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Shrinking of Chemically Cross-Linked Polymer Networks in the Postgel Region

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Summary

In this paper, the syneresis behaviors in the post-gel region of hydrogels of hydroxyethylcellulose (HEC) and its hydrophobically modified analogue (HM-HEC) were investigated by means of a new high precision swell-ratio-tester. The gels were prepared by cross-linking cellulose ether derivatives with divinyl sulfone (DVS) in alkaline solution at various cross-linker concentrations and temperatures. Increasing the cross-linker density promotes a faster shrinkage of the gel, and a more compressed gel. The compression of the 1 wt % HEC gel starts at an earlier time at 40°C than at 25°C, because the increased mobility of the chains is more favorable to a faster formation of interpolymer cross-links. The results from the deswelling measurements show that the hydrophobic modification of the polymer yields less contracted gels. This novel finding is ascribed to the fact that some of the hydroxyl groups for the formation of intermolecular cross-links are deactivated through the incorporated hydrophobic groups at these sites.

Keywords

Deswelling, syneresis, hydrogels, hydroxyethylcellulose.

Introduction

As early as the 1950s, attempts were made for the development and use of environmental sensitive materials in various applications. These attempts ultimately resulted in the discovery of a new class of polymer substances commonly known as hydrogels. Hydrogels are three-dimensional networks made of polymer chains cross-linked by physical or chemical bonds, in an aqueous environment [1-5]. Chemical gels do not dissolve in contact with liquid phases but, depending on the external conditions, they may swell or shrink. This behavior is utilized in many applications within different areas such as biotechnology, bioengineering, pharmacology, medicine, agriculture, and the food industry [6]. Gels may undergo reversible or discontinuous volume changes in response to alterations of the environmental conditions, such as solvent composition [7-11], temperature [7,8,10,12-19], pH

[15,18,19], cross-linker density [16], salinity [19-24], ion complexation [25,26], and electric fields [27].

In this work, shrinking measurements have been carried out on semidilute aqueous gels of hydroxyethylcellulose (HEC) and its hydrophobically modified analogue (HM-HEC) in the presence of various concentrations of the chemical cross-linker divinyl sulfone (DVS). HEC is a hydrophilic non-ionic polysaccharide with many interesting properties that makes it useful for the development of products such as cosmetics, personal care products, and drug delivery systems. The HM-HEC sample has hydrophobic hexadecyl (C16) groups attached to the polymer backbone. The chemical structures of the polymers are displayed in Figure 1.

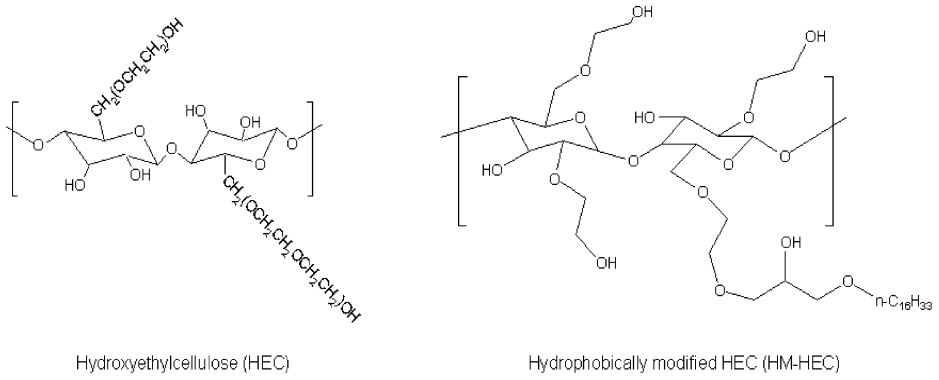

Figure 1. Chemical structures of HEC and the hydrophobically modified HEC employed in this work.

At alkaline conditions (pH ≈ 11.8; the reaction only proceeds at high pH values) and sufficiently high polymer and cross-linker concentrations, the aqueous solutions of HEC or HM-HEC will undergo a sol-gel transition through a cross-linker reaction via hydroxyl groups [28-30]. In the postgel region, the contraction of the gels under various conditions of polymer concentration, levels of crosslinker addition, and temperature is monitored over a long period of time (ca. 24 h) with the aid of a high precision swell-ratio-tester. This new device is capable of measuring the shrinkage of the polymer gel network by following the changes in the height of the probe in contact with the sample undergoing shrinkage. By applying this new and simple instrument, the shrinkage rate of the sample can be monitored with a good time-resolution, and therefore the complications that may be encountered in the classical gel swelling/shrinking experiments, where the sample is dried and weighted at different times, can be avoided.

The aim of this work is to gain insight into the kinetics of the deswelling behavior of HEC and HM-HEC gels at different conditions in the postgel region. This will give us important information about the extent and duration of the chemical cross-linking process in the postgel region. The novel feature of this investigation is the presentation of a detailed picture of the extent and kinetics of the syneresis in these systems. To the best of our knowledge, results with this experimental technique have not been reported before. Furthermore, the effects of crosslinking density, polymer concentration, temperature, and hydrophobicity on the gel compression and deswelling kinetics of this type of gels have not been investigated. Polymer hydrogels

are employed in many drug release applications, where small drug molecules embedded in the gel matrix are to be released in a controlled manner. In this context, it is crucial to know how the contraction of the gel-network in the postgel region will affect the porosity of the gel-matrix and thereby the release-rate of the drug molecules.

Experimental

Materials

In this study a HEC sample with the commercial name Natrosol 250 GR (Lot no. V-0403) was obtained from Hercules, Aqualon Division. The degree of substitution of hydroxyethyl groups per repeating anhydroglucose unit of the polymer is 2.5 (given by the manufacturer). The weight average molecular weight of this sample was determined to be approximately 400 000 by means of intensity light scattering [31]. The same HEC sample was also used as the precursor for the synthesis of its hydrophobically modified analogue. The crosslinking agent DVS was purchased from Merck and utilized without further purification. Millipore water was used for the preparation of all solutions. The other reagents for the synthesis of the HM-HEC were: glycidyl hexadecyl ether (2,3-epoxypropyl hexadecyl; $C_{19}H_{38}O_2$), technical grade, Sigma-Aldrich, and 3-chloro-2-hydroxy-1-propanesulfonic acid sodium salt hydrate ($C_3H_6ClNaO_2S.xH_2O$; 95 %), Sigma-Aldrich. Dilute HEC solutions were dialyzed against Millipore water for at least 1 week to remove salt and other low molecular weight impurities, and thereafter the polymer was isolated by freeze-drying. Regenerated cellulose with a molecular weight cutoff of 8000 (Spectrum Medical Industries) was used as dialyzing membrane.

Synthesis of HM-HEC

The HM-HEC polymer was synthesized according to a standard procedure that has been described elsewhere [32]. In this synthesis, 50 g of the above mentioned hydroxyethyl cellulose, 400 g of 88 % isopropyl alcohol (ARCUS), and 3.5 g of a 48 % aqueous solution of sodium hydroxide were introduced into a 1000-ml glass separable reactor, equipped with a mechanical stirrer, thermometer, and condenser tube, to prepare a slurry. This mixture was stirred at room temperature for 30 min in a nitrogen atmosphere. An amount of 9.7 g of glycidyl hexadecyl ether was added to the slurry, and the reaction proceeded at 80°C for 8 hours. After the completion of the hydrophobization reaction, the liquid reaction mixture was neutralized with acetic acid, and the product was collected by filtration. The reaction product was washed twice with 500 g of 80 % acetone (acetone/water = 4:1V/V) and then twice with 500 g of acetone, and dried at 70°C for 24 hours under reduced pressure to remove rests of acetone. By this procedure, 44.8 g of the HM-HEC polymer was obtained. The polymer was then dialyzed against Millipore water for 7 days in order to remove the low molecular weight impurities, and thereafter freeze-dried. The chemical structure and purity of the HM-HEC was ascertained by ^{1}H-NMR spectrum making use of deuteron-DMSO as a solvent with a Bruker AVANCE DPX 300 NMR spectrometer (Bruker Biospin, Fällanden, Switzerland) operating at 300.13 MHz at 298.2 K. The ^{1}H chemical shift in DMSO-d_6 is referred to the residual C_2HD_5-SO proton (2.50 ppm) of C_2D_6SO. The hydrophobic modification degree (glycidyl hexadecyl ether groups) was determined from the peak ratios between anisomeric protons and the methyl protons

of the glycidyl hexadecyl chain. The degree of substitution by the hydrophobic group (glycidyl hexadecyl ether group) calculated from the ^{1}H-NMR spectrum was 1 mol %.

Sample Preparation

In this work, the measurements have been carried out in the semidilute regime on 1 wt % and 2 wt % hydrogels of HEC and 2 wt % of HM-HEC in the presence of three different concentrations of the cross-linker DVS. The overlap concentration c* was determined from viscosity measurements [30] on dilute aqueous solutions of HEC. The intrinsic viscosity ([η]) is found to be 4.02 wt %$^{-1}$ and from the relation c* = 1/[η] the value of c* = 0.25 wt %, which suggests that the considered polymer concentrations are well in the semidilute regime. Measurements of HEC and HM-HEC gels were carried out at 25°C, and some deswelling experiments on the HEC samples were also conducted at an elevated temperature (40°C). The polymers were dissolved in aqueous alkaline (NaOH) media with a pH of 11.8 (at this pH the cross-linker reaction proceeds). The solutions were prepared by weighing the components, and the samples were homogenized by stirring at room temperature for one day. The addition of cross-linker has no effect on the pH of the samples. The prescribed amount of DVS (in the range of 15-60 μl/g of polymer solution) was added to the sample and a fast homogenization of the solution was performed.

Gel Swelling Experiments

The SRT-1^{TM} swell-ratio-tester, purchased from the Cambridge Polymer Group, Inc., Boston, MA, can be used to measure the swelling/shrinkage properties of polymer gels. The instrument is capable of measuring swelling ratios at temperatures up to 150°C (with a temperature accuracy of ± 0.1°C) with a position resolution of ± 15 μm. The instrument utilizes a laser micrometer to measure the displacement of a probe in contact with the gel sample, thereby producing the transient and steady-state change in height of the sample as it swells or shrinks (see Figure 2). If the sample is assumed to be isotropic, the change in volume can be readily determined. If the sample is non-isotropic, samples can be placed in several orientations to determine the degree of anisotropy. The samples in this study are found to be isotropic.

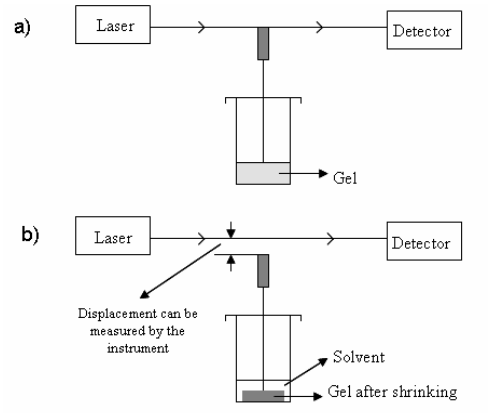

Figure 2. Schematic picture of the swell-ratio-tester.

The chamber lid of the swell-ratio-tester was removed and 2 ml (h ≈ 4.06 mm) of the sample was transferred into the stainless steel chamber. To avoid evaporation of the solvent, the free surface of the sample was always covered with a thin layer of low-viscosity silicone oil. Thereafter the chamber lid was replaced and the experiment was started when the solution was transformed into an incipient gel, which could be observed visually by tilting the flask containing the rest of the sample [14]. All the measurements were started in the post-gel regime just after the gel point of the considered sample. Before an experiment was started, a piece of very thin filter paper (the height of the sample was not affected by this filter) was placed on the top of the gel to prevent the probe from penetrating the gel. The ceramic probe rod was inserted through the hole in the lid, and the height of the probe was monitored as a function of time by a laser beam detection device. The apparatus is interfaced to a PC, and data are collected through a software package provided by the manufacturer.

Results and discussion

Deswelling of HEC Hydrogels

It has been observed [15,25] for other gelling polymer systems with a chemical crosslinker that contraction of the gel networks occurs in the course of time. Little attention has been paid to the kinetics of the crosslinking process of polysaccharide gels in the postgel domain. The shrinking (deswelling) or swelling of a gel or a film can be probed accurately as a function of time for different types of hydrogels with the aid of the present swell-ratio-tester. The shrinking of the gel can be described by the following relationship:

$$\Gamma\ (\%) = (h_t/h_0) \cdot 100 \qquad (\mathbf{1})$$

where Γ is the swelling ratio, h_0 and h_t are the heights of the sample in the initial state and at the time of measurement, respectively.

To provide a more detailed description of the kinetics of the shrinking process, the data are analyzed in the framework of an empiric quantitative model. The data for both HEC and HM-HEC hydrogels at different conditions are well fitted by means of the following fitting equation

$$\Gamma(\,t\,) = (\,100 - P\,)\,\exp\,[-\,(\,t\,/\,t_r\,)^{\alpha}\,\ln\,(\,100 - P\,)] + P \qquad (\mathbf{2})$$

where P is the final plateau value of the swelling ratio parameter Γ, t is the time of measurement, t_r is the relaxation time, which refers to the time where the shrinkage of the sample terminates (the time for the onset of the plateau at long times), and α is an exponent.

Figure 3 shows the results (determined from eq 1) from the shrinking experiments, together with the curves fitted with the aid of eq 2, for the HEC samples (1 wt % and 2 wt %) in the presence of different cross-linker concentrations. It is evident that the shrinking rate, at a given polymer concentration, is substantially affected by the cross-linker concentration. The results reveal that the initial shrinking commences earlier as the level of added cross-linker increases, and the amplitude of shrinkage to the final stage is higher. It is interesting to note that the cross-linker reaction proceeds over a long time, and as expected the results indicate that the reaction is

terminated at an earlier time for a system with a high cross-linker concentration. A close inspection of the data suggests that the cross-linking process continues over a longer time for the gel with the higher polymer concentration, which may be ascribed to the higher number of active "sites" for cross-linking with this more concentrated sample.

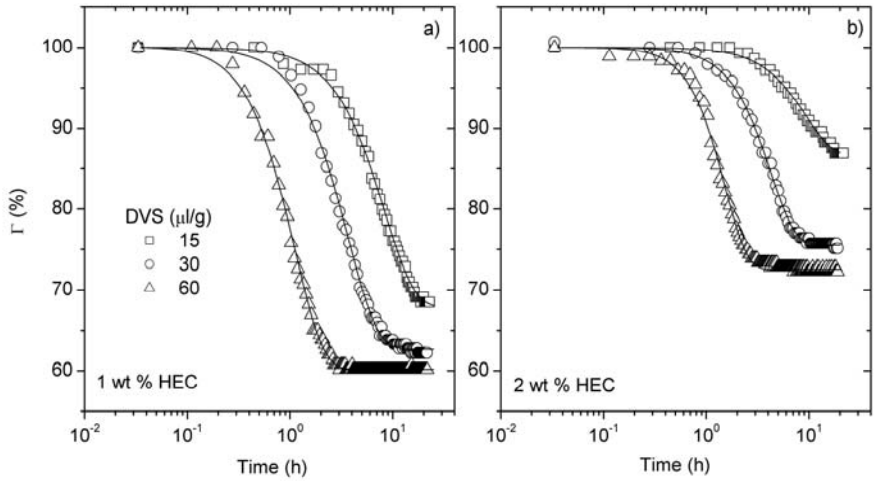

Figure 3. Time dependencies of the swelling ratio for 1 wt % (a) and 2 wt % (b) HEC gels in the presence of different cross-linker concentrations. (□ every 50 point is shown, ○ every 30 point is shown, Δ every 10 point is shown). The lines are fitted with the aid of eq. 2.

These findings suggest that the deswelling process commences earlier and the degree of compression at the final stage is more pronounced for a gel with a higher cross-linker density. An increase in DVS concentration promotes a faster evolution of the gel because of a higher probability for intermolecular cross-links, and this is expected to lead to a more compacted gel network. In this context we may note that previously it has been observed [29] that the turbidity of HEC gels rises over a long time in the postgel region, and this effect is strengthened as the cross-linker concentration is increased. In this study we have also noticed a similar behavior for the HM-HEC systems.

Figure 4 shows the results for the relaxation time t_r and the equilibrium gel compression P, obtained from the fitting of the data with eq 2, for the HEC gels at different polymer and cross-linker concentrations. The results demonstrate that a high concentration of cross-linker leads to a shorter relaxation time for both HEC samples. It is obvious that at higher levels of DVS addition, the magnitude of HEC concentration has little effect on the relaxation time, whereas t_r is faster for the highest polymer concentration in the presence of a small amount of DVS. At a low crosslinker addition, the higher number of active "sites" in the more concentrated HEC sample will favor a faster cross-linker reaction, whereas at sufficiently high cross-linker concentrations this effect should be reduced. We note that for the higher polymer concentration (2 wt %) the degree of compression is less (see Figure 4b). This can probably be ascribed to the higher density of polymer chains in the gel matrix and more entanglements. As a result the gel network is less prone to contract.

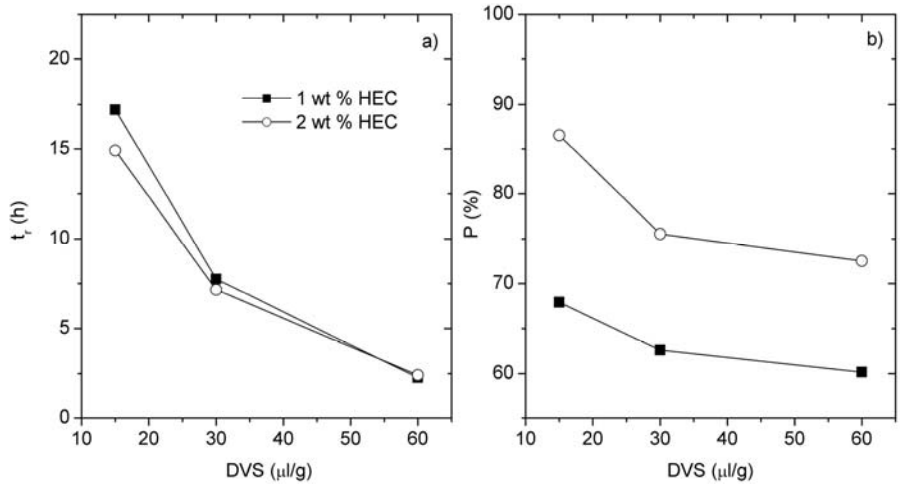

Figure 4. (a) Plot of t_r versus cross-linker concentration for 1 wt % and 2 wt % HEC. (b) Plot of P as a function of cross-linker concentration for 1 wt % and 2 wt % HEC.

Effect of Temperature on Shrinking of the HEC Hydrogels

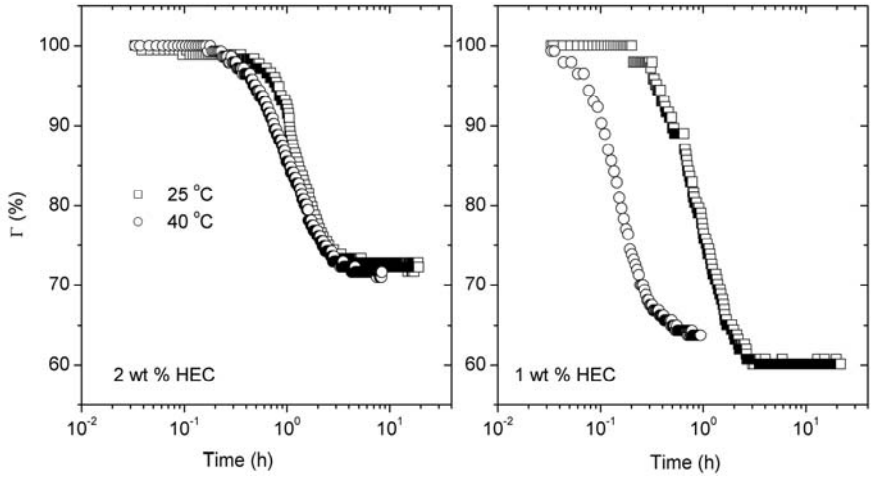

Figure 5. Time dependencies of swelling ratio for 1 wt % and 2 wt % HEC samples in the presence of 60 μl/g DVS at 25°C and 40°C.

Figure 5 shows the temperature effect on the shrinking behavior of 1 wt % and 2 wt % HEC postgels in the presence of 60 μl/g DVS. The results for the HEC sample of the lowest concentration reveal that the time at which the gel begins to shrink is shifted toward shorter time with increasing temperature. This can probably be attributed to enhanced mobility of the polymer chains and cross-linker molecules at elevated temperature. In this stage, the augmented collision of active "sites" promotes a faster formation of intermolecular cross-links and thereby an earlier outset of the shrinking process. At the higher polymer concentration, only a small effect is visible because the

growth of entanglements subdues the temperature-induced augmented mobility of the polymer chains, and the cross-linking situation is virtually unaltered. We notice again that due to higher chain density in the gel matrix for the 2 wt % sample, the degree of compression at longer times is less pronounced than for the 1 wt % HEC gel.

Deswelling Properties of HM-HEC Hydrogels

In semidilute aqueous solutions of HM-HEC, strong associations are mediated through intermolecular hydrophobic interactions, and the conjecture is that the addition of a cross-linker agent to this system should yield a gel with different swelling properties than the corresponding gel from the unmodified HEC. In the case of the 1 wt % HM-HEC sample, it was not possible to produce mechanically stable gels in the considered cross-linker concentration range (15-60 μl/g). The reason for this may be that the number of effective hydroxyl groups accessible for intermolecular cross-linking (some groups have been consumed in the reaction to attach hydrophobic groups onto the chains) of the polymer chains is reduced and the reactivity of the groups may be decreased so that no stable gel network is formed. In addition, the bulky hydrophobic groups on the polymer backbone may course steric hindrance problems during the cross-linking process. At higher polymer concentration, the increased number of accessible hydroxyl groups and more entanglements will facilitate the gelation of the sample. Therefore, only 2 wt % HM-HEC gels are examined here.

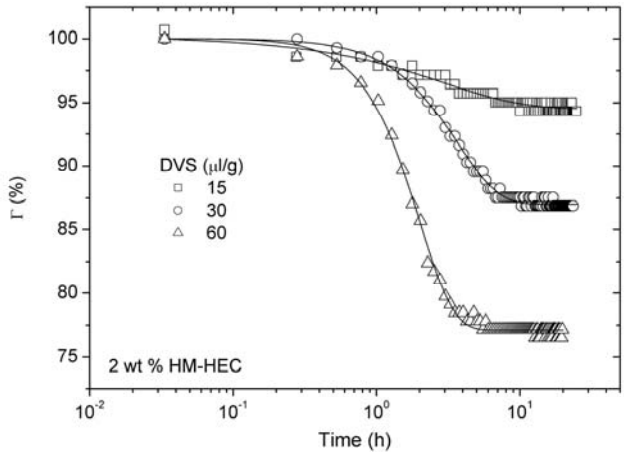

Figure 6. Time dependencies of Γ for 2 wt % HM-HEC solutions in the presence of different cross-linker concentrations (every 30 point is shown). The lines are fitted with the aid of eq. 2.

Results from the shrinking experiments of 2 wt % samples of HM-HEC with different cross-linker concentrations are depicted in Figure 6. It is obvious that a higher level of cross-linker addition leads to an earlier onset of the syneresis and more contracted gels. The general behavior is reminiscent of the features observed for the HEC samples, but the characteristics of the plateau domains at long times are different. To evaluate the differences between the HEC and HM-HEC gels quantitatively, the values of the characteristic parameters t_r and P are plotted as a function of the DVS

concentration in Figure 7. In the presence of the lowest cross-linker concentration, the value of t_r is much shorter for the HM-HEC sample than for the HEC gel, whereas for the higher two cross-linker concentrations the relaxation times are virtually the same for the two systems. The incorporation of hydrophobic groups will reduce the number of reactive hydroxyl groups somewhat (1 mol % of attached hydrophobic groups use up some OH groups) and steric hindrance may decrease the reaction rate of forming crosslinks. Under these conditions, the probability of forming effective crosslinks is least at the lowest level of crosslinker addition, whereas at higher crosslinker concentrations the enhanced probability of forming crosslinks will suppress the difference in shrinking kinetics between the systems. We should bear in mind that the shrinking in the postgel is considered, and at this stage a large amount of DVS has already been consumed, especially when the original crosslinker concentration is low.

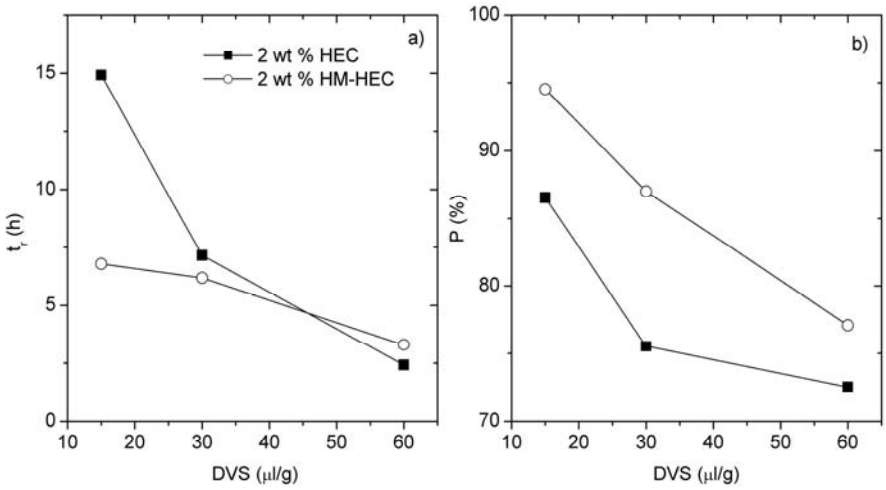

Figure 7. (a) Plot of t_r versus cross-linker concentration for 2 wt % of HEC and HM-HEC. (b) Plot of P as a function of cross-linker concentration for 2 wt % of HEC and HM-HEC.

A comparison of the plateau values (P) of the shrinking postgels at long times for the HEC and HM-HEC systems (see Figure 7b), discloses that the compression of the gel in the postgel region is more palpable for the HEC sample than for the corresponding HM-HEC gel. This difference in behavior can probably be traced to decreased reactivity and less number of reacting sites of HM-HEC and it is possible that the network structure is different for HM-HEC due to the hydrophobic associations.

Conclusions

In this work, shrinking kinetics and swelling ratio of chemically cross-linked gels of hydroxyethylcellulose and its hydrophobically modified analogue have been monitored over a long time after gelation with the aim of a high precision swell-ratio-tester. It is shown that measurements with this apparatus can provide quantitative information about deswelling kinetics and the extent of shrinkage of chemically cross-linked gels. This knowledge is essential in the physical chemical characterization of gels that undergo changes in course of time.

The rate of deswelling depends on many variables such as cross-linker density, polymer concentration, hydrophobicity, and temperature. It was demonstrated that an increased cross-linker density leads to an earlier onset of syneresis, and more compressed gels. The results show that in the presence of higher polymer concentration, the degree of compression of the gels declines. The faster and earlier outset of shrinking of HEC hydrogels at elevated temperatures is ascribed to enhanced mobility of the chains, which promotes a more efficient formation of interpolymer cross-links. The hydrophobic modification of the polymer results in a reduced number of accessible hydroxyl groups for the formation of cross-linked gels. Consequently, at the same conditions of polymer and cross-linker concentrations, the HM-HEC gels are less contracted compared with the HEC gels. The smaller shrinkage and earlier decay to the plateau region for the HM-HEC sample at the lowest level of cross-linker addition can be attributed to steric hindrance and less number of hydroxyl groups, leading to a reduced efficiency of the cross-linker reaction.
An important finding of this work is that hydrophobicity and polymer concentration can be employed as variables to tune the contraction of the gel-matrix in the postgel region. This effect can be utilized to modulate the porosity of the hydrogel, and thereby the drug release characteristics in controlled drug delivery.

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