

Thermogelation Hydrogels of Methylcellulose and Glycerol–Methylcellulose Systems

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Received 24 November 2004; accepted 25 June 2005

DOI 10.1002/app.23375

Published online in Wiley InterScience (www.interscience.wiley.com).

ABSTRACT: The effects of the concentrations of methylcellulose (MC) solutions and glycerol as a additive on gel properties were investigated with rheological, test-inversion-tube, and breakthrough-vacuum methods. The results showed that glycerol favored the sol–gel transition of MC solutions, and the gel temperature was approximately proportional to the glycerol volume ratio; however, the gel

strength decreased as the glycerol volume ratio increased. To further understand the gel structure, rubber elasticity theory was cited and proved to be consistent with the experimental results. © 2006 Wiley Periodicals, Inc. *J Appl Polym Sci* 100: 4120–4126, 2006

Key words: methylcellulose; glycerol hydrogel; rheology

INTRODUCTION

Some aqueous solutions of hydrophobically modified natural polymers or synthetic polymers, such as *N*-isopropylacrylamide copolymers, poly(ethylene glycol–propylene glycol–ethylene glycol), and hydrophobic chitosan, undergo a thermosensitive sol–gel transition upon heating or cooling.¹ These in situ thermoreversible hydrogels are more feasible for macromolecular drug delivery, drug release, tissue barriers, and tissue engineering because of their simplicity and safety.²

In the family of thermoreversible gelling polymers for hydrogels, hydrophobically modified cellulose derivatives, such as methylcellulose (MC) and hydroxypropyl methylcellulose, are some of the largest members. MC is the simplest derivative of cellulose, made via hydrophobic substitution by methyl groups, and is widely used as a binder or thickener in pharmaceuticals, food, ceramics, and paint. MC is water-soluble only with an optimum level of the degree of methyl substitution (typically between 1.7 and 2.0). Lower or higher substituted cellulose is insoluble in water.³

In the past decade, many studies^{3–10} have been carried out to investigate the behavior in water of MC. At low temperatures, water molecules are presumed to form cagelike structures to surround the hydrophobic methoxyl groups, causing MC to become water-soluble. The dissolving process of MC in water is exothermic, so cooling the solution is effective in bringing about complete dissolution and aids in solution stability. Takeshi and Matao¹¹ investigated the viscoelastic properties of aqueous solutions of MC with three types of rheometers. They concluded that the structural networks in solutions that are formed by MC molecular entanglement, which depends on the concentration of MC at a certain temperature, become closer with increasing temperature, and the corresponding viscoelastic mechanism varies from intermolecular interactions such as entanglement to intramolecular motion with increasing frequency. As the temperature is increased, solutions of MC will gel, yet these gels will liquefy to the original consistency upon cooling. Because of the difficulty in obtaining a precise distribution of the substituents, the mechanism of gelation of MC is still not well understood. On the basis of observations of the gelation process by rheometry and microdifferential scanning calorimetry, at present, most people think that, with the temperature increasing, the cagelike structures are distorted, and this allows the interaction of the hydrophobic methoxyl groups, which is mainly dependent on the temperature, and then results in the formation of hydrophobic aggregates and subsequently in the formation of a gel.

Previously, many studies have been conducted on the gel properties of MC solutions, such as the gel temperature and gel strength. These properties have been proved to be determined as functions of the

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Contract grant sponsor: Teaching and Research Award Program for Outstanding Young Teachers in Higher Education Institutions of the Ministry of Education; contract grant number: 2002.

Contract grant sponsor: Key Research Project of the Ministry of Education of the People's Republic of China; contract grant number: 02041.

molecular weight, degree of methyl substitution, concentration, and presence of additives.³ In particular, some additives, such as various salts, alcohol, glycol, and glycerol, can affect the gel temperature. There have been many studies conducted on the effects of various salt additives.^{12–15} However, few works have been conducted on the effects of alcoholic additives. In this work, MC solutions of various concentrations were prepared by a traditional method, and various volumes of glycerol were added to the MC solutions under stirring conditions. Their gel temperatures, gel strengths, and rheological properties were measured, and the effects on the mechanism of gelation and the gel structure of MC were investigated with rheological methods.

EXPERIMENTAL

Materials

MC in a powder form was purchased from HeDa Co. (Shandong, China). The viscosity of a 2 wt % aqueous solution at 20°C, supplied by the manufacturer, was about 400 cp. The average molecular weight of MC was 130,000, and its average degree of methyl substitution was 1.8.

Preparation of the MC solutions and samples

The aqueous solutions were prepared by the slow dissolution of dried MC powder in hot deionized water (ca. 70°C) with stirring until they were cooled to room temperature; then, these samples were transferred to a refrigerator and were kept at about 5°C for 24 h to ensure complete dissolution. The final solutions were clear and transparent.

On the other hand, various volumes (5, 10, 15, 20, and 25 mL) of glycerol were slowly added to clear 50-mL solutions of MC at room temperature with stirring for 1 h and then were kept in a refrigerator at about 5°C for 24 h. The ratio of the glycerol volume to the water volume (G/W) was used to label the samples; for example, when 5 mL of glycerol was added to 50 mL of an MC solution, the sample was labeled G/W = 1:10.

Gel temperature measurements

The gel temperatures of various solutions were measured by the test-tube-inversion method.¹⁴ About 5 mL of each sample was placed in a glass test tube, which was then kept in a constant-temperature water bath for 10 min. The temperature at which the sample did not flow when the tube was inverted was used as the reversible sol–gel transition temperature, that is, the gel temperature. Otherwise, the bath temperature

was quickly increased by 1°C, and then the measurement was conducted as previously described.

Gel strength measurements

The gel strength of MC solutions or glycerol–MC systems was measured by the breakthrough–vacuum method.¹⁶ About 25 mL of an MC solution or glycerol–MC system was transferred to a colorimetric tube; after deaeration, it was kept in a constant-temperature water bath for 30 min to obtain a gel. The tube, which was connected to a pump, was quickly put into the gel, and the biggest value on the vacuum meter, that is, the breakthrough vacuum, was written down. Every sample was measured three times, and the average value was used as the gel strength for the sample.

Rheological measurements

A rheometer with a 4-cm (4°) cone and a 60-cm plate was used to measure the dynamic viscoelastic functions, such as the shear storage modulus (G') and loss modulus (G''), as functions of time, temperature, or angular frequency. Temperature sweeps were performed at a rate of 2°C/min from 30 to 80°C at 1.0 Hz and at a shear strain amplitude of 5%, and frequency sweeps were carried out from 100 Hz to 0.01 Hz at a certain temperature at 4.7 Pa. Low-viscosity silicone oil was placed around the periphery surface of the sample, which was held between the cone and plate to avoid dehydration.

RESULTS AND DISCUSSION

Thermal gelation of pure MC solutions

MC solutions of the proper concentration will undergo a reversible sol–gel transition upon heating. Just as explained previously, this unique thermal behavior is mainly caused by the hydrophobic association of methoxyl groups and is known to vary considerably with the type and degree of substitution, concentration, molecular weight, and additives. The effects of the concentration and additives are discussed.

Figure 1 shows the temperature dependence of G' and G'' for 10 g/L MC solutions with a heating rate of 2°C/min. As shown in Figure 1, there was a crossover between G' and G'' at 52.4°C. The whole G' curve can be divided into three parts. The first part was below 40°C; G' decreased slowly as the temperature increased, showing the typical thermal behavior of an entanglement liquid. A gradual increase in G' was observed from about 40 to 60°C, which can be considered to be caused by the partial formation of aggregates or clusters through hydrophobic association.

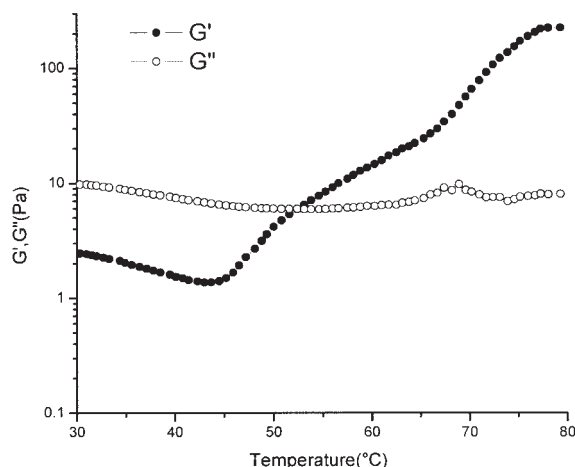


Figure 1 G' and G'' as functions of temperature for 15 g/L MC at 1 Hz and a strain amplitude of 5% with a heating rate of 2°C/min.

Then, G' increased sharply between 60 and 75°C, and a plateau formed at 75°C, indicating that a gel structure had formed. On the other hand, the G'' curve is simpler and more inconspicuous than G' . G'' slightly decreased with increasing temperature but began to increase from the crossover point. This rheogram describes the thermal behavior of MC solutions in detail and proves the gelation mechanism partly.

The results for G' for five concentrations are shown in Figure 2. In all cases, G' was a monotonically increasing function of temperature, and the increases of the other four concentrations were all similar to that of the 10 g/L MC solution, in agreement with previous reports. For the three moderate concentrations, G' was roughly independent of the concentration from 30 to about 60°C, whereas for the higher concentration or the low concentration (25 and 5 g/L), the modulus

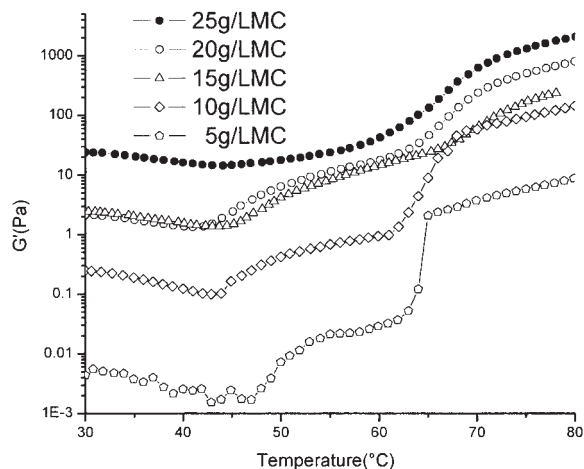


Figure 2 Variation of G' for various concentrations of MC solutions as a function of temperature at 1 Hz and a strain amplitude of 5% with a heating rate of 2°C/min.

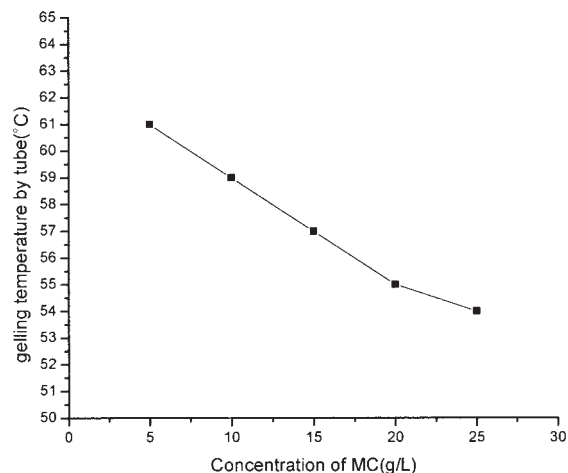


Figure 3 Gel temperatures for various MC concentrations, tested by the test-tube-inversion method.

was significantly different from those of the former three. However, the modulus at all concentrations began to increase rapidly at 60°C, and the terminal plateau height increased with increasing concentration. Figure 2 shows that the G' curve of the 5 g/L MC solution was not as smooth as those for the other four concentrations, and the terminal plateau was lower than the others, indicating that a quite weak gel was formed. In the literature, a 10 g/L MC solution is considered to have a critical concentration; that is, only at and above 10 g/L can a gel be formed. Certainly, the critical concentration depends on the degree of substitution and molecular weight. In this article, 10 g/L was taken as a critical concentration according to the experimental results.

Figure 2 shows that the gel temperature little depended on the concentration, but an imperceptible effect was well determined through the test-tube-inversion method, as shown in Figure 3. Figure 3 illustrates that the gel temperature had a linear relationship with the concentration. The total number of hydrophobic methoxyl groups linearly increased with the concentration, and so hydrophobic interactions could occur at a lower temperature, leading to a linear decrease in the gel temperature.

Figure 2 also shows that the gel strength increased with the concentration, in agreement with the gel strength measurement. Figure 4 shows the evolution of the gel strength for various concentrations at 65°C.

Effects of various additives on the gel temperature

On the basis of the hypothesis of cage-like MC–water structures, additives, which may protect or disrupt these structures, can affect the gel properties. According to these rules, some water-soluble small molecules and polymers were added to MC solutions to investi-

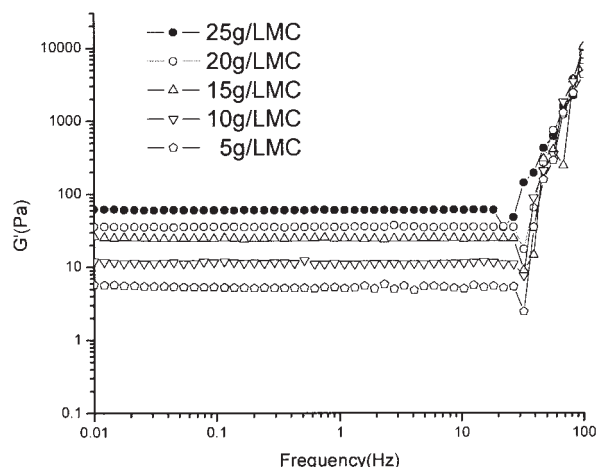


Figure 4 G' as a function of frequency for various concentrations of MC at 65°C.

gate the effect on the gel temperature through the test-tube-inversion method. According to our experimental results, the variations of the gel temperature could be divided into three types. For ethanol and propylene glycol, these molecules acted as surfactants and interacted with both water molecules and MC chains. To a certain degree, the solubility of MC in water was enhanced in the presence of ethanol or propylene glycol, as can be observed from the fact that the solutions became more clear and transparent. Thus, the gel temperature was notably increased. On the other hand, glycerol or xylitol can remarkably promote gelation at low temperatures. Some have suggested that the decrease in the gel temperature is due to the dehydration of the polymer because of their great affinity for water. However, for polymers such as poly(ethylene glycol), poly(vinyl alcohol), and polyvinyl pyrrolidone, the effect on the gel temperature is not as distinct as that for small molecules. The gel temperature was a little reduced by the addition of polymer additives but depended little on the added amounts. One reason for this phenomenon was exit competition between the polymers and MC molecules for the solubility in water, so the solubility of MC in water was reduced by the addition of the polymers and resulted in a decrease in the gel temperature. Because glycerol favored the gelation of MC solutions, glycerol–MC systems were investigated in detail.

Mechanism of the thermal gelation and gel properties of glycerol–MC systems

Previously, many studies had been carried out on the effects of additives on the gel temperature, yet few had studied the mechanism of thermal gelation of additive–MC solutions, especially glycerol–MC systems. From the previous discussion, we knew that the phase transition of MC solutions was promoted in the

presence of glycerol. Moreover, it was conceivable that the effect of glycerol on the transition was related to the amounts of the addition. In this study, the process of the sol–gel transition and the characterization of the gel properties were mainly determined by a rheological method; in addition, the test-tube-inversion method and gel strength measurements were used.

Figure 5 presents the temperature dependence of G' and G'' for a glycerol–MC system ($G/W = 3 : 10$) at a heating rate of 2°C/min. As shown in Figure 5, an obvious distinction can be observed in comparison with Figure 1. There was no crossover point during the whole temperature sweep, and the G' curve is above G'' curve for the whole time. The increase in G' proceeded in two steps. G' initially slowly increased with temperature and then sharply increased with temperature until a quasi-plateau was reached. The temperature at which G' sharply increased shifted to a lower temperature in the presence of glycerol. However, the behavior of G'' was similar to that of a pure MC solution. This transform of the gelation can be considered to be due to the great affinity of glycerol for water. As a polyhydric alcohol, glycerol has a strong affinity for water, and at the same time, it is a good plasticizer for MC because of hydrogen bonds with MC chains. When glycerol is added to MC solutions, it can disrupt the cage-like structures and interact with both water molecules and MC chains. This pseudosurfactant function may help to protect the water–MC structures and result in the gel temperature increasing. However, according to our experimental results, glycerol can remarkably reduce the gel temperature. This is because glycerol has a great affinity for water and leads to a strong hydration interaction that promotes the destruction of the cages. At the same time, glycerol acts as a plasticizer, and this makes the MC chains move easily. Thus, the hydrophobic association

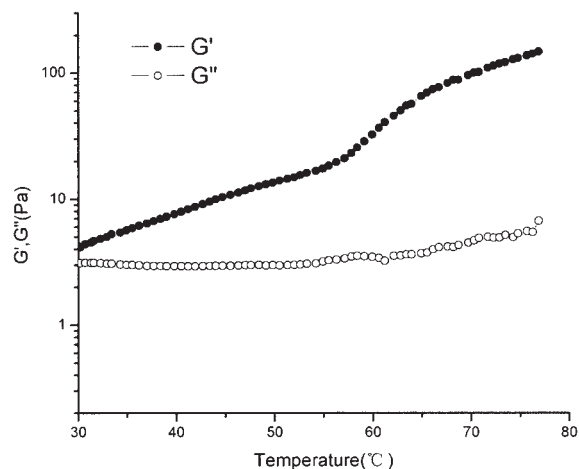


Figure 5 G' and G'' as functions of temperature for the glycerol–MC system ($G/W = 3 : 10$) at 1 Hz and a strain amplitude of 5% with a heating rate of 2°C/min.

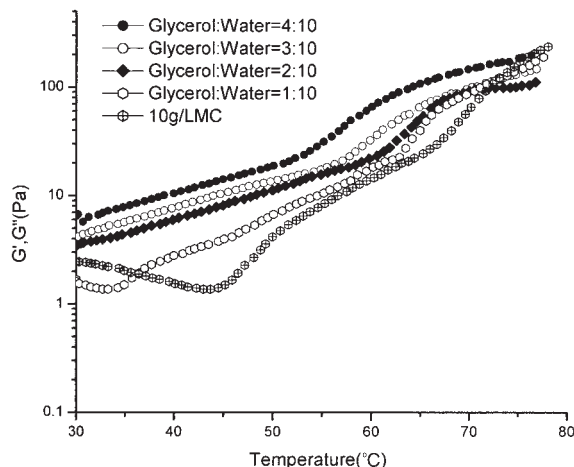


Figure 6 Variation of G' for a 10 g/L MC solution and various glycerol–MC systems as function of temperature at 1 Hz and a strain amplitude of 5% with a heating rate of 2°C/min.

between methyl groups can occur at a lower temperature. This shows that the effect of glycerol on the breaking of hydrogen bonds is similar to those of salts and increasing the temperature.¹⁵

Figure 6 illuminates the temperature dependence of G' for 10 g/L MC solutions with various glycerol volume ratios. As shown in Figure 6, G' was a monotonically increasing function of temperature. With the glycerol volume ratio increasing, the curve shifted to a lower temperature. This showed that the gel temperature gradually decreased with the glycerol volume ratio increasing. Moreover, as shown in Figure 7, the gel temperature was approximately proportional to the glycerol volume ratio, as tested by the test-tube-inversion method.

Frequency sweeps were carried out to further examine the structure of MC in aqueous solutions and

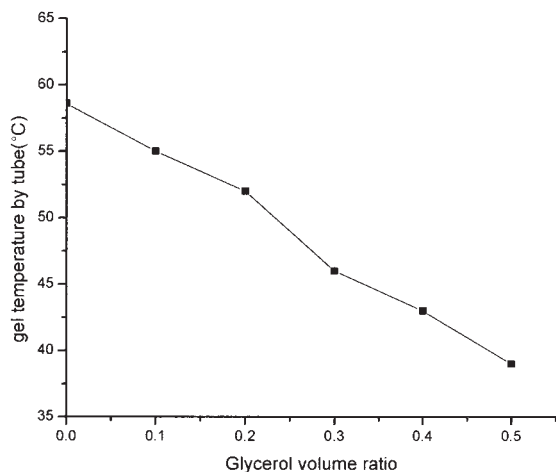


Figure 7 Gel temperatures for various glycerol–MC systems, tested by the test-tube-inversion method.

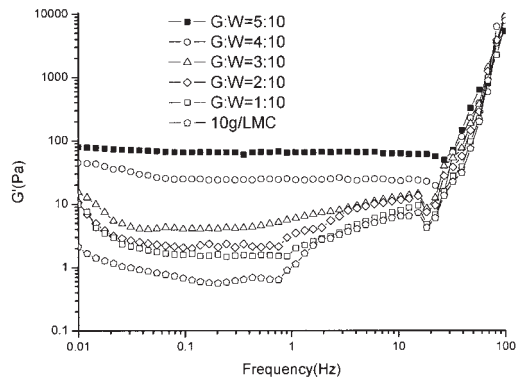


Figure 8 G' as a function of frequency for a 10 g/L MC solution and various glycerol–MC systems at 55°C.

gels. To observe the various states of various glycerol–MC systems, from the temperature range of gelation (40–70°C), we chose 55°C. As shown in Figure 8, for high concentrations of glycerol, G' exhibited a weak dependence on the frequency, which was defined as the gel state.⁸ However, for a low concentration of glycerol or with no glycerol at all, G' was strongly dependent on the frequency. The G' curves were all similar and nearly overlapped. At lower frequencies between 0.01 and 1 Hz, there was a plateau in these G' curves, indicating that a weak gel had formed. From these results, the conclusion can be drawn that the addition of glycerol affected the gel temperature and that glycerol–MC systems with various glycerol volume ratios had a wide gel temperature range.

These results can be explained by a thermodynamic analysis: the hydrophobic interaction of cellulose molecules in an aqueous solution happens only when the difference of the Gibbs free energy (ΔG) is negative at a given constant temperature T :

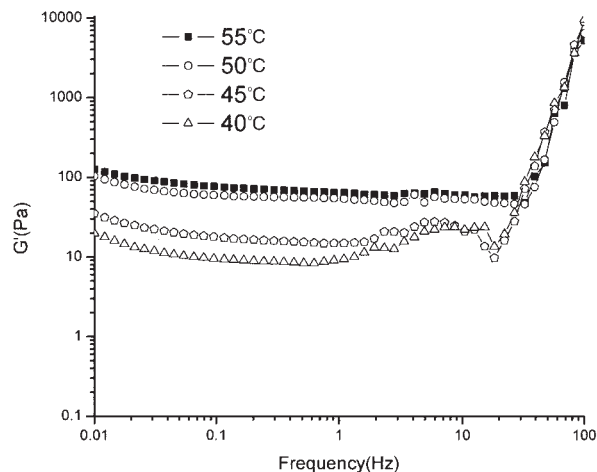


Figure 9 G' for the glycerol–MC system ($G/W = 5:10$) as a function of frequency at different temperatures.

TABLE I
G' at Different Temperatures at 1 Hz

Glycerol volume ratio	G' (Pa)					
	50 °C	55 °C	60 °C	65 °C	70 °C	75 °C
0:10	4.18	8.48	14.7	24.5	65.4	190
1:10	9.02	16.1	25.8	42.9	91.4	235
2:10	14.5	20.1	25.3	35.7	68.4	103
3:10	13.5	17.4	32.4	65.4	101	131
4:10	18.9	31.6	66.3	108	147	186

$$\Delta G = \Delta H - T\Delta S < 0 \quad (1)$$

where ΔH and ΔS are the differences of enthalpy and entropy, respectively. When cellulose self-associates in an aqueous solution, ΔH should be positive because the gelation process is an endothermic process, as confirmed by the preliminary results of microdifferential scanning calorimetry analysis (not shown).^{9,15} Thus, ΔS should be more positive to meet the requirement of $\Delta G < 0$ during the gelation process. However, this seems to be in contradiction with the results of hydrophobic interactions of MC molecular chains in aggregates. Such an interesting question can be resolved only by the consideration of the small molecules, including water and glycerol. In the glycerol–MC systems, small molecules such as water and glycerol, because of the hydrogen bonds, were fixed onto the MC chains to form cagelike structures, exhibiting some degree of order in the solution. Heating supplied the activation energy to disrupt these cagelike structures, resulting in the hydrophobic interaction of MC. Moreover, the destruction of the cagelike structures was more prominent as a contribution to the change of entropy than the aggregates of hydrophobic interaction. Thus, when a gel formed in the end, ΔS of the system was positive (i.e., $\Delta S > 0$). At the same time, the dehydration of polymers due to the great affinity of glycerol for water resulted in less required heating to meet the requirement of $\Delta G < 0$. In other words, the glycerol–MC systems had lower gel temperatures than the MC solutions. Moreover, for the test-tube-inversion method, ΔS from a solution to a gel was approximately equal, so the gel temperature had a linear relationship with the glycerol volume ratio.

The second distinction in Figure 6 is that the terminal plateau of the G' curves of samples with lower volume ratios of glycerol or samples without glycerol are higher than those of higher volume ratios. This is due to the variety of gel strengths for the various glycerol–MC systems. To study the changes, we took the G' values in Figure 6 at several temperatures (50, 55, 60, 65, 70, and 75°C) for all the glycerol–MC systems and listed the results in Table I.

Table I shows that the G' values with the same concentration of glycerol all increased with tempera-

ture. However, for the same temperature, the G' values as functions of the various concentrations of glycerol were more complexed. At lower temperatures (50, 55, and 60°C), the G' values generally increased with the concentration, yet at higher temperatures (65, 70, and 75°C), the G' values of low concentrations of glycerol gradually exceeded those of high concentrations. One reason for this phenomenon may be that at lower temperatures, glycerol promoted the formation of gels; it seems that the more glycerol was added, the better the gel formed, and this resulted in the increase in the G' values with glycerol volume ratio increasing. At higher temperatures, the temperature effect was predominant in forming a gel, and at the same time, glycerol played an important role as a plasticizer, so the G' values of lower concentrations of glycerol gradually exceeded those of higher concentrations.

To study the temperature effect on the gel strength, frequency sweeps for different concentrations of glycerol were carried out. As shown in Figure 9, for the glycerol–MC system ($G/W = 5 : 10$), G' showed little dependence on frequency, and with the temperature increasing, the plateau became wide. Also, the plateau of the G' curves at high temperatures was higher than that at low temperatures. In the MC solutions, the temperature played an important role in the sol–gel transition. With the temperature increasing, the cagelike water–MC structures were gradually disrupted, and this resulted in hydrophobic association and eventually gel formation. Just as reported in a previous article,⁹ at high temperatures, the MC solutions could quickly form gels, and the strength was better than that at low temperatures. This phenomenon may be due to a higher crosslinking density because the total number of hydrophobic aggregates increased with increasing temperature. Because the mechanism of gelation of the glycerol–MC systems was similar to that of MC, the gel strength with increasing temperature followed the same pattern. In other words, the gel strength of the glycerol–MC systems also increased with the temperature.

Interestingly, the aforementioned results can all be explained by the rubber elasticity theory. Here we present only the form of the rubber elasticity theory

used to analyze the structures of hydrogels prepared in the presence of a solvent. G' is then¹⁷

$$G' = \frac{\rho R T \bar{r}_0^2}{M_c \bar{r}_f^2} \left(1 - \frac{2M_c}{M_n} \right) \quad (2)$$

where ρ is the density of the polymer, R is the universal gas constant, and T is the absolute experimental temperature. The front factor, \bar{r}_0^2/\bar{r}_f^2 , is the ratio of the end-to-end distance in a real network versus the end-to-end distance of isolated chains. In the absence of knowledge concerning these values, \bar{r}_0^2/\bar{r}_f^2 is often approximated as 1. M_n is the number-average molecular weight of the polymer, and M_c is the desired molecular weight between crosslinks. From this equation, for the same glycerol–MC system, ρ was a constant, although M_c increased with increasing temperature and G' still increased with temperature, as confirmed by the experimental results. For the same temperature of gelation, M_c increased with the glycerol volume ratio increasing, and ρ decreased with the glycerol volume ratio increasing; therefore, in the end, G' decreased with the glycerol volume ratio increasing, and this was also consistent with our experimental results.

CONCLUSIONS

The effect of glycerol on the thermoreversible sol–gel transition behavior of MC solutions, such as the gel temperature and gel strength, has been investigated with the test-tube-inversion method and rheological method.

Glycerol favors the sol–gel transition of MC solutions. In the presence of glycerol, because of hydration and plasticization, glycerol–MC systems can gel at low temperatures. The gel temperature measured by the

test-tube-inversion method exhibits a linear relationship with the glycerol volume ratio.

The temperature sweeps in the rheological study show that the curves of G' shift to lower temperatures with the glycerol volume ratio increasing. However, the gel strength is a little reduced by the addition of glycerol. This indicates that the mechanism of gelation of glycerol–MC systems is a bit different from that of salt–MC systems, in which the gel strength is independent of the salt concentration.

The frequency sweeps of the rheological study show that the gel strength is related to the temperature. For a glycerol–MC system, the plateau of the G' curve is heightened with the temperature at which the glycerol–MC system forms a gel. This is because a high temperature can increase the crosslinking density and result in the gel strength increasing. Also, we have illustrated this phenomenon from the rubber elasticity theory.

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