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Intelligent hydrogels based on radiation induced copolymerization of *N*-isopropylacrylamide and Kappa carrageenan

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Abstract

A series of blended hydrogels composed of poly-*N*-isopropylacrylamide (polyNIPAAm) and Kappa carrageenan have been prepared by γ-irradiation. The hydrogels obtained by this method were transparent and elastic and the gel strength was improved greatly. Measurements showed that the polyNIPAAm/Kappa carrageenan blends were hydrogels, which not only had pH and temperature sensitivities, but also exhibited a chloride ion-induced phase transition.

Keywords: Kappa carrageenan; *N*-isopropylacrylamide; Blend hydrogel; Radiation; Intelligent hydrogels

1. Introduction

Poly-*N*-isopropylacrylamide (polyNIPAAm) hydrogel, which is a typical intelligent hydrogel used in the biomedical field with a lower critical solution temperature (LCST) of about 35 °C, has been studied extensively in recent years (Bhalerao, Varghese, Lele, & Badiger, 1998; Chen & Hoffman, 1995; Feil, Bae, Feijen, & Kim, 1992; Huglin, Liu & Velada, 1997; Park & Hoffman, 1993; Sasaki, Kawasaki, & Maeda, 1997; Serizawa, Uemura, Kaneko, & Akashi, 2002; Shibayama, Mizutani, & Nomura, 1996; Shin, Jhon, Lee, & Yuk, 1998; Vesterinen, Dobrodumov, & Tenhu, 1997; Wang, Fang, & Hu, 2001). Such hydrogels can be used in many fields including drug delivery systems, bioseparation and other biotechnology applications (Morra & Cesinell, 1995; Rosiak & Ulanski, 1999; Takashi & Kohei, 1996; Zhai, Yi, Shu, Wei, & Ha, 1998). However, the low mechanical strength of pure polyNIPAAm hydrogel in the swollen state seriously limits its application. In our laboratories, some research on the modification of polyNIPAAm hydrogels has been done by incorporation of linear polymers into the polyNIPAAm hydrogels in order to form semi-interpenetrating network polymers (IPNs), or full-IPNs, or by grafting copolymerization of NIPPAm onto the matrix. PolyNIPAAm-based biomaterials with suitable mechanical properties were obtained, but their temperature sensitivity and swelling behaviour was decreased (Li, Zhai, Yi, Gao & Ha, 1999; Lu, Zhai, Li, & Ha, 2000; Zhai, Li, Yi & Ha, 2000).

Kappa Carrageenan is a hydrophilic polysaccharide that exists as matrix material in numerous species of seaweed (Nijenhuis, 1997). Chemically, it is a linear, sulfated polysaccharide, composed of a repeating D-galactose and 3,6-anhydro-D-galactose units. Recently, Kappa carrageenan was found to enhance the properties of synthetic hydrogels by incorporation into the water-soluble polymer systems such as polyethylene oxide and poly-*N*-vinyl pyrrolidone (PVP) (Tranquilan-Aranilla, Yoshhi, Dela Rose, & Makuuchi, 1999; Zhai, Ha, Yoshii & Makuuchi, 2000).

In this work, Kappa Carrageenan has been incorporated into polyNIPAAm hydrogels under the action of radiation. It was expected that the incorporation of Kappa carrageenan would overcome the low mechanical properties of polyNIPAAm hydrogels on one hand, and also extend the biomedical applications of polyNIPAAm hydrogels on the other hand.

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2. Experimental

2.1. Materials

Kappa carrageenan samples (WG-115) were obtained from Copenhagen Pectin A/S of Denmark. NIPAAm were purchased from Kishita Corp. Ltd, Japan. *N*,*N*′-methylene-bis-acrylamide (Bis) and other reagents were purchased from Beijing Chemical Works.

2.2. Preparation of the polyNIPAAm/Kappa carrageenan blend hydrogels

Kappa carrageenan solutions were prepared by dissolving Kappa carrageenan in distilled water at 80 °C for 2 h. The hot Kappa carrageenan solution was mixed with NIPAAm, Bis solution, and then poured into a glass tube of diameter 15 mm. The final concentrations in the mixture of Kappa carrageenan, NIPAAm and Bis were 5, 5 and 0.1%, respectively. The samples were cooled and then irradiated at room temperature by a ^{60}Co-γ source.

2.3. Measurement of gel strength

After irradiation, the hydrogel was cut into cylinders with a 15 mm diameter and 20 mm height for testing. Gel strength was measured by 75% compression and decompression of gel samples between the plates of a Strograph-R1 Material Tester with a crosshead speed of 50 mm/min.

2.4. Swelling behaviour

PolyNIPAAm/Kappa carrageenan gel samples were dried to constant weight at 52 °C in a vacuum oven and were immersed in distilled water to be swollen. The swelling ratio (*R*) (based on swelling kinetics) and equilibrium degree of swelling (EDS) (swelling capacity) were calculated as follows, respectively:

$$R(\%) = W_t/W_0 \times 100 \tag{1}$$

$$\mathrm{EDS}(\%) = W_e/W_0 \times 100 \tag{2}$$

where W_0 is initial mass of dried hydrogel; W_t and W_e are the masses of the swollen hydrogels at time *t* and at equilibrium, respectively.

2.5. Determination of the concentration of chloride ion in swelling solution

When polyNIPAAm/Kappa carrageenan gel samples were swollen, chloride ions were released from the gels into the solution. The concentration of chloride ion in the swelling solution was determined by means of a chloride ion selective electrode.

3. Results and discussion

3.1. Preparation of the polyNIPAAm/Kappa carrageenan blend hydrogels

When Kappa carrageenan, NIPAAm, Bis aqueous solutions were cooled down to room temperature, physically crosslinked Kappa carrageenan gels were obtained. Intramolecular bridges were formed first by an ionic bond between K^+ and the sulfate group and secondly by electrostatic forces of attraction between K^+ and the 3,6-anhydro-D-galactose residues in Kappa carrageenan (Fig. 1). K^+ was incorporated in the form of potassium chloride during the extraction procedure of Kappa carrageenan manufacture, i.e. the Kappa carrageenan is not pure. The incorporation of K^+ obviously can increase the gel strength of Kappa carrageenan gels (Watase & Nishinari, 1982). NIPAAm molecules were dispersed homogeneously in the network of Kappa carrageenan gels. When the mixture was irradiated by γ-rays, the polymerization and crosslinking of NIPAAm occurred. The blended hydrogel is believed to have the structure of an IPN.

Of course, radiation grafting of NIPAAm onto Kappa carrageenan was not eliminated. Fig. 2 shows the influence of Kappa carrageenan concentration and the level of the radiation dose on the gel strength of polyNIPAAm/Kappa carrageenan blended hydogels. The inset in Fig. 2 is a magnified figure showing the change of gel strength of pure polyNIPAAm hydrogel as a function of the radiation dose. The gel strength of pure polyNIPAAm hydrogel increased with increased dose and then leveled off around 10 kGy. However, the gel strength of pure polyNIPAAm hydrogel was very low and showed weak mechanical properties. After incorporating Kappa carrageenan into the polyNIPAAm hydrogels, the gel strength improved greatly. The gel strength of the blended hydrogels was raised with the increase in the dose from 0 to 2 kGy, and above 10 kGy decreased. When the radiation dose was lower than 10 kGy, in Kappa carrageenan/NIPPAm/H_2O mixtures, the polymerization and crosslinking of NIPAAm was the predominant reaction and after that, the degradation of Kappa carrageenan was no longer protected by the above reaction. This is similar to the situation in a Kappa carrageenan/PVP blend system (Zhai, Ha, Yoshii & Makuuchi, 2000). Kappa carrageenan is a kind of radiation degradation susceptible material, which on irridation, decreases in molecular weight, and the degradation of Kappa carrageenan could be protected and prevented by other reactions under low

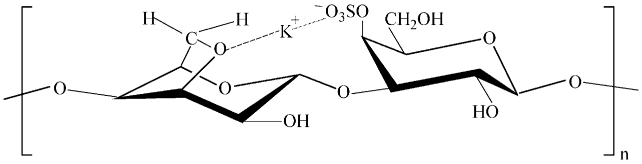

Fig. 1. Possible model of intramolecular K^+ bridging in Kappa carrageenan in aqueous solution at low temperature.

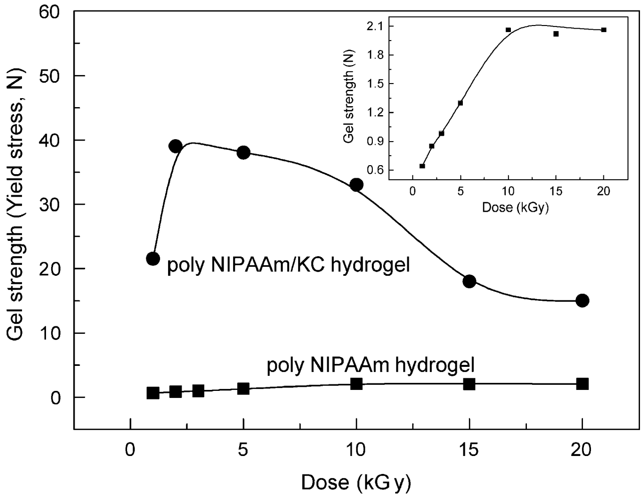

Fig. 2. Gel strength of polyNIPAAm hydrogels and polyNIPAAm/Kappa carrageenan (KC) blended hydrogels.

radiation doses. Therefore, in order to obtain transparent and elastic blended hydrogels with higher gel strength and swelling capacity, the radiation dose should not be higher than 2 kGy (2 kGy was applied in the following experiment).

3.2. The environmental responsiveness of polyNIPAAm/Kappa carrageenan blend hydrogels

3.2.1. The chloride ion-induced phase transition

The swelling kinetics of the blended gels at different temperature is shown in Figs. 3 and 4. When the swelling temperature was lower than 35 °C (the LCST of polyNIPAAm hydrogel), the swelling ratio increased with the time. But when the temperature was higher than 35 °C, the swelling curves appeared unusually to show a decreasing tendency after 5–10 h, and this tendency became more obvious with increasing temperature.

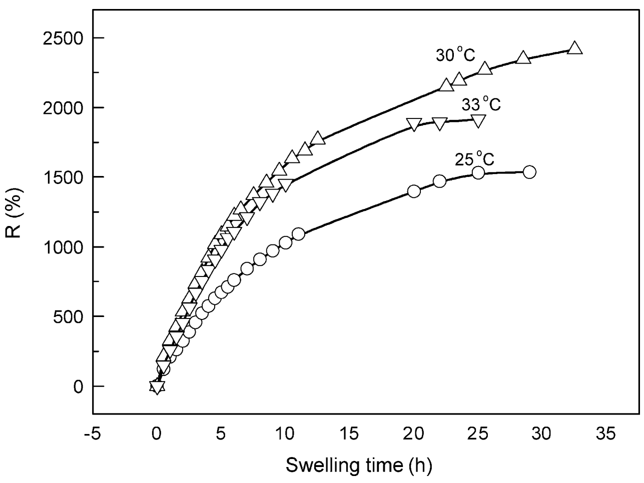

Fig. 3. Swelling behaviour of polyNIPAAm/Kappa carrageenan blended hydrogels at temperatures lower than the LCST of the polyNIPPAm gel.

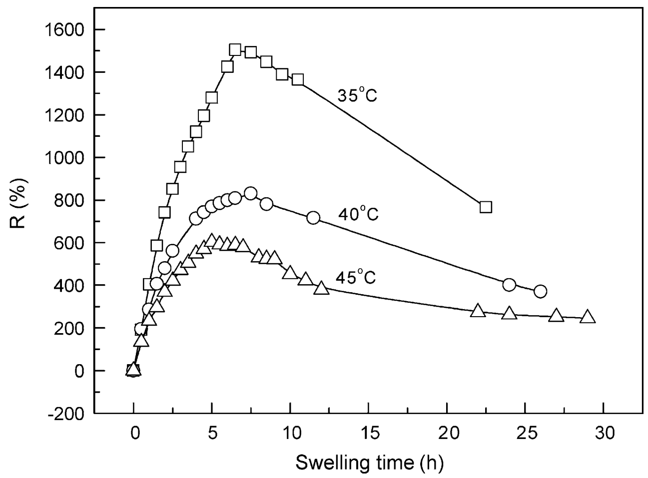

Fig. 4. Swelling behaviour of polyNIPAAm/Kappa carrageenan blended hydrogels at temperatures higher than the LCST of the polyNIPPAm gel.

This kind of phenomenon could be explained by a chloride-induced phase transition (Park & Hoffman, 1993). According to Park and Hoffman results, the polyNIPAAm gel demonstrates an unusual sodium chloride induced phase transition. This means that the gel collapses sharply at a critical sodium or potassium chloride concentration, which depends on the temperature. In fact, the chloride ions play a major role in this phase transition.

In our case, the blended gel containing polyNIPAAm also possesses a chloride ion-induced phase transition. This procedure accounts for the behaviour shown in Fig. 4. In fact, the Kappa carrageenan, as one component of the blended gels contains significant amounts of chloride ions in the form of potassium chloride, which was added during precipitation of Kappa carrageenan as part of the Kappa carrageenan manufacturing process. These chloride ions would be released from the blend gels gradually into the swelling aqueous solution. The concentration of chloride ion released in the swelling solution was measured by the chloride ion selective electrode. Fig. 5 shows the release

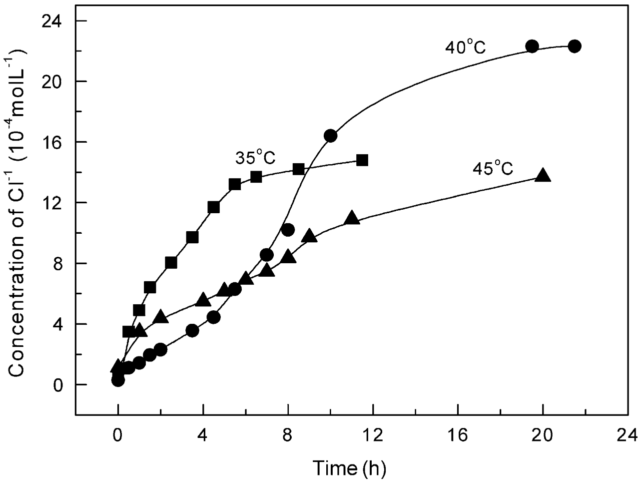

Fig. 5. Release of chloride ion from polyNIPAAm/Kappa carrageenan blended hydrogels into the swelling solution.

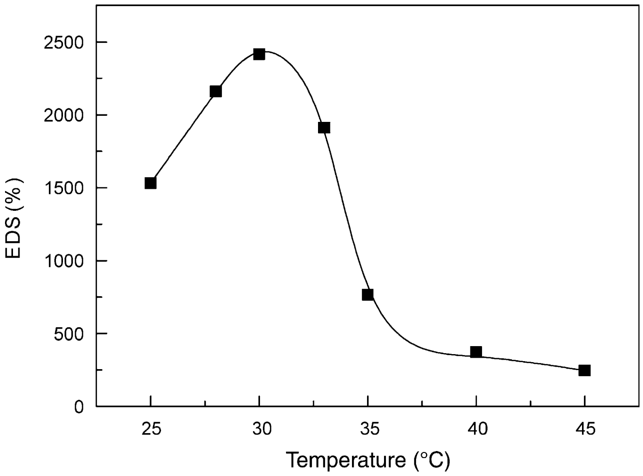

Fig. 6. Temperature-dependent phase transition of polyNIPAAm/Kappa carrageenan blended hydrogels.

process of chloride ions from the blended gels into water. The blended gels started to shrink when the concentration of chloride ion in the solution reached a certain degree, which was named as the critical concentration for the chloride ion-induced phase transition. Comparing Fig. 4 with Fig. 5, the critical concentrations of the chloride ion-induced phase transition were found to be 6.5×10^{-4}, 8×10^{-4} and 1.3×10^{-3} for 45, 40 and 35 °C, respectively. At lower temperature (<33 °C), the critical concentration of the chloride ion was quite high. It was much higher than the equilibrium concentration of chloride ion that could be achieved in this work. Therefore, the phase transition of the blended gels could not appear at temperatures lower than the LCST of polyNIPPAm gel.

3.2.2. Temperature-dependent phase transition

The EDS data plotted against the swelling temperature is shown in Fig. 6 from which it can be concluded that the blended gel containing polyNIPAAm still has obvious temperature sensitivity; the LCST was about 35 °C similar to that of pure polyNIPAAm hydrogel. The increase in the EDS of the blend hydrogel with temperature from 25 to 30 °C is attributed to the increase in the swelling capacity of the Kappa carrageenan gel at higher temperature.

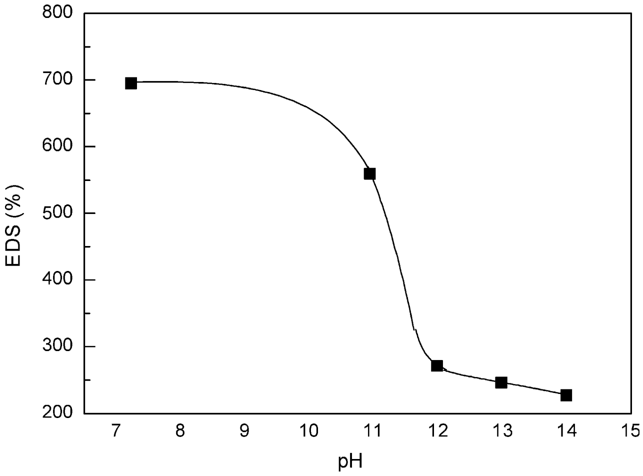

Fig. 7. pH-dependent phase transition of polyNIPAAm/Kappa carrageenan blended hydrogels.

3.2.3. pH-dependent phase transition

One of the components of the blended gel is Kappa carrageenan, which is a strong anionic polymer due to the half-ester sulfated moieties. Therefore, it is expected that the blended gel should have a pH response in basic medium. The results are shown in Fig. 7. In order to eliminate the influence of ionic strength, sodium sulfate was added into the aqueous solution for the swelling studies of the blended gels at different pH. Because of salting-out effects, the EDS values were obviously lower than those in pure water. Fig. 7 shows that polyNIPAAm/Kappa carrageenan blended gels exhibit a pH-dependent phase transition.

4. Conclusion

Transparent and elastic blended hydrogels composed of Kappa carrageenan and polyNIPAAm have been obtained by γ-irradiation technology. Gel strength was improved largely after incorporating Kappa carrageenan into the polyNIPAAm hydrogels. The blended gels were found to have temperature, and pH sensitivity and to exhibit a chloride ion-induced phase transition.

References

Bhalerao, V. S., Varghese, S., Lele, A. K., & Badiger, M. V. (1998). Thermoreversible hydrogel based on radiation induced copolymerisation of poly(*N*-isopropyl-acrylamide) and poly(ethylene oxide). *Polymer*, *39*(11), 2255–2260.

Chen, G., & Hoffman, A. S. (1995). Graft copolymers that exhibit temperature induced phase transitions over a wide range of pH. *Nature (London)*, *373*(6509), 49–52.

Feil, H., Bae, Y. H., Feijen, J., & Kim, S. W. (1992). Mutual influence of pH and temperature on the swelling of ionizable and thermosensitive hydrogels. *Macromolecules*, *25*, 5528–5530.

Huglin, M. B., Liu, Y., & Velada, L. (1997). Thermoreversible swelling behavior of hydrogels based on *N*-isopropylacrylamide with acidic comonomers. *Polymer*, *38*(23), 5785–5791.

Li, J., Zhai, M. L., Yi, M., Gao, H. C., & Ha, H. F. (1999). Radiation grafting of thermo-sensitive polyNIPAAm onto silicone rubber. *Radiation Physics and Chemistry*, *55*, 173–178.

Lu, X. Q., Zhai, M. L., Li, J. Q., & Ha, H. F. (2000). Radiation preparation and thermo-response swelling of interpenetrating polymer networks composed of poly NIPAAm and PMMA. *Radiation Physics and Chemistry*, *57*, 477–480.

Morra, M., & Cesinell, C. (1995). Thermal recovery of cells cultured on polyNIPAAm surface-grafted polystyrene dishes. *Polymer: Preprint*, *36*(1), 55–56.

Nijenhuis, K. T. (1997). Carrageenans. In *Thermoreversible networks*, Berlin: Springer, pp. 203-252.

Park, T. G., & Hoffman, A. S. (1993). Sodium chloride-induced phase transition in nonionic poly(*N*-isopropylacrylamide) gel. *Macromolecules*, *26*, 5045–5048.

Rosiak, J. M., & Ulanski, P. (1999). Synthesis of hydrogels by irradiation of polymers in aqueous solution. *Radiation Physics and Chemistry*, *55*, 139–151.

Sasaki, S., Kawasaki, H., & Maeda, H. (1997). Volume phase transition behavior of *N*-isopropylacrylamide gels as a function of the chemical potential of water molecules. *Macromolecules*, *30*, 1847–1848.

Serizawa, T., Uemura, M., Kaneko, T., & Akashi, M. (2002). Rapid and controlled deswelling of porous poly(*N*-isopropylacrylamide) hydrogels prepared by the templating of interpenetrated nanoporous silica particles. *Journal of Polymer Science, Polymer Chemistry*, *40*(20), 3542–3547.

Shibayama, M., Mizutani, S., & Nomura, S. (1996). Thermal properties of copolymer gels containing *N*-isopropylacrylamide. *Macromolecules*, *29*, 2019–2024.

Shin, B. C., Jhon, M. S., Lee, H. B., & Yuk, S. H. (1998). Temperature-induced phase transition of semi-interpenetrating polymer networks composed of poly(*N*-isopropyl acrylamide) and hydrophilic polymers. *European Polymer Journal*, *34*(2), 171–174.

Takashi, A., & Kohei, S. (1996). Glucose-sensitive lower critical solution temperature changes of copolymers composed of NIPAAm and phenylboronic acid moieties. *Polymer Journal*, *l28*(4), 371–374.

Tranquilan-Aranilla, C., Yoshhi, F., Dela Rosa, A. M., & Makuuchi, K. (1999). Kappa-carrageenan-polyethylene oxide hydrogel blends prepared by gamma irradiation. *Radiation Physics and Chemisry*, *55*, 127–131.

Vesterinen, E., Dobrodumov, A., & Tenhu, H. (1997). Spin-labeled polyelectrolyte gels based on poly(*N*-isopropylacrylamide). Effects of the network structure and the gel collapse on the EPR spectra. *Macromolecules*, *30*, 1311–1316.

Wang, M. Z., Fang, Y., & Hu, D. D. (2001). Preparation and properties of chitosan-poly(*N*-isopropylacrylamide) full-IPN hydrogels. *Reactive and Functional Polymers*, *48*(1–3), 215–221.

Watase, M., & Nishinari, K. (1982). The rheological study of the interaction between alkali metal ions and Kappa-carrageenan gels. *Colloid and Polymer Science*, *260*, 971–975.

Zhai, M. L., Ha, H. F., Yoshii, F., & Makuuchi, K. (2000). Effect of kappa-carrageenan on the properties of poly(*N*-vinyl pyrrolidone)/kappa-carrageenan blend hydrogel synthesized by γ-radiation technology. *Radiation Physics and Chemistry*, *57*, 459–464.

Zhai, M. L., Li, J., Yi, M., & Ha, H. F. (2000). The swelling behavior of radiation prepared of semi-interpenetrating polymer networks composed of polyNIPAAm and hydrophilic polymers. *Radiation Physics and Chemistry*, *58*, 397–400.

Zhai, M. L., Yi, M., Shu, J., Wei, J. S., & Ha, H. F. (1998). Radiation preparation and diffusion behavior of thermally reversible hydrogels. *Radiation Physics and Chemistry*, *52*, 313–316.