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Thermally Reversible Hydrogels for Drug Delivery Obtained by Radiation

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Introduction

Hydrogels are polymer networks which absorb and retain significant amounts of water and can be used as matrices for the immobilization of enzymes and cells in biocatalysis and for the controlled release of drugs (Gehrke and Lee 1990).

In recent years much effort has been directed towards "intelligent" hydrogels which reversible swell in water in response to environmental changes such as temperature, pH, electric field, light, ionic strength (Okano and Yoshida, 1993). The negative thermosensitivity is observed for hydrogels prepared from polymers which exhibit a lower critical solution temperature (LCST) and it has been assumed that such a temperature is a function of a suitable balance between hydrophilic and hydrophobic groups in the polymer chain (Taylor and Cerankowski, 1975).

In this work we reported the radiation synthesis of hydrogels based on acryloyl-L-proline methyl ester (A-ProOMe) with hydrophilic or hydrophobic moieties in the polymer chain. Acetaminophen (paracetamol) an analgesic and antipyretic drug, was entrapped and the effect of the hydrophilic/hydrophobic balance on its release was investigated. It was also of interest to synthesize a new thermoresponsive hydrogels by copolymerization of A-ProOMe with an acrylic derivative of acetaminophen, which was synthesized in our laboratories, and to investigate the swelling and the hydrolytical degradation.

Experimental

Materials

A-ProOMe was synthesized according to the method already described by Yoshida *et al.* (1992). 4-acryloyloxy acetanilide (AOA) was synthesized in our laboratories. N,N-dimethylacrylamide (DMAA), 2-cyanoethyl acrylate (CEA) and trimethylolpropane trimethacrylate (TMPTMA), acryloyl chloride, 4-hydroxyacetanilide (paracetamol) from Sigma Chemical Co. were used as received.

Synthesis of AOA

AOA was synthesized through the reaction at 0^0C of acryloyl chloride and 4-hydroxyacetanilide dissolved in NaOH/solution and dioxane. AOA formed by precipitation was filtered and purified by a double precipitation with cool water.

Synthesis of Thermoresponsive Hydrogels

The hydrogels were prepared by radiation-induced polymerization of mixtures of the related monomers using γ-rays from a ^{60}Co source at the dose rate of 0.36 Gy/s at room temperature after flushing nitrogen. After irradiation, the polymer was washed with cool water to remove the unreacted monomer. Solid and transparent samples were obtained in a cylindrical form by separating the product from the mold in which they were contained.

Determination of Swelling

The swelling ratio, Sw, of the hydrogels at the equilibrium in water was calculated as follows:

$$Sw = \frac{W - W_0}{W}, \qquad (1)$$

where W and W_0 are the weights of the swollen and dried samples, respectively.

Drug Loading

Copolymer hydrogels with entrapped 10% acetaminophen were prepared by irradiation at 25°C of the homogeneous solutions of the related monomers in different proportions. Some runs were carried out adopting a different procedure by immersing the lyophilized copolymer gels in a saturated aqueous solution of acetaminophen at 5°C for 3 days.

Drug Release from Thermoresponsive Discs

Hydrogel discs with the entrapped acetaminophen by radiation were allowed to swell in distilled water at 37°C. The concentration of the drug released was assayed by means of a UV Pharmacia LKB-Ultraspec III spectrophotometer at the wavelength of 246 nm.

Results and Discussion

In this work hydrogels based on A-ProOMe were synthesized and hydrophilic/hydrophobic balance of the polymer chain was changed in the attempt at investigating the effects on thermosensitivity and on release of a model drug. To this purpose DMAA, a hydrophilic monomer, and CEA and TMPTMA, both hydrophobic monomers, were selected, the latter is a crosslinking agent.

From the swelling data an inverse function of temperature was observed. Moreover, as the concentration of TMPTMA decreases the swelling increases. The hydrogels containing more than 3%

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crosslinking agent show a continuous decrease of swelling with increasing temperature while for the concentrations lower than 3% a transition phase is observed. This effect is more pronounced for hydrogels containing CEA. When hydrogels were obtained by irradiation of A-ProOMe in the presence of hydrophilic DMAA swelling decreases with increasing temperature and a discontinuous transition is attained at low concentration of DMAA only.

In this work several hydrogels based on A-ProOMe were used for entrapping acetaminophen which was allowed to be released at 37°C, a temperature above the transition temperature and thus suitable for "squeezing" the drug.

Figure 1 shows the release of acetaminophen from copolymer hydrogels obtained by radiation polymerization of the monomer mixtures with the dissolved drug. Despite some scattering of the data points, it can be seen that the highest release rate occurred with the most swellable matrix bearing DMAA. On the contrary, for the hydrogels with the hydrophobic crosslinking agent, the higher the amount of the latter, the lower the extent of release was.

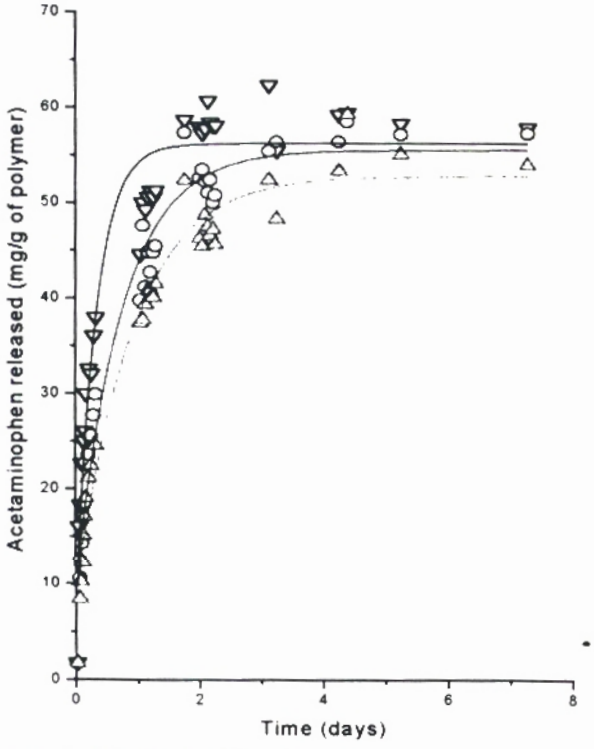

Figure 1. Release profile at 37°C of acetaminophen form matrices obtained by radiation-induced polymerization of the mixtures in the w/w ratio: A-ProOMe/DMAA/TMPTMA 95/5/1(V); A-ProOMe/TMPTMA 99/1(O); A-ProOMe/TMPTMA 97/3(Δ).

Figure 2 shows the release of acetaminophen from bearing AOA covalently attached to the macromolecular support through the hydrolyzable ester functional group. In this case the mechanism of drug release significantly differs from that described in the Figure 1 in which the drug was entrapped in the polymer matrix. Actually, from the Figure 1 it can be seen that the time that the acetaminophen release took to reach a "plateau" was 2-3 days, i.e. approximately the same time for the hydrogel samples to reach the swelling equilibrium in water at the different temperatures, while the "plateau" time for poly(A-ProOMe-co-AOA) was much longer, about 20 days. It can be therefore concluded that in this case from the kinetic point of view the drug release is mostly determined by the hydrolysis process and not by the molecular diffusion.

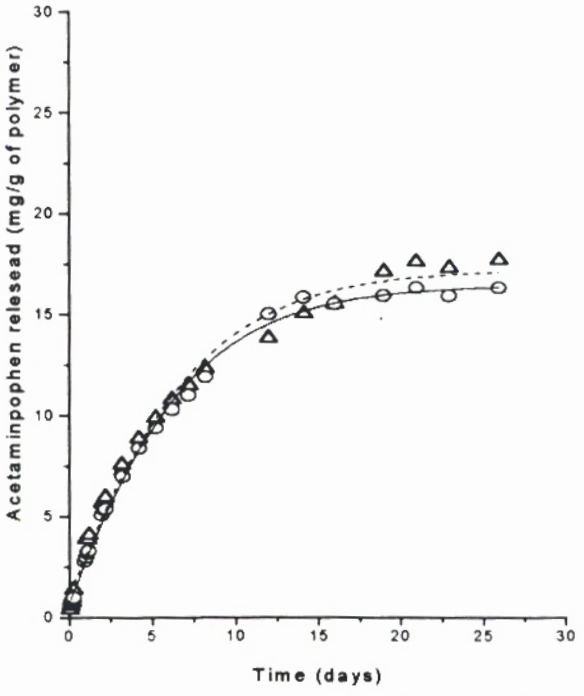

Figure 2. Release profile at 37°C and ph=8.5 of acetaminophen from matrices obtained by radiation-induced polymerization on the mixtures A-ProOMe/AOA/TMPTMA in the w/w ratio 80/20/1 (Δ) and 90/10/1 (O).

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Acknowledgments

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