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Kinetics of dextran crosslinking by epichlorohydrin: A rheometry and equilibrium swelling study

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ABSTRACT

Curing behavior and gel properties of dextran are investigated during its crosslinking by epichlorohydrin (ECH) using rheometry and equilibrium swelling studies. Each ECH/anhydroglucose unit of different molar ratio (0.16–0.99) was added to a known volume of aqueous dextran solution (25%, w/w) in the presence of sodium hydroxide (1.2–3.6 M) as a catalyst. Gel point was investigated as a function of the reactants concentration. The rheological behavior of the curing gels was evaluated using a rheokinetic model. Swelling behavior of the cured, cylindrical specimens was also studied gravimetrically. Increasing NaOH and ECH concentrations significantly increased the crosslinking reaction rate leading to shorter gel points, which was attributed to more ionization of hydroxyl functional groups of dextran due to higher NaOH concentrations. Degree of swelling *vs.* the reaction time was decreased sharply as a direct function of increasing NaOH and ECH concentrations up to certain levels, which then leveled off. In contrast, higher NaOH concentrations increased the swelling ratio probably due to the alkaline induced degradation of dextran chains.

1. Introduction

Hydrogels are three-dimensional polymeric networks capable of swelling rapidly and retaining large quantities of water in their swollen structure (Hoffman, 2002). The unique properties of hydrogels such as biocompatibility and hydrophilicity render them highly useful in different applications especially in medical and pharmaceutical fields (Cadée et al., 2000) *e.g.*, controlled drug delivery systems. Three-dimensional network structures of hydrogels can be formed by means of either a chemical or a physical gelation process. In a physical gelation process, weak intermolecular forces like van der Waals forces, electrostatic attractions, hydrogen bonding, and hydrophobic interactions can be utilized to physically crosslink polymer chains together. The covalent bonds between polymer chains provide chemically crosslinked gels (Silioc, Maleki, Zhu, Kjøniksen, & Nyström, 2007). Different synthetic and naturally derived polymers including polysaccharides have been reported to fabricate well-characterized hydrogels (Imren, Lu, & Guner, 2006).

Dextran, a polysaccharide mainly consisting of 1,6-α-D-glucosidic bonds, has found particular importance in biomedical applications due to its excellent hydrophilic nature and biocompatibility. Dextran is also a colloidal and water soluble polymer which does not impair cell viability in biological systems due to its inertness (Coviello, Matricardi, Marianecci, & Alhaique, 2007; Hennink, Franssen, Dijk-Wolthuis, & Talsma, 1997). Because of these unique properties, dextran has been used for many years as a blood plasma expander to maintain or replace blood volume after severe hemorrhage, or as a carrier for a variety of therapeutic agents including antibiotics, anticancer drugs, peptides, proteins and enzymes (Coviello et al., 2007; Heinze, Liebert, Heublein, & Hornig, 2006).

Dextran hydrogels can be formed by different methods including photocrosslinking of its derivatives (Kim, Won, & Chu, 1999a) or crosslinking by chemical reaction of complementary groups using various functional organic and inorganic compounds resulting in swollen aqueous gels (Imren et al., 2006). In the latter report, characteristics of the resulting hydrogels were directly dependent on the nature of the crosslinking agents used. There are several studies on the synthesis and characterization of dextran-based hydrogels prepared using epichlorohydrin (ECH), *N*,*N*′-methylenebisacrylamide (MBAm), phosphorus oxychloride ($POCl_3$) or glutaraldehyde (GA) (Can, Denizli, Guner, & Rzaev, 2005; Denizli, Can, Rzaev, & Guner, 2004; Güner, Akman, & Rzaev, 2001; Imren, lu, & Guner, 2010). Various researchers have reported the effects of different crosslinking agents or functionalization of dextran molecules by introducing hydrophilic or hydrophobic adducts on the properties of finally formed hydrogels (Kim, Won, & Chu, 1999b; Sun, Shen, Ho, Kusuma, & Gerecht, 2009; Zhang, Won, & Chu, 1999). However, the kinetics of gelation and the effect of reaction

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Table 1
Rheological parameters of Dex/ECH systems with different composition.[a]

Sample code	NaOH conc. (mol/l)	Molar ratio of ECH/AGU[b]	t^* (s)	G' [c] (Pa)	t_0 (s)	τ (s)
D1.2E16	1.2	0.16	2870	49	2630	6257
D1.2E33	1.2	0.33	1760	1980	1585	2920
D1.2E66	1.2	0.66	1620	4670	1490	2879
D1.2E99	1.2	0.99	1840	1690	1550	2952
D1.8E16	1.8	0.16	1510	1600	1285	2899
D1.8E33	1.8	0.33	1190	7830	1100	2630
D1.8E66	1.8	0.66	1150	11,430	1035	2583
D1.8E99	1.8	0.99	1210	9600	1130	2656
D2.4E16	2.4	0.16	1130	3410	1050	2762
D2.4E33	2.4	0.33	1080	12,200	990	2525
D2.4E66	2.4	0.66	940	31,500	900	2480
D2.4E99	2.4	0.99	1010	23,700	955	2597
D3.6E16	3.6	0.16	1420	900	1255	2834
D3.6E33	3.6	0.33	1270	2830	1135	2602
D3.6E66	3.6	0.66	1180	6760	1010	2532
D3.6E99	3.6	0.99	1320	1280	1100	2903

[a] Dextran concentration (25%, w/v) is constant for all samples.
[b] Anhydroglucose unit.
[c] Final G' values are reported at 5000 s.

components concentration on the kinetics of dextran crosslinking reaction are more or less neglected.

Here, we report chemical crosslinking of dextran in aqueous alkali solutions using epichlorohydrin as a crosslinking agent. Sodium hydroxide was used as a catalyst for the reaction and as a proton scavenger. Gel structure was studied by rheometry as a function of the crosslinking reaction parameters including the crosslinker and sodium hydroxide concentrations. Network structure was also elucidated through equilibrium swelling studies to obtain equilibrium swelling ratio and swelling rate constant. Crosslinking reaction kinetics was followed by rheometry and swelling studies. Finally, a rheokinetic model, which was originally developed for the curing of elastomers, was used to describe the rheological behavior of the hydrogels.

2. Experimental

2.1. Materials

USP grade dextran 70 (M_n = 45,040 g mol^{-1}, PDI = 1.47) was purchased from Pharmacosmos A/S (Holbaek, Denmark). Epichlorohydrin and NaOH were of analytical grade and used as supplied by Merck Chemicals Co. (Darmstadt, Germany). Deionized water (HPLC grade) was prepared in house using reverse osmosis technique (AquaMax 311, YoungLin Instruments, Anyang, South Korea) and used in preparation of solutions.

2.2. Methods

2.2.1. Preparation of solutions

Dextran solutions (25%, w/w) were prepared by dissolving known weights of dextran in aqueous NaOH (1.2–3.6 M) solutions. The solutions were homogenized by high-speed centrifugal mixing (SpeedMixer^{TM}, DAC150 FVZ-K, Hauschild, Germany) at 3000 rpm for 15 min at room temperature. ECH was added to each mixture with ECH/anhydroglucose units of different molar ratio (0.16–0.99) in order to investigate its effect on the crosslinking reaction rate. Compositions of the mixtures are shown in Table 1.

2.2.2. Rheological tests

Kinetics of the crosslinking reaction was followed in time sweep mode using an MCR 300 rheometer (Anton Paar Physica, Germany) with cone-and-plate geometry having a cone angle of 2° and a diameter of 50 mm. A known volume of test solution containing prescribed amounts of polymer, crosslinking agent, and catalyst *i.e.*, NaOH was transferred into the rheometer cell after a fast homogenization as previously described. Rheometric studies started at 5 rad/s^{-1} frequency and 5% strain under constant temperature at 40 °C. The strain percentage was found to be within the linear viscoelastic region for dextran gels by performing a strain sweep test. The free surface of the sample was covered with a thin layer of low-viscosity silicone oil to prevent evaporation of the solvent. Viscoelastic response of the samples was virtually unaffected by this thin layer (Silioc et al., 2007).

2.2.3. Dynamic swelling measurements

To characterize the network structure, dynamic swelling experiments were carried out. To this end, the polymer mixtures with the same compositions as described earlier (Table 1), were transferred into appropriate Teflon molds. After addition of the crosslinking agent and thorough homogenization, samples were incubated at 40 °C and orbitally shaken at 150 rpm. After 24 h, hydrogels were removed from the molds and placed in distilled water for 7 days to remove the sol fraction. Hydrogels were then dried in an oven at 40 °C until no weight loss was detected. Dried hydrogels were weighed and placed in distilled water at room temperature for swelling studies. The swollen hydrogels were weighed every hour after surface blotting. The swelling ratio was then determined using Eq. (1) as:

$$SR(\%) = \left[\frac{M_t - M_0}{M_0}\right] \times 100 \tag{1}$$

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

The average molecular weight between crosslinks ($\overline{M_c}$) was determined using Eq. (2) which is derived according to Flory–Rehner theory (Flory & Rehner, 1943) modified by Peppas, Hilt, Khademhosseini, and Langer (2006).

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

In this equation, M_n is the number-average molecular weight of dextran (45,040 g mol^{-1}), V_1 is the molar volume of water (18 cm^3/g), υ is the partial specific volume of dextran (0.62 cm^3/g), χ is the Flory–Huggins interaction parameter between polymer–solvent (0.473 for dextran–water (Imren et al., 2006)), $\nu_{2,r}$ is the polymer volume fraction of the hydrogel immediately after crosslinking before immersion in water and $\nu_{2,s}$ is the swollen polymer volume fraction.

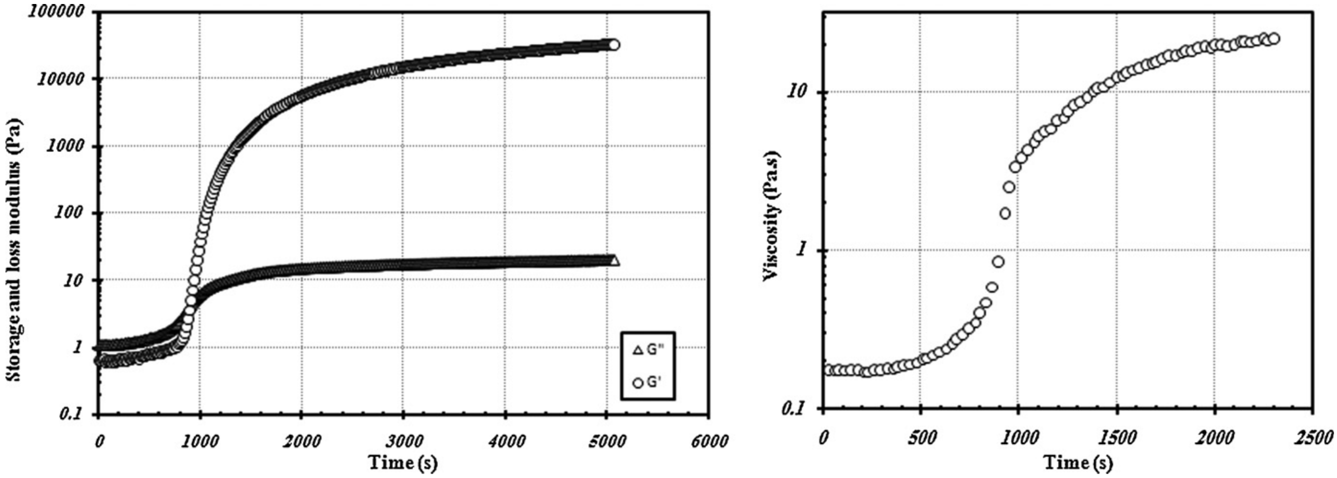

Fig. 1. The evolution of storage and loss modulus during gelation for sample D2.4E66 and determination of gel point by detecting the crossover point of the curves.

Average distance between crosslinks in the hydrogel, hydrogel mesh size (ξ), in the swollen state was calculated using the following equation (Imren et al., 2006):

$$\xi = \left(\upsilon_{2,s}\right)^{-1/3}\sqrt{\overline{r_0}^2} \tag{3}$$

where $\sqrt{\overline{r_0}^2}$ is the average distance between two adjacent crosslinks in the solvent-free state. For dextran, the relationship between $\sqrt{\overline{r_0}^2}$ and number-average molecular weight can be given as follows (Imren et al., 2006).

$$\sqrt{r_0{}^{-2}} = 0.071\sqrt{M_n} \tag{4}$$

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

$$\xi = 0.071\left(\upsilon_{2,s}\right)^{-1/3}\sqrt{M_c} \tag{5}$$

3. Results and discussion

3.1. Rheological tests

To gain insight into the kinetics of crosslinking process of dextran/ECH systems the rheometry experiments were carried out to follow the development of the dynamic mechanical properties during the reaction. One of the cardinal kinetics characteristics of any curing reaction is gel point (t^*) which is an indication of the transition from a viscous liquid to solid state. Gel point can be determined by rheological methods by assessing the intersection of storage and loss modulus, maximum of tan δ or the time at which viscosity increases drastically (Malkin & Kulichikhin, 1991; Winter & Chambon, 1986; Xing, Nierling, & Lechner, 2004). Here, due to good agreement between the results obtained following gel point determination by various methods, the intersection point of storage and loss moduli curves was registered and reported. Rheograms depicted in Fig. 1 (sample D2.4E66) show the results for determining the gel point by tracing the intersection of storage and loss modulus and time at which viscosity increases drastically in rotational rheometry studies.

The effect of ECH concentration on the gelation kinetics was studied by plotting storage and loss moduli against time. It is evident in Fig. 1 that before the gel point, lower G' relative to G'' is an indication of viscous behavior of samples, but after that, gel formation results in G' of a higher value than G'', showing the domination of elastic response. Using the crossover point of G' and G'', the time to gelation was determined for dextran (25%, w/w solution) in the presence of various amounts of ECH as reported in Table 1. In all cases, the values of t^* are decreased and final storage modulus is increased with incremental ECH/anhydroglucose unit molar ratio up to 0.66. This is due to the increasing number of possible active sites for crosslinking of dextran and consequent increment in crosslinking density, which favors faster gelation. By increasing ECH concentration to higher values (0.99 M ratio), a reversed behavior was observed. In other words, samples containing 0.99 M ratio of ECH/anhydroglucose unit showed higher t^* and lower G' than samples containing 0.66 M ratio. For better comparison, the values of final storage modulus (G' values at $t = 5000$ s) of all samples with different molar ratios are plotted against ECH concentration (Fig. 2). The same behavior is reported for starch/anhydroglucose unit hydrogel, which has almost similar structure to dextran (Kartha & Srivastava, 1985a; Kulicke, Aggour, Nottelmann, & Elsabee, 1989).

Low aqueous solubility of ECH at higher concentrations (>0.66 M ratio) leads to phase separation and consequent formation of heterogeneous network structure. This effect is accompanied by formation of a network containing domains with different crosslinking densities. This heterogeneous microstructure decreases the strength of hydrogels and final storage modulus.

Furthermore, formation of ECH dimer, glycerol and chlorohydrin are considered as side reaction products, which possibly form in the presence of large amounts of ECH under alkaline conditions. These products are shown schematically in Fig. 3 (Kartha & Srivastava, 1985b). Consumption of ECH molecules in these side reactions reduces the efficiency of crosslinking reaction and subsequently the storage modulus of the hydrogels.

The effect of NaOH concentration on the kinetics of crosslinking reaction was observed by gel point values as they are reported in Table 1. By increasing the NaOH concentration, t^* values drop to reach an optimum value and then they increase. To investigate its effect on the hydrogel strength, changes in the storage modulus *vs.* time are shown in Fig. 4 for samples with different NaOH concentrations at constant ECH concentration (0.33 M ratio). As is observed, augmentation of storage modulus with increases in NaOH concentration continues until the NaOH concentration exceeds 1.8 M, probably due to more ionized hydroxyl groups, so the number of active sites for crosslinking of dextran increases. At the highest NaOH concentration (*i.e.*, 3.6 M), the final storage modulus decreases against the previously observed trend. This phenomenon can be attributed to degradation of polysaccharide chains under highly alkaline media (Roberts & Cameron, 2002; Ragheb,

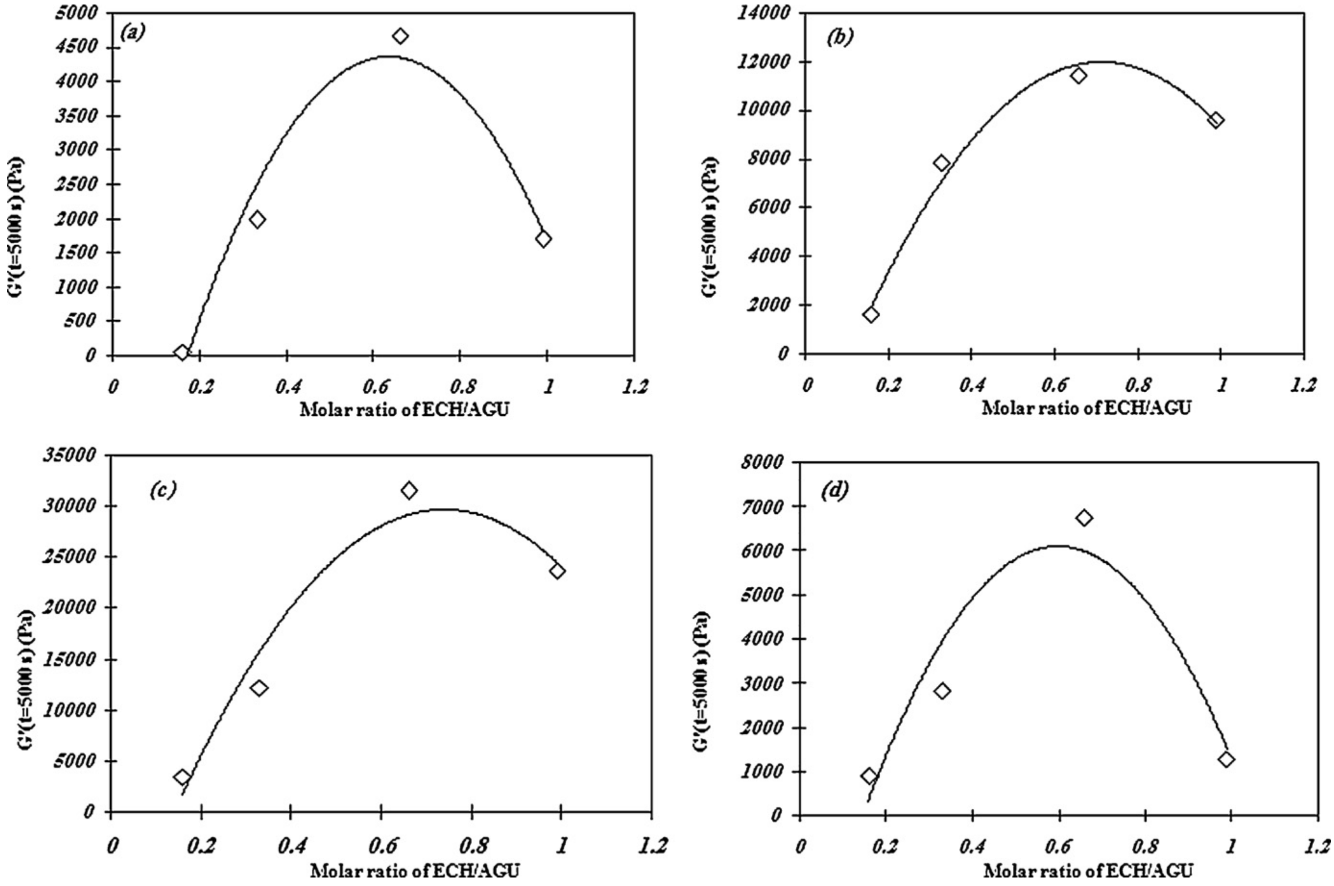

Fig. 2. Effect of ECH concentration on final storage modulus for hydrogels with NaOH concentration of (a) 1.2 M, (b) 1.8 M, (c) 2.4 M, (d) 3.6 M.

Thalouth, & Tawfik, 1995; Ragheb, Thalouth, & Tawfik, 1996) and intensifies with increasing NaOH concentration. This would, in turn, shorten dextran chains and weaken the strength of the prepared hydrogel. In this case, higher polymer concentrations would be required to form an integrated dextran gel. At constant dextan concentration (25%, w/w), NaOH concentration of about 2.4 M seems to be the optimal value for gelation of dextran at 40 °C.

3.2. Swelling tests

As it is stated above, a unique property of a hydrogel lies in its high capacity to uptake water and swell to an equilibrium level. The mechanical properties and applicability of hydrogels for different biological purposes are strongly influenced by their water content. Thus, the swelling property of hydrogels is an important factor in regulating many of their other properties (Zhang et al., 1999). Swelling properties, regardless of being evaluated dynamically or in equilibrium state, is commonly used to characterize a polymeric network structure due to the inverse relationship between the swelling capacity of a polymer network and its corresponding crosslinking density.

In the present work, swelling behavior of Dex/ECH hydrogels was followed up for 48 h. Dynamic swelling behavior of the hydrogels is depicted in Fig. 5a using different concentrations of the crosslinking agent (ECH) prepared using 1.8 M NaOH concentration. It is obvious that the swelling capacity of all samples is increased by time, but after a certain period of time all of them reach their equilibrium swelling state. Increasing the ECH concentration showed a significant effect on water uptake capacity of the hydrogels and the absolute value of equilibrium swelling ratio. Comparative analysis of swelling profiles and equilibrium values for the samples with different amounts of ECH confirm the presence of a critical concentration for ECH concentration. This is in agreement with the rheometric data. Decreases in the value of equilibrium swelling by increasing the ECH/anhydroglucose unit molar ratio from 0.16 to 0.66 are due to the increases in crosslinking density of the networks. However, at higher concentrations (0.99 M ratio) aggregation of ECH molecules results in greater extent of side reactions, which would impede the process of gelation. Equilibrium swelling ratios

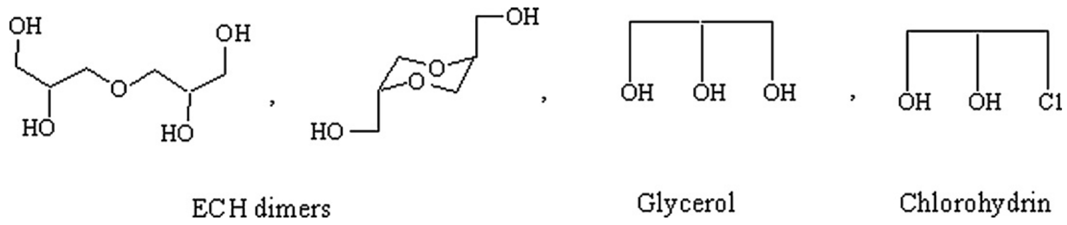

Fig. 3. Schematic illustration of the byproducts as a result of possible side reactions which are occurred in alkaline pH and high ECH concentrations.

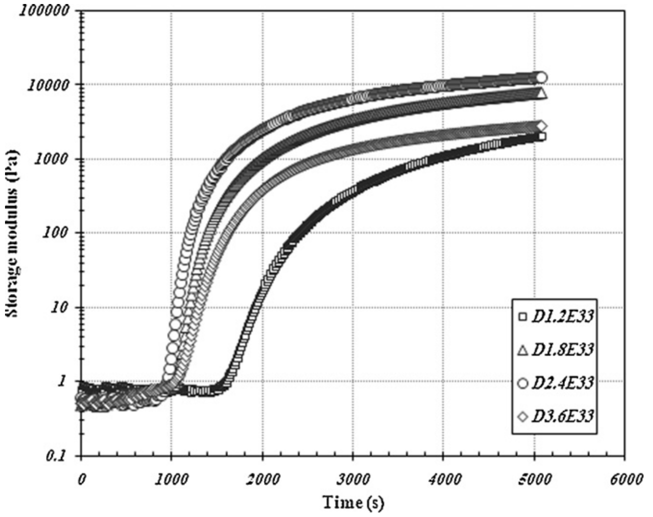

Fig. 4. Effect of NaOH concentration on storage modulus of hydrogels at 0.33 M ratio of ECH/AGU.

Table 2
Swelling parameters of dextran/ECH systems with different composition.

Sample code	S_{eq} (%)	M_c (g mol^{-1})	ξ (nm)	n	$S^{\dagger}_{eq}$[a] (%)	k_∞
D1.2E16	1883	5541	16.1	0.64	2083	1.7
D1.2E33	941	4623	13.5	0.607	1000	1.43
D1.2E66	695	3870	11.5	0.636	729	1.43
D1.2E99	1541	4549	13.5	0.584	1607	2.16
D1.8E16	1100	4940	14.2	0.667	1182	1.48
D1.8E33	842	4527	13.4	0.512	892	1.32
D1.8E66	559	3805	11.3	0.613	574	1.26
D1.8E99	1289	4318	12.3	0.512	1329	2.21
D2.4E16	1917	5300	15.1	0.585	2020	1.84
D2.4E33	1400	4795	13.9	0.568	1447	1.69
D2.4E66	831	4080	12	0.568	892	1.31
D2.4E99	1146	4212	12.3	0.525	1223	1.42
D3.6E16	2560	5901	16.4	0.61	2691	1.98
D3.6E33	1613	4724	13.4	0.603	1666	1.8
D3.6E66	916	4399	12.9	0.631	925	1.53
D3.6E99	1457	5240	15	0.511	1404	2.17

[a] $S^{\dagger}_{eq}$ values are obtained from model.

of the hydrogels are provided in Table 2, together with their corresponding $\overline{M_c}$ and ξ values. As seen, the hydrogels characteristic parameters express lower efficiency of crosslinking at higher concentrations. From Table 2 the value of 0.66 ECH/anhydroglucose unit molar ratio is confirmed for reaching the highest crosslinking density and hence viscoelastic properties.

Our results also proved that NaOH induces two comparative reactions in parallel. The first is introduction of intermolecular crosslinks passing *via* the side-chain alcoholate (Dx-ONa) formation stage. The second is chain scission of dextran molecules through the polysaccharide alkali degradation (Roberts & Cameron, 2002). The former reaction proceeds toward network formation leading to stronger network, but the latter increases the free chain ends, which do not contribute to an ideal network structure. According to the obtained results (Table 2) at higher NaOH concentrations, equilibrium swelling values increase due to the more progress of alkali degradation reaction. The turning point values obtained from swelling experiments is different from the data obtained from the rheological experiments. This can be attributed to different methods of the swelling and rheometry studies adopted, which provide different analytical sensitivity for these techniques toward detecting microstructure of the networks. However, both of them showed that at higher NaOH concentrations alkali degradation of dextran was intensified. The values of M_c and ξ demonstrated the occurrence of structural changes in dextran networks by changes in the crosslinking agent and catalyst concentration.

4. Modeling

4.1. Rheokinetics

Since application of hydrogels is dependent on their mechanical properties, we attempted to find a kinetic model for dextran crosslinking, which can better predict physical or mechanical properties of the fabricated hydrogels. Due to the elastic properties of dextran-based hydrogels in their swollen state, a kinetic model developed by Hsich, Yanyo, and Ambrose (1984) and Hsich (1982) was applied on the results. This model basically describes the curing behavior of elastomeric systems, and the changes in the physical or mechanical properties during crosslinking reaction could thus be followed. The crosslinking is interpreted in terms of the mean square fluctuations of thermodynamic ordering parameters:

$$\frac{G'_\infty - G'_t}{G'_\infty - G'_0} = \exp\left[-\left(\frac{t-t_0}{\tau}\right)^{\beta}\right] \tag{6}$$

Here, τ and β are fitting parameters, which are interpreted as a characteristic of the relaxation time and width of the relaxation spectrum, respectively. The chemical relaxation time is different from structural relaxation time, which describes how rapidly the reaction takes place and it is proportional to the reciprocal of the rate constant for the reaction (Hsich et al., 1984). The induction time, t_0, which is different for each sample, is presented in Table 1. As is shown in Fig. 6, the model is fitted to the experimental data.

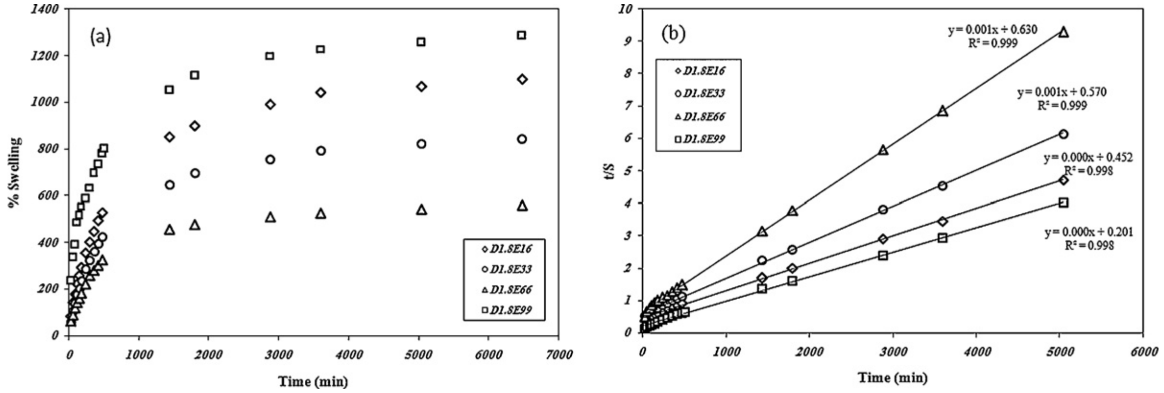

Fig. 5. Effect of ECH concentration on (a) dynamic swelling behavior and (b) the second-order swelling kinetics of dextran hydrogels.

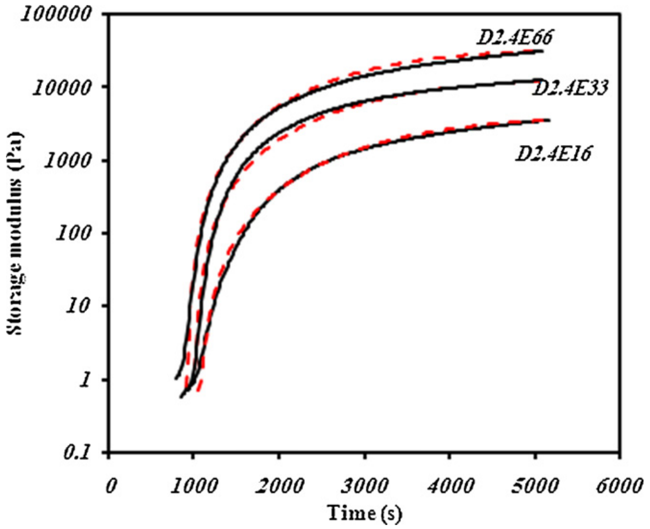

Fig. 6. Storage modulus *vs.* time for some of dextran hydrogels: (—) experimental data; (- - - -) theoretical calculation.

The chemical relaxation time is also presented in Table 1. The results showed that increasing ECH and NaOH concentrations to optimum values reduces the value of τ, therefore, increasing the rate constant of the reaction. This leads to the same conclusion as stated earlier and confirms the presence of areas having different crosslinking densities *i.e.*, structural heterogeneity due to dextran crosslinking by ECH.

4.2. Diffusion

Diffusion of water molecules into dextran hydrogels leads to swelling. Thereby diffusion characteristics were calculated from dynamic swelling data using the following equation (Can, Denizli, Kavlak, & Guner, 2005; Can, Kirci, Kavlak, & Guner, 2003):

$$F = \frac{M_t}{M_{\inf}} = kt^n \tag{7}$$

where M_t and M_{inf} denote the amount of water diffused into the gel at time, t, and infinite time (at equilibrium), respectively; k is a kinetic constant and n is swelling exponent which can interpret the type of water diffusion. For sample, in cylindrical shapes, Fickian diffusion, which appears when polymer chains have a high mobility, corresponds to $n < 0.5$, whereas $0.5 < n < 1.00$ indicates that diffusion behavior is non-Fickian and penetration of water into the polymer core is slow (Ganji, Vasheghani-Farahani, & Vasheghani-Farahani, 2010). The plot of $\ln F$ against $\ln t$ for the initial 60% of swelling yielded a straight line. The n exponent was calculated from slope of the lines (Table 2). Our findings showed that water diffusion into all samples of different compositions follows non-Fickian behavior.

The rate of swelling of dextran/ECH hydrogel was studied in cylindrical form samples. The weight gain of the hydrogels is a characteristic of water uptake, which leads to swelling of the network. For extensive swelling of dextran-based hydrogels in aqueous environment, the following equation can be used (Katime, Velada, Novoa, & Apodaca, 1996; Rodriguez, Alvarez-Lorenzo, & Concheiro, 2003). This equation represents a second order kinetics profile

$$\frac{t}{s} = A + Bt \tag{8}$$

where $A = 1/k_\infty^2$ is the reciprocal of initial swelling rate of the gel and $B = 1/S_{eq}$ is the reciprocal of the equilibrium swelling.

Fig. 5b shows an example of linear regression of swelling data, which expresses the transport mechanism referred in Eq. (8) and k_∞ and S_{eq} values were calculated and they are presented in Table 2. In general, higher k_∞ indicates that the swelling process is quicker. Thereby, as chains are more crosslinked, the slower swelling rate would be predictable. The values of S_{eq}, determined using Eq. (8), are compared with equilibrium swelling values obtained from experimental data. As it is shown there is a good agreement between these values. In fact, studies of kinetic parameters give deep insight into the structure of the crosslinked polymer.

5. Conclusion

Oscillatory rheometry of Dex/ECH systems provided useful information on kinetics of Dex crosslinking showing short pot life depending on the gel compositions. As the final storage modulus is directly related to the strength of hydrogels, comparative analysis of its values give reasonable information on the polymeric network structure. It is found that a different correlation exists between the network crosslinking density and ECH concentration in low and high concentration regimes of ECH. At higher levels of ECH concentration, the side reactions intensify leading to lower crosslinker agent efficiency. Although the presence of NaOH is essential for reaction to be effective, at higher alkaline concentrations dextran molecules undergo degradation resulting in a significant decrease in the hydrogel properties. These phenomena are confirmed by swelling experimental studies, which result in determination of the equilibrium swelling values. A diffusion characteristic and a second order kinetic equation were used to achieve more exact information on the properties of final hydrogel. Finally regarding the elastic behavior of dextran hydrogels, a rheokinetics model, derived for crosslinking of elastomers, was used for better analysis of rheological data.

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