Cephazoline Sodium Release from Poly(*N*-isopropyl acrylamide-*co*-*N*,*N*-dimethylacrylamide) Hydrogels

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ABSTRACT: Hydrogels are hydrophilic polymers that swell to an equilibrium volume in the presence of water, preserving their shape. The dynamic swelling behavior of poly(*N*-isopropylacrylamide-*co*-*N*,*N*-dimethylacrylamide) [poly(NIPA-*co*-DMA)] copolymers at 37°C was investigated. It was observed that the swelling degree in the copolymers decreases with the *N*-isopropylacrylamide content. In addition, the liberation mechanism was found to be Fickian. Diffusion coefficients according to Fick's law as a function of the *N*-isopropylacrylamide concentration and results of the release process are reported. The kinetics of cephazoline sodium release from poly(NIPA-*co*-DMA) hydrogels with different compositions was studied. © 2004 Wiley Periodicals, Inc. J Appl Polym Sci 91: 3433–3437, 2004

Key words: hydrogels; drug delivery systems; hydrophilic polymers

INTRODUCTION

The field of biomaterials is advancing rapidly nowadays. Hydrogels seem to be one of the most promising types of materials for biomedical applications. They usually show good biocompatibility in contact with blood, body fluids, and tissues. The ability of hydrogels to swell as well as their ability to release trapped particles into surrounding medium is often used as a drug-delivery system.[1–4] Hydrogels are most often defined as a two-component system, where one of the components is a hydrophilic polymer insoluble in water because of its structure crosslinking and the second one is water. These systems may swell in water up to a certain equilibrium state and retain their original shape. The hydrophilicity of these materials is due to the presence of water-compatible groups such as —OH, —COOH, —$CONH_2$, and —SO_3H, and those are related to the existence of capillary areas and differences in osmotic pressure.

The aim of this work was to use temperature-sensitive hydrogels based on *N*-substituted acrylamide derivates for drug release. In this case, *N*-isopropylacrylamide and *N*,*N*-dimethylacrylamide were used. The drug employed in this study was cephazoline. The release kinetics of cephazoline from dry as well as swollen poly(*N*-isopropylacrylamide-*co*-*N*,*N*-dimethylacrylamide) crosslinked hydrogels in aqueous solutions was studied. The swelling process was also analyzed.

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EXPERIMENTAL

Materials

N-Isopropylacrylamide (NIPA; Fluka, Basel, Switzerland; HPLC grade) and *N*,*N*-dimethylacrylamide (DMA; Fluka, HPLC grade) were employed as monomers, and potassium persulfate ($K_2S_2O_8$; Merck, HPLC grade), as an initiator. *N*,*N*-Methylenebisacrylamide (NMBA; Fluka, HPLC grade). NMBA was employed as a crosslinking agent. Cephazoline was supplied by Pharmaceutic Laboratories Reynaldo Gutiérrez (Havana, Cuba). Distilled water with a 10 μS conductivity was employed in the swelling and release studies.

Polymerization

Hydrogels was synthesized by radical polymerization. The feed mixtures are given in Table I. The initiator was $K_2S_2O_8$ (1.0 wt %) and the crosslinking agent was NMBA (0.25 wt % with respect to the total weight of the monomers) (see Fig. 1). Water was used as a sol-

TABLE I
Composition of Reaction Mixture

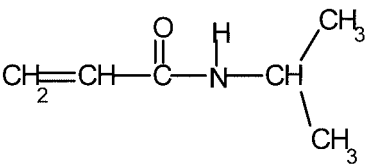
Samples	NIPA (wt %)	DMA (wt %)
M_1	100	0
M_2	70	30
M_3	50	50
M_4	30	70
M_5	0	100

vent. The solution was degassed in a nitrogen atmosphere in glass test tubes. Polymerization was carried out at 60°C for 8 h.

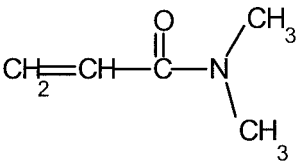
The resultant crosslinked polymer rods were immersed in water for 2 weeks to remove any possible residual monomers and uncrosslinked polymer and then dried again to determine the percentage gelation:

$$\text{Gelation}(\%) = \frac{m_g}{m_0} \times 100$$

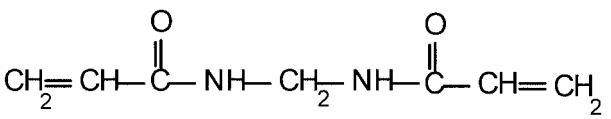
where m_0 is the initial weight of the dry gel (xerogel), and m_g, the weight of dry gel after water extraction. Discs were obtained from the hydrogel rods. Then,



N-isopropylacrylamide



N,N′-dimethylacrylamide



N,N′-methylenebisacrylamide

Figure 1 Chemical structures of the monomer units and the crosslinking agent.

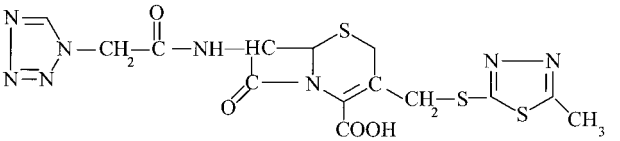


Figure 2 Chemical structure of cephazoline sodium.

they were dried at 40°C for several days to a constant weight. The thickness of the dry disc was 1.0 ± 0.05 mm.

Swelling

Dynamic swelling experiments were performed by placing the dry disc (xerogel) in a distilled water bath at 37.0 ± 0.1°C and measuring their weight increase as a time function. The swelling degree W is expressed as the water weight in hydrogels at any instant during swelling[5]:

$$W = \frac{(\text{weight of swollen disc} - \text{weight of dry disc})}{\text{weight of dry disc}} \quad (1)$$

Loading of hydrogels

Polymer discs were loaded with cephazoline (see Fig. 1) by soaking them in an aqueous solution of the drug (2.26×10^{-3} g/L). The swollen drug-loaded gels were then either used directly in the release experiments or dried at ambient temperature for several days at 40°C to a constant weight.

Drug release

Release experiments were performed by placing the polymeric disk containing the drug on a holder into distilled water at 37.0 ± 0.1°C. The volume of the water in the Pyrex glass tubes was 10 mL. To follow the cephazoline sodium (Fig. 2) release, the water present in the Pyrex tubes glass was extracted several times. Later, 10 mL of distilled water was added into the same Pyrex glass tubes to follow the release study again. The concentration of cephazoline was measured by UV spectroscopy (Secoman, S.1000 Model). The detection wavelength was 261 nm. The amount of drug released at any selected time was calculated from the cephazoline calibration curve.

RESULTS AND DISCUSSION

Equilibrium swelling degree

A fundamental relationship exists between the swelling of a polymer in a solvent and the nature of both of them. Swelling studies were performed gravimetrically following eq. (1). The swelling curves of poly-

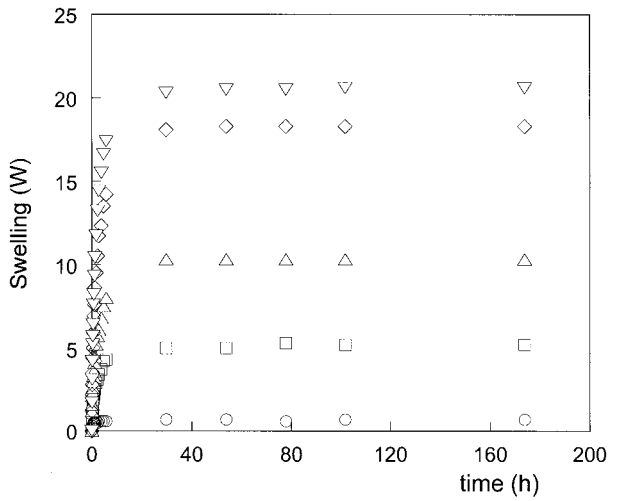


Figure 3 Swelling isotherms of the poly(NIPA-*co*-DMA) hydrogels with different compositions at 37°C: (○) M1; (□) M2; (△) M3; (◇) M4; (▽) M5.

(NIPA-*co*-DMA) hydrogels with different compositions are shown in Figure 3.

As Figure 3 shows, swelling increases with time, but, later, constant swelling values are observed. These swelling values can be considered as an equilibrium swelling degree, and they are given in Table II.

As shown in Table II, equilibrium-swelling values increase as the NIPA content decreases. This behavior can be due to the great steric impediment of the isopropyl group present in this monomer structure. The hydrophilic capacity of a hydrogel increases when the content of DMA in poly(NIPA-*co*-DMA) increases because CH_3 groups of DMA are smaller than is the isopropyl group of NIPA.

The penetration rate of water for each polymer was determined by the method described by Peppas et al.[6,7] using eq. (2):

$$\nu = \frac{1}{2\rho A}\left(\frac{dW_g}{dt}\right) \tag{2}$$

where ν is the penetration rate; dW_g/dt, the slope of the plot of weight increase versus time; ρ, the density of water at 37°C; and A, the area of one of the faces of the disc.

TABLE II
Experimental Data of Equilibrium Swelling and Penetration Rates for Poly(NIPA-*co*-DMA) Hydrogels at 37°C

Samples	NIPA content	Equilibrium swelling	Penetration rate ($\times 10^{-3}$ cm/s)
M_1	100	0.7	0.59
M_2	70	5.3	8.66
M_3	50	10.3	14.17
M_4	30	18.3	23.03
M_5	0	20.6	28.22

TABLE III
***n* and *k* Values for the Water Diffusion into Poly(NIPA-*co*-DMA) Hydrogels**

Samples	NIPA content	n	$k \times 10^2$ (h^{-n})
M_1	100	0.49 ± 0.02	23.10 ± 0.03
M_2	70	0.48 ± 0.01	28.80 ± 0.02
M_3	50	0.49 ± 0.01	30.20 ± 0.03
M_4	30	0.50 ± 0.02	31.70 ± 0.03
M_5	0	0.49 ± 0.02	46.80 ± 0.03

The values obtained are reported in Table II. These results agree with the swelling equilibrium ones: The more isopropyl groups there are, the more difficult the water penetration is, because of the steric impediment created in the hydrogel structure.

Diffusion

When a dry hydrogel is brought into contact with water, water diffuses into the hydrogel and the hydrogel swells. Diffusion involves migration of water into preexisting or dynamically formed spaces among hydrogel chains. Swelling of the hydrogel involves a larger-scale segmental motion, resulting, ultimately, in an increase of the separation distance among hydrogel chains.[8]

Analysis of the mechanisms of water diffusion in swellable polymeric systems has received considerable attention in recent years, because of the important applications of swellable polymers in biomedical, pharmaceutical, environmental, and agricultural engineering fields.[9] To determine the nature of water diffusion into hydrogels, eq. (3) was used:

$$\frac{M_t}{M_\infty} = kt^n \tag{3}$$

where M_t and M_∞ denote the amount of solvent diffused into the hydrogel at time t and infinite time (at equilibrium), respectively; k is a constant related to the structure of the network; and the exponent n is a characteristic coefficient of transport. For slab shapes, $n \cong 0.50$ corresponds to Fickian diffusion, whereas $0.50 < n < 1.00$ indicates that diffusion is of the non-Fickian type. This equation is applied to the initial stages of swelling and plots of $\ln(M_t/M_\infty)$ versus $\ln t$ yield straight lines to almost a 60% increase in the mass of the hydrogel.[10]

The values of the diffusion constant calculated from the slopes of the lines and the k constant values, calculated from the intercept, for poly(NIPA-*co*-DMA) hydrogels, are listed in Table III. As shown, the values of the diffusion exponent range between 0.48 and 0.50,

TABLE IV
Diffusion Coefficient Values and Statistical Treatment of Poly(NIPA-*co*-DMA) Hydrogels at 37°C

Samples	NIPA content	$D \times 10^7$ cm^2/s	Experimental correlation coefficient
M_1	100	2.30	0.99882
M_2	70	4.23	0.99025
M_3	50	5.06	0.99792
M_4	30	5.16	0.98247
M_5	0	15.90	0.99489
Critic correlation coefficient (r)		0.652	
Freedom degrees (L)		16	
Trust interval (α)		0.999	

indicating that the diffusion of water into poly(NIPA-*co*-DMA) hydrogels fits a Fickian behavior.

Following eq. (3), when k is $4(D/\pi l^2)^{1/2}$ and $n = 0.50$, the relationship between M_t/M_∞ and $t^{1/2}$ yields straight lines with an excellent correlation coefficient (see Table IV). The diffusion coefficient, D_i, was calculated from the slopes of the lines.

For long times, Schott[11] suggested a theoretical model for the diffusion-controlled swelling. The Fick's law of diffusion related to the one-dimensional swelling of films considers that the diffusion coefficient of the penetrating agent (solvent or solution) and film thickness remain constant during the entire swelling process.[12–14] For extensive swelling, the film thickness l obviously does not remain constant. However, it has been demonstrated that, for a second-order swelling kinetic, the inverse of the average rate of swelling (t/W) is related to the time of treatment by the linear eq. (4):

$$\frac{t}{W} = A + Bt \tag{4}$$

where W is the swelling of the hydrogel at time t, and A and B are two coefficients whose physical sense can be interpreted as follows: At a long time of treatment, $Bt \gg A$ according to eq. (4) and $B = 1/W$ is the reciprocal of the equilibrium swelling. On the other hand, at very short times of treatment, $A \gg Bt$, eq. (4) is

$$\lim_{t \to 0}\left(\frac{dW}{dt}\right) = \frac{1}{A} \tag{5}$$

Therefore, the intercept $1/A$ represents the initial swelling rate. The plots obtained by the application of our swelling data to eq. (4) are shown in Figure 4.

In all cases (see Table V), straight lines with an excellent correlation coefficient are obtained. This fact demonstrates that the swelling behavior of these systems follows a second-order diffusion kinetic (critic correlation coefficient < experimental correlation coefficient values).

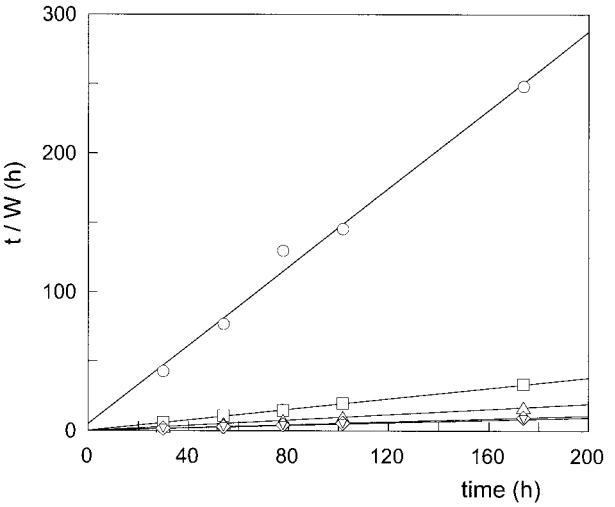


Figure 4 Variation of the inverse rate of swelling versus the swelling time for hydrogels with different compositions: (○) M1; (□) M2; (△) M3; (◇) M4; (▽) M5.

Drug release

The kinetics of cephazoline release from the glassy poly(NIPA-*co*-DMA) hydrogels with different compositions are presented in Figure 5. The cephazoline release depends on the NIPA content: The higher the content of NIPA the slower is the release rate obtained. The cephazoline-release percentages are shown in Table VI.

The solute release data may be analyzed with eq. (3), where, in this case, (M_t/M_∞) is the solute fractional release; t, the release time; k, a kinetic constant characteristic of the drug/polymer system; and n, a characteristic exponent of the drug-release mechanism. That equation describes the release kinetics of drugs

TABLE V
Statistical Treatment of Swelling Data [Using Eq. (5)] for Hydrogels with Different NIPA Contents

Samples	NIPA content		Experimental correlation coefficient
M_1	100		0.99871
M_2	70		0.99970
M_3	50		0.99991
M_4	30		1.00000
M_5	0		0.99999
Critic correlation coefficient (r)		0.898	
Freedom degrees (L)		3	
Trust interval (α)		0.999	

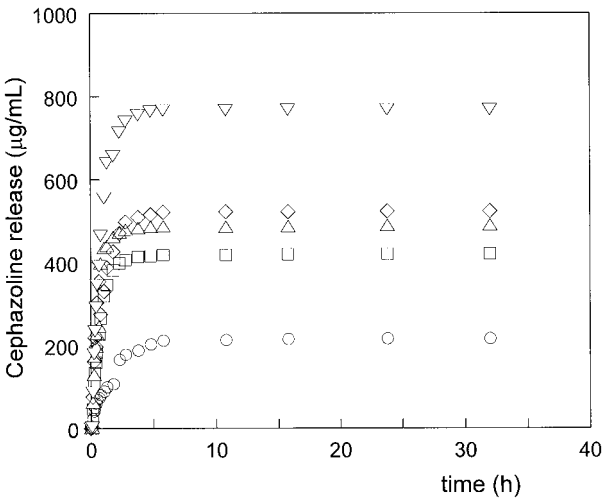


Figure 5 Cephazoline-release curve from dry poly(NIPA-*co*-DMA) hydrogels with different compositions: (○) M1; (□) M2; (△) M3; (◇) M4; (▽) M5.

which diffuse by a Fickian mechanism. For this case, $n = 0.50$ and k is given by eq. (6):

$$k = 4\left(\frac{D_i}{\pi l^2}\right)^{1/2} \tag{6}$$

where D_i is the diffusion coefficient for drug delivery and l is the thickness of the disc containing the drug.

The diffusion coefficient of cephazoline in equilibrium swelling was measured by drug-release experiments from the hydrogels in a solution of cephazoline. The diffusion coefficient was calculated from the slope of the release curve according to following equation:

TABLE VI
Cephazoline-release Percentage from Poly(NIPA-*co*-DMA) Hydrogels at 37°C

Samples	Cephazoline-release percentage
M_1	22.0 ± 0.1
M_2	42.1 ± 0.1
M_3	49.0 ± 0.1
M_4	52.8 ± 0.1
M_5	76.7 ± 0.1

TABLE VII
Values of *n*, *k*, and diffusion coefficient, *D*, of the cephazoline-release kinetics from Poly(NIPA-*co*-DMA) Hydrogels

Samples	NIPA content	n	$k \times 10^2$ (h^{-n})	D (cm^2/s) $\times 10^7$
M_1	100	0.49	63.79 ± 0.02	43.35 ± 0.02
M_2	70	0.48	65.74 ± 0.02	49.20 ± 0.02
M_3	50	0.51	71.40 ± 0.01	52.90 ± 0.05
M_4	30	0.50	73.26 ± 0.01	56.82 ± 0.04
M_5	0	0.50	87.84 ± 0.02	73.20 ± 0.05

$$D_i = \frac{\pi l^2}{16}\left[\frac{d(M_t M_\infty)}{dt^{1/2}}\right]^2$$

The values for k, n, and D of the cephazoline-charged hydrogels are listed in Table VII. The release index obtained for the release kinetics from the swollen hydrogels (see Table VII) suggests that this is a diffusion-controlled process.

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