Syntheses of Hydroxypropyl Methylcellulose Phthalate Hydrogels in Na₂CO₃ Aqueous Solutions with Electron-Beam Irradiation

Ling Xu,[1] Naotsugu Nagasawa,[2] Fumio Yoshii,[2] Tamikazu Kume[2]

[1]*China Institute of Atomic Energy, Beijing 102413, People's Republic of China*
[2]*Takasaki Radiation Chemistry Research Establishment, Japan Atomic Energy Research Institute, Watanuki-machi, Takasaki-shi, Gunma-ken, 370-1292, Japan*

ABSTRACT: Novel cellulose ether hydrogels were prepared by the radiation-induced crosslinking of hydroxypropyl methylcellulose phthalate (HPMCP) in a solution of Na₂CO₃. The effects of several factors, such as the HPMCP concentration, Na₂CO₃ concentration, absorbed dose, and dose rate, on the crosslinking of HPMCP were investigated in detail. An increase in the HPMCP concentration resulted in an increasing content of the gel fraction, and this meant that the crosslinking probability increased as well. Na₂CO₃ was essential for dissolving HPMCP in water, and a 4–5% Na₂CO₃ aqueous solution was optimal for the crosslinking of HPMCP. The dose rate also affected the radiation crosslinking of HPMCP; hydrogels with higher gel fractions and transparency could be formed at lower dose rates. The ratio of degradation to crosslinking of the gel was calculated according to the Charlesby–Rosiak equation, and it showed good agreement with the experimental results. Some important properties, such as the swelling kinetics, ion and ionic strength dependence, and pH dependence, of the HPMCP hydrogels were also investigated. The HPMCP hydrogels possessed excellent swelling rates and swelling ratios in some solvents, such as water and methanol, with a high hydrogen-bonding parameter. © 2003 Wiley Periodicals, Inc. J Appl Polym Sci 89: 2123–2130, 2003

Key words: hydrogels; irradiation; swelling; crosslinking

INTRODUCTION

Hydrogels are widely used as biomedical materials, such as wound dressings, controlled-release drug delivery systems, dental materials, and implants, because of their high affinity to water and insolubility in water. A few studies have been reported on the absorption of organic compounds by hydrogels made from proteins.[1] Natural polymer-based hydrogels seem to be interesting materials for various purposes because of their biodegradability.

Cellulose ethers, such as methylcellulose, hydroxypropyl cellulose (HPC), carboxymethyl cellulose (CMC), and hydroxypropyl methylcellulose (HPMC), generally show no evidence of toxicity to rats, dogs, or humans;[2] they are approved by the Food and Drug Administration for food and drug uses. The chemical crosslinking of these polymers has been reported;[3] however, crosslinkers used for chemical crosslinking usually are toxic and, as a result, have limited applications in the food, drug, and pharmaceutical industries. Radiation crosslinking has advantages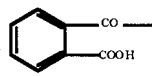 over chemical crosslinking because crosslinkers are not required in the fabrication process; this leads to high purity of the hydrogel products. Cellulose and its derivatives are usually considered radiation-degradable polymers. However, some scientists recently have reported that concentrated aqueous solutions of cellulose ethers, such as CMC and HPC, could be crosslinked under the action of ionizing radiation.[4–7]

Hydroxypropyl methylcellulose phthalate (HPMCP), a cellulose ether with a phthalate functional group, is widely used in the pharmaceutical industry because it is less susceptible to hydrolysis than cellulose acetate phthalate. Weiß et al.[8,9] reported that the coacervate formation of HPMCP is both pH- and temperature-dependent, so HPMCP could be used for the microencapsulation of some drugs by simple coacervation. However, only a few studies have been reported on the processing and properties of this polymer, whereas hydrogels based on this polymer have not been disclosed. An investigation into the radiation crosslinking of HPMCP would be helpful for studies on the formation of hydrogels based on cellulose derivatives on account of its novel structure.

In this study, the effects of several factors, such as the HPMCP concentration, Na₂CO₃ concentration, absorbed dose, and dose rate, on the crosslinking of HPMCP and the properties of its hydrogels were investigated in detail.
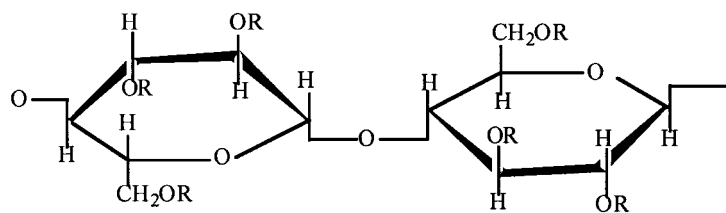
Scheme 1 R = −H, —OCH$_3$ (MeO), —CH$_2$CH(OH)CH$_3$ (HPO), and [benzene ring with CO and COOH] (CB).

EXPERIMENTAL

Materials

HPMCP (HP-55), obtained from Shinetsu Chemical Co., Ltd. (Tokyo, Japan), was used as received. The chemical structure of the cellulose ethers is shown in Scheme 1. The degrees of substitution of MeO, HPO, and CB were 1.9, 0.25, and 0.65, respectively. The acid value was 123 mg of KOH/g of polymer. The weight-average molecular weight was 4.5×10^4.[10]

The other chemicals used were analytical-grade. Highly purified water was used for the aqueous solutions.

Sample preparation and irradiation

Unless otherwise stated, 5% Na$_2$CO$_3$ was used as the solvent for all the samples. Appropriate amounts of HPMCP and 5% Na$_2$CO$_3$ were mixed, stirred, and kept at room temperature for a few days until the solution was homogeneous. Low-concentration HP-MCP samples were placed directly into the plastic bags to be irradiated. The high-concentration samples were very viscous and easily transformed into sheets 0.5 mm thick with a cold press machine. Samples meant for irradiation in air were kept in plastic bags and then heat-sealed. Samples to be irradiated were kept in plastic bags, with the air in the bags removed by a vacuum pump before the heat sealing.

Electron-beam irradiation (2 MeV) was performed with an RDI Dynamitron accelerator (Radiation Dynamics, Inc., NY). A beam current of 1 mA was used. Unless otherwise stated, the dose rate was kept to 1 kGy per pass.

Gel fraction

After irradiation, the obtained polymer gel was immersed in a 5% Na$_2$CO$_3$ aqueous solutions for 2 days for the removal of the sol part of the polymer. After that, Na$_2$CO$_3$ adhering to the samples was washed off thoroughly with distilled water, and then the gel was dried in vacuum at 50°C for 48 h. The gel fraction was determined as follows:

$$\text{Gel fraction (\%)} = (G_d/G_i) \times 100 \quad (1)$$

where G_i is the initial weight of dried samples and G_d is the weight of the insoluble part after extraction with a solvent.

Swelling ratio

The hydrogel sheets were cut into a round shape with a diameter of 20 mm and dried in 50°C in a vacuum. The dry hydrogels were weighed. After that, the dry hydrogels were immersed in solutions at 25°C until equilibrium (for the measurement of the equilibrium degree of swelling) or kept for a certain time (for the measurement of the swelling kinetics). The gels were taken out of the solution and then weighed, after excess surface solution was wiped off, until equilibrium was reached. The swelling ratio of the hydrogels was calculated with the following equation:

$$\text{Swelling ratio} = (G_s - G_d)/G_d \quad (2)$$

where G_s and G_d are the weights of swollen and dry samples, respectively.

The solutions and buffers used to investigate the pH dependence were formulated according to ref. 11 and adjusted to 0.1M by the addition of NaCl.

RESULTS AND DISCUSSION

Radiation-induced crosslinking

Because of its regular structure and array of hydroxyl groups, cellulose has a high degree of crystallinity and hydrogen bonding in the crystalline regions,[2] which lead to low accessibility and low solubility in water; therefore, cellulose is a radiation-degradation polymer. However, added functional groups, either strong alkaline solutions or organic solvents, could increase the amorphous areas of cellulose so that the accessibility of such a cellulose derivative would be increased.

HPMCP is insoluble in water but has good organosolubility because of its high degree of substitution of hydrophobic groups. It can dissolve in alkaline solutions and some organic solvents and crosslink by radiation in a highly viscous state. According to the results shown in Table I, an Na$_2$CO$_3$ solution was

TABLE I
Gel Fraction of HPMCP Gels Synthesized in Different Solvents

Solvent	Water	5% Na$_2$CO$_3$	Methanol	Methyl acetate	Acetone
Gel fraction (%)	Insoluble	78	32	31	20

The HPMCP concentrations in 5% Na$_2$CO$_3$ and organic solvents were 30 and 50%, respectively. The dose was 100 kGy.

chosen as the solvent for this study to achieve hydrogels with hydrophilicity and higher gel fractions.

Figure 1 shows the relationship between the gel fraction and irradiation dose of the hydrogels with different initial HPMCP concentrations. For irradiation doses lower than 50 kGy, C—O bond scission due to attack by the alkaline solution on the main chain of cellulose was the main reaction in the system, faster than the crosslinking of the polymer. Therefore, no gel was formed. After a certain irradiation dose, namely, the gelation dose, the crosslinking reaction overwhelmed chain scission, a hydrogel was formed rapidly, and then the gel fraction leveled off. Compared with the gelation dose of HPC, which is around 10 kGy,[6] the higher gelation dose for HPMCP is assumed to be caused by (1) the existence of charged groups generated by the reaction between the carboxyl group and Na$_2$CO$_3$ and (2) the comparatively low molecular weight of the used polymer.

The radiation-induced crosslinking of HPMCP is also affected by the initial polymer concentration. The insert in Figure 1 shows the effect of the initial polymer concentration on the gel fraction at the irradiation dose of 80 kGy. The gel fraction increased slowly with increasing polymer concentrations up to 35%, and then it decreased quickly with a further increase in the polymer concentration. The gel fraction of 40% HPMCP was lower than that of 35% HPMCP. This phenomenon was caused by the phase separation of the 40% solution; that is, the solution was inhomogeneous at this concentration.

p_0/q_0, the ratio of degradation to crosslinking, was calculated according to the Charlesby–Rosiak equation:[12]

$$s + \sqrt{s} = \frac{p_0}{q_0} + \left(2 - \frac{p_0}{q_0}\right)\frac{D_v + D_g}{D_v + D} \qquad (3)$$

where s is the sol fraction and p_0 and q_0 are the degradation and crosslinking density, respectively. p_0 represents the level of scission, and q_0 represents the level of crosslinking, of these polymers. D is the absorbed dose, and D_v is the virtual dose. The calculation for each polymer was performed with Gelsol software kindly provided by Rosiak (Technical Uni-
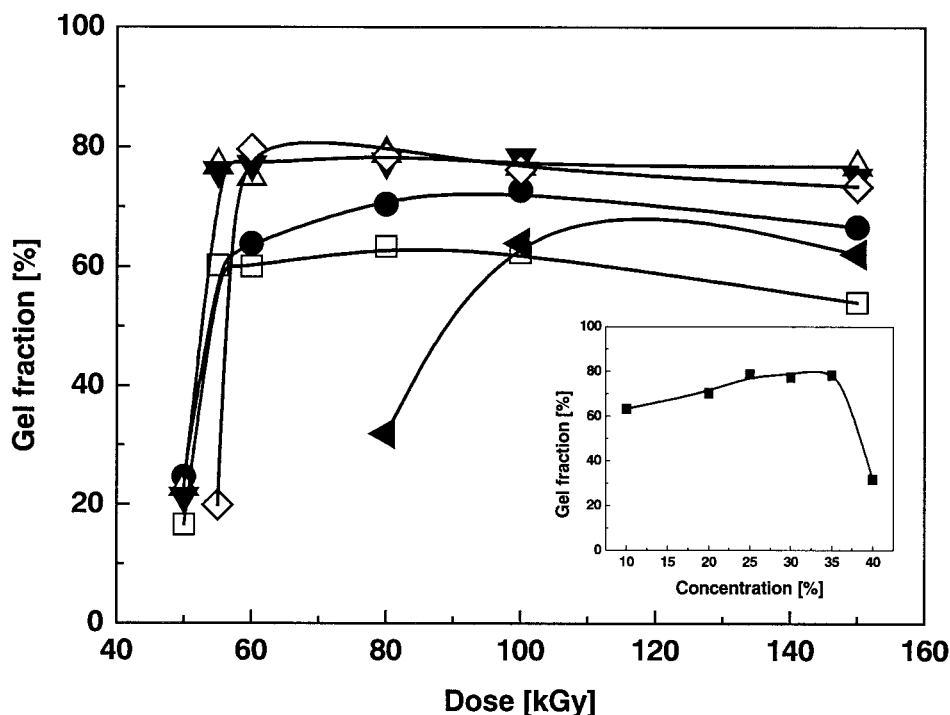

Figure 1 Influence of the HPMCP concentration on the radiation crosslinking: (□) 10, (●) 20, (△) 25, (▼) 30, (◇) 35, and (◀) 40%.
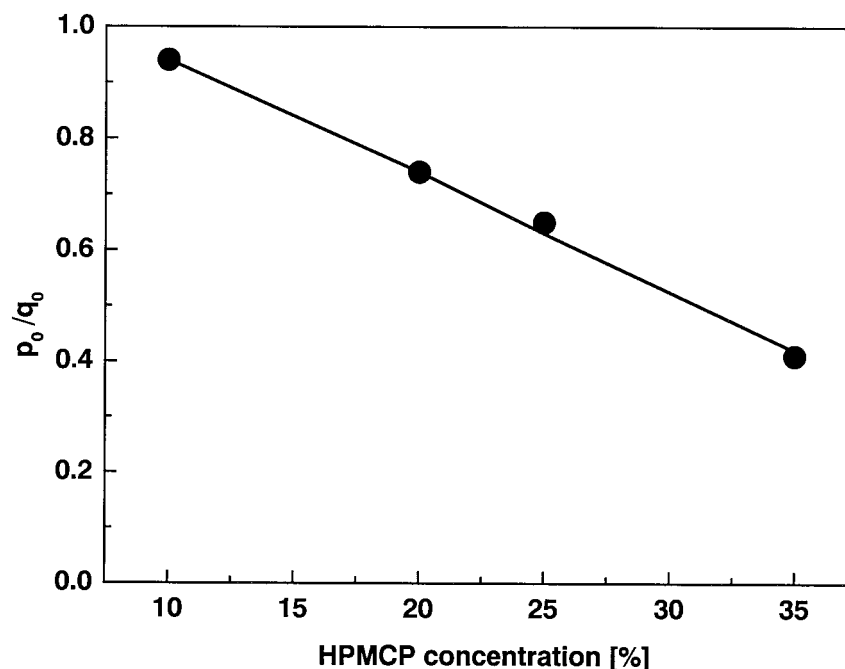
Figure 2 Relationship between p_0/q_0 and the HPMCP concentration.

versity, Lodz, Poland). The relationship of the calculated p_0/q_0 values and the gelation doses with the concentration of HPMCP is illustrated in Figure 2. The calculated gelation dose was in good agreement with the experimental results, as shown in Figure 1.

When a polymer solution is subjected to radiation, reactive intermediates are formed on the macromolecules. These macroradicals undergo various reactions that cause intermolecular crosslinking or chain scission. At a low concentration of HPMCP ($<10\%$), the density of the radicals was not high enough to recombine on different chains, so the polymers underwent a radiation-degradation mechanism. At a higher polymer concentration, polymer chains interpenetrate, and the probability of two recombining radicals localized on different chains is relatively higher. For HPMCP, when the concentration was 10–35%, the gel fraction of each dose increased with increasing polymer concentration. When the concentration of HPMCP increased, the p_0/q_0 ratio decreased, and this also implied that intermolecular crosslinking, which caused gel formation, became the dominant reaction.

Figure 3 demonstrates the influence of the Na_2CO_3 concentration on the gel formation. The irradiation dose was 80 kGy. Na_2CO_3 had a negative impact on the crosslinking of the polymer. The gel fraction decreased with an increasing concentration of Na_2CO_3. For example, by the irradiation of 20 g of HPMCP in 80 mL of a 4% Na_2CO_3 solution with an 80-kGy dose, a hydrogel with a 68% gel fraction was obtained. We also found that the gel fraction decreased significantly when the Na_2CO_3 concentration was greater than 6%. Despite this, Na_2CO_3 was essential for the polymers to

dissolve in water, and higher concentrations of the polymers could only be obtained with higher concentration Na_2CO_3 solutions. Hydrogels with higher gel fractions could be obtained when the amounts of the polymer and water were adjusted to an optimum ratio, that is, around the neutral point of the polymer.

These results imply that, when polymers are mixed with a solution, the carboxyl group reacts with Na_2CO_3 to form sodium carboxylate, and the hydrogels are formed from the Na type of the polymers. When an excessive amount of Na_2CO_3 is added to the solution, there is a negative effect of the charged groups on crosslinking, and the decreasing compatibility between the Na_2CO_3 solution and HPMCP causes the gel fraction to decrease. However, when there is insufficient Na_2CO_3, some of the polymer cannot dissolve in the solution, and this causes a two-phase solution and leads to a decrease in the gel fraction.

The effect of the dose rate on the radiation-induced crosslinking of 30% HPMCP is shown in Figure 4. The dose rate of 1 kGy/pass produced a higher gel fraction than 10 kGy/pass and 5 kGy/pass. High dose rates may generate tens of radicals, or even more than a hundred, simultaneously on each chain. Under these conditions, the probability and yield of intermolecular recombination are greatly reduced, so intramolecular recombination plays a bigger role. Therefore, the probability of crosslinking decreases.[13] Because the major part of the absorbed radiation energy is converted into heat, at a lower dose rate, heat generated from irradiation is easier to release to the environment, and as a result, fewer bubbles form. Consequently, hydrogels
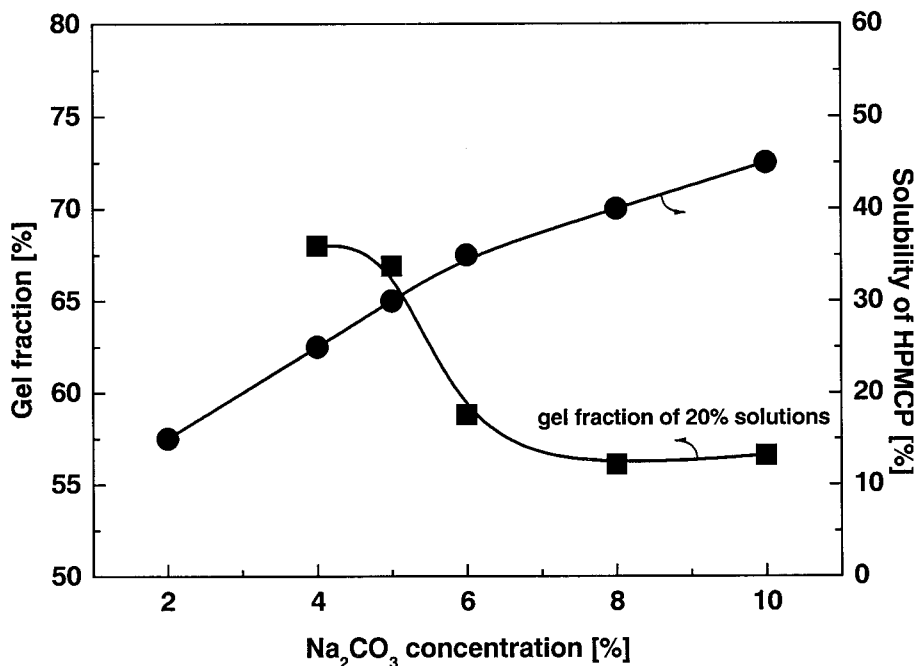
Figure 3 Influence of the Na$_2$CO$_3$ concentration on the radiation crosslinking of HPMCP.

with high clarity can be obtained with a lower dose rate. Therefore, 1 kGy/pass was chosen for the synthesis of the HPMCP hydrogels.

Swelling behavior

Figure 5 shows the swelling kinetics of HPMCP hydrogels in distilled water, 0.15M NaCl, and methanol.

The HPMCP hydrogel was synthesized by 80-kGy irradiation of a 35% HPMCP solution. The hydrogels were polyelectrolytes because a charged group was formed during the dissolution procedure. When chains forming a network contain ionizable groups, because intermolecular coulombic, hydrogen-bonding, and polar forces are present, the mobile counterions present in gels develop a large swelling pres-
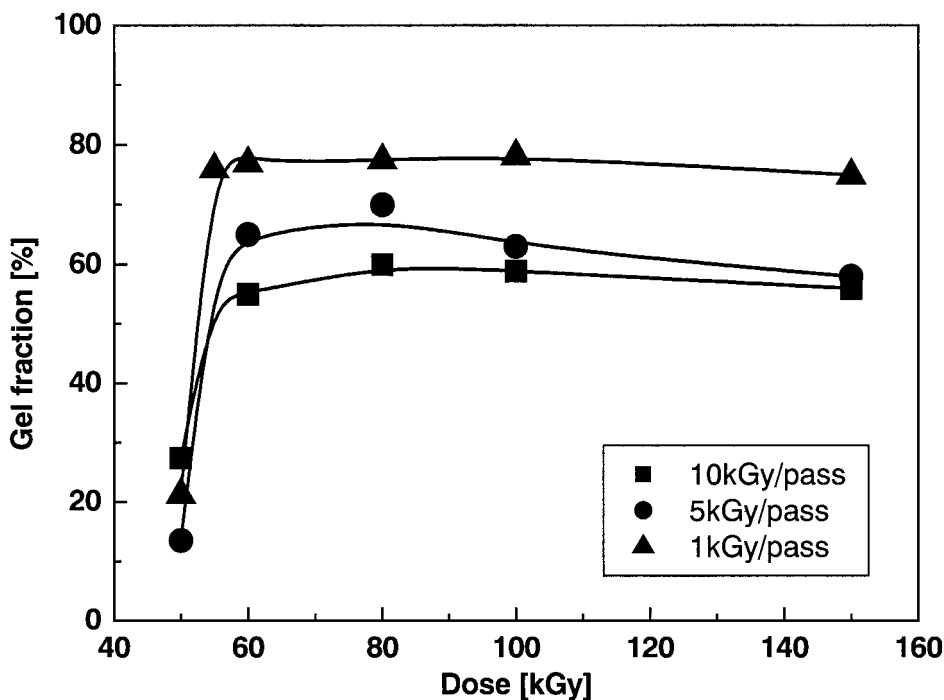

Figure 4 Influence of the dose rate on the radiation crosslinking of HPMCP.
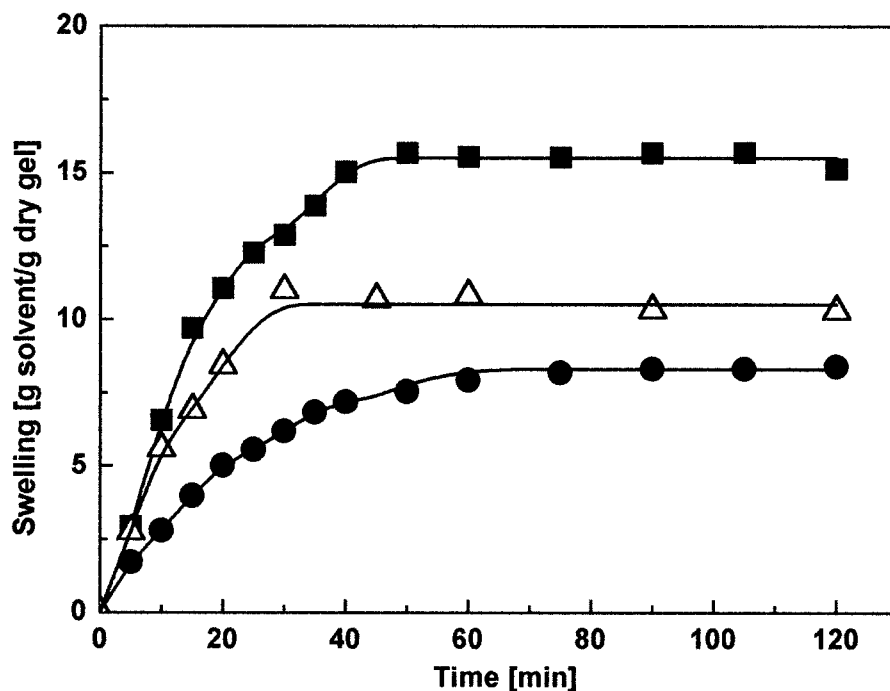
Figure 5 Swelling kinetics of HPMCP hydrogels in different solvents: (■) water, (●) 0.15M NaCl, and (△) methanol.

sure;[13] therefore, polymer interactions are enhanced and cause a very high sorption rate. As shown in Figure 5, the hydrogels reached an equilibrium swelling ratio within 50 min and then leveled off. This sorption rate was rather high compared with that of general neutral hydrogels, which need several hours or days to attain equilibrium swelling.

The HPMCP hydrogels possessed ion and ionic strength dependence. Figure 6 demonstrates the swelling behavior, in water, aqueous solutions, and methanol, of HPMCP hydrogels synthesized with different irradiation doses. With an increasing absorbed dose, although the gel fraction of the hydrogels did not change remarkably, the crosslink density increased.
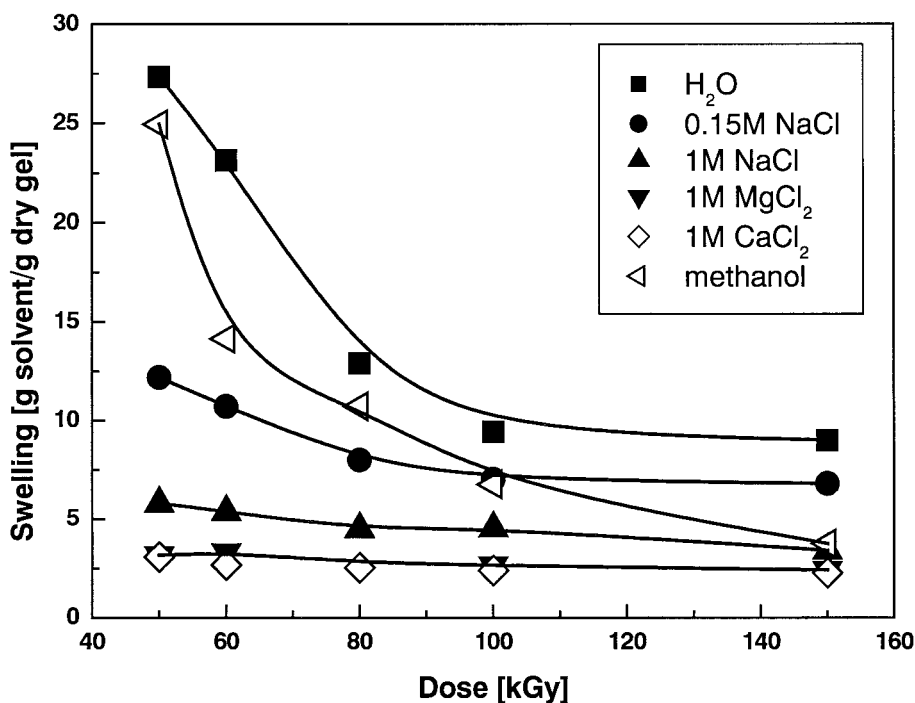

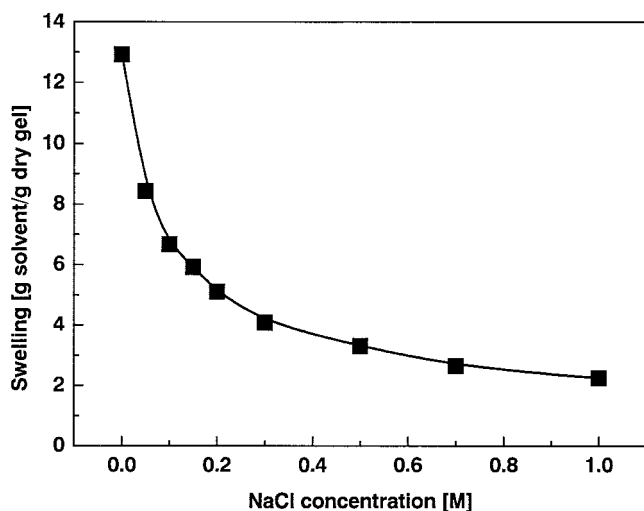**Figure 6** Swelling behavior of HPMCP hydrogels in different solvents.

Figure 7 Ionic strength dependence of HPMCP hydrogels.

Because strongly crosslinked polymers inhibit the interactions between polymer chains and solvent molecules, the swelling ratio decreases quickly, especially in water, with increasing crosslink density. At the gelation dose, a relatively low number of intermolecular bonds exist in the hydrogels, and solvents can easily penetrate and are retained inside the crosslinked matrix of the polymer. The swelling ratios of the HPMCP hydrogels in water, 0.15M NaCl, and methanol were 27, 12, and 25 g of solvent/g of dry gel, respectively. When the absorbed dose reached 80 kGy, the swelling ratios in the aforementioned solvents de-

creased to 13, 8, and 11 g of solvents/g of dry gel, respectively.

In addition, the swelling ratio is highest in distilled water, and in methanol, it is a little lower than that in water. However, both are clearly higher than that in salt aqueous solutions. The lower swelling ratio in salt aqueous solutions is assumed to be caused by the salt-out effect, which can destroy hydrogen bonding between the polymer and water. In particular, the swelling ratios of the hydrogels were lower in divalent ionic solutions than in single-valence ionic solutions. With the same valence, Ca^{2+} and Mg^{2+} did not have a significant difference on the swelling behavior of HPMCP hydrogels.

Figure 7 shows the swelling ratio of HPMCP hydrogels as a function of the concentration of the NaCl solution. The hydrogel was prepared from a 35% solution and with a 80-kGy irradiated dose. The increase in the NaCl solution concentration led to an increase in the osmotic pressure of the solution and a decrease in the excess osmotic pressure of the network; therefore, the swelling ratio of the hydrogels decreased. When the concentration of NaCl was increased from 0 to 1M, the swelling ratio decreased from 12.9 to 2.2 g of solvent/g of dry gel.

Figure 8 demonstrates that the HPMCP hydrogels apparently had a pH dependence on the swelling ratio. It is well known that, below pK_a values, carboxylic acid groups are in the form of COOH. As the pH of the solution increased, COOH became ionized (COO$^-$), and the resulting electrostatic repulsion
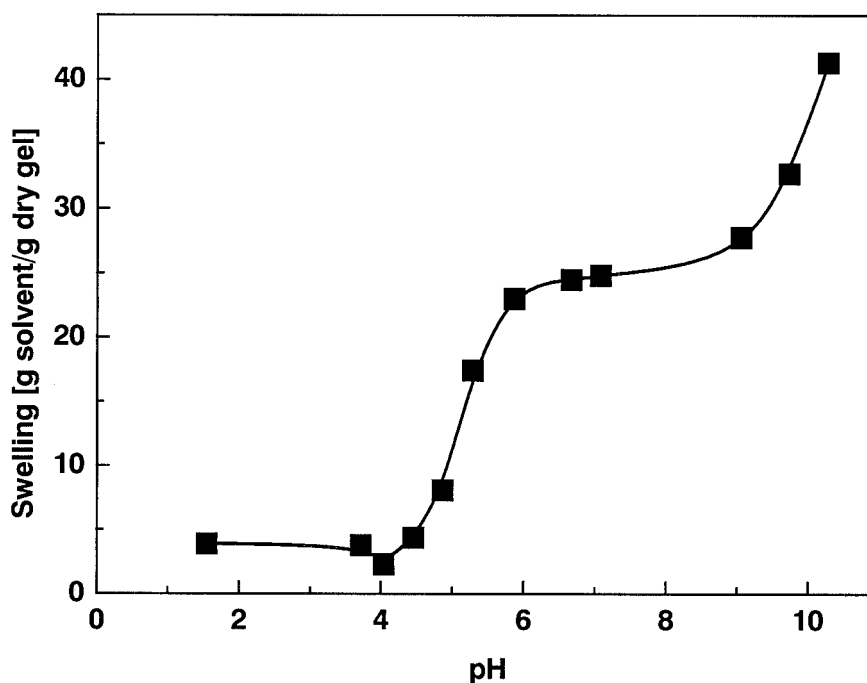

Figure 8 pH dependence of the swelling ratio of HPMCP hydrogels.

caused the hydrogels to swell.[14] For HPMCP hydrogels, their swelling ratio was rather low when the pH was lower than 4 and increased significantly in the pH range of 4–5.2 because of COOH changing into COO^-. In the pH range of 6–9, the swelling ratio was stable because most of the COOH was already changed into COO^-. It is well known that, under alkaline conditions, cellulose is subjected to β-elimination and, therefore, causes degradation.[2] For HPMCP hydrogels, when the pH was above 9, the swelling ratio increased again because of the alkaline degradation of the hydrogels. In higher alkaline buffers, that is, pH > 12, the hydrogels were totally degraded. For pH-sensitive hydrogels, either acid or basic groups were contained in the network: the phthalate substituents were responsible for the pH dependence of the swelling ratio of HPMCP hydrogels. As the pH sensitive range of HPMCP is similar to the pH in the stomach, it should have potential applications in controlled-release drug systems.

CONCLUSIONS

HPMCP hydrogels were prepared by the ionizing radiation-induced crosslinking of HPMCP in Na_2CO_3 aqueous solutions. An increase in the HPMCP concentration resulted in an increasing gel fraction and decreasing p_0/q_0, which meant that the crosslinking probability increased as well. Na_2CO_3 had a negative effect on the crosslinking of the hydrogels, but it was essential for dissolving the polymers in water. Hydrogels with higher gel fractions and clarity were obtained in the lower dose rate range (e.g., 1 kGy/pass).

The HPMCP hydrogels possessed high sorption rates and swelling ratios in strong polarity solvents such as water and methanol. They also had ion and ionic strength dependence as well as pH dependence.

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