according to the model of Flory and Rehner,[18] modified by Peppas and Merril[19] for gels in which the crosslinks are introduced in solution [eq. (2)].

$$\frac{1}{M_c} = \frac{2}{M_n} - \frac{[(\nu/V_1)(\ln(1-\nu_{2,s}) + \nu_{2,s} + \chi\nu_{2,s}^2)]}{\nu_{2,s}[(\nu_{2,s}/\nu_{2,r})^{1/3} - 1/2(\nu_{2,s}/\nu_{2,r})]} \quad (2)$$

In this equation M_n is the number-average molecular weight of dextran (46,800 Da), V_1 is the molar volume of water (18 cm^3/g), ν is the partial specific volume of dextran (0.62 cm^3/g), χ is the Flory-Huggins interaction parameter between polymer and water (0.473),[20] $\nu_{2,r}$ is the polymer fraction of the hydrogel in a relaxed state, $\nu_{2,s}$ is the polymer fraction of maximum swelling, and $\nu_{2,r}$ and $\nu_{2,s}$ were calculated from the weight of the gels before immersing to the water and after equilibrium swelling, respectively.

The hydrogel mesh size (ξ) in the swollen state was calculated using the following equation[21]

$$\xi = (\nu_{2,s})^{-1/3}\sqrt{r_0^{-2}} \quad (3)$$

where $\sqrt{r_0^{-2}}$ is the average distance between two adjacent crosslinks in the solvent-free state. For dextran the

relationship between $\sqrt{r_0^{-2}}$ and number-average molecular weight can be given as follows.[22]

$$\sqrt{r_0^{-2}} = 0.071\sqrt{M_n} \quad (4)$$

Substitution of eq. (4) in eq. (3) and replacing M_n by M_c gives eq. (5).

$$\xi = 0.071\ (\nu_{2,s})^{-1/3}\sqrt{M_c} \quad (5)$$

Structure analysis of dextran hydrogels

The Fourier transform infrared (FTIR) analysis was done to identify the atomic structure of the hydrogels. The vacuum-dried samples were mixed with KBr powder and pressed into tablets under vacuum. The spectra were collected on a Mattson 1000 FTIR spectrophotometer at the wavelength range of 400–4000 cm^{-1} with a resolution of 4 cm^{-1}.

Thermal analysis of dextran hydrogels

Thermogravimetric analysis (TGA) was carried out with a thermogravimetric analyzer (Seteram, France) in dynamic nitrogen atmosphere at a heating rate of 10°C/min and temperature interval between 25 and 500°C.

RESULTS AND DISCUSSION

Water-soluble polymers with hydroxyl groups (e.g., dextran) can be crosslinked using functional crosslinking agents. To establish crosslinking, rather drastic conditions (appropriate temperature program, base-aqueous medium) have to be applied. In this study, dextran hydrogels were prepared by crosslinking of dextran with organic functional crosslinking agents such as MBAm, ECH, and GA. The proposed mechanisms of crosslinking reactions were summarized below for each dextran/crosslinker system and were illustrated in Scheme 1 for dextran/ECH hydrogel as an example.

Dextran/MBAm hydrogel

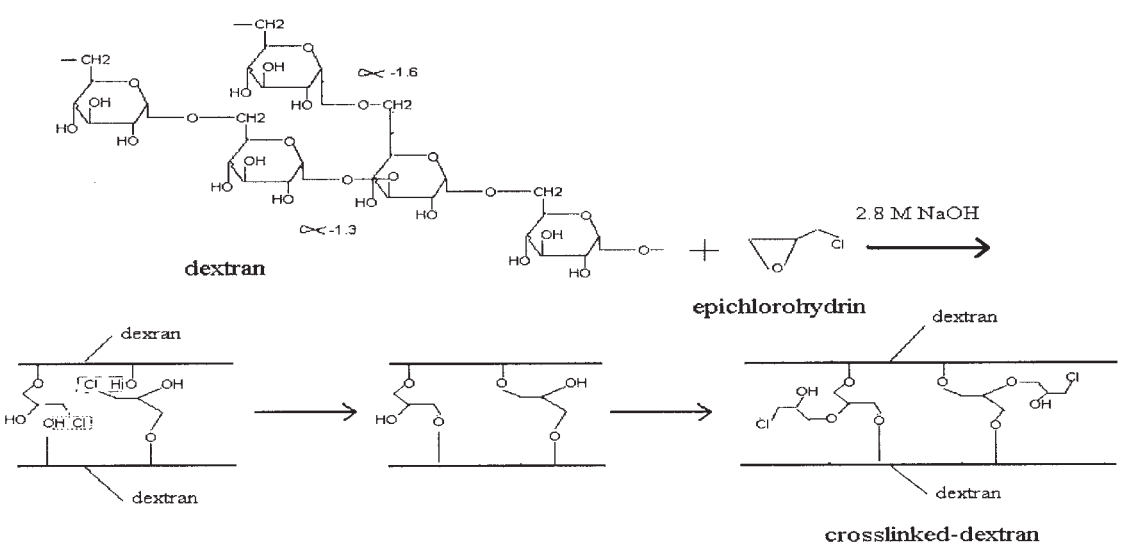
It is well known that (metha)acrylamides undergo to charge transfer isomerizated polymerization in the presence of sodium alkoholate (R—ONa) with the formation of poly-β-alanine (—CH_2—C(CH_3)—CO—NH—).[23] Probably, this reaction can also be realized in the studied dextran/MBAm system with simultaneous opening of acrylic double bonds in the presence of NaOH. MBAm is a polyfunctional monomeric crosslinker. Dextran is crosslinked with MBAm through side-chain reaction of dextran hydroxyl groups with amine groups of MBAm.

Dextran/ECH hydrogel

In the first stage of the reaction of dextran with ECH, the opening of epoxy groups with formation of free chlorohydrin fragments in the side chain of linear macromolecules is proceeded. The chlorohydrin fragments formed can be easily transformed to an epoxy functionality by dehydrochlorination in the presence of NaOH. Dehydrochlorination reaction between two macromolecules containing OH and Cl-substitute, respectively, is realized providing formation of crosslinking structure[16] (Scheme 1).

Dextran/GA hydrogel

At first, double bond of C=O group in aldehyde structure opens and it crosslinks with hydroxyl groups of dextran (Scheme 1).



Scheme 1 Crosslinking reaction of dextran with ECH.

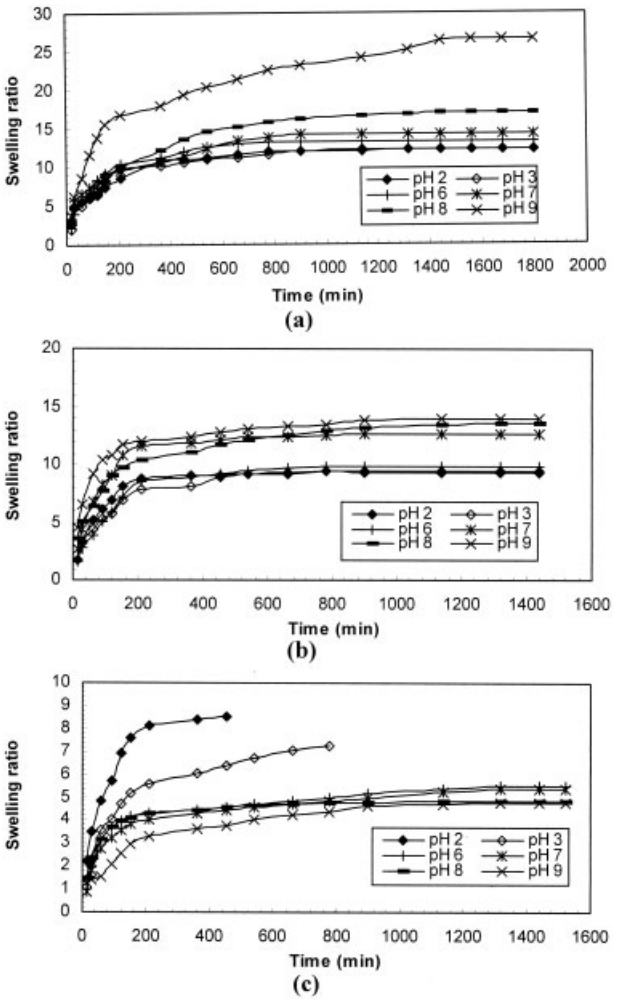


Figure 1 Dynamic swelling curves of dextran hydrogels as a function of swelling medium pH. (a) Dextran-MBAm (50%) hydrogel, (b) Dextran-ECH (50%) hydrogel, and (c) Dextran-GA (50%) hydrogel.

To understand the effect of crosslinker ratio on the synthesis of dextran hydrogels crosslinking reaction was performed in different crosslinker ratios. Dextran/crosslinker mixtures containing less than 30% GA, 40% ECH, 50% MBAm (wt %) do not lead to the stable hydrogel formation. On the other hand, crosslinking ratios higher than 50% MBAm, 60% GA, and 80% ECH causes phase separation and lead to nonhomogenous structures. This is why, dextran hydrogels were prepared with 50% MBAm, 40; 50; 60; 80% ECH and 30; 40; 50; 60% GA.

As expected for reactions between dextran and crosslinker, the curing time and step by step increase of reaction temperature are important for the degree of completion of the crosslinking reaction within the hydrogel network.[13] Our results showed that while the reaction temperature has a strong effect on the completion of crosslinking reaction, the applied temperature program increased the mechanical stability of the hydrogels. Mechanical weakness is an undesired property of the hydrogel as it potentially could result in release of drug because of cracking induced by mechanical stress in the stomach or small intestine. Therefore, it was decided to realize the crosslinking reactions with an appropriate temperature program by depending upon crosslinker type. For MBAm: 24 h at 25°C; for ECH: 2 h at 25°C, 60 h at 37.5°C; for GA: 2 h at 25°C, 24 h at 37.5°C, and 168 h at 50°C.

Swelling properties

pH-Sensitive dextran hydrogels offer great advantages for colon-specific protein release by protecting drugs from enzymatic hydrolysis in the upper GI tract and enhancing drug release at colon via extensive gel

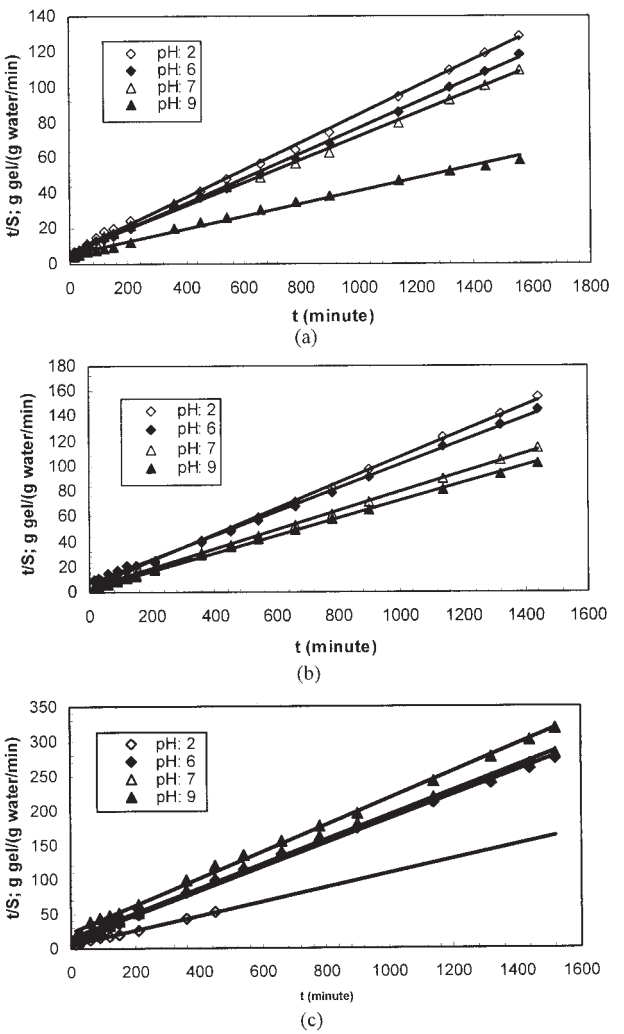


Figure 2 Representation of the second-order swelling kinetics (t/S vs. t plots) as a function of pH for three hydrogels. (a) Dextran-MBAm (50%) hydrogel, (b) Dextran-ECH (50%) hydrogel, and (c) Dextran-GA (50%) hydrogel (straight lines: data obtained from mathematical model; points: experimental data).

TABLE I
Swelling Parameters of the Dextran-Crosslinker Systems in Different pHs at 37°C

Hydrogel[a]	pH	S_{eq}, experimental (g water/g dry gel)	S_{eq}, model (g water/g dry gel)	$(dS/dt)_0$ (g water/g gel min)	r^2
Dx-MBAm	2	12.0	12.9	0.12	0.998
	3	12.2	12.9	0.15	0.999
	6	13.1	14.1	0.16	0.999
	7	14.2	15.3	0.16	0.996
	8	16.8	18.7	0.17	0.996
	9	26.5	28.2	0.18	0.994
Dx-ECH	2	9.2	9.6	0.09	0.998
	3	9.4	10.0	0.11	0.999
	6	9.8	10.6	0.12	0.998
	7	12.6	13.1	0.13	0.999
	8	13.5	14.2	0.14	0.999
	9	14.0	14.4	0.15	0.999
Dx-GA	2	8.5	9.6	0.11	0.999
	3	7.3	7.8	0.09	0.999
	6	5.5	5.7	0.08	0.997
	7	5.4	5.6	0.07	0.999
	8	4.8	5.1	0.06	0.998
	9	4.7	4.9	0.04	0.996

[a] Crosslinker ratio is 50% (wt) for all hydrogels.

swelling and degradation. In this study, pH-sensitivity of the dextran hydrogels was investigated by depending upon the nature of crosslinking agents. To study the behavior of hydrogels in contact with solution at different pH values, we analyzed the dynamic swelling of hydrogels immersed in buffered solutions at pH values in the range 2.0–9.0 at 37°C. The kinetic curves of swelling for the 50% crosslinker containing hydrogels are illustrated in Figure 1. It is clearly seen that the swelling capabilities of all hydrogels are increased by time, but after a certain period they show constant swelling behavior, and process is transformed equilibrium swelling state. While the water contents of dextran/MBAm and dextran/ECH hydrogels are higher at basic medium than acidic medium, dextran/GA hydrogel exhibited higher water content at acidic medium than basic medium. These differences among the swelling properties of dextran hydrogels might be attributed to the different functional groups of crosslinkers.

Dextran/GA hydrogel was completely dissolved after 6 h immersion at acidic media, whereas the dextran/MBAm and dextran/ECH hydrogels were relatively more stable in all pHs up to a 1-month period.

During the swelling process hydrogel dimensions obviously do not remain constant. Therefore, swelling kinetics of hydrogels was evaluated by means of second-order kinetics proposed by Schott.[24]

For extensive swelling, the reciprocal of the average rate of swelling (t/S) is related to the time of treatment by the linear equation:

$$t/S = A + Bt \tag{6}$$

where S is the swelling or solvent uptake at time t, $B = 1/S_{eq}$, the inverse of the maximum swelling, and $A = 1/(dS/dt)_0$, the reciprocal of the initial swelling rate.

The figures [Figs. 2(a)–(c)] obtained by the application of eq. (6) to the data in Figure 1 give straight lines (t/S vs. t) with excellent correlation coefficients. This result demonstrates that swelling process of dextran hydrogels follow a second-order diffusion kinetics, independent of the pH of the medium. The swelling parameters calculated from eq. (6) are listed in Table I together with experimental S values. The effectiveness of crosslinking agents on the equilibrium swelling values decreases in the following order: MBAm $\gg$ ECH $\gg$ GA.

The results obtained allow to simply reflect the possibility of the formation of hydrogel with different type and functionality in the dextran/crosslinker systems.

TABLE II
Network Properties of Dextran Hydrogels Synthesized in This Study

Hydrogel	Crosslinker (wt %)	$\nu_{2,r}$	$\nu_{2,s}$	M_c (g/mol)	ξ (nm)
Dx-MBAm	50	0.228	0.032	7300	19.2
Dx-ECH	40	0.581	0.025	7400	21.0
	50	0.306	0.031	7000	19.0
	60	0.246	0.035	6800	18.0
	80	0.108	0.048	5600	14.6
Dx-GA	30	0.087	0.051	5400	14.0
	40	0.112	0.051	5300	13.9
	50	0.103	0.054	5000	13.3
	60	0.097	0.054	5000	13.2

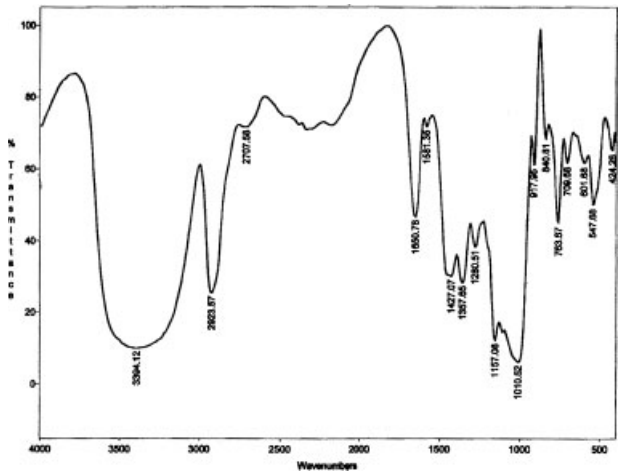


Figure 3 FTIR spectrum of dextran.

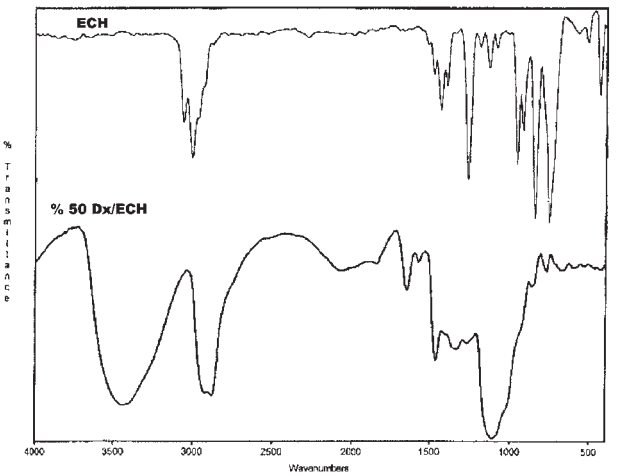


Figure 5 FTIR spectra of ECH and dextran crosslinked with ECH.

M_c and ξ values

One of the most important structural parameters characterizing the hydrogels is the average molecular weight between two consecutive crosslinks (M_c). The value of M_c for dextran hydrogels was estimated according to the Flory-Rehner model. The determination of M_c has great practical significance and it was realized by eq. (2). M_c values are given in Table II, together with the ξ values. M_c values for all hydrogels are higher than 5000 g mol^{-1}, this is why, all hydrogels synthesized here can be considered as loosely crosslinked networks. Comparison of M_c values given in Table II indicated that M_c is affected by crosslinking conditions, above all by the nature, and concentrations of the chosen crosslinking agent. The decreasing order of effectiveness of the crosslinkers in reducing the M_c is: MBAm ≫ ECH ≫ GA.

Hydrogel mesh size, ξ, is an important parameter to predict the release behavior of macromolecule, e.g., protein release from hydrogels. The calculated mesh sizes of hydrogels are in the range of 13–21 nm, which means that it will not likely result in a screening effect for most protein drugs. Because the hydrodynamic diameters of most proteins are smaller than 13 nm, such as for BSA (7.7 nm) and IgG (11.3 nm).[25]

FTIR results

FTIR spectra of dextran, polyfunctional crosslinking agents, MBAm, ECH, GA, and dextran crosslinked with these agents are presented in Figures 3–6. The changes in the band positions and intensities observed from the IR spectra of parent crosslinking

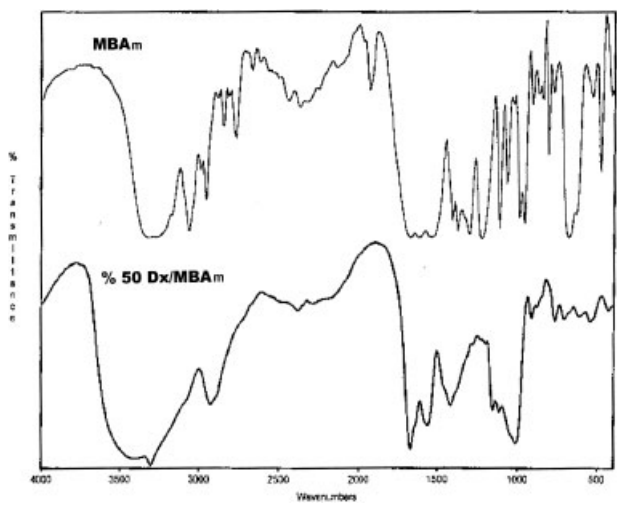


Figure 4 FTIR spectra of MBAm and dextran crosslinked with MBAm.

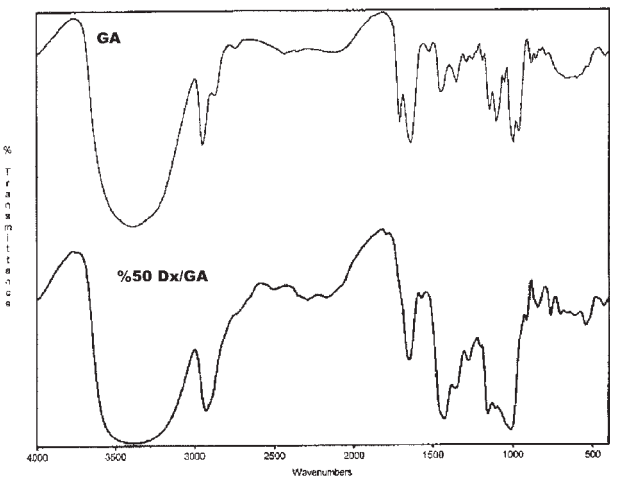


Figure 6 FTIR spectra of GA and dextran crosslinked with GA.

TABLE III
IR Spectral Data of *N,N′*-methylenebisacrylamide (MBAm) and Dextran Crosslinked with MBAm (50%)

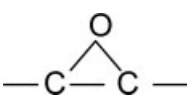
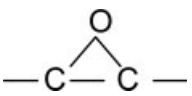
MBAm	Dx-MBAm	Assignments
3326,3270 b		N—H stretching, free and H-bonded
	3425 b	O—H stretching
	3308 sp	N—H stretching
3072 s	da -sh	Subst. amide
2960 sp	2923 b	C—H stretching
	1665, 1634	C=O ternary
1665, 1615 sp	sh -di	amide (—$CONR_2$)
1540 sp	1560 di	N—H bonding
1417 w	da	C—N stretching
1386, 1312 m	da	CO—NH—R stretching
1230 sp	da	C—N stretching
1120 s	di	C—O—C stretching
990, 958 s	da	N—H rocking
	1014 s	C—O stretching (alcohol)
680 s	di	N—C=O stretching
481 s	di	C—C=O stretching

All values are per centimeter (cm^{-1}) and the spectra were recorded in KBr. s, strong; sp, sharp; w, weak; sh, shoulder; m, medium; da, disappeared; b, broad; di, decreased intensity.

agents and the dextran/MBAm, dextran/ECH, and dextran/GA hydrogels are also summarized in Tables III–V. As evident from these data, the following changes of the main absorption bands are observed:

For dextran/MBAm system; (1) Appearance of new absorption bands of 1634 cm^{-1} and 1014 cm^{-1} corresponding to C=O ternary amide (—$CONR_2$) and C—O stretching, respectively. (2) Disappearence of 1417 cm^{-1} (C—N stretching), 1386, 1312 cm^{-1} (CO—NH—R stretching), 1230 cm^{-1} (C—N stretching) and 990, 958 cm^{-1} (*N*—H rocking). (3) Remarkable decrease in intensity at 1560 cm^{-1} (*N*—H bonding), 1120 cm^{-1} (C—O—C stretching), 680 cm^{-1} (*N*—C=O stretching) and 481 cm^{-1} (C—C=O stretching).

TABLE IV
IR Spectral Data of Epichlorohydrin (ECH) and Dextran Crosslinked with ECH (50%)

ECH	Dx-ECH	Assignments
	3444 b	O—H stretching
3010 s	2917, 2880 s	C—H stretching
	1647 s	O—H bonding
1436 m	1467 m	C—C stretching (ring)
1269 s	di	epoxy ring
		
	1107 b	C—O stretching (alcohol)
965 m	di	C—O stretching
853 s	di	epoxy ring
		
753 s	di	C—Cl stretching

For dextran/ECH system; (1) Appearance of a new absorption bands at 1107 cm^{-1}, corresponding to C—O stretching. (2) remarkable decrease in intensity at 1269 cm^{-1} (epoxy ring), 956 cm^{-1} (C—O stretching), 853 cm^{-1} (epoxy ring) and 753 cm^{-1} (C—Cl stretching).

TABLE V
IR Spectral Data of Glutaraldehyde (GA) and Dextran Crosslinked with GA (50%)

GA	Dx-GA	Assignments
	3383 b	O—H stretching
2950, 2880, s, m	2930 s	C—H stretching
1715 s	1715 di- sh	C=O stretching (aliphatic aldehyde)
1647 s	1653 s	C=O stretching
1455 m	1436 s	C—H bonding
1150 m	1157 m	C—O—C stretching
1107 m	da	C—O stretching
1008 s	da	C—O stretching
	1014 s	C—O stretching (alcohol)
971 s	da	CH_2—CHO

For dextran/GA system; (1) remarkable decrease in intensity of 1715 cm^{-1} (aliphatic aldehyde C=O stretching). (2) disappearance of 1107 and 1008 cm^{-1} (C—O stretching) and 971 cm^{-1} (CH2—CHO stretching).

These experimental observations indicated that crosslinking occurs through the side-chain reactions of dextran hydroxyl groups with amino groups of MBAm, epoxy ring and Cl group of ECH, and carbonyl group of GA.

Thermal degradation

The data of TGA of the dextran hydrogels are illustrated in Figure 7. Each hydrogel contains water and the onset of thermal degradation is higher than 200°C (Table VI). While the thermal degradation occurs sharply for dextran, dextran/ECH, and dextran/GA, the presence of MBAm in the hydrogel leads to the thermal degradation in three stages. The first stage began at ~ 180°C, second stage at 265°C follows it, and then maximum degradation occurs at the third stage at about 300°C. As clearly indicated before, crosslinking occurs through the hydroxyl groups of dextran. During the crosslinking reaction, MBAm can show different crosslinking tendencies with each hydroxyl group due to the conformational changes of dextran. As a result, different thermal

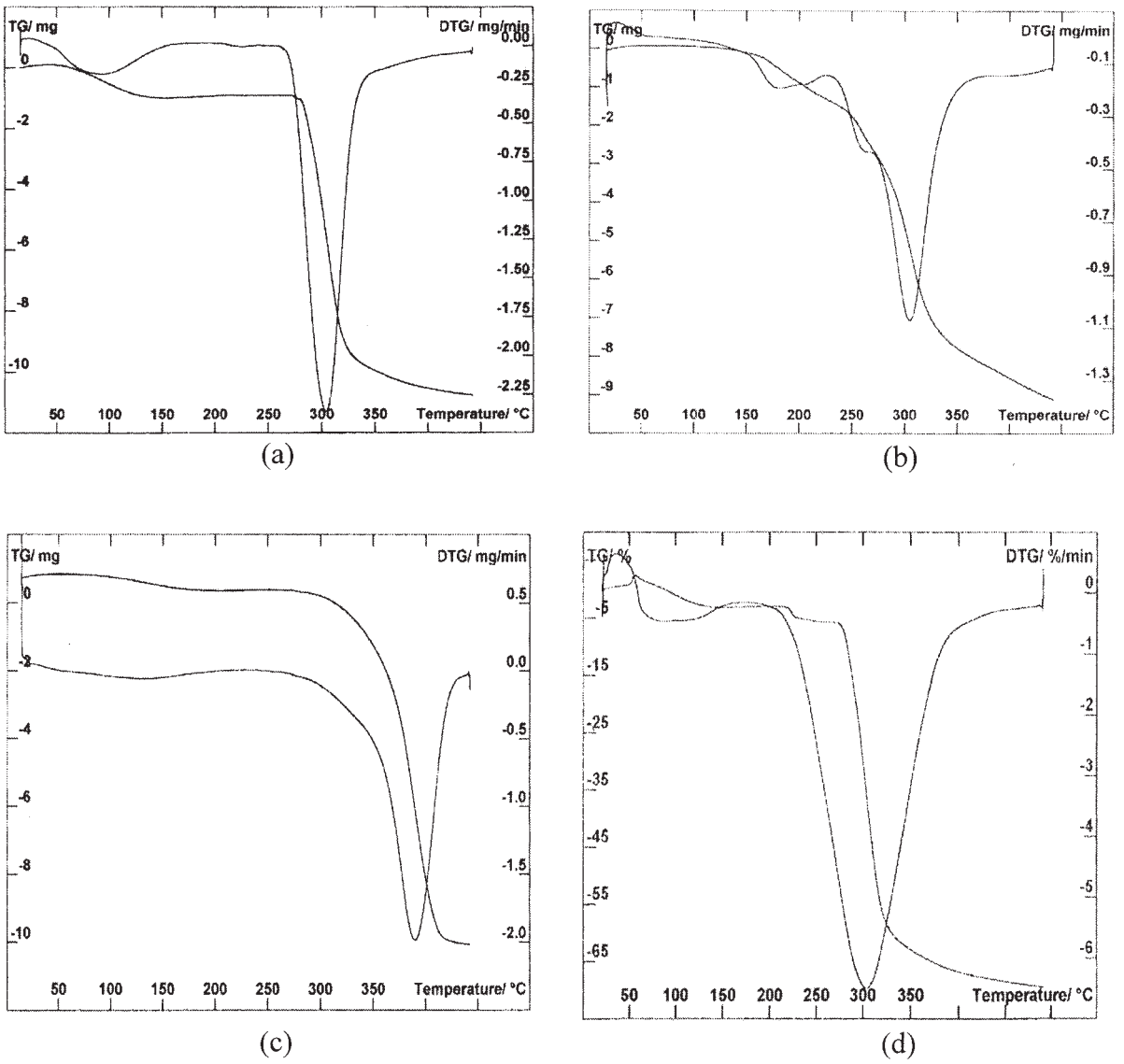


Figure 7 TGA curves of (a) dextran, (b) dextran-MBAm, (c) dextran-ECH, and (d) dextran-GA hydrogels in nitrogen atmosphere at a heating rate of 10°C/min.

degradation stages could be observed. Thermal stability of these hydrogels decreases with change of crosslinker nature in the following way: GA ≫ ECH ≫ MBAm.

TABLE VI
Information Obtained from the TGA

Hydrogel[a]	Humidity (wt %)	Onset of thermal degradation (°C)	The temperature of maximum weight loss (°C)
Dextran	7.16	211	300
Dx-MBAm	9.86	221	355
Dx-ECH	2.85	252	304
Dx-GA	3.92	273	388

[a] Crosslinker ratio is 50% (wt) for all hydrogels.

Since almost all the biotechnological and biomedical applications need easily sterilizable materials, a high degradation temperature (i.e., above 120°C) offers advantage such as those applications.

References

1. Hennink, W. E.; van Nostrum, C. F. Adv Drug Deliv Rev 2002, 54, 13.
2. Gehrke, S. H. Drugs Pharm Sci 2000, 102, 473.
3. Walker, G. J. In International Review of Biochemistry, Biochemistry of Carbohydrates II, Vol. 16; Manners, D. J., Ed.; University Park Press: Baltimore, 1978.
4. Torchilin, V. P.; Tischenko, E. G.; Smirnov, V. N.; Chazov, E. I. J Biomed Mater Res 1977, 11, 223.
5. Klotz, U.; Kroemer, H. Clin Pharmacokinet 1987, 12, 123.
6. Torres-Lugo, M.; Peppas, N. A. Macromolecules 1999, 32, 6646.

7. Larsen, C.; Johansen, M. Int J Pharm 1985, 27, 205.
8. Larsen, C.; Horboe, E.; Johansen, M.; Olesen, H. P. Pharm Res 1989, 5, 995.
9. Van den Mooter, G.; Samyn, C.; Kinget, R. Pharm Res 1994, 11, 1737.
10. Hennink, W. E.; Franssen, O.; Van Dijk-Wolthuis, W. N. E.; Talsma, H. J Controlled Release 1997, 48, 107.
11. Edman, P.; Ekman, B.; Sjoholm, I. J Pharm Sci 1980, 69, 838.
12. Hovgaard, L.; Brøndsted, H. J Controlled Release 1995, 36, 159.
13. Brøndsted, H.; Andersen, C.; Hovgaard, L. J Controlled Release 1998, 53, 7.
14. Kim, S. H.; Won, C. Y.; Chu, C. C. Carbohydr Polym 1999, 40, 183.
15. Van, D.-W.; Franssen, O.; Talsma, H.; Steenbergen, M. J.; Kettenes-vab den, B.; Hennink, W. E. Macromolecules 1995, 28, 6317.
16. Güner, A.; Akman, Ö.; Rzaev, Z. M. O. React Funct Polym 2001, 47, 55.
17. Chiu, H. C.; Hsu, Y. H.; Lin, P. J. J Biomed Mater Res 2002, 61, 146.
18. Flory, P. J.; Rehner, R. J Chem Phys 1943, 11, 521.
19. Peppas, N. A.; Merril, E. W. J Polym Sci Polym Chem Ed 1976, 14, 459.
20. De Jong, S. J.; Van Eerdenbrugh, B.; Van Nostrum, C. F. J Controlled Release 2001, 71, 261.
21. Peppas, N. A.; Moynihan, H. J.; Lucht, L. M. J Biomed Mater Res 1985, 19, 397.
22. Gekko, K. In Solution Properties of Polysaccharides; Brant, D. A., Ed.; ACS Symposium Series, Vol. 150: American Chemical Society: Washington, DC, 1981; p 415.
23. Avramoglou, D. L.; Josefonvicz, J. J Biomed Mater Res B Appl Biomater 1999, 48, 578.
24. Schott, H. J Macromol Sci Phys 1992, 31, 1.
25. Merrill, E. W.; Dennison, K. A.; Sung, C. Biomaterials 1993, 14, 1117.