THERMALLY REVERSIBLE HYDROGELS BASED ON 2-METHOXYETHYLACRYLATE (MOEA) AS DRUG DELIVERY SYSTEMS

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Abstract

Hydrogels of poly(N,N-dimethylacrylamide-*co*-2-methoxyethylacrylate) and poly(acrylamide-*co*-2-methoxyethylacrylate) have been synthesised by radiation polymerization in dimethylformamide solution with trimethylolpropane trimethacrylate as a crosslinker. In this work, it is reported the investigations about the release *in vitro* of gentamicin sulphate, an antibiotic entrapped in the hydrogels, in aqueous solutions. The result indicate that the release occurs practically in the first 24h, the release rate is constant over a period of 35 hours and without displaying any significant burst effect. The evidence observed also indicates that the solute transport in the beginning of release is controlled by Fickian diffusion and fractional release of gentamicin is initially linear when plotted against the square root of time, as expected for a Fickian process.

Keywords: poly(N,N-dimethylacrylamide-*co*-2-methoxyethylacrylate), poly(acrylamide-*co*-2-methoxyethylacrylate), thermoresponsive hydrogel, gentamicin, delivery system.

Introduction

The field of biomaterials has made rapid progress over the past years, mainly as a result of attempts to replace body tissues with natural and synthetic materials. One of the most promising classes of materials for biomedical applications seems to be the hydrogels.[1]

"Intelligent hydrogels" which reversibly swell in water in response to environmental changes such as temperature, pH, electric field, light, ionic strength have been developed.[2-4].

With regard to thermosensitivity, in some cases it can be negative, i.e., hydrogels shrink when the temperature increases.[5] Qualitatively, this behaviour is the result of extensive hydrogen bonding at low temperature, making the gel hydrophilic. Above the critical temperature, this hydrogel bounding is disrupted and polymer-polymer interactions dominate; as a consequence, the hydrogel becomes more hydrophobic.

Controlled drug delivery technology represents one of the most advanced areas of science. Such delivery systems offer numerous advantages compared to conventional dosage forms including improved efficacy, reduced toxicity, and improved patient compliance. All controlled release systems aim to improve the effectiveness of drug therapy.

The thermoresponsive behaviour of poly(N,N-dimethylacrylamide-co-2-methoxyethylacrylate) gels was investigated by Mueller[6,7] and the phase behaviour of their thermotropic aqueous copolymers solutions by Huglin[8,9]. In this work, a series of thermoresponsible copolymer hydrogels is prepared by gamma ray-induced copolymerization in dimethylformamide (DMF) solution of 2-methoxyethylacrylate (MOEA) with acrylamide (Am) and dimethylacrylamide (DMAA) in the presence of a small amount of a crosslinker, e.g., trimethylolpropane trimethacrylate (TMPTMA).

We have studied the dynamic swelling behaviour of the different hydrogels at different temperatures; the degree of swelling as a function of temperature and the normalised sorption curves, determining the diffusion coefficients at 5, 10 and 37 ^{o}C by gravimetry already reported in the 1st International Conference on Polymer Modification Degradation and Stabilisation, September 3-7, 2000 in Palermo, Italy.

In this work it is also reported the *in vitro* release in aqueous solution of gentamicin sulphate, an antibiotic, entrapped in the hydrogels by the adsorption method.

Experimental

Materials

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

Copolymerization of thermoresponsive hydrogels

The hydrogels based on MOEA were obtained by radiation-induced polymerization of the mixtures MOEA/DMAA and MOEA/Am in 50 % DMF in the presence of 1 %

TMPTMA, using γ-rays from a ^{60}Co source at a dose rate of 0.14 Gy/s at room temperature in N_2 atmosphere.

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.

Swelling measurements and behaviour

Hydrogel samples were swollen up to the equilibrium at different temperatures. The water transport was derived by dynamic swelling that was followed by measuring gravimetrically the water uptake as a function of time (time intervals of 30 min) at the temperatures of 5^o, 10^o and 37^oC. Measurements were taken in triplicate and standard deviations were calculated.

1

Drug loading and "in vitro" release

The lyophilized hydrogels were immersed in a 10 μg/mL solution of gentamicin for 5 days at 5^oC and lyophilized again. The amount of drug loaded was evaluated gravimetrically Hydrogel discs with the loaded gentamicin were immersed in a 50 mL of water at 37^oC and, at fixed times, 500 μL aliquots were taken and immediately replaced by pure water. The concentration of the drug released was assayed by UV at 335 nm after reaction with o-phathalaldehyde as reported in the literature.[10]

Results and Discussion

The comonomer feed compositions for the systems DMAA/MOEA and Am/MOEA are reported in the Table I.

The swelling rates of hydrogels as a function of both temperature and composition of hydrophilic monomers DMAA and Am indicate that the swelling ratio increases with the increasing of the amount of the monomers.

Data correlation for characterising the kinetics of solvent sorption by hydrogels was performed by assuming that the water uptake can be described by a one-dimensional Fickian diffusion process, this is, radial diffusion can be neglected compared to axial one. This condition is satisfied if $d << H$, where d and H are the sample diameter and thickness, respectively.

Table I. Feed composition of mixtures DMAA/MOEA and Am/MOEA in the ratio (w/w) in 50% DMF solution with 1% TMPTMA.

Sample	DMAA	Am	MOEA
1	25	-	75
2	20	-	80
3	15	-	85
4	10	-	90
5	-	25	75
6	-	20	80
7	-	15	85
8	-	10	90

It can be shown that the non-dimensional instantaneous water uptake M^* is a function of the Fourier number Fo and can be obtained as:[11]

$$M^* = \frac{4}{\sqrt{\pi}}\sqrt{Fo}\left\{1+2\sqrt{\pi}\left[\sum_{n=1}^{\infty}(-1)^n \text{ ierfc}\left(\frac{n}{2\sqrt{Fo}}\right)\right]\right\} \quad (1)$$

where:

$$M^* = \frac{M}{M_\infty} \quad (2)$$

$$Fo = \frac{Dt}{H^2} \quad (3)$$

In Eq. (2) M is the instantaneous water uptake and M_∞ is the asymptotic water uptake (attained at infinite time). In Eq. (3), t is the time and D is the diffusion coefficient. For $M^* \leq 0.8$, Eq. (1) can be reasonably approximated by:

$$M^* \cong \frac{4}{\sqrt{\pi}}\sqrt{Fo} \quad (4)$$

Based on Eq. (4), the data can be fitted with a linear correlation of the form:

$$M^* = B\sqrt{t} \quad (5)$$

where the slope B results:

$$B = \frac{4}{H}\sqrt{\frac{D}{\pi}} \quad (6)$$

The experimental data was correlated by using Eq. (5). For each experiment a mean value $\overline{\left(\frac{D}{H^2}\right)}$ was calculated from Eq. (6). Since the film thickness did not remain constant in the experiments, the mean value $\overline{H}$ was taken for the selected data. A mean diffusion coefficient can be calculated from these values. Several repetitions of the experiments were performed in order to improve data reliability.

MOEA is a hydrophobic monomer and, hence, its homopolymer is completely insoluble in water. However, if hydrophilic monomers, such as DMAA or Am, are added to the MOEA polymerization, the swelling behaviour and the rate of water uptake increase. These informations are important for the identification of polymers that could expand slowly to allow a prolonged solute release.

As it can be seen from the data of the Tab. II for DMAA/MOEA and Am/MOEA hydrogels, the mean diffusion coefficient increases with temperature.

It can be observed a significant variation in the diffusion coefficient for different temperatures, while the range of variation as a function of their chemical composition is smaller.

Table II. Diffusion coefficients for MOEA/DMAA or Am copolymers.

		***D* (10^{-7} *cm*^{2}/*s*)**		
	Composition	**5 ^oC**	**10 ^oC**	**37 ^oC**
DMAA/MOEA	25/75	2.2 ± 0.4	2.2 ± 0.4	6.0 ± 0.6
	20/80	6.0 ± 0.6	2.5 ± 0.6	6.3 ± 0.5
	15/85	2.3 ± 0.3	1.9 ± 0.2	5.5 ± 0.4
	10/90	1.3 ± 0.2	0.9 ± 0.1	4.7 ± 0.4
Am/MOEA	15/85	1.7 ± 0.2	1.3 ± 0.3	4.8 ± 0.4
	10/90	1.1 ± 0.1	1.0 ± 0.2	4.0 ± 0.3

Changes in the diffusion coefficient for temperatures below Lower Critical Solution Temperature LCST (corresponding to the data at 5^o and 10^oC) for the different hydrogels (Fig. 1) are not significative, within the experimental errors.

The fractional drug release profile of gentamicin in DMAA/MOEA copolymers hydrogel with ratio 20/80 (w/w) at 37^oC are shown in Fig.2. The result indicate that the release occurs practically in the first 24 hours followed by a slow release. In order to clarify

the release mechanism the release drug fraction (M_t/M_∞) was plotted as function of the square root of time, according to the mathematical model proposed for Fick diffusional mechanism.[12]

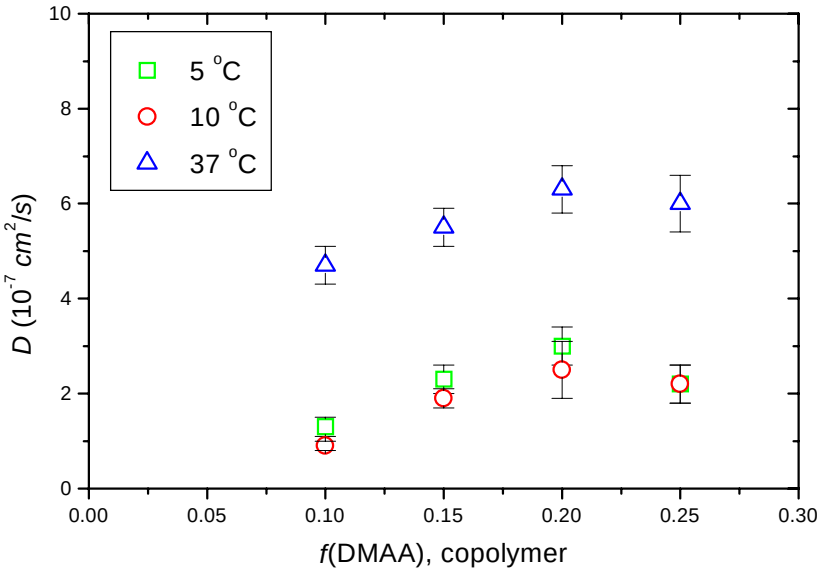

Fig. 1. Values of the diffusion coefficient, *D*, versus copolymer chemical composition, weight fraction of DMAA, at various temperatures.

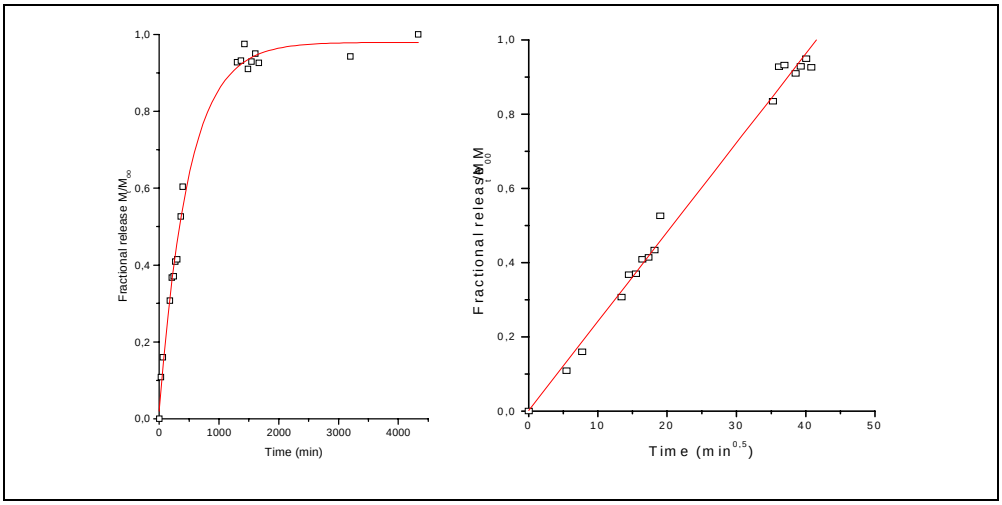

Figure 2. Release profile *in vitro* of gentamicin at 37°C in water from poly (MOEA-*co*-DMAA) in the ratio 80/20 (w/w).

The experimental results shown in Fig.2 indicate that, for this sample, the solute transport in the beginning of release is controlled by Fickian diffusion, the fractional release of gentamicin is initially linear when plotted against the square root of time.

These thermoresponsive hydrogels based on MOEA offer interesting possibilities in the field of drug delivery systems and absorption-extraction processes.

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