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Radiation Physics and Chemistry 66 (2003) 155–159

Radiation Physics and Chemistry

www.elsevier.com/locate/radphyschem

Water and drug transport in radiation-crosslinked poly(2-methoxyethylacrylate-*co*-dimethyl acrylamide) and poly(2-methoxyethylacrylate-*co*-acrylamide) hydrogels

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Received 29 March 2002; accepted 22 May 2002

Abstract

Hydrogels of poly(*N*,*N*′-dimethylacrylamide-*co*-2-methoxyethylacrylate) and poly(acrylamide-*co*-2-methoxyethylacrylate) have been synthesized by radiation polymerization in dimethylformamide solution with trimethylolpropane trimethacrylate as a crosslinker. In this work, some investigations on the in vitro release of gentamicin sulphate, an antibiotic entrapped in the hydrogels, are reported. The kinetics of drug release from hydrogels matrices were examined and the results indicate that the release for the proposed geometry practically occurs in the first 24 h. The fractional cumulative release of the drug from the DMAA/MOEA matrices is linear when plotted against the square root of time, pointing out a Fickian process. On the other hand, AAm/MOEA matrices showed an initial non-Fickian behaviour, probably indicating a comparable rates of Fickian diffusion and polymer relaxation.

Keywords: Poly(*N*,*N*′-dimethylacrylamide-*co*-2-methoxyethylacrylate); Poly(acrylamide-*co*-2-methoxyethylacrylate); Thermoresponsive hydrogel; Polymeric drug delivery system

1. Introduction

The field of biomaterials rapidly progressed in the last years, mainly as a result of attempts at replacing body tissues with natural and synthetic materials. One of the most promising classes of materials for biomedical applications seems to be represented by polymer hydrogels (Rosiak et al., 1995).

"Intelligent hydrogels" which reversibly swell in water in response to environmental changes, such as temperature, pH, electric field, light, ionic strength, have recently been investigating (Okano and Yoshida, 1993; Hoffman, 1995; Galaev, 1995; Kost and Langer, 2001). With regard to thermosensitivity, in some cases it can be negative, i.e., hydrogels swell when the temperature decreases. It is believed that this behaviour is the result of extensive polymer-water interactions at low temperature, especially specific hydrophobic–hydrophilic balancing effects and configuration of the side groups. Above a critical temperature, i.e. the lower critical solution temperature (LCST), this hydrogel-water bonding is disrupted, thus giving rise to polymer-polymer interactions. As a consequence, the hydrogel becomes more hydrophobic (Yoshida et al., 1996; Souza et al., 1998; Kost and Langer, 2001).

Controlled drug delivery technology represents one of the most advanced areas of science since offers numerous advantages compared to conventional dosage forms including a higher efficacy, reduced toxicity, and improved patient's compliance. All controlled release

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0969-806X/03/$ - see front matter
PII: S0969-806X(02)00283-9

systems aim at improving the effectiveness of drug therapy (San Roman et al., 1994; Uhrich et al., 1999).

The thermoresponsive behaviour of poly(*N*,*N*′-dimethylacrylamide-*co*-2-methoxyethylacrylate) gels (Mueller, 1991, 1992) and the phase behaviour of their thermotropic aqueous copolymer solutions (El-Ejmi and Huglin, 1996, 1997) were investigated. In this work, a series of thermoresponsive copolymer hydrogels were prepared by gamma-ray induced copolymerization in dimethylformamide solution of 2-methoxyethylacrylate (MOEA) with acrylamide (AAm) and *N*,*N*′-dimethylacrylamide (DMAA) in the presence of a small amount of a crosslinker, e.g., trimethylolpropane trimethacrylate (TMPTMA).

In a previous work we studied the dynamic swelling behaviour of these hydrogels (Martellini et al., 2002). Normalized water sorption and dynamic swelling curves where built for each sample by gravimetric measurements carried out at different temperatures, i.e. 5°C, 10°C and 37°C. From these curves, the degree of swelling was determined and the diffusion coefficient calculated assuming a Fickian behaviour (Crank and Park, 1968).

In the present work, determinations of solute permeability in thermosensitive hydrogels based on MOEA through the in vitro release in aqueous solution of gentamicin sulphate are reported. This antibiotic was entrapped in the hydrogels by using the adsorption method. These measurements were made with the purpose of characterizing these hydrogels as drug delivery systems.

2. Experimental

2.1. Materials

MOEA was obtained from Polysciences Ltd. DMAA, AAm and TMPTMA were obtained from Aldrich Chemical Co. and used as received. Gentamicin sulphate was obtained from Polysciences Ltd.

2.2. Copolymerization of thermoresponsive hydrogels

The hydrogels based on MOEA were obtained by radiation-induced copolymerization at room temperature in N_2 atmosphere of the mixtures MOEA/DMAA and MOEA/AAm in different proportions dissolved in 50% dimethylformamide in the presence of 1% TMPTMA. The dose rate was 0.14 Gy/s and total dose 10 kGy.

The hydrogels were obtained in a cylindrical form and cut into 6 mm diameter and 2 mm height discs that were repeatedly washed with cool water to remove the unreacted monomer and solvent excess. The swelling percentage, Sw, was determined as the ratio of the weight of water with respect to the weight of the hydrogel swollen at the equilibrium.

2.3. Drug loading and "in vitro" release

The lyophilized hydrogels were immersed in a 10 μg/ml solution of gentamicin sulphate for 5 days at 5°C and lyophilized again. The amount of drug loaded was evaluated gravimetrically. Hydrogel discs with the loaded drug were immersed in 50 ml of water at 37°C and, at fixed times, 500 μl aliquots were taken and immediately replaced by pure water. The concentration of the drug released was assayed using a UV/vis spectrophotometer at a wavelength of 335 nm after reaction with *o*-phthalaldehyde as reported in the literature (Zhang et al., 1994).

3. Results and discussion

One of the most interesting characteristics of the copolymers here described is their capability of swelling at different temperatures to form hydrogels with physicochemical properties depending on the composition and the temperature of the medium.

Recently, the influence of the temperature and hydrophilicity on water transport of copolymeric hydrogels of the hydrophobic MOEA with the hydrophilic DMAA or AAm (Martellini et al., 2002) were studied and the LCST determined. For the mixtures DMAA/MOEA in the ratio 10/90, 15/85, 20/80 and 25/75 (w/w), the LCST values were 15°C, 25°C, 39°C and 32°C, respectively. According to the literature (Taylor and Cerankowski, 1975), it can be observed that the LCST values increase as the amount of the hydrophobic component decreases. In the present work, swelling behaviour of copolymers was carried out by determination of the dynamic swelling expressed as the variation of the degree of hydration as a function of the swelling time at the temperatures of 5°C, 10°C and 37°C (see Fig. 1). MOEA is a hydrophobic monomer and, hence, its homopolymer is completely insoluble in water. However, if hydrophilic monomers, such as DMAA or AAm, are added to the polymerizing MOEA, the swelling behaviour and the rate of water uptake increase. From the figure it can be seen that with increasing the amount of the hydrophilic monomer, the swelling ratio Sw increases with time rapidly at the beginning, reaching a constant value thereafter; in other words, the higher the DMAA or Am content, the larger the affinity of the gel for water. The previous results (Martellini et al., 2002) denoted that diffusion and swelling followed a Fickian diffusion mechanism indicating that molecular relaxation process did not exert any significative influence. These informations are

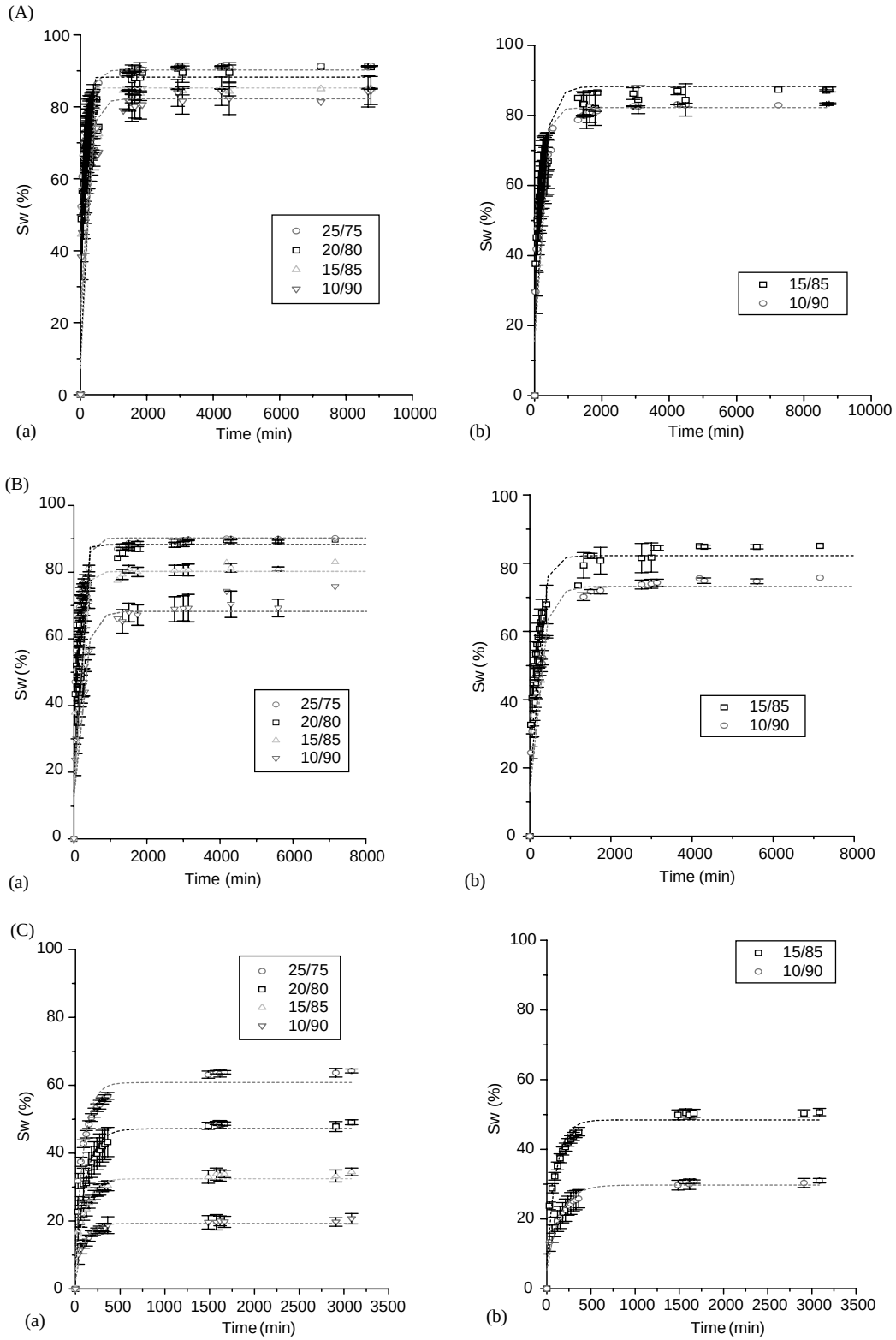

Fig. 1. Dynamic swelling kinetics at the temperatures of 5°C (A), 10°C (B) and 37°C (C) of the MOEA hydrogels with DMAA (a) and AAm (b). The composition of the mixtures DMAA/MOEA and AAm/MOEA in the ratio w/w are indicated in the inset. Error bars represent standard deviations for three experiments.

important for the identification of polymers that could expand slowly to allow a prolonged solute release.

It is known that the release from hydrogels is usually controlled by a combination of mechanisms such as Fickian diffusion, drug dissolution rate and relaxation rate of the polymer chains. The release of water soluble drugs from dehydrated hydrogel matrices generally involves the simultaneous absorption of water and

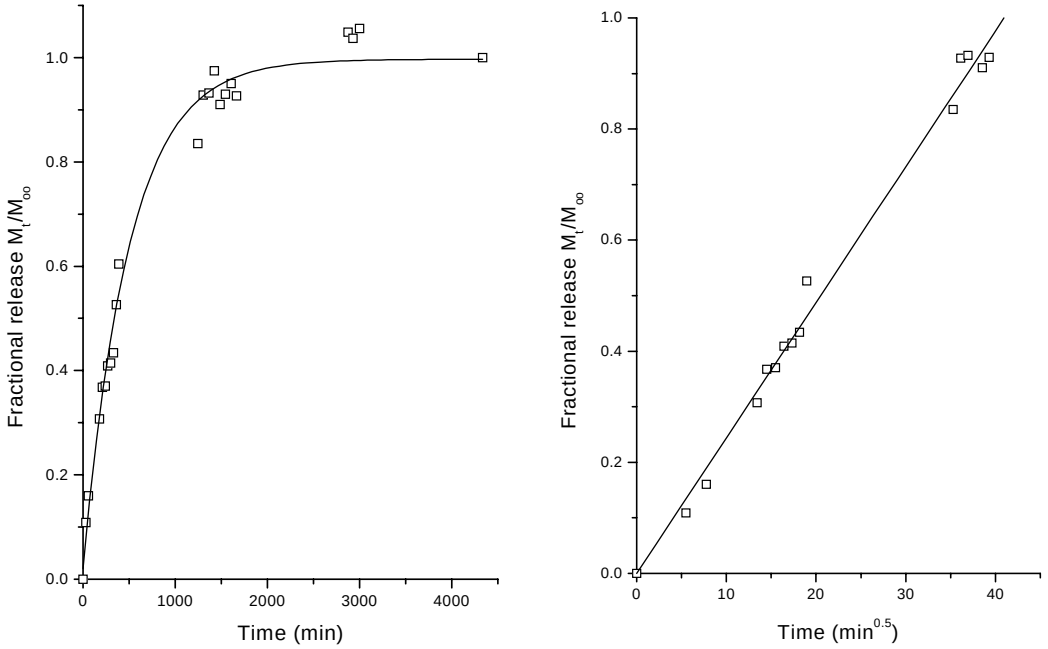

Fig. 2. Release profile in vitro of gentamicin sulphate at 37°C in water from poly(MOEA-*co*-DMAA) in the ratio 80/20 (w/w).

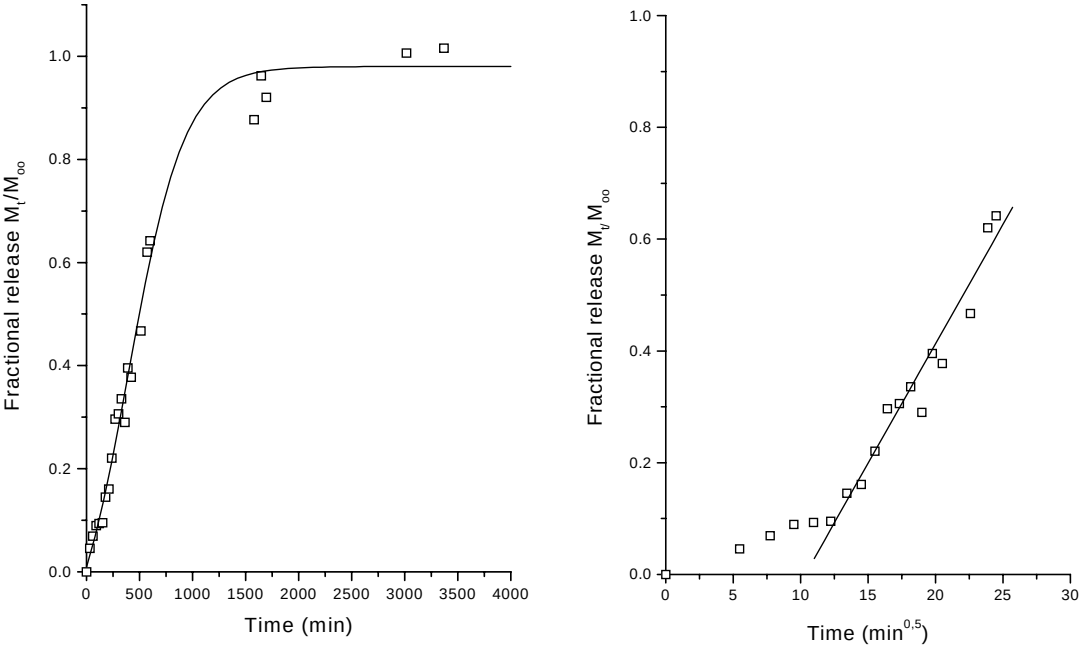

Fig. 3. Release profile in vitro of gentamicin sulphate at 37°C in water from poly(MOEA-*co*-AAm) in the ratio 85/15 (w/w).

desorption of drug through the swollen matrix. Depending on the rate of polymer relaxation at the glass/rubbery swelling front, the swelling process and the associated drug release may exhibit Fickian or non-Fickian behaviour. Typically, for a polymer slab, Fickian diffusion is characterized by square root time dependence in both the amount diffused and the penetrating diffusion front position (Lee, 1985; Korsmeyer, 1991; Caliceti et al., 2001).

Figs. 2 and 3 show the fractional gentamicin sulphate cumulative release, expressed as M_t/M_∞, where M_t and M_∞ are the amounts of drug released at the times t and infinite, respectively, as a function of time for poly(MOEA-*co*-DMAA) and poly(MOEA-*co*-AAm) matrices, respectively. The extent of release of both copolymers reaches the equilibrium value after about 30 h. The release of the drug from the DMAA/MOEA matrices is linear when plotted against the square root of time, suggesting a Fickian process (Fig. 2). On the other hand, the release profile reported in Fig. 3 for AAm/MOEA matrices indicate that the gentamicin sulphate release during the first stage could be influenced for the relaxation of polymer chains. Thus, AAm/MOEA matrices shown an initial non-Fickian behaviour indicating similar rates of Fickian diffusion and polymer relaxation. The release by Fickian diffusion occurs after 4 h.

The data were fitted according to the mathematical elaboration proposed for Fickian diffusion from moderately swelling slabs (Ritger and Peppas, 1987) and the diffusion coefficient D at 37°C for poly(MOEA-*co*-DMAA) was found to be $D = 3.8 \pm 0.1 \times 10^{-7}\,\mathrm{cm}^2/\mathrm{s}$. This result is in agreement with the Fickian behaviour previously found (Martellini et al., 2002) for the water transport through the DMAA/MOEA hydrogels.

Acknowledgement

This work was financially supported by CNPq.

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