RADIATION SYNTHESIS OF HYDROGELS FOR BIOMEDICAL APPLICATIONS

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ABSTRACT

Thermally reversible hydrogels were synthesized by radiation-induced copolymerization of acryloyl-L-proline methyl ester with hydrophilic or hydrophobic monomers. The preparation of this copolymers has the purpose to obtain materials for biomedical application as drug delivery systems. Acetaminophen, an analgesic and antipyretic drug, was entrapped into some thermoresponsive hydrogels. It was found that the release profiles of drug can be controlled by copolymer porosity, hydrophilicity and changing the environmental temperature.

I. INTRODUCTION

Radiation processing is a well-established technology which has led to commercial exploitation in a wide range of fields, such as sterilization of medical devices, crosslinking of wires and cables, production of heat-shrinkables films, curing of coatings, "doping" of semiconductors and so on.

Radiation chemistry applied to bioengineering takes essentially two roads: (a) synthesis of polymeric gels (hydrogels) used as carriers for immobilization of biologically active as well as for drug delivery systems and (b) modification on polymeric materials both for immobilization of biocomponents and for biomedical uses [1].

This work describes the study of radiation induced polymerization to obtain thermoresponsive gels based on acryloyl-L-proline methyl ester for controlled release of drugs. The gel systems were synthesized by γ-rays from a ^{60}Co source at a dose rate of 0.36 Gy/s and at room temperature after flushing nitrogen.

In recent years, thermoresponsive gels have received much interest, and their applications to sensors, drug delivery systems, intelligent materials, and actuators have been proposed [2,3]. We have studied the synthesis, phase transitions of gels based on acryloyl polymers with pendant amino acid such as proline. These gels have a potential applicability as drug delivery systems because they contain a naturally occurring amino acid constituent.

This work describes the synthesis and swelling behavior of gels consisting of polymers having acryloyl-L-proline methyl ester (A-ProOMe), which have a lower critical solution temperature (LCST) of 17°C in water. Also we report the *in vitro* release of an analgesic and antipyretic drug from the gels of different composition and according to changes in environmental temperature.

II. EXPERIMENTAL

Materials A-ProOMe was synthesized according to the method already described [4]. N,N-dimethylacrylamide (DMAA), 2-cyanoethyl acrylate (CEA), trimethylolpropane trimethacrylate (TMPTMA) from Aldrich Chemical Co., and 4-hydroxyacetanilide (acetaminophen), from Sigma Chemical Co., were used as received.

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. 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 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 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 at 10, 30 and 37°C.

III. RESULTS AND DISCUSSION

In this work hydrogels based on A-ProOMe were synthesized by radiation and the hydrophilic/hydrophobic balance of the polymer chains was changed in the attempt on investigating the effects on thermosensitivity and on release of a model drug. For this purpose, DMAA, a hydrophilic monomer, CEA and TMPTMA, both hydrophobic monomers, were selected.

The effect of crosslinking density on the swelling behaviour of the A-ProOMe copolymer gels was investigated by preparing the gels with various amounts of crosslinking agent.

The results of our experiments revealed that the transition temperatures and the swelling ratios of the DMAA/A-ProOMe and CEA/A-ProOMe copolymer gels were changed in proportion to the monomer ratio used in copolymerization. As expected, changes in hydrophobicity of the gel bring about changes in the swelling behaviour. Therefore, the crosslinking density strongly affected the swelling ratios.

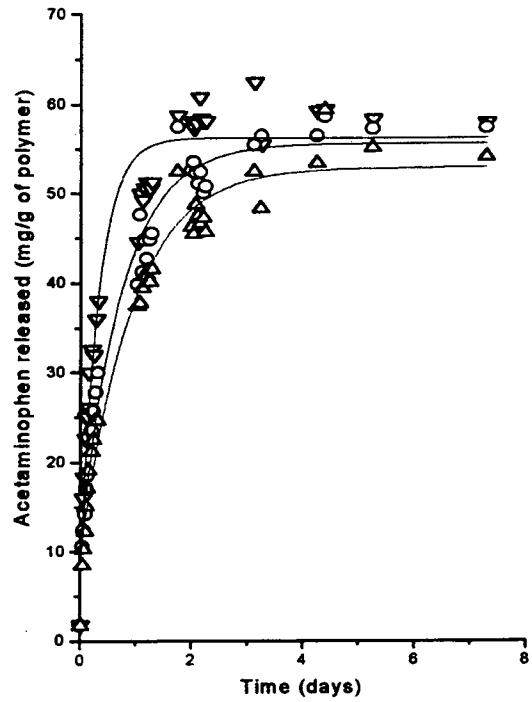

Figure 1: Release profile at 37°C of acetaminophen from matrices obtained by radiation-induced polymerization of mixtures in the w/w ratio: A-ProOMe/DMAA/TMPTMA 95/5/1 (▽); A-ProOMe/TMPTMA 99/1 (○); ProOMe/TMPTMA 97/3 (△).

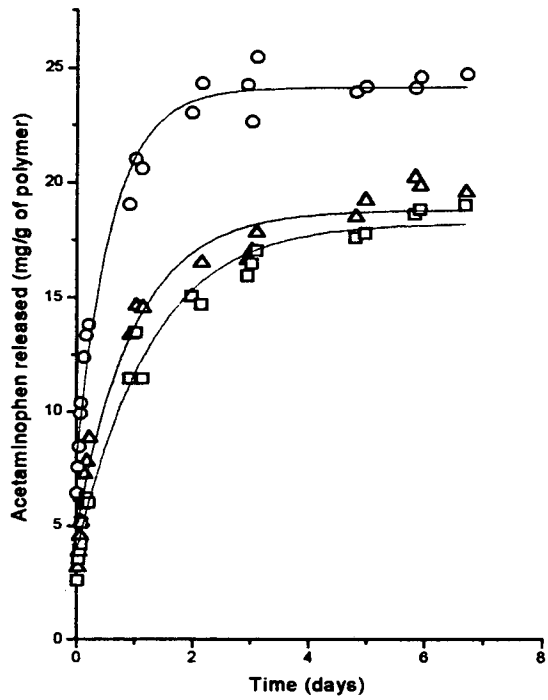

Figure 2: Release profile at 37°C of acetaminophen from matrices obtained by radiation-induced polymerization of mixtures in the w/w ratio: A-ProOMe/DMAA/TMPTMA 95/5/1 (○); A-ProOMe/TMPTMA 99/1 (△); ProOMe/CEA/TMPTMA 95/5/1 (□).

Figures 1 and 2 shows the results of the cumulative acetaminophen release at 37°C from the different A-ProOMe copolymer gels.

Figure 1 shows the release of acetaminophen from copolymer hydrogels obtained by radiation polymerization of the monomer mixtures with the dissolved drug. It can be seen that the highest release rate occurred with the most swellable matrix bearing DMAA.

The hydrophilicity effect is still more evident in the release curves, reported in Fig. 2, referring to the hydrogels loaded with acetaminophen in a saturated solution of the drug at 5°C. Actually, the highly swellable hydrogel obtained with DMAA as the hydrophilic component shows an extent of release much higher than less swellable hydrogels with the hydrophobic TMPTMA and CEA.

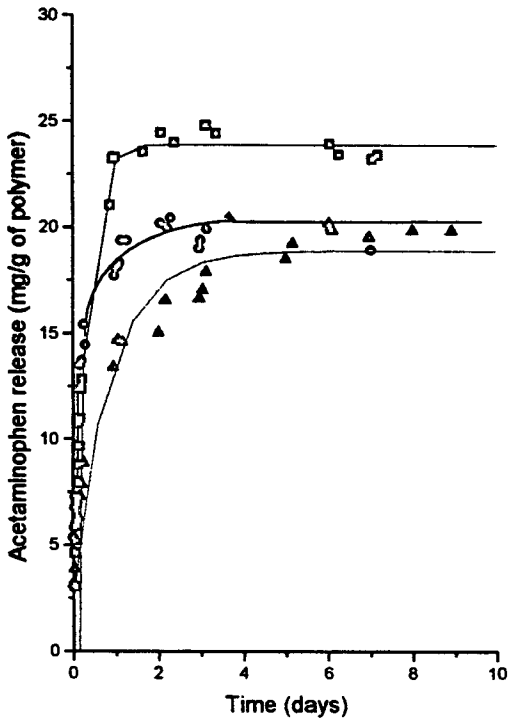

Figure 3: Release profile of acetaminophen from A-ProOMe/TMPTMA 99/1 obtained by radiation-induced polymerization at different temperatures: 10°C (□); 30°C (O); and 37°C (Δ).

This release behaviour agrees with the free volume theory. An important aspect of this theory is the hydration or swelling of the polymer. This swelling essentially increases the amount of free volume in the matrix to increase the diffusivity of solutes.

In this paper the effect of temperature on the release of model drug from A-ProOMe hydrogel is described. Figure 3 shows the release of acetaminophen from thermoresponsive discs at different temperatures. It can be seen that the release rate varies with the temperature. The rate of drug release at the temperature below the phase transition temperature (10°C) was higher than the release rate at the temperature above the phase transition temperature. This may be due to the fact that hydrogels are little hydrated at temperatures above the phase transition temperature.

In this thermoresponsive gels, the diffusivity of solutes will be a function of both temperature and swelling of the gels due to the hydrophobic/hydrophilic balance.

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Capes, CNPq.

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