THERMOSENSITIVE HYDROGELS OBTAINED BY RADIATION-INDUCED POLYMERIZATION

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INTRODUCTION

Thermally reversible hydrogels are a new class of hydrogels which are attracting much interest for a number of applications in biotechnology and biomedicine [1]. They exhibit a lower critical solution temperature (LCST), i.e. they swell if they are cooled below LCST and shrink if they are warmed above it. It has been shown that such a temperature is a function of a suitable balance between hydrophilic and hydrophobic groups in the polymer chain [2].

Ionizing radiation enables hydrogels with the proper design and function to be prepared [3-5]. By this technique new acrylic and methacrylic hydrogels bearing α-amino acid groups in the polymer chain have been obtained and used as matrices for the controlled release of drugs [6].

In this work the synthesis by γ-radiation of hydrogels based on acryloyl-L-proline methyl ester (A-ProOMe) and their thermo-responsiveness as a function of temperature are reported.

EXPERIMENTAL

A-ProOMe was synthesized according to the method already described [6]. N,N-dimethylacrylamide (DMAA) and trimethylolpropane trimethacrylate (TMPTMA) were from Aldrich Chemical Co. and used as received.

Poly(A-ProOMe) was prepared by radiation-induced polymerization the related monomer at the dose rate of 0.36 Gy/s and at roo temperature after flushing nitrogen. In the same experimental conditior hydrogels were obtained by irradiating mixtures of A-ProOMe with th other comonomers at different compositions. The specimens were allowe to swell in cool water for several days to remove the unreacted monomer.

Hydrogel samples were equilibrium swollen in water at differe temperatures and weighted after wiping the excess surface wate Subsequently, they were dried for 24 hrs in a vacuum heater and weighte again. The swelling ratio, Sw, was calculated from the ratio of the mass water absorbed and that of the dried samples.

RESULTS AND DISCUSSION

Several hydrogels based on A-ProOMe bearing hydrophilic hydrophobic moieties in the polymer chain were prepared by radiation ar the hydrophilic/hydrophobic balance was changed in the attempt investigating the effects on thermoresponsive behaviour.

First of all, the LCST of pure poly(A-ProOMe) was determined. To th purpose, the polymer was left in water at 6^{o}C where it was complete soluble. Every hour the temperature was increased by 1^{o}C until th transparent polymer solution became suddenly opaque. This temperatur was taken as the LCST of poly(A-ProOMe) and it was found to be 17^{o}C.

Irradiation of mixtures of A-ProOMe with the hydrophilic DMAA in th presence of TMPTMA, a crosslinking agent, gives rise to hydrogels whos swelling ratios as a function of temperature are reported in Fig. 1. It can b seen that the swelling ratio decreases with increasing temperature and discontinuous transition is attained at low DMAA concentrations only. I agreement with previous observations [2], these hydrogels made mor hydrophilic by the presence of DMAA show a shift of the transitio temperature towards higher values, for example for the hydrogel obtaine by irradiation of the mixture A-ProOMe/DMAA/TMPTMA in the ratio 95/5/ this value is 20^{o}C.

The swelling-deswelling curves when the temperature was cycle between 6^{o}C and 35^{o}C for 24 hrs at each temperature are shown in Fig. where swelling at the lowest temperature and shrinking at the highes temperature is observed. The hydrogels were allowed to swell a equilibrium at 6^{o}C and the swelling values for the samples in the rati

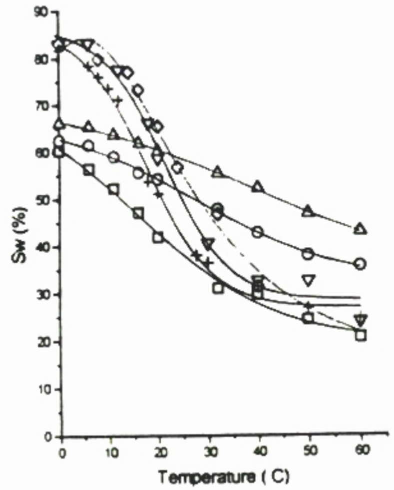

Fig. 1. Swelling ratio as a function of temperature of the hydrogels obtained by polymerization of the mixtures A-ProOMe/DMAA/TMPTMA in the ratio (w/w): 99.5/0.5/1 (+); 98/2/1 (◇); 95/5/1 (▽); 95/5/3 (△); 80/20/3 (○); 70/30/3 (□).

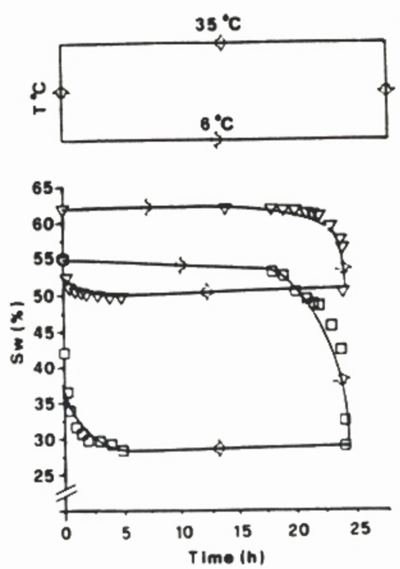

Fig. 2. Swelling-deswelling kinetics of the hydrogels obtained by polymerization of the mixtures A-ProOMe/DMAA/TMPTMA in the w/w ratio 70/30/3 (▽) and 90/10/3 (□) in response to the temperatures of 6°C and 35°C.

70/30/3 and 90/10/3 were 62% and 55%, respectively. After that, th temperature was raised at 35°C and every hour a swelling measuremer was carried out. A rapid loss of weight due to the shrinking wa ascertained until a new equilibrium was attained after 5-6 hrs, the swellin values for the two samples being 50% and 30%, respectively. After 24 h the temperature was again lowered at 6°C, the specimens started to swe until the same extent of swelling before determined at this temperatur was reached. As expected, the sample with the highest amount of th hydrophilic moiety DMAA showed the highest swelling values at both 6° and 35°C.

Work is now in progress with the aim of using the hydrogels befor described as drug delivery systems for the controlled release of a analgesic and antipyretic drug.

REFERENCES

[1] A.S. Hoffman, "Intelligent" polymers in biotechnology and medicin *Macromol. Symp.* **98**, 645 (1995).

[2] L.D. Taylor and L.D. Cerankowsi, Preparation of films exhibiting balanced temperature dependence to permeation by aqueou solutions - A study of lower consolute behavior, *J. Polym. Sci. Polyr Chem. Ed.* **13**, 2551 (1975).

[3] M. Carenza, Recent achievements in the use of radiatio polymerization and grafting for biomedical applications, *Radiat. Phy Chem.* **39**, 485 (1992).

[4] I. Kaetsu, Radiation synthesis of polymeric materials for biomedic and biochemical applications, *Adv. Polym. Sci.* **105**, 81 (1993).

[5] J.M. Rosiak, Radiation formation of hydrogels for drug delivery, *Controlled Release* **31**, 9 (1994).

[6] M. Yoshida, M. Asano, M. Kumakura, R. Katakai, T. Mashimo, I Yuasa and H. Yamanaka, Thermo-responsive hydrogels based c acryloyl-L-proline methyl ester and their use as long-actir testosterone delivery systems. *Drug Des. Delivery* **7**, 159 (1991).