Pergamon

Radiat. Phys. Chem. Vol. 52, Nos 1–6, pp. 295–299, 1998

Printed in Great Britain

PII: S0969-806X(98)00156-X

0969-806X/98 $19.00 + 0.00

INTELLIGENT DRUG DELIVERY SYSTEMS OBTAINED BY RADIATION

FLAVIA MARTELLINI,[1] OLGA Z. HIGA,[1] ERZSEBET TAKACS,[2] AGNEZA SAFRANJ,[2] MASARU YOSHIDA,[3] RYOICHI KATAKAI[4] AND MARIO CARENZA[5]

[1] Instituto de Pesquisas Energéticas e Nucleares - IPEN/CNEN - SP, Sao Paulo, Brazil, [2] Institute of Isotopes, Hungarian Academy of Sciences, H-1525 Budapest, Hungary, [3] Department of Material Development, Japan Atomic Energy Research Establishment, Takasaki, Gunma 370-12, Japan, [4] Department of Chemistry, Faculty of Engineering, Gunma University, Kiryu, Gunma 376, Japan, [5] Istituto di Fotochimica e Radiazioni d'Alta Energia, C.N.R., Sezione di Legnaro, Padova, Italy

ABSTRACT

Radiation-induced polymerization of acryloyl-L-proline methyl ester, an α-aminoacid-containing monomer, in the presence of a crosslinking agent and a hydrophilic monomer gave rise to polymer hydrogels whose water content at equilibrium was found to decrease as the swelling temperature increased. Some hydrogel samples were obtained with entrapped acetaminophen, an analgesic and antipyretic drug. It was ascertained that the release of the drug was controlled by both the hydrophilicity of the polymer matrices and the environmental temperature.

KEYWORDS

Thermosensitive hydrogel; radiation polymerization; poly(acryloyl-L-proline methyl ester); acetaminophen; controlled release.

INTRODUCTION

Some polymers show a reverse thermodynamic behaviour when dissolved in water: upon heating they precipitate out of solution whereas at low temperatures they dissolve (Taylor and Cerankowski, 1975), the polymeric chains turning from the extended configuration to the globular one. A polymer solution that exhibits this behaviour has a Lower Critical Solution Temperature (LCST). In the same way, the corresponding hydrogels swell at temperatures lower than LCST and shrink above it.

There are many advances in the development of thermosensitive hydrogels obtained by the chemical method for modulating drug delivery (Hoffman, 1995; Tsuruta, 1996). High energy radiation is a suitable technique that allows the synthesis of "smart" hydrogels responsive to a wide range of stimuli (Kaetsu, 1966).

Much attention has been directed in recent years toward the synthesis by γ-radiation of hydrogels bearing α-amino acid groups as matrices for a slow release of drugs (Yoshida *et al.*, 1991, 1992, 1995, 1996). We report here an investigation on radiation polymerization and crosslinking of hydrogels based on acryloyl-L-proline methyl ester (A-ProOMe), their thermo-responsiveness and their use for the controlled release of acetaminophen, an analgesic and antipyretic drug.

EXPERIMENTAL

The synthesis of A-ProOMe monomer was carried out as previously described (Yoshida *et al.*, 1991). Trimethylolpropane trimethacrylate (TMPTMA) and N, N-dimethylacrylamide (DMAA) were from Aldrich Chemical Co. and used as received.

Both poly(A-ProOMe) homopolymer and related hydrogels were obtained by radiation polymerization of A-ProOMe at room remperature and at the dose rate of 0.36 Gy/s (total dose = 25 kGy) after flushing nitrogen. After irradiation, the samples were repeatedly washed with cool water to remove the unreacted monomer.

The swelling in water at the equilibrium of hydrogels at different temperatures was determined from the ratio of the mass of water absorbed with respect to that of swollen samples.

Acetaminophen, a Sigma Chemical Co. product, was loaded as follows. Hydrogels in a shape of discs obtained by radiation polymerization were lyophilized and then immersed in a saturated aqueous solution of the drug at 5°C for 72 hrs. Afterwards, the discs were removed from the solution, transferred into liquid nitrogen and lyophilized again.

For the determination of the released drug, hydrogel discs with entrapped acetaminophen were transferred to a tube containing 20 ml of water at the established temperatures and, at fixed times, 20 µl aliquots were taken and immediately replaced by pure water. The concentration of the released drug was assayed by means of a UV Pharmacia LKB-Ultrospec III spectrophotometer at the wavelength of 246 nm.

RESULTS AND DISCUSSION

Pure poly(A-ProOMe) obtained by radiation-induced polymerization was found to be soluble in water at temperatures below 17°C while above it a phase separation occurred. Thus, this temperature was taken as the LCST of the polymer.

Irradiation of A-ProOMe in the presence of TMPTMA, a crosslinking agent, gave rise to hydrogels and in Table 1 the swelling at equilibrium at the temperatures of 0°, 10° and 20°C and at different concentrations of TMPTMA are shown. Not surprisingly, increasing concentrations of the latter bring about decreasing swelling percentages while, for the same concentration of the crosslinking agent, decreasing swelling values with increasing temperature are observed.

Table 1. Percent of swelling of the hydrogels obtained by radiation-induced polymerization of the mixtures A-ProOMe/TMPTMA as a function of both temperature and amount of TMPTMA

Swelling (%)	T (°C)	TMPTMA (%)
82	0	0.5
67	0	3.0
54	0	6.0
40	0	10.0
73	10	0.5
55	10	3.0
46	10	6.0
35	10	10.0
41	20	0.5
39	20	3.0
36	20	6.0
28	20	10.0

It should be noted that this behaviour is in agreement with the SEM analysis of cross-section structures of hydrogel samples previously observed (Martellini *et al.*), *i.e.* as the swelling temperatures increase the pore sizes decrease.

Much effort has been recently directed towards obtaining tailor-made responsive hydrogels for a wide variety of applications (Bae *et al.*, 1990; Kost and Langer, 1991; Shibayama and Tanaka, 1993; Hoffman, 1995), taking into account that an alteration of the subtle balance of hydrophilic and hydrophobic groups in the polymer chain affects their thermosensitivity (Taylor and Cerankowski, 1975). To this purpose, hydrogels were prepared by irradiation A-ProOMe in the presence and in the absence of hydrophilic DMAA. From the swelling data reported in Fig. 1, an inverse function of temperature can be observed and, moreover, a shift of LCST from 17°C for hydrogels A-ProOMe/TMPTMA to 20°C for hydrogels A-ProOMe/DMAA/TMPTMA is discernible.

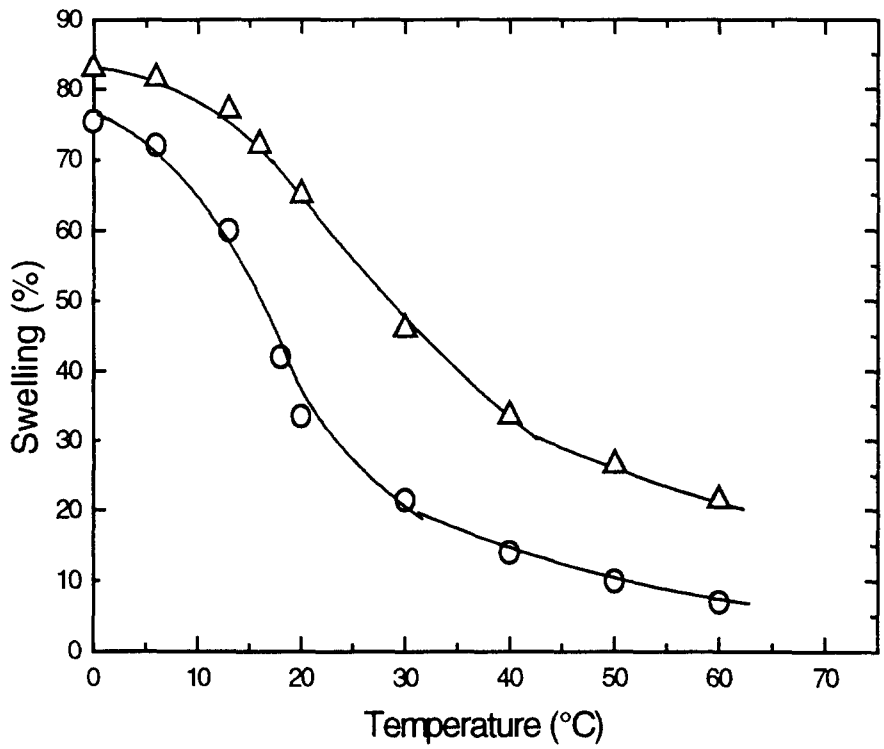

Figure 1. Swelling percentage as a function of temperature of the hydrogels obtained by radiation polymerization of the mixtures A-ProOMe/TMPTMA in the ratio (w/w) 99/1 (○) and A-ProOMe/DMAA/TMPTMA in the ratio (w/w) 98/2/1 (△).

In this work hydrogels A-ProOMe/TMPTMA in the ratio 99/1 were loaded with acetaminophen in a saturated solution of the drug at 5°C and the release profiles at the temperatures of 10°, 30° and 37°C are shown in Fig. 2. It can be seen that the extent of release increases as the *milieu* temperature decreases, in other words the diffusion of acetaminophen depends on swellability of the matrices which, as shown before, is the higher the lower temperature. To this regard, it is not surprising that hydrogels with an enhanced swelling due to the presence of hydrophilic moieties in the polymer chain were found to give rise to a still higher release rate (Martellini *et al.*).

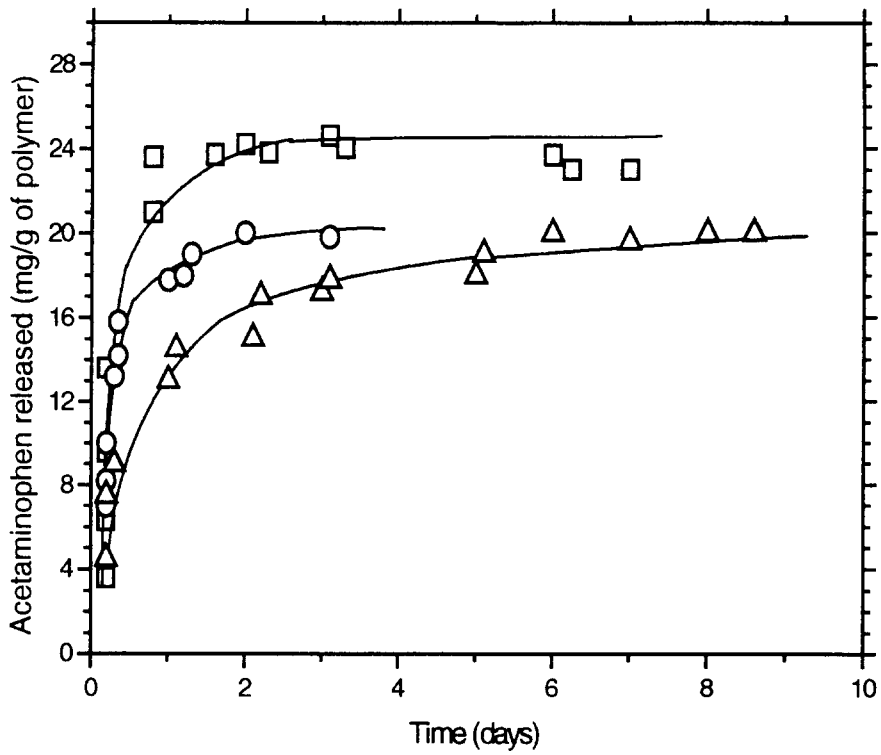

Figure 2. Release profile at 10°C (□), 30°C (○) and 37°C (△) of acetaminophen from matrices obtained by radiation polymerization of the mixture A-ProOMe/TMPTMA in the ratio 99/1 (w/w).

ACKNOWLEDGEMENTS

The authors wish to express their appreciation to Mr. D. Ceccato for his kind assistance.

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