STUDY OF THERMORESPONSIVE HYDROGELS FOR DRUG DELIVERY

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ABSTRACT

Thermoresponsive copolymer hydrogels were prepared by radiation induced polymerization based on acryloyl-L-proline methyl ester and the relationship between swelling behavior of gels and the copolymerization ratio was studied experimentally. The effect of crosslinking density and hydrophilic or hydrophobic monomers ratio on the swelling behavior of the hydrogels, and the "in vitro" rate release of a model drug were investigated. The results revealed that the transition temperature of A-ProOMe copolymers changed in proportion to the monomer ratio used in copolymerization and that the crosslinking density strongly affected the swelling. The rate of drug release from the thermo responsive gels can be different by changing the hydrophilic or hydrophobic component in the gels.

Key word: Thermoresponsive hydrogels, drug delivery, poly(acryloyl-L-proline methyl ester), LCST hydrogels, phase transition.

INTRODUCTION

In drug delivery , the term "hydrogel" is reserved polymeric networks which absorb and retain significant amounts of water maintaining a distinct three-dimensional structure(1). The permeability of hydrogels to water, drugs, and other solutes is easily adjusted over a broad range by changing the precursor, crosslinker, or synthesis conditions. These properties makes them interesting materials as carriers for immobilization of active compounds.

In order to design drug delivery system, the development of "intelligent" polymers that respond to environmental changes, for example, pH, ionic strength, temperature, and electric field, is of the greatest importance (2) They have been also termed "stimuli-sensitive", and "smart" gels. The property which often changes most dramatically is the swollen volume. The negative thermosesitivity, i.e. hydrogels shrink when the temperature increase, is observed for hydrogels prepared from polymers which exhibit a lower critical solution temperature (LCST). It has been assumed that such a temperature is a function of a suitable balance between hydrophilic and hydrophobic groups in the polymer chain (3).

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.

We also described the synthesis of a new thermoresponsive hydrogels by copolymerization of A-ProOMe with an acrylic derivative of acetaminophen. This monomer was synthesized in our laboratories to investigate the swelling and the hydrolytical degradation

EXPERIMENTAL

Materials

A-ProOMe was synthesized according to the method already described (4). 4-acryloyloxy acetanilide (systematic name: 4-acetamidophenyl acrylate), (AOA) was synthesized in our laboratory. N,N-dimethylacrylamide (DMAA), 2-cyanoethyl acrylate (CEA), trimethylolpropane trimethacrylate (TMPTMA) and acryloyl chloride, from Aldrich Chemical Co., and 4-hydroxyacetanilide (acetaminophen), 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 an alkaline 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. The small cylinders were cut into a 5 mm diameter and 1.5 mm height discs which were allowed to

contained. The small cylinders were cut into a 5 mm diameter and 1.5 mm height discs which were allowed to swell in cool water for several days to remove the unreacted monomer.

Determination of Swelling

Hydrogels samples were equilibrium swollen at different temperatures and weighed after wiping the excess surface water. Subsequently, they were dried for 24 hrs in a vacuum heater and 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 A-ProOMe containing both the drug and DMAA, CEA, AOA and TMPTMA 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 5°C for 24 hrs. 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

Hydrogels based on A-ProOMe were synthesized by radiation and the hydrophilic/hydrophobic balance of the polymer chains was changed in the attempt at investigating the effects on the thermosensitivity and on the 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.

The swelling of A-ProOMe/TMPTMA hydrogels as a function of both temperature and concentration of crosslinking agent were observed. An inverse function of temperature was observed, i.e. as the concentration of TMPTMA decreases the swelling increases. The hydrogels containing more than 3% crosslinking agent show a continuous decrease of swelling with increasing temperature while for the concentrations lower than 3% a transition temperature is observed. This effect is more pronounced for hydrogels containing CEA. The hydrogels obtained in the presence of hydrophilic DMAA showed a swelling decreases with increasing temperature and a discontinuous transition is attained at low concentration of DMAA gives rise to an increase of the transition temperature.

Acetaminophen was incorporated into the hydrogels by means of radiation-induced polymerization in order to examine the thermo-responsiveness as a means for controlled drug release. The *in vitro* drug release data from poly(A-ProOMe-co-DMAA-co-TMPTMA), 95/1, and poly(A-ProOMe-co-TMPTMA) 99/1, and 97/3 (Figure 1) showed that highest release rate occurred with the most swellable matrix obtained with DMAA as the hydrophilic component. The hydrogels with hydrophobic crosslinking agent, the higher the amount of the latter, the lower the extent of release was.

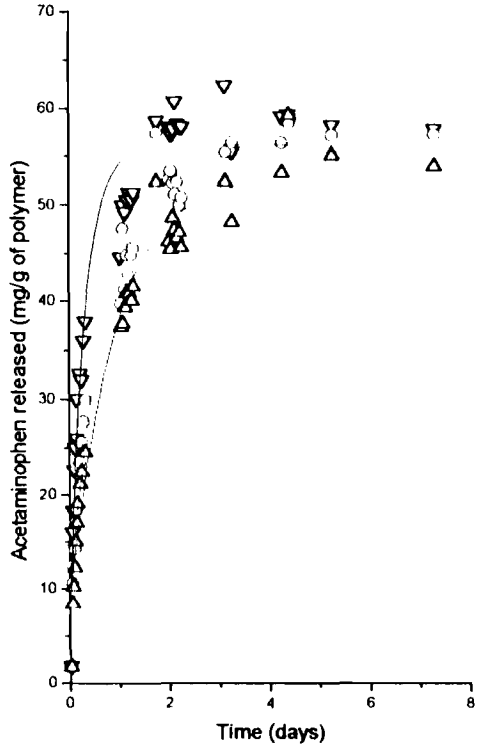

Figure 1: Release profile at 37°C of acetaminophen from matrices obtained by radiation-induced polymerization of mixtures in the w/w ratio: A-ProOMe/DMAA/TMPTMA 95/5/1 (∇); A-ProOMe/TMPTMA 99/1 (○); ProOMe/TMPTMA 97/3 (Δ).

The Figure 2 shows the release of acetaminophen referring to the hydrogels loaded with the drug in a saturated solution of the acetaminophen at 5°C. The highly swellable hydrogel obtained with DMAA as the hydrophilic component shows a release extent much higher than less swellable hydrogels with the hydrophobic TMPTMA and CEA.

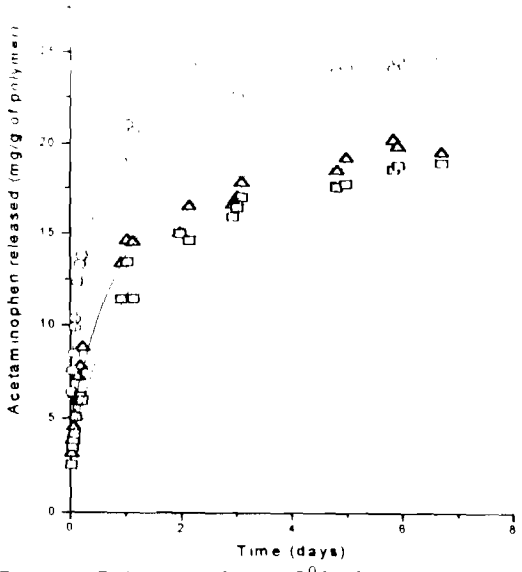

Figure 2: Release profile at 37^{0}C of acetaminophen from matrices obtained by radiation-induced polymerization of mixtures in the w/w ratio: A-ProOMe/DMAA/TMPTMA 95/5/1 (O); A-ProOMe/TMPTMA 99/1 (Δ); ProOMe/TMPTMA 97/3 ( ).

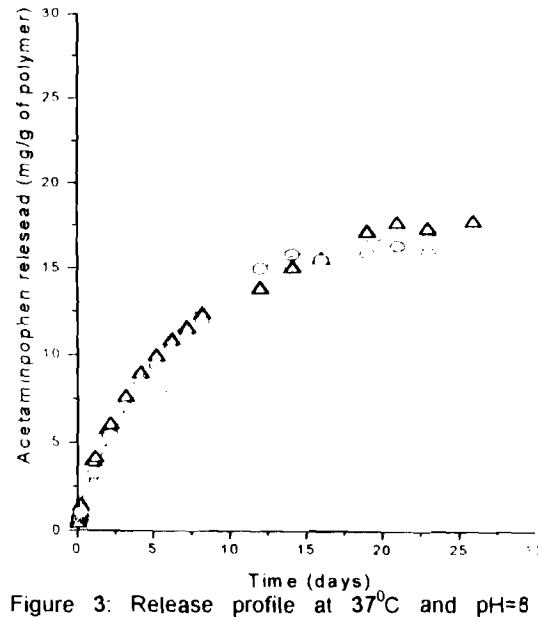

Figure 3: Release profile at 37^{0}C and pH=8.5 of acetaminophen from matrices obtained by radiation-induced polymerization of mixtures A-ProOMe/AOA/TMPTMA in the w/w ratio 80/20/1 (Δ) and 90/10/1 (O).

The preparation of several methacrylic derivatives of acetaminophen showed that both homopolymer and copolymers of 4-methacryloyloxy acetanilide underwent alkaline hydrolysis with release of acetaminophen (5). It was of interest to investigate if a similar behaviour occurred also in the case of copolymers of A-ProOMe with AOA.

Figure 3 shows the release of acetaminophen from hydrogels 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 Figures 1 and 2 in which the drug was entrapped in the polymer matrix.

The delivery process of acetaminophen from the latter occurs by diffusion mechanism, thus depending on the time of swelling equilibrium in water. The time that acetaminophen release took to reach a "plateau" for poly(A-ProOMe-co-AOA) was much longer, about 20 days. It can therefore be concluded that in the case from the kinetic point of view the drug release is mostly determined by the hydrolysis process and not by the molecular diffusion.

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