# Effect of Hydrophobic Modification on Rheological and Swelling Features during Chemical Gelation of Aqueous Polysaccharides

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Rheological characteristics during chemical gelation with the cross-linker ethylene glycol diglycidyl ether (EGDE) of semidilute aqueous solutions of hydroxyethylcellulose (HEC) and of two hydrophobically modified analogues (HM-1-HEC and HM-2-HEC) are reported. In addition, rheological features of gelling samples (dextran and its hydrophobically modified analogue (HM-dextran)) of a different structure have been examined. Some swelling experiments on these gels in the postgel region are also reported. The gelation time of the hydroxyethylcellulose systems decreased with increasing cross-linker concentration, and incorporation of hydrophobic units of HEC resulted in a slower gelation. The time of gelation for the dextran system was only slightly affected by the incorporation of hydrophobic groups (HM-dextran). At the gel point, a power law frequency dependence of the dynamic storage modulus ($G' \propto \omega^{n'}$) and loss modulus ($G'' \propto \omega^{n''}$) was observed for all gelling systems with $n' = n'' = n$. The attachment of hydrophobic moieties on the dextran chains had virtually no impact on the value of $n$ ($n = 0.77$), and the percolation model describes the incipient dextran gels. By increasing the number of hydrophobic groups of the HEC polymer, the value of $n$ for the corresponding incipient gel drops significantly, and the value of the gel strength parameter increases strongly. Incorporation of hydrophobic units in the HEC chains promotes the formation of stronger incipient gels because of the contribution from the hydrophobic association effect. The frequency dependence of the complex viscosity reveals that all the investigated gels become more solidlike in the postgel domain. Far into the postgel region, the hydrophobicity of HEC plays a minor role for the strength of the gel network, whereas the values of the complex viscosity are significantly higher for HM-dextran than for the corresponding dextran gel. The swelling experiments on HEC, HM-1-HEC, and HM-2-HEC systems disclose that the degree of swelling of the postgels in water is quite different, depending on the relative distance from the gel point at which the cross-linker reaction is quenched. At a given distance from the gel point, the swelling of the HEC gel is less pronounced than for the corresponding hydrophobically modified samples. At this stage, the swelling of the HM-dextran gel is stronger than for the dextran gel.

## Introduction

Hydrogels can be produced through the introduction of intermolecular cross-links in semidilute aqueous polymer solutions. As a result, a stable chemically or physically cross-linked gel network evolves, which is able to swell rapidly and retains large volumes of water in its swollen three-dimensional structure.[1−3] Hydrogels are considered as functional materials for application in fields such as controlled drug delivery,[4,5] protein adsorption,[6] enzyme and cell encapsulation,[7,8] cell gene therapy,[9] recyclable absorbents,[6] bioseparation,[10] and artificial muscles[11] among others. Either a chemical or a physical gelation process can form the network structure of a hydrogel. In a semidilute polymer solution with an appropriate cross-linker agent, the polymer chains are gradually interconnected during the chemical gelation by covalent bonds to form a permanent gel network. In a physical gelation process, various forces, such as van der Waals, electrostatic attraction, hydrogen bonding, and hydrophobic interactions, can be employed to bind polymer chains together to form a gel.

In some respects, physical and chemical gels resemble the corresponding polymer solutions, but cross-links provide unique features of the gel matrix such as moderate rigidity, capability of shape retention, and gradual release of small drug molecules. In view of the latter aspect, special attention has been paid to drug delivery devices based on biocompatible polysaccharides.[12,13] However, the high solubility of polysaccharides in aqueous media is often responsible for the premature release of solutes, and the drug release features can be improved if the biopolymer is chemically modified through the incorporation of a few hydrophobic groups in the hydrophilic polymer backbone. In this way the polymer becomes less water-soluble.

In this work, the chemical gelation of semidilute aqueous solutions of hydroxyethylcellulose with different amounts of hydrophobic groups is monitored with the aid of rheology and some swelling experiments. To compare the gelling features of these cellulose derivative samples with a polysaccharide of a different nature, the gelation behavior of semidilute aqueous solutions of dextran and a hydrophobically modified analogue was studied by means of rheology and swelling measurements. In aqueous solutions, the hydroxyethylcellulose chains are extended and rather rigid, while dextran is a branched hydrophilic polysaccharide with a simpler backbone structure, and in solution the molecules exhibit a compact coil conformation. The results will show that the difference in structure between the polysaccharides will influence the gelation characteristics in a fundamental way.

The impact of cross-linker and polymer concentration on the gelation process has been studied previously for other polymer systems,[14−17] but the consequence of the degree of hydrophobicity of the polymer on chemical gelation is unknown. In the present study, effects of cross-linker concentration and hydrophobicity of the polymer, as well as polymer structure on the gelation process, are reported. The principal objective of this study is to understand how the degree of hydrophobicity of the

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polymer and polysaccharide structure will affect the gelation process far into the postgel region at different levels of cross-linker addition. The usual employed chemical cross-linker agents, such as divinylsulfone are toxic, which would limit the biomedical applications of the hydrogel. The cross-linker agent ethylene glycol diglycidyl ether (EGDE) that is utilized in this work is much less toxic and a very promising agent.

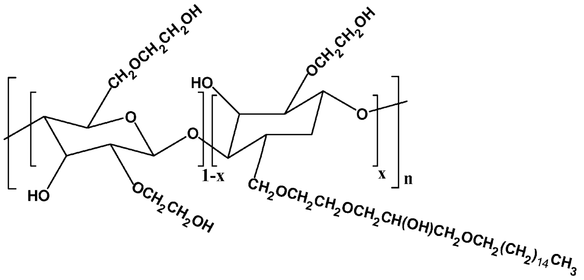
To gain insight into factors that influence the chemical gelation process, changes of the rheological characteristics and some swelling properties of the systems in the course of gelation far beyond the gel point will be scrutinized. To the best of our knowledge, this issue has not been addressed in detail before and is important for the understanding of hydrogels for controlled drug delivery applications. It will be shown in this work that the incorporation of a few hydrophobic groups in hydrophilic hydroxyethylcellulose chains will yield gelling systems with different rheological characteristics. The comparison of chemical gelation of polysaccharides of different architecture will demonstrate that the structure of the polymer affects the gelling properties of the system. The findings from gelling systems of quite different nature may lead to the development of hydrogels with properties that can be modulated for certain applications, e.g., controlled drug delivery.

## Experimental Section

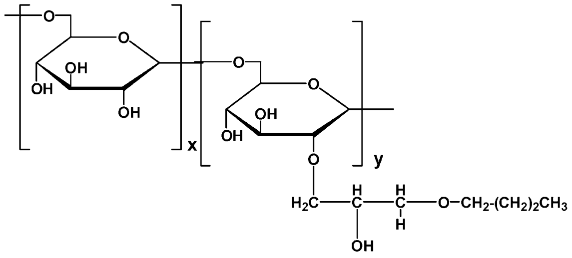
**Materials and Solution Preparation.** In this work, a hydroxyethylcellulose (HEC) sample with the trade name Natrosol 250 GR (lot. no. A-0382), obtained from Hercules, Aqualon Division, was utilized as a reference and as the precursor for the synthesis of the hydrophobically modified analogues. The molar degree of substitution of hydroxyethyl groups per repeating anhydroglucose unit is 2.5 (given by the manufacturer) for this HEC sample. The weight-average molecular weight ($M_w = 400\ 000$) of this HEC has previously been determined[18] by intensity light scattering at 25 °C. The dextran sample was purchased from ACROS chemicals (no. 40626), and it was employed as a reference and precursor for the synthesis of a hydrophobically modified analogue. The sample was characterized by means of size-exclusion chromatography coupled to multi-angle light scattering and refractive index detectors. The weight-average molecular weight and polydispersity index ($M_w/M_n$) of this fraction were determined[19] to be $6.2 \times 10^5$ and 1.8, respectively. The cross-linker agent ethylene glycol diglycidyl ether (EGDE) was supplied by Aldrich, Germany and used without further purification. The chemical structures of the cross-linker agent and the hydrophobically modified analogues of HEC and dextran are depicted in Figure 1.

The two hydrophobically modified polymers (HM-1-HEC and HM-2-HEC) were synthesized according to a standard procedure,[20] the details and characterization of the samples have been described elsewhere,[21] and only a brief summary is given below. The difference between HM-1-HEC and HM-2-HEC is the molar degree of substitution of glycidyl hexadecyl ether groups, where the substitutions of the former and the latter are 1 mol % and 2 mol %, respectively. After completion of the hydrophobization reactions, acetic acid neutralized the liquid reaction mixtures, and the products were collected by filtration. The products were washed thoroughly with acetone and dried at 70 °C for 24 h under reduced pressure to remove contents of acetone. The molar degrees of hydrophobic substitution of the HEC sample are only 1 mol % and 2 mol %, and under this condition the hydrophobic groups prefer to be bound to the OH groups on the longer side chains rather than the OH functions of the backbone. In this study, we use a commercial HEC sample as the start material to produce hydrophobic analogues with a similar structure.

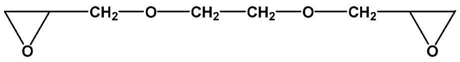
Dextran was allowed to react with butyl glycidyl ether in the presence of 1 M NaOH at ambient temperature under nitrogen atmosphere for 48 h. Then, the crude product was precipitated twice with ethanol, dialyzed against deionized water for 24 h, and freeze-dried. The hydrophobic content of the polymer was determined by $^1$H NMR in $D_2O$.



Hydrophobically modified HEC
(HM-1-HEC, x=0.01;HM-2-HEC, x=0.02)



Hydrophobically modified dextran (HM-dextran)



Ethyleneglycol diglycidylether (EGDE)

**Figure 1.** Schematic illustration of the chemical structures of the hydrophobically modified hydroxyethylcellulose (HM-1-HEC and HM-2-HEC), HM-dextran, and the cross-linker agent EGDE.

The chemical structure and purity of the HM-HEC samples and HM-dextran were ascertained by $^1$H NMR (deuteron-DMSO as a solvent for HM-HEC and $D_2O$ as a solvent for HM-dextran) with a Bruker AVANCE DPX300 NMR spectrometer (Bruker Biospin, Fällanden, Switzerland) operating at 300.13 MHz at 298.2 K. The hydrophobic modification degrees (glycidyl hexadecyl ether groups) of the HM-HEC samples were determined from the peak ratios between the anisomeric protons (4.9 ppm) and the methyl protons (0.8 ppm) of the glycidyl hexadecyl chain. The molar degree of substitution of the hydrophobic groups of the samples determined from NMR analysis were 1 mol % (HM-1-HEC) and 2 mol % (HM-2-HEC). The hydrophobically substituted content of the HM-dextran sample was calculated from the $^1$H NMR spectrum from the peak ratios between the anisomeric protons (4.9 ppm) and the methyl protons (0.8 ppm) of the glycidyl butyl chain, and the degree of substitution of hydrophobic groups was approximately 1.7 mol %.

To remove salt and other low-molecular-weight impurities, dilute HEC, HM-1-HEC, HM-2-HEC, dextran, and HM-dextran solutions were thoroughly dialyzed against Millipore water (7 days) and isolated by freeze-drying. Regenerated cellulose with a molecular weight cutoff of about 8000 (Spectrum Medical Industries) was utilized as dialyzing membrane.

All aqueous solutions were prepared by weighing the components. Semidilute aqueous solutions with a fixed polymer concentration of 2 wt % for the hydroxyethylcellulose samples and 5 wt % for dextran and HM-dextran were prepared by dissolving the polymers in 1 M NaOH at room temperature, followed by stirring over night to obtain homogeneous solutions. To obtain sufficiently stable gels of the cellulose derivatives for the swelling experiments, we needed a polymer concentration of 2 wt %, which is ca. 8 times the overlap concentration ($c^* = 0.25$ wt %). However, if we should have the same degree of overlap for the dextran samples ($c^* = 2.7$ wt %), the gelation process is too fast to be monitored in the rheometer. Therefore, we have chosen a concentration of 5 wt % for the dextran samples, which corresponds to about twice the overlap concentration. The strong alkaline conditions (pH ≈ 13−14) are necessary for the cross-linking reaction to proceed in the mixture. Prior to measurement, prescribed amounts of the cross-linker agent EGDE were added to the solutions under vigorous stirring, and shortly afterward the experiments were commenced. The concentrations of the cross-linker agent used were 5 wt %, 10 wt %, and 15 wt % (wt % refers to the weight of the cross-linker added to the weight of the total polymer solution) for the HEC, HM-1-HEC, and HM-2-HEC solutions, while for the dextran and HM-dextran solutions the cross-linker concentration was always 10 wt %. The cross-linking reaction in solutions of the unmodified and hydrophobically modified polymers occurs between the cross-linker molecules and hydroxyl groups on the polymer chains. The addition of cross-linker agent does not affect the pH of the solution.

**Rheology.** Oscillatory sweep and stress relaxation experiments were carried out in a Paar-Physica MCR 300 rheometer using a cone-and-plate geometry, with a cone angle of 1° and a diameter of 75 mm. This geometry was employed in all measurements. To prevent evaporation of the solvent, the free surface of the sample was always covered with a thin layer of low-viscosity silicone oil (the value of the viscosity is practically not affected by this layer). The measuring device is equipped with a temperature unit (Peltier plate) that gives an effective temperature control (±0.05 °C) over an extended time for the temperature (25 °C) considered in this work. In the oscillatory shear experiments, the values of the strain amplitude were checked to ensure that all measurements were carried out within the linear viscoelastic regime, where the dynamic storage modulus ($G'$) and loss modulus ($G''$) are independent of the strain amplitude. The measurements were carried out over a broad angular frequency ($\omega$) interval.

In a stress relaxation experiment, the sample is subjected to a rapid applied small strain, which is held constant for the remainder of the measurement, and the decay of stress in the viscoelastic material is monitored as a function of time. From this type of experiment, the stress relaxation modulus $G(t) = \sigma(t)/\gamma_0$, the ratio of stress to the fixed strain, can be determined.

**Swelling Experiments.** The SRT-1 swell-ratio-tester, purchased from the Cambridge Polymer Group, Inc., Boston, MA, can be used to measure the swelling/shrinkage properties of polymer gels as they respond over time at equilibrium conditions.[22] The instrument is capable of measuring swelling/shrinkage ratios at temperatures up to 150 °C (with a temperature accuracy of ± 0.1 °C). 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. If the sample is assumed to be isotropic, the change in volume can be readily determined. If the sample is nonisotropic, samples can be placed in several orientations to determine the degree of anisotropy. The samples in this study are found to be isotropic.

After adding the cross-linker to the polymer solution and stirring properly, the sample was transferred into a Teflon holder, which was placed inside the larger stainless steel chamber of the instrument. A picture of the equipment together with the Teflon holder is shown in Figure 2. The sample was allowed to gel inside the Teflon cell to produce a well-defined cylindrical gel piece for the swelling experiment. In the postgel regime the Teflon cell can be removed easily, and a piece of the gel will remain at the bottom of the chamber cell. This gel was formed at high pH, because the cross-linking of the network proceeds at alkali conditions. However, at a chosen distance from the gel point in the postgel region, the pH of the gel system is lowered and this quenches the cross-linking reaction.

Before the commencement of a swelling experiment, 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, and the ceramic probe was inserted through the hole in the lid covering the sample chamber. The gel piece was thereafter well covered by solvent (water), which was added through a second hole in the lid.

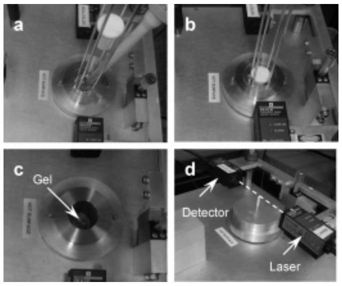


**Figure 2.** A picture of the swelling instrument with some components is shown. (a) Polymer solution was transferred into a Teflon holder after adding the cross-linker. (b) The gelation of the sample took place in the holder. (c) The holder was removed at the desired $\epsilon$, and a piece of the gel was left at the bottom of the chamber cell and it was surrounded by water. (d) Displacements of the probe-rod during the swelling process are registered by means of the laser and the detector.

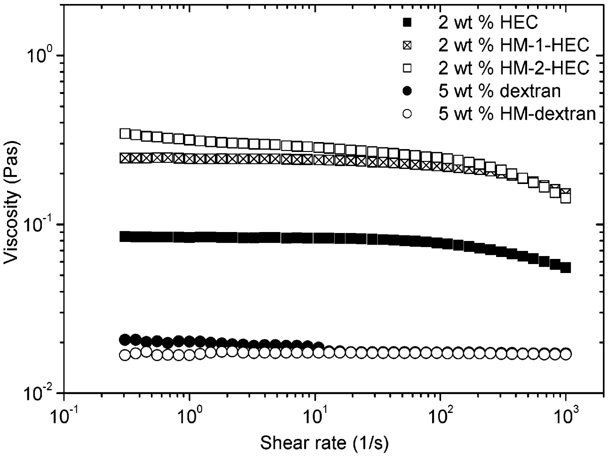


**Figure 3.** Shear rate dependence of the viscosity (in the absence of cross-linker agent, but all the samples are dissolved in 1 M NaOH) for 2 wt % solutions of HEC, HM-1-HEC, and HM-2-HEC and for 5 wt % solutions of dextran and HM-dextran.

The height of the probe was monitored as a function of time by a laser beam detection device. In this way, the time evolution of the swelling of the gel piece immersed in the solvent was monitored. The apparatus was interfaced to a PC, and data were collected by means of a software package provided by the manufacturer.

The swelling or shrinking of a gel or a film can be probed accurately as a function of time by following the change of the height of the sample with the aid of the present swell-ratio-tester. The swelling of the gel can be determined by the following relationship:

$$\mathrm{SR}\ (\%) = \frac{h_t - h_0}{h_0} \cdot 100 \qquad (1)$$

where SR 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.

## Results and Discussion

**Rheological Properties.** Before the gelation features of the systems are presented and discussed, it may be instructive to compare the viscosity behaviors of the polymer solutions in the absence of cross-linker agent. Figure 3 shows the effects of shear rate on the measured viscosity for the solutions of the unmodified and hydrophobically modified polymers that are used in the gelling experiments presented below. The results for the dextran systems reveal that the viscosity is low and virtually Newtonian over the considered shear rate domain. There is

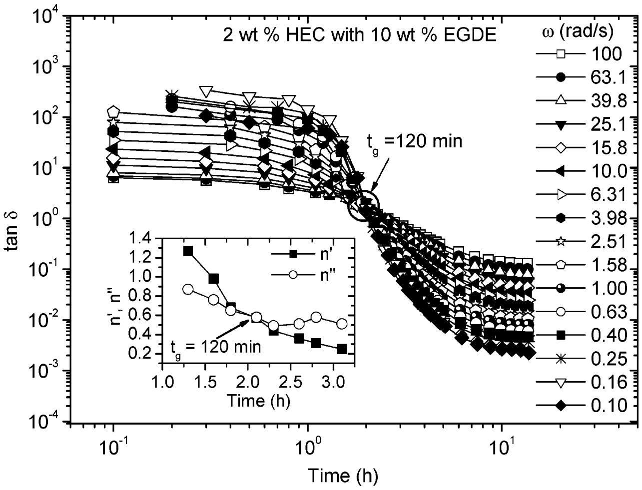


**Figure 4.** Illustration of methods for the determination of the gel point. Viscoelastic loss tangent as a function of time for the system and frequencies indicated. The inset plot shows changes of the apparent exponents' n′ for the storage and n″ for the loss moduli during the course of gelation.

almost no effect of the hydrophobic interaction on the viscosity, which may suggest that most of the hydrophobic moieties reside inside the compressed structure. For the hydroxyethylcellulose systems, on the other hand, the intermolecular hydrophobic association effect is evident, and shear thinning is clearly observed for the sample with the highest degree of hydrophobicity. This diversity in behavior between the dextran and the hydroxyethylcellulose systems can be ascribed to differences in the network structure. In the former case, the network consists of compact coils that are close-packed, whereas for the latter systems the extended and rigid chains associate and may even form some entanglements.

The gel point during a chemical cross-linking process of a polymer solution can be determined by observation of a frequency-independent value[23] of the loss tangent, tan $\delta$ ($= G''/G'$), obtained from a multifrequency plot tan $\delta$ versus time. A typical example is presented in Figure 4 for a system with 2 wt % HEC in the presence of 10 wt % cross-linker. The common feature observed for all gelling HEC and HM-HEC solutions is that the loss tangent is frequency dependent and decreases during the gel formation, indicating that the systems become more and more elastic. The time of gelation $t_g$ is identified at the point where a frequency-independent value of the loss tangent is observed. An alternative method[24] to determine the gelation time is to plot against time the "apparent" viscoelastic exponents $n'$ and $n''$ ($G' \sim \omega^{n'}$; $G'' \sim \omega^{n''}$) calculated from the frequency dependence of G′ and G″ at each time of measurement and observing a crossover where $n' = n'' = n$ (see the inset plot of Figure 4). Both methods yield the same gelation times for the considered polymer systems.

Effects of cross-linker concentration and degree of hydrophobic modification on the gelation time are illustrated in Figure 5. It is evident in all cases that the values of $t_g$ decrease with increasing concentration of the cross-linking agent. As the cross-linker density rises, the probability of forming cross-links in the system increases, and this favors a faster gelation. At a given cross-linker concentration the time of gelation becomes longer as the number of hydrophobic groups of the polymer increases, probably because the number of "active sites" for cross-linking of the polymer network declines. This is ascribed to the fact that some of the hydroxyl groups for cross-linking were consumed in the chemical reaction when hydrophobic moieties were attached to the HEC chains. The reduction of reactive hydroxyl groups prolongs the gelation time. In addition, the cross-linker reaction may be slowed down because of steric hindrance caused by the hydrophobic moieties. As is illustrated in the inset of Figure 5, where the relative gelation time ($t_g/t_{g,5}$) (where $t_{g,5}$ is the gelation time for the samples containing 5 wt % EGDE) is plotted as a function of the cross-linker concentration, the difference in gelation time between the polymer samples seems to be virtually unaffected by the level of added cross-linker agent.

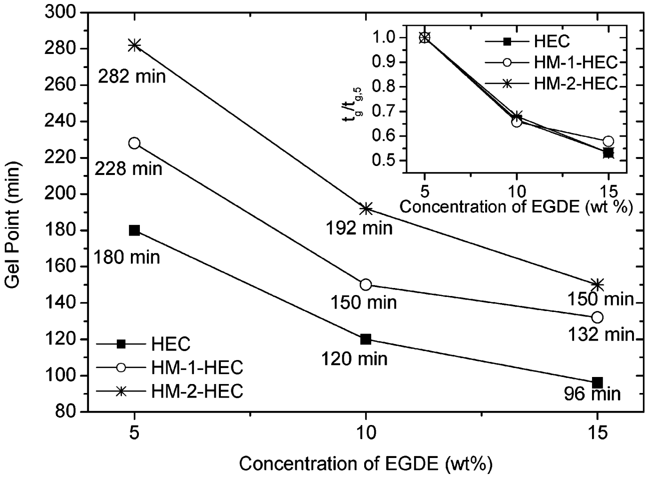


**Figure 5.** Effect of cross-linker concentration on the gelation time for 2 wt % samples of HEC, HM-1-HEC, and HM-2-HEC. The inset plot shows the effect of cross-linker concentration on the relative gelation time.

The rheological behavior of an incipient gel can be described in terms of a simple power law between dynamic moduli and angular frequency[25]

$$G' = G''/\tan\delta = S\omega^n\Gamma(1-n)\cos\delta \qquad (2)$$

where Γ(1 − n) is the Legendre gamma function, $n$ is the viscoelastic exponent, and $S$ (Pa s$^n$) is the gel strength parameter,[25] which depends on the cross-linking density and the molecular chain flexibility and is considered to be a material parameter. The phase angle $\delta$ between stress and strain is independent of angular frequency but proportional to the value of the viscoelastic exponent[25]

$$\tan\delta = G''/G' = \tan(n\pi/2) \qquad (3)$$

These results suggest that the following scaling relation describes the incipient gel:

$$G'(\omega) \propto G''(\omega) \propto \omega^n \qquad (4)$$

This type of power law behavior at the gel point is illustrated in Figure 6 for the unmodified and the hydrophobically modified HEC samples in the presence of 10 wt % of EGDE. The most interesting finding is the strong drop of the value of $n$ as the number of attached hydrophobic groups to the polymer chains increases. The same trend is also observed at the other levels of cross-linker addition, and the value of $n$ is virtually not affected by the different cross-linker concentrations studied in this work for any of the considered hydroxyethylcellulose samples (HEC, HM-1-HEC, or HM-2-HEC). This is consistent with rheological studies[16,17] on other gelling polymer systems, where no effect of cross-linker addition on the value of $n$ was reported.

By using the same methods for the determination of the gel point ($t_g$) as described above, the times of gelation for 5 wt %

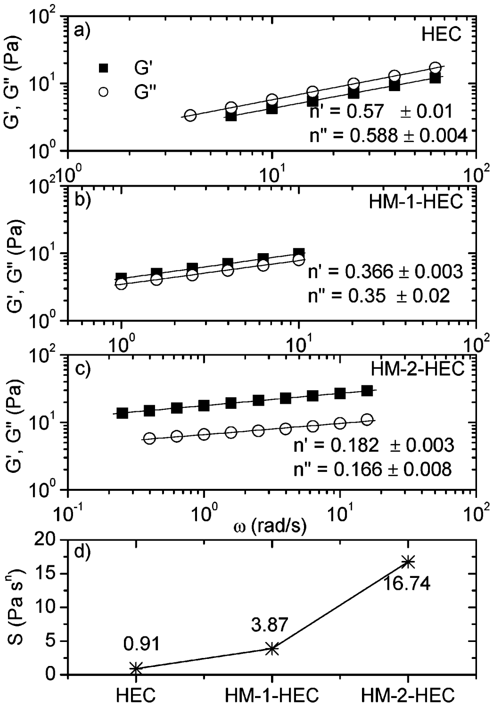


**Figure 6.** (a, b, c) Illustration of power law behavior of the dynamic moduli for 2 wt % incipient gels of HEC, HM-1-HEC, and HM-2-HEC in the presence of 10 wt % cross-linker agent. (d) Plot of the gel strength parameter (see eq 2) for the HEC, HM-1-HEC, and HM-2-HEC systems with 10 wt % EGDE.

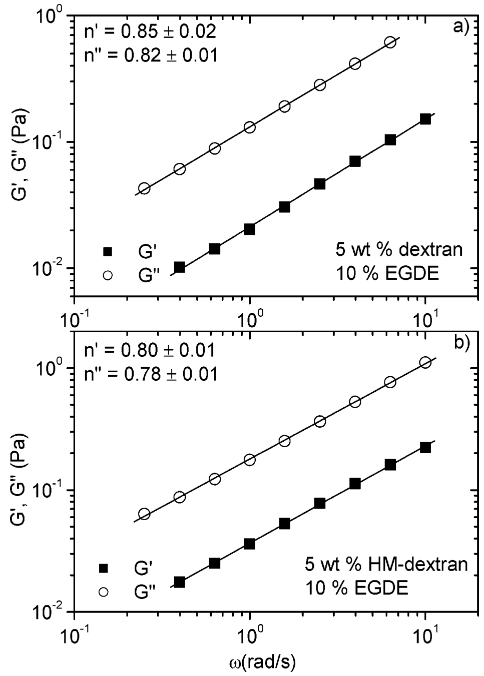


**Figure 7.** The frequency dependencies of the dynamic moduli for the incipient gels of the systems indicated.

solutions of dextran and HM-dextran in the presence of 10 wt % EGDE are 114 and 96 min, respectively. This reveals that the gelation time ($t_g$) is only slightly affected by the hydrophobic modification. At the gel point, parallel lines are observed for the frequency dependencies of the dynamic moduli in a log−log plot (cf. Figure 7), and the viscoelastic exponent $n$ is 0.83 and 0.79 for the incipient gels of dextran and HM-dextran, respectively.

The formation of incipient gels and the value of the viscoelastic exponent are features that are frequently analyzed in the framework of the percolation model, which describes the fraction of chemical bonds at the gel point to establish the connectivity of a sample-spanning cluster. In the interpretation of the viscoelastic exponent, two main models, which take into account the fractal geometry of polymer clusters and their intrinsic irregular structure, have been elaborated. Based on a suggested[26,27] isomorphism between the complex modulus and the electric conductivity of a percolation network with randomly distributed resistors and capacitors, a value of $n = 0.72$ was predicted. In the other approach,[28] the Rouse model, which assumes no hydrodynamic interaction between polydisperse polymeric clusters, together with percolation statistics, yielded a value of $n = 2/3$. Several investigations in the literature[15−17,25,29] on gelling systems of various natures seem to support the percolation approaches with values of $n$ around 0.7. However, there are oscillatory shear studies[22,25,30−33] on different gelling systems that indicate $n$ is not a constant but takes values in the range $0 < n < 1$, depending on factors such as structure of the species in the reaction mixture, the stoichiometric ratio, the gel preparation method, and also molecular weight and polymer concentration.

It is evident that the values of the viscoelastic exponent observed for the hydroxyethylcellulose systems (Figure 6a−c) cannot be accommodated within the percolation model. In this context it is interesting to notice a different approach[34] in which the relation between viscoelastic and structural properties of systems of cross-linking polymers near the gel point was considered in the framework of a mechanical ladder model, consisting of springs and dashpots which mimic the rheological characteristics. For ladderlike structures, this model predicts a power law in frequency for the complex shear modulus, with an exponent $n = 0.5$. It was argued in the analysis of this model that the role of additional cross-links is to decrease the value of $n$. Experimental studies[14−16,29] on chemically cross-linked incipient gels have revealed that as the polymer concentration increases lower values of $n$ are usually obtained. This effect was ascribed to entanglement effects at higher polymer concentrations. In the light of the aspects above, the observed drop of $n$ with increased number of hydrophobic groups (from $n = 0.57$ (HEC) to $n = 0.18$ (HM-2-HEC)) can probably be attributed to enhanced intermolecular associations due to the growth of the intermolecular hydrophobic interactions. As will be seen below, the incipient gel network is strengthened by the hydrophobic interactions. The values of the power law exponent for incipient gels of dextran ($n = 0.83$) and HM-dextran ($n = 0.79$) are fairly close to that predicted from the percolation model. In this case, we visualize a situation where the close-packed spherelike molecules are interconnected through cross-links to form a sample-spanning cluster in the spirit of the percolation approach. For the incipient gels of hydroxyethylcellulose and the hydrophobic analogues, the chains are intertwined and probably also entanglements are formed. The evolution of connectivity for the gel network is more intricate for this system. In this case, the extended polymer chains are expected to form a transient network in the semidilute regime before the cross-linker is added.

It is obvious from Figure 6d that the gel strength parameter $S$ rises as the hydrophobicity of HEC is increased; this reflects augmented hydrophobic associations, and probably the chain rigidity is also enhanced. This finding suggests that the hydrophobic tails of the polymer contribute to the formation of a "harder" incipient gel. For the incipient dextran and HM-dextran gels, the values of the $S$ are 0.03 ± 0.01 (Pa s$^n$) and 0.05 ± 0.01 (Pa s$^n$), respectively. These values are much lower

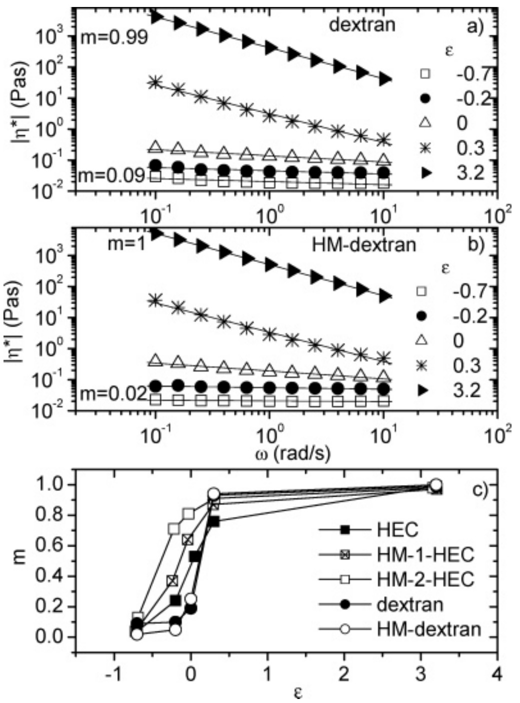


**Figure 8.** Frequency dependence of the complex viscosity (log−log plot) at different stages during the gelation process for 2 wt % samples of HEC and HM-2-HEC in the presence of 10 wt % cross-linker agent.

than for the hydroxyethylcellulose samples, and there is virtually no effect of attached hydrophobic groups on the value of *S*, which suggests that, in contrast to the HEC systems, the hydrophobic interactions contribute very little to the gel strength of the incipient gel network. This behavior, as well as the much lower *S* values for the dextran systems can probably be traced to the compact conformation of the cross-linked molecules as compared to the extended HEC and HM-HEC chains, where both entanglements and hydrophobic association effects more easily can come into play.

To follow the evolution of the viscoelasticity in the course of a gelation process, it is convenient to introduce the complex viscosity, with its absolute value given by[35]

$$|\eta^*(\omega)| = \frac{(G'^2 + G''^2)^{1/2}}{\omega} \tag{5}$$

In an analogous way as for the dynamic moduli, we may describe the frequency dependence of the absolute value of complex viscosity in terms of a power law[36] $|\eta^*| \propto \omega^{-m}$, where the complex viscosity exponent *m* for an incipient gel is directly related to *n* through $m = 1 - n$. Values of *m* close to zero announce liquidlike behavior, whereas values of *m* approaching 1 suggest solidlike response of the system.

The frequency dependencies of the complex viscosity, as measured in small amplitude oscillatory shear experiments, at different stages (where $\epsilon = (t - t_g)/t_g$, *t* is the considered time and $t_g$ is the time of gelation, is the relative distance from the gel point) during the gelation process for aqueous solutions of HEC and HM-2-HEC in the presence of 10 wt % cross-linker agent are displayed in a log−log plot in Figure 8a,b. An analogous plot for the dextran and HM-dextran systems is depicted in Figure 9a,b. The general picture that emerges for all gelling systems is that at early stages in the pregel domain ($\epsilon < 0$), weak frequency dependence of $|\eta^*|$ is found (liquidlike behavior), whereas as the gel evolves, a progressively stronger dependence is observed and a solidlike response (*m* is close to 1) is approached far beyond ($\epsilon \gg 0$) the gel point. This feature, which is observed for all the gelling samples, clearly shows that the cross-linking reaction proceeds far into the postgel region, and the large number of cross-linked chains raises the elastic response of the systems.

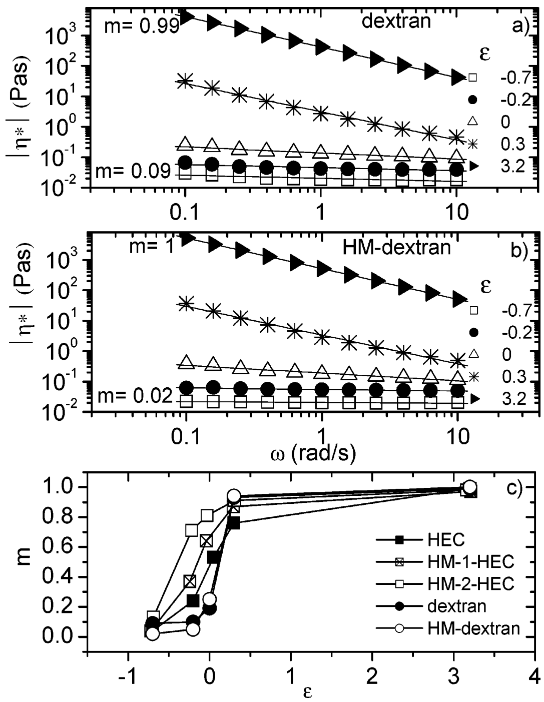


**Figure 9.** (a, b) Frequency dependence of the complex viscosity (log−log plot) at different stages during the gelation process for 5 wt % samples of dextran and HM-dextran in the presence of 10 wt % cross-linker agent. (c) Plot of the power law exponent *m* ($|\eta^*| \sim \omega^{-m}$) for 2 wt % samples of HEC, HM-1-HEC, and HM-2-HEC and 5 wt % samples of dextran and HM-dextran in the presence of 10 wt % cross-linker agent.

In Figure 9c, the change of the power law exponent *m* in the course of gelation is illustrated for all the polymer systems in the presence of 10 wt % of the cross-linker agent. In the course of gelation, the values of *m* at a given $\epsilon$ in the pregel and gel region for the hydroxyethylcellulose system become higher as the number of attached hydrophobic tails to the polymer chains increases. At this stage, we also note that the values of *m* for the dextran and HM-dextran systems are significantly lower than the corresponding ones for the cellulose derivative systems. This finding indicates that the elastic response is weaker, and more fragile incipient gel networks are evolved for the dextran and HM-dextran systems because of a more compact structure and nonentangled chains of the interconnected molecules. However, far beyond the gel point the value of *m* is practically the same for all the gelling polymer systems. These findings may be rationalized in the following way. At stages up to the gel point and somewhat beyond, the hydrophobic moieties of the hydroxyethylcellulose chains act as stickers and form intermolecular bridges in addition to the junction zones formed through the chemical cross-linking reaction. As a result, a stronger network evolves due to the involvement of the hydrophobic interactions. When it comes to the dextran systems, our conjecture is that a large fraction of the hydrophobic moieties is buried inside the coil structure, and the contribution of intermolecular hydrophobic interactions to the gelation process is weak. This indicates that the number of OH sites for interpolymer cross-linking is somewhat less for HM-dextran. This may explain the lower values of *m* for this polymer in the pregel domain in comparison with those of dextran.

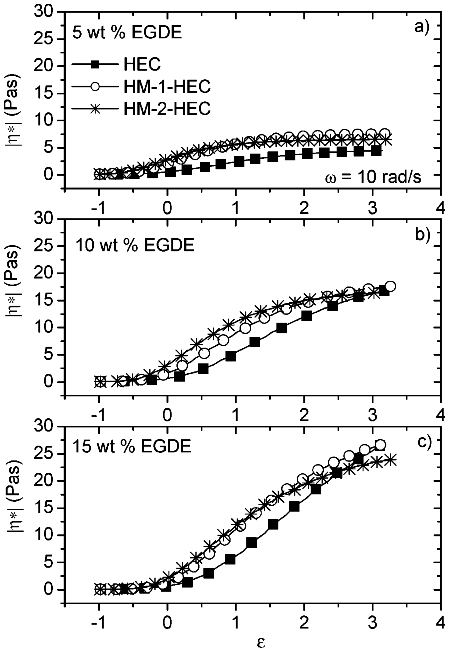


**Figure 10.** Time evolution of the complex viscosity (at an angular frequency of 10 rad/s) in the course of gelation for 2 wt % samples of HEC, HM-1-HEC, and HM-2-HEC in the presence of different concentrations of the cross-linker EGDE. The symbols have the same meaning in all panels.

Far into the postgel region most of the “active sites” on the polymer chains for interpolymer cross-links have been used up, and strongly cross-linked networks are created for all the systems. At this stage the contribution from the weaker hydrophobic interactions plays an insignificant role to the frequency dependence of the complex viscosity.

A comparison of the growth of the complex viscosity (at a fixed angular frequency of 10 rad/s) during the gelation process of 2 wt % solutions of HEC, HM-1-HEC, and HM-2-HEC at diverse levels of cross-linker addition is shown in Figure 10.

In the course of gelation, the elastic response rises for all systems, and this trend becomes more pronounced as the EGDE concentration increases. At the lowest cross-linker concentration, the values of $|\eta^*|$ are, over the whole $\epsilon$-domain, significantly higher for the hydrophobically modified analogues than for HEC, whereas at the higher levels of cross-linker addition the complex viscosity data for the unmodified and the hydrophobically modified samples virtually overlap each other at high values of $\epsilon$. This observation suggests that at a deficiency of cross-linker, the polymer network is relatively weak even far beyond the gel point, and the interactions of the hydrophobic tails contribute notably to the strength of the network. However, at higher cross-linker densities, the impact of the hydrophobic interactions on the viscoelasticity in the far postgel region (large values of $\epsilon$) is negligible because a large fraction of the OH groups of the polymer has reacted and formed a strong network. At this stage, even smaller values of $|\eta^*|$ may be expected for the hydrophobically modified samples since some of their OH groups have been consumed during the attachment of the hydrophobic moieties to the polymer chains.

Evolution of $|\eta^*|$ in the course of the gelation process for dextran and HM-dextran in the presence of 10 wt % cross-linker concentration is shown in Figure 11.

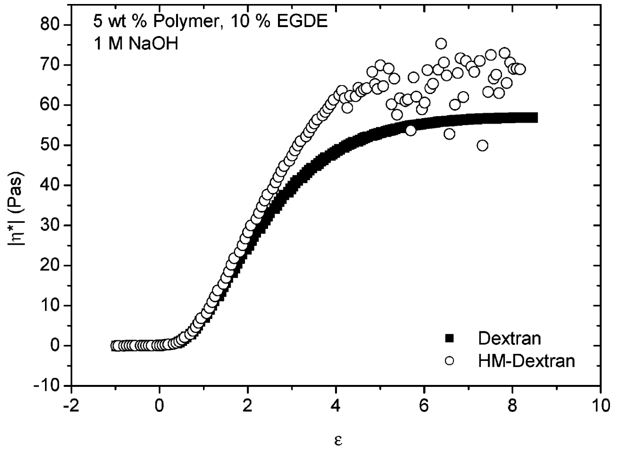


**Figure 11.** Time evolution of the complex viscosity (at an angular frequency of 10 rad/s) in the course of gelation for 5 wt % samples of dextran and HM-dextran in the presence of 10 wt % of EGDE.

For the dextran and HM-dextran systems a different picture emerges for the time evolution of the cross-linking process. In this case, the values of $|\eta^*|$ for the two samples overlap with each other in the pregel region and in the initial stage of the postgel regime, suggesting that the hydrophobic moieties do not affect the gelation process. However, far beyond the gel point significantly higher values of $|\eta^*|$ are observed for the HM-dextran sample. In the cross-linking process of dextran, we may assume that both intrapolymer and interpolymer cross-links are formed, whereas for the HM-dextran a reduced number OH sites for intramolecular cross-linking are available because hydrophobic groups occupy a great part of the OH functions in the interior of the compact species. As a consequence of this, a more efficient interpolymer cross-linked network will develop in the course of time for HM-dextran because most of the EGDE molecules participate in intermolecular cross-linking of the compact polymer coils. Since the degree of hydrophobic modification of the HM-dextran sample is fairly low, there are plenty of active OH sites on the surface of the polymer coils available for intermolecular cross-linking. Very far into the postgel region ($\epsilon > 4$), a large scatter in the experimental data for the HM-dextran gel is an evident feature at this stage. This may indicate that a more fragile gel structure is evolved, composed of weaker (hydrophobic interactions in the interior of the connected coils) and stronger (chemical cross-links of chains) domains of connected chains. This heterogeneity in the morphology of the gel network may give rise to fluctuations in the values of the complex viscosity. In dextran gels, both intrapolymer and interpolymer cross-links are established through the chemical cross-linker, and this may promote the growth of a more uniform network.

The decay of the relaxation modulus $G(t)$ (determined from stress relaxation measurements) during the gel formation process is shown in Figure 12 for 2 wt % solutions of HEC, HM-1-HEC, and HM-2-HEC in the presence of 5 wt % EGDE. The general trend is parallel for the three systems, namely that the relaxation function exhibits a pronounced shift in the decay time toward higher values as the gel evolves. In the pregel region, large scatter is observed in the stress relaxation data for the unmodified sample due to weaker network associations. The general picture that emerges is that as more and more chains are cross-linked in the course of gelation, the decay of the relaxation process becomes slower. This is another demonstration that the gel network is gradually strengthened during a long period of time after the gel point and that a more solidlike material evolves.

To compare the relaxation behavior of the gels in the beginning of the postgel region, the relaxation modulus $G(1)$ at a given time ($t = 1$ s) is plotted versus $\epsilon$ for the indicated gel samples with a cross-linker concentration of 5 wt % (see Figure

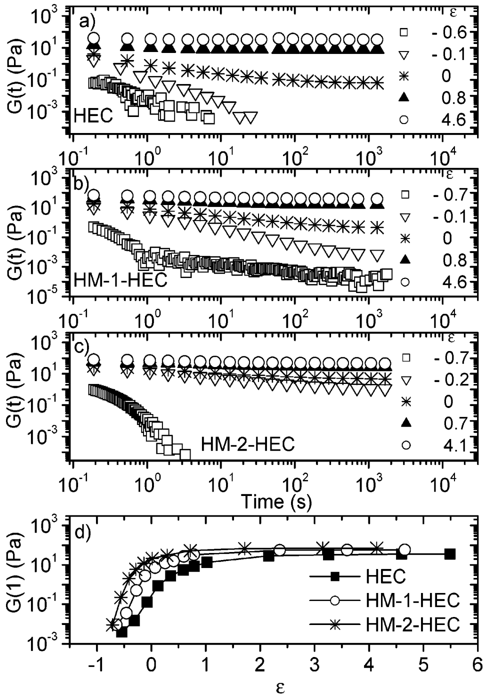


**Figure 12.** (a, b, c) Time dependence of the shear relaxation modulus at different stages of gelation for the 2 wt % samples indicated at a cross-linker concentration of 5 wt %. (d) Plot of the shear relaxation modulus $G(1)$ at a fixed time (1 s) versus $\epsilon$.

12d). Around the gel point, the relaxation is slowed down more as the hydrophobicity of the polymer rises due to the impact of the hydrophobic interactions on the cross-linking zones. However, at sufficiently high values of $\epsilon$ the values of $G(1)$ for the three systems are almost the same, which again emphasizes that at this stage the hydrophobic associations play a minor role for the strength of the gel network.

**Swelling Properties.** To gain some information about the swelling kinetics of matured gels, some of the gels were quenched at different stages ($\epsilon = 8$ and $\epsilon = 24$) in the postgel region by lowering the pH, gel pieces prepared for measurement were immersed in the solvent, and the swelling ratio (SR) was monitored during a long time after gelation. The swelling characteristics of a hydrogel can be determined by fitting the data with the aid of the following Voigt-based relationship[37,38]

$$S_t = S_0(1 - e^{-t/\tau}) \qquad (6)$$

where $S_t$ is swelling ratio at time $t$, $S_0$ is equilibrium swelling ratio, $t$ is time for swelling, and $S_t$ and $\tau$ are "rate parameters".

In Figure 13, the swelling ratio as a function of time for 2 wt % samples of HEC and HM-2-HEC (with 15 wt % cross-linker) is shown at two different values of $\epsilon$, together with fitted curves by means of eq 6. The values of $\tau$ and $S_0$ for the systems are collected in Table 1. Let us first discuss the results for the HEC samples at different distances from the gel point (Figure 13a). The results suggest that a higher value of $\epsilon$ promotes a faster rate of water uptake (lower value of $\tau$) and a smaller degree of swelling (smaller value of $S_0$) than for the corresponding gel at an earlier stage of gelation. The faster swelling at $\epsilon = 24$ may be attributed to a more pronounced heterogeneity of the gel network at this late stage of the cross-linking process. This inhomogeneity of the gel network gives rise to some large pores, which may facilitate the transport of solvent into the gel matrix. The difference in the swelling degree between the gels may be rationalized in the following way. At an early state in the postgel region, the gel network is loose and it can swell considerably when exposed to a good solvent, whereas at a later stage of the gelation process several additional cross-links have been established and a rigid network is developed. This network reaches its equilibrium state at a fairly low swelling ratio, because the heavily cross-linked gel matrix is stiff and this restricts the degree of swelling of the gel. This conjecture is compatible with the rheological findings for the HEC system, where a progressively stronger gel network is found to evolve as the relative distance from the gel point is increased.

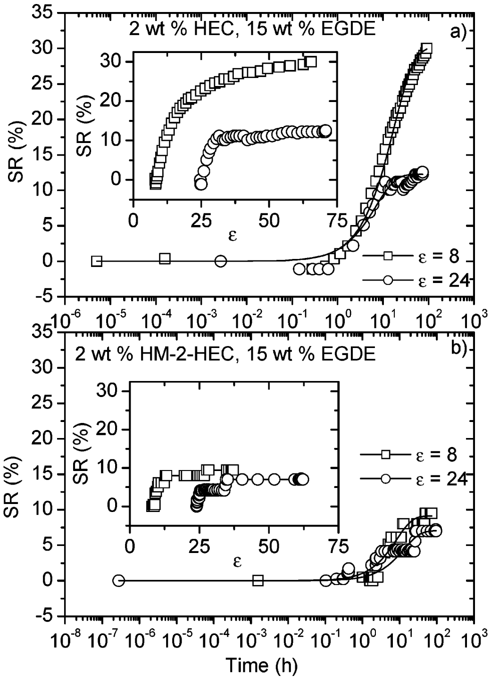


**Figure 13.** Time evolution of the swelling ratio at two different stages in the postgel region for 2 wt % samples of HEC (a) and HM-2-HEC (b) with 15 wt % of cross-linker. The gel samples were quenched at two different stages in the postgel region, and the swelling ratios were monitored over time. The inset plots show a comparison of the swelling ratio as a function of time at two different stages during the gelling process. The solid curves in the panels have been fitted to the data points with the aid of eq 6. The values of the fitted parameters are collected in Table 1.

**Table 1.** Values of Fitted Parameters with the Aid of Eq 6 for the Systems and Values of $\epsilon$ Indicated

| | ($\epsilon = 8$) | | ($\epsilon = 24$) | |
|---|---|---|---|---|
| systems | $\tau$ (h) | $S_0$ | $\tau$ (h) | $S_0$ |
| HEC | 17.7 | 30.1 | 6.8 | 12.3 |
| HM-2-HEC | 7.7 | 8.9 | 13.2 | 7.0 |
| dextran | 22.3 | 13.8 | - | - |
| HM-dextran | 22.9 | 25.9 | - | - |

Effect of distance from the gel point for the HM-2-HEC sample reveals a different behavior than for the HEC system (cf. Figure 13b and Table 1). In this case the rate of water uptake is faster at a low value of $\epsilon$, which indicates that a tighter network (higher value of $\tau$) is formed as the cross-linking process proceeds. The degree of swelling is almost unaffected by the value of $\epsilon$ for the HM-2-HEC gel.

The swelling features of HEC and dextran gels and the corresponding hydrophobically modified samples (HM-2-HEC and HM-dextran) at $\epsilon = 8$ are compared in Figure 14. It is evident from Figure 14 and Table 1 that the degree of swelling is less pronounced for HM-2-HEC than for HEC, and the rate of water uptake is faster for the hydrophobically modified

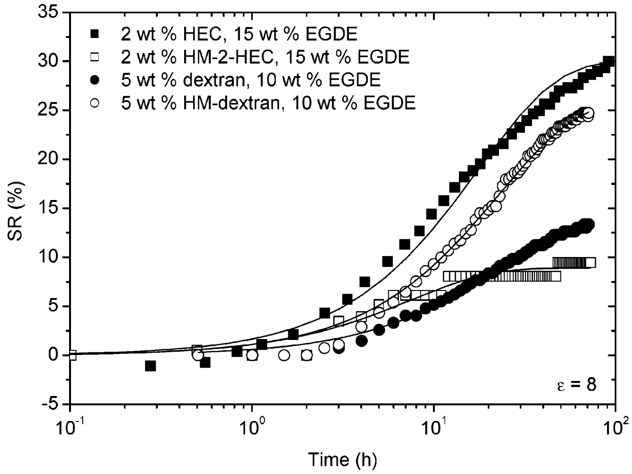


**Figure 14.** A comparison of swelling at $\epsilon = 8$ for the gels of HEC, HM-2-HEC, dextran, and HM-dextran. The solid curves have been fitted to the data points with the aid of eq 6. The values of the fitted parameters are collected in Table 1.

analogue. The polymer with hydrophobic groups attached to the chains should have a lower tendency for water uptake[38] than the more hydrophilic HEC. In addition, the hydrophobic interactions may promote the growth of a more rigid network that is less inclined to swell. Because of the hydrophobic interactions, the gel network is presumably more heterogeneous, and this should favor a faster penetration of solvent molecules into the gel piece. An alternative explanation of the fast swelling of HM-HEC may be that because of the spacious substituents, which are able to adjust a certain distance between the chains, the polymer structure is more easily accessible to solvent penetration.

A peculiar effect is found when the swelling of dextran and HM-dextran gels is compared (see Figure 14 and Table 1). In this case the rate of water uptake ($\tau$) is practically the same, but the swelling is more pronounced for the hydrophobic counterpart in contrast to that observed for the cellulose derivatives. This difference in behavior can probably be traced to structural differences between the systems as discussed above (cf. Figure 11). The more fragile structure of the HM-dextran gel is more prone to swell than the uniform structure of the dextran gel. However, the strongest swelling for these systems is detected for the HEC gel, which probably is associated with the fact that this gel matrix is composed of fairly extended chains of a hydrophilic nature.

## Conclusions

In this work, we utilized rheological and swelling methods to examine the effect of hydrophobicity on the gelation behavior of semidilute aqueous solutions of hydroxyethylcellulose and its hydrophobically modified analogues (HM-1-HEC and HM-2-HEC) in the presence of different cross-linker concentrations. As a comparison, similar experiments were also conducted on gelling systems of dextran and HM-dextran, polysaccharides with a different architecture. This study shows that the incorporation of hydrophobic groups on the HEC chains momentously affects the gelling properties of the system, whereas hydrophobic modification of dextran has a much smaller influence on the gelation process. In this work, we have found that the architecture of the network forming the gel matrix is crucial for the gelling and swelling features of the system. The gel networks of HEC and its hydrophobically modified counterparts are build-up of extended and more or less intertwined chains, whereas the gels of dextran and HM-dextran are composed of compact coils that are close-packed and connected through chemical cross-links. Our conjecture is that in the case of HM-dextran the hydrophobic moieties are predominantly in the interior of the structures, whereas for the HM-HEC systems the extended structure of the chains makes them more accessible to interpolymer associations. A schematic illustration of the association behaviors of these systems is displayed in Figure 15. The main results can be summarized in the following way: (1) As the number of attached hydrophobic groups of HEC increases, the time of gelation becomes longer because the number of active OH sites for interpolymer cross-linking decreases. The incorporation of hydrophobic groups on dextran chains has an insignificant impact on the gelation time. (2) At the gel point, the storage and loss moduli show a power law behavior for all the systems, $G' \propto G'' \propto \omega^n$, with angular frequency $\omega$. At a fixed HEC concentration and a given cross-linker density, the value of $n$ drops considerably, and the values of the gel strength parameter and the complex viscosity increase strongly for the incipient gels as the number of hydrophobic groups attached to the HEC chains rises. These features suggest augmented association strength of the gel network, and that the elasticity of the incipient gel is enhanced by the presence of an increasing number of hydrophobic tails. The attachment of hydrophobic moieties to the compact dextran chains has virtually no effect on the value of $n$, and the incipient gels can be described in the framework of the percolation model. At the gel point, the low values of $S$ for the dextran and HM-dextran gels signify that the gel networks are much weaker than for the cellulose derivatives. (3) The frequency dependence of the complex viscosity reveals that all the gels become more solidlike ($m$ is close to 1) in the postgel domain, and for the HEC systems this effect is strongest for the most hydrophobic gel. A similar behavior appears from the stress relaxation measurements on the gelling HEC systems. However, far into the postgel region for the HEC samples the contribution from the hydrophobic units to the strength of the gel network is weak because at this stage the network is heavily cross-linked and the input of hydrophobic interactions is negligible. The picture that emerges for the dextran systems is quite different. In this case a plot of $|\eta^*|$ versus $\epsilon$ yields curves that collapse onto each other beyond the gel point. At longer distances from the gel point, higher values of $|\eta^*|$ are observed for the hydrophobically modified analogue. Far beyond the gel point, strong fluctuations in the complex viscosity data for HM-dextran are visible, and this behavior is ascribed to the evolution of a fragile gel structure. The significant differences in behavior between the HEC and dextran gel systems are attributed to fundamental dissimilarities in the architecture of the polysaccharides in solution. (4) The swelling experiments disclosed that the degree of swelling of the HEC postgels in water was quite different depending on the relative distance from the gel point at which the cross-linker

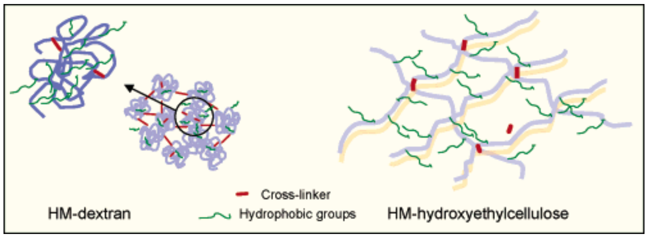


**Figure 15.** A schematic illustration of the association and gelation behaviors in systems of hydrophobically modified dextran and hydroxyethylcellulose.

reaction was quenched. At an early stage in the postgel region, the degree of swelling is more marked than for the corresponding gel far into the postgel region. The reason is that the former gel network is more flexible and allows a greater degree of swelling than the stronger cross-linked gel. The strongly cross-linked HEC gel ($\epsilon = 24$) is more heterogeneous and exhibits a faster water uptake than that at $\epsilon = 8$. The influence of the value of $\epsilon$ on the degree of swelling and the rate of water uptake in the gel is less accentuated for the hydrophobically modified HEC (HM-2-HEC). At a given relative distance from the gel point ($\epsilon = 8$), the swelling is less pronounced for the hydrophobically modified HEC sample, but the uptake of water is faster for this gel system. The swelling at $\epsilon = 8$ is more pronounced for HM-dextran than for dextran. This was associated with the development of a more soft and fragile HM-dextran gel at this stage with a larger swelling capacity.

The findings from this study have shown that by changing the architecture or the hydrophobicity of the polymer, the cross-linker density, and the time of curing the gel, the features of the gel can be tuned. This makes it possible to tailor-make hydrogels for certain applications, e.g., for controlled drug delivery.

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