Design of a Drug Delivery System Based on Poly(acrylamide-*co*-acrylic acid)/Chitosan Nanostructured Hydrogels

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ABSTRACT: To obtain biodegradable materials for biomedical applications, new biopolymeric hydrogels based on blends of polyacrylamide nanoparticles and chitosan have been prepared. In this work, we have studied the behavior of the diffusion of ascorbic acid (V-C) from poly(acrylamide-*co*-acrylic acid)/chitosan nanostructured hydrogels. The process involves the synthesis of nanoparticles of polyacrylamide by inverse microemulsion polymerization and their complexation with chitosan dissolved in an acrylic acid aqueous solution. We have studied the effect of the concentration of the polyacrylamide nanoparticles, which are crosslinked with *N,N′*-methylenebisacrylamide, in the delivery of V-C. The results indicate that the drug delivery operates by a non-Fickian mechanism. Also, we have obtained the diffusion coefficient for V-C in gels for different nanoparticle concentrations, using a modified form of Fick's second law that takes into account dimensional changes in the hydrogels during drug release. © 2007 Wiley Periodicals, Inc. J Appl Polym Sci 106: 3939–3944, 2007

Key words: chitosan; drug delivery systems; hydrogels; nanoparticles; nanotechnology

INTRODUCTION

The shape stability and water insolubility of hydrogels are the results of the presence of three-dimensional linkages. The swelling in a hydrogel is the result of cohesive and dispersive forces that affect the polymeric chains, and the result of these balances is the criterion that determines the relationship between the mechanical behavior and the stability of the polymeric network.[1–3] Generally, the cohesive forces not only are due to covalent links (chemical gels) but also can be related to electrostatic forces or dipole–dipole bonds (physical gels); however, it is important to consider that the swelling behavior of any hydrogel also depends on the nature of the polymer, the polymer–solvent compatibility, and the degree of crosslinking. For example, the polymer elasticity combined with polymer–solvent mixing contributes to the overall swelling process.[4,5] The drug absorption in polymer networks and the resultant delivery of the active components from the charged matrix have been widely studied for the case of nanoparticles involved in the delivery process,[6–9] and for the case of the use of biodegradable polymers.[6,8,10] There are many interesting applications of drug delivery systems based on nanomaterials and biodegradable systems. These systems permit better control of the time of residence and concentration of the drug in the human body; they also allow the delivery of the drug to specific places or cells in the body and go through certain tissue barriers such as the intestine. For example, Langer and Peppas[8] identified at least five kinds of hydrogel systems for controlled drug delivery: swelling-controlled release systems, environmentally responsive hydrogels, neutral hydrogels [acrylamide (AM)-based hydrogels], bioadhesive hydrogels, glucose-sensitive hydrogels, dendrimers, and star polymers. Each of them shows specific advantages and uses.

Recently, chitosan has been used widely in drug delivery applications. Chitosan is a polysaccharide; its sugar backbone consists of β-1,4-linked glucosamine with a high degree of N-acetylation. Because chitosan exhibits favorable biological properties such as nontoxicity, biocompatibility, and biodegradability, it has attracted great attention in the pharmaceutical and biomedical fields.[11] The cationic character and presence of reactive functional groups in its molecule provide interesting possibilities for its use in controlled-release systems, and many of these applications have been reported in the last few years.[11–18] Networks formed by the ionic crosslinking of chitosan are mainly used for delivery

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purposes; the properties of pH-dependent drug delivery systems can be controlled by the experimental conditions during preparation, and they generally exhibit pH-sensitive swelling and drug release by diffusion through their porous structure.[16] In the case of chitosan networks formed by polyelectrolyte complexation, the systems also exhibit pH-sensitive and ion-sensitive swelling, and they can also be used for controlled drug delivery. However, these systems are more complex to prepare in comparison with chemical hydrogels. Physical chitosan-based systems show interesting properties, such as bacteriostatic activity in wound healing or biocompatibility with living systems.[17]

In controlled drug delivery, drug release occurs by one of three main mechanisms: diffusion, chemical reaction, and solvent activation.[8] The first of these mechanisms is the most widely used in the pharmaceutical industry; there are two main types of drug distribution mechanics: a reservoir in which the drug is surrounded by a polymer barrier and a matrix in which the drug is generally uniformly distributed through the polymer. In either case, diffusion through the polymer is the rate-limiting step. When a polymeric matrix is put in contact with a drug's concentrated solution, this solution pierces the structure and forms a gel phase in the wet section. The gel phase formation is accompanied by a reduction of the mechanical resistance of the material due in part to an increase in the permeability in the wet region;[19] these phenomena can be useful in the delivery of bioactive materials (drugs, insecticides, fertilizers, etc.).

A drug delivery system is a dosage mechanism containing an element that exhibits temporal and/or spatial control over the drug release. Most of the oral drug delivery systems are matrix-based systems; swellable matrices are prepared by the compression of a powdered mixture of a hydrophilic polymer and a drug.[20] In general, the drug delivery process exhibits anomalous behavior different from Fickian diffusion, in which the molecular relaxation is either much faster or very slow and is not observable. In the case of non-Fickian diffusion, the process depends on the experimental temperature related to the glass-transition temperature of the hydrogel and the thermodynamic compatibility between the solvent and the hydrogel. If such thermodynamic compatibility is favorable, the glass-transition temperature is lowered below the experimental temperature, and the hydrogel swells to a rubbery state with an important volume expansion;[4,21,22] in this case, the relaxation and diffusion interact, and the transport behavior cannot be described by a Fickian law. Such transport is called non-Fickian diffusion or anomalous transport. Thomas and Windle[21] considered these molecular relaxations to be time-dependent mechanical deformation in the polymer in response to the swelling stress.

Sánchez-Díaz et al.[23] reported the diffusion coefficient for hydrogel systems containing polyacrylamide nanoparticles, but in these systems, the nanoparticles were dispersed only in an aqueous solution of AM that eventually formed a polyacrylamide hydrogel. The gels synthesized for this work contained nanoparticles that were dispersed in a mixture formed by AM and chitosan solutions. The chitosan chains were trapped by the polyacrylamide hydrogel, forming a semi-interpenetrating network. Also, it is important to consider that the chitosan was dissolved in an aqueous acrylic acid solution. Acrylic acid exhibits a structural similarity to AM; it has a carboxylic group that makes it highly hydrophilic.[24] Then, when it forms a copolymer with AM, it is expected to have a more open matrix that permits higher swelling and release rates.

The dimensional changes in the polymeric matrix due to the drug diffusion show a nonisotropic swelling behavior in which the thickness of the sample increases faster than the diffusion area.[24–26] Here we report the determination of the diffusion coefficients for drug delivery from nanostructured polyacrylamide/chitosan hydrogels; these values have been calculated, with the dimensional changes of the hydrogel during drug release being taken into account. Ascorbic acid (V-C) has been selected as a convenient model drug because its solubility in water allows a high loading of the drug into the polymer matrix from concentrated solutions and because its release into water can be followed by UV spectroscopy.

EXPERIMENTAL

Materials

Sodium bis(2-ethylhexyl)sulfosuccinate (AOT; 98% pure) from Fluka (Guadalajara, Mexico) was dried and stored in a desiccator jar before use. Acrylic acid (99% pure) from Scientific Polymer, AM (99% pure) from Aldrich (Guadalajara, Mexico), 2,2′-azobisisobutyronitrile (AIBN) from Dupont (Guadalajara, Mexico), 2,2′-azobis(2-amidinopropane)dihydrochloride (V-50) from Wako Chemicals (Guadalajara, Mexico), V-C (99% pure) from Merck, high-performance liquid chromatography grade toluene (Merck), and chitosan (99% pure; weight-average molecular weight $= 1.08 \times 10^6$ g/mol) from Aldrich were used as received. *N*,*N*′-Methylenebisacrylamide (NMBA; Scientific Polymer) was recrystallized from methanol. Distilled and deionized water was used.

Hydrogel preparation

Nanostructured hydrogels were synthesized by a two-stage polymerization process. First, AM was

polymerized at 50°C for 1 h with AIBN [weight of AIBN (m_{AIBN})/weight of acrylamide (m_{AM}) = 0.01] in an inverse (water-in-oil) microemulsion to generate the nanoparticles. The composition of the parent microemulsion was 68.4 wt % toluene, 17 wt % AOT, and 14.6 wt % of a 50 wt % AM aqueous solution. After the polymerization, the toluene was eliminated in a rotary evaporator, and the surfactant was removed from the particles by repeated washing with toluene. To preserve the identity of the particles during drying and the following redispersion in water, for the second-polymerization stage, NMBA [weight of NMBA (m_{NMBA})/m_{AM} = 0.01] was added to the microemulsion recipe before polymerization. For the second stage, the nanoparticles were dispersed in an aqueous solution of AM, a chitosan solution (1 wt % chitosan dissolved in a 1 wt % acrylic acid aqueous solution), and NMBA [m_{NMBA}/m_{AM} = 0.01; this dispersion was polymerized at 50°C with V-50 [weight of V-50 ($m_{V\text{-}50}$)/m_{AM} = 0.01] for 24 h. The concentration of particles (AM) in the dispersion ranged from 0 to 50 wt % with respect to the monomer (AM).

The size of the nanoparticles was measured with a Malvern (Guadalajara, Mexico) 4700C quasielastic light scattering apparatus. The measured diffusion coefficients were presented in terms of the apparent diameters by means of Stokes' law under the assumption that the viscosity was that of the continuous phase. The particle size in the inverse microemulsion was 53 nm.

The nanostructured hydrogels, obtained in the shape of rods, were cut into disks. The disks were immersed in flasks containing 500 mL of water for several days to remove any possible residual monomer. Then, the hydrogels were removed and dried at room temperature (25°C). To produce materials with similar dimensions, the dried disks were carefully sanded until the diameter varied between 10 and 12 mm and the thickness ranged from 1.5 to 2 mm.

Drug delivery measurements

The previously weighed xerogels were loaded with V-C by immersion in a saturated drug aqueous solution (333 g/L) until equilibrium was reached. The loaded hydrogels were dried at room temperature (25°C) for a week and weighed to obtain the concentration of V-C in the xerogels. The diameter of the xerogel (L_x) and the diameter of the hydrogel at any selected time during the release (L_{Ht}) were measured (within ±0.05 mm) with a micrometer.

The loaded xerogels were immersed in 200 mL of distilled water at 25°C and constantly stirred. With the objective of following the kinetics of the delivery, 5-mL samples were taken at different times to measure the V-C concentration in a UV spectrophotometer (Genesis 10, Thermo, Guadalajara, Mexico); to make the analysis, 1 mL of the sample was diluted to 100 mL with distilled water. These diluted samples were used to measure the absorbance in the UV spectrophotometer with a wavelength of 258 nm. With the absorbance and the calibration curve for V-C, we obtained the released concentration (mg/L). To determine the amount of V-C, we took into consideration the dilutions made and the total volume (for the first measure, the total volume was 200 mL; for the second, it was 195 mL; and so on). The amount of the drug released at any given time (M_t) was calculated from the calibration curve and the absorbance of the sample. The maximum weight available for release (M_∞) was determined by gravimetric measurements. The fractional release (F_t) was then calculated as $F_t = M_t/M_\infty$.

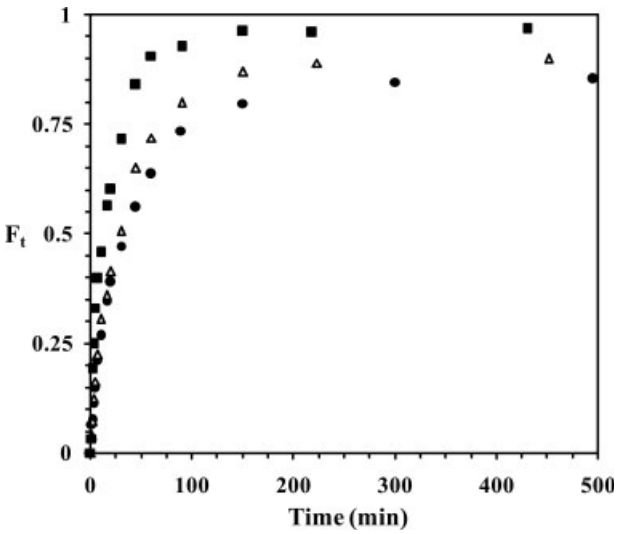

Figure 1 Release profiles of V-C at 25°C from poly(acrylamide-*co*-acrylic acid)/chitosan nanostructured hydrogels in water with different quantities of nanoparticles: (■) 50, (△) 30, and (●) 0 wt %.

RESULTS AND DISCUSSION

The kinetics of the release of V-C from the poly (acrylamide/acrylic acid)/chitosan hydrogels are presented in Figure 1, which shows that the release of V-C depends on the fraction of polyacrylamide nanoparticles added to the polymeric matrix. At a low nanoparticle percentage, the release rate decreases.

The release data were analyzed with eq. (1), in which F_t is defined as M_t/M_∞:

$$\frac{M_t}{M_\infty} = kt^n \tag{1}$$

where t is the release time, k is the kinetic constant of the system, and n is a characteristic exponent for

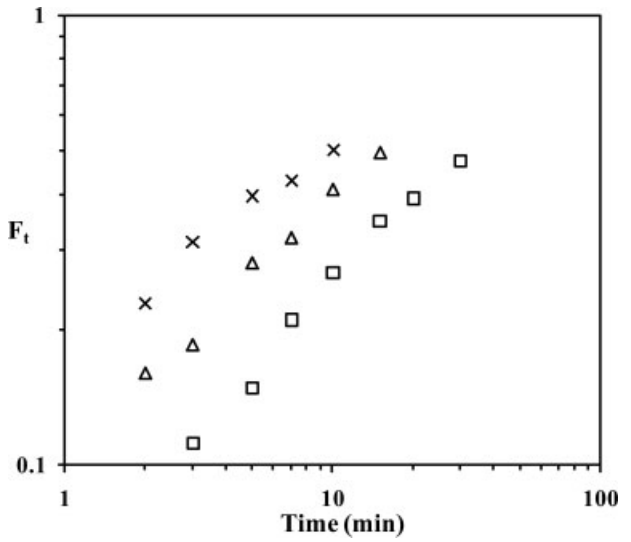

Figure 2 Log–log release profiles for hydrogels with nanoparticle concentrations of (□) 0, (△) 10, and (×) 40 wt %.

the drug release. This equation describes the release kinetics of a drug when it diffuses with Fickian behavior. For these cases, $n = 0.5$, and k is given by

$$k = 4\left(\frac{D_i}{\pi h^2}\right)^{1/2} \quad (2)$$

where D_i is the diffusion coefficient for the drug delivery mechanism and h is the thickness of the loaded disc.

The experimental release data were plotted in accordance with eq. (1) in a log–log scale. Figure 2 presents an example of these plots and corresponds to the hydrogel with 30% nanoparticles. In this figure, we can observe the changes in the slope of the lines that the experimental points (F_t vs time) produce; these changes in the slope suggest that the release rate is not a constant. The system presents two different diffusional behaviors: V-C diffusion from the charged polymer disc to the surrounding medium is the controlling mechanism (slope I), and water diffusion inside the charged hydrogel is more important than the V-C release (slope II). It is important to take into account that eq. (1) describes an approximation and could be inadequate to represent all the diffusional profiles; the equation is used typically for low-release fractions, and there are no uniform criteria, but generally $F_t \leq 0.4$ is accepted.[27]

Exponent n in eq. (1) was determined from slope I in Figure 2. The n values show that the V-C release from the hydrogel follows an anomalous mechanism or non-Fickian diffusion ($n > 0.5$). The diffusion process is partially controlled by the viscoelastic relaxation in the three-dimensional network during the water penetration. The values of n are used with eq. (1) to determine k; the values of n and k for the different weight percentages of nanoparticles are reported in Table I. Also, we can observe that the k values are proportional to the nanoparticle concentration added to the polymeric matrix. A possible explanation is related to the structure of the gels. The polymer matrix becomes more open as the concentration of nanoparticles increases, and this allows a less sinuous and easier exit route for the V-C molecules.[23]

TABLE I
Kinetics of V-C Release from Poly(acrylamide-*co*-acrylic acid)/Chitosan Nanostructured Hydrogels

Polyacrylamide nanoparticle concentration (wt %)	n	k (min^{-n})
0	0.6478	0.0563
10	0.6590	0.0910
20	0.5979	0.1108
30	0.5551	0.1002
40	0.5303	0.1578
50	0.5016	0.1495

The diffusion coefficient of V-C in the gels was measured by drug release experiments with the gels in water. The diffusion from the charged polymeric matrix can be considered a one-dimensional phenomenon when the dimensions of the cylinder thickness are small with respect to the diameter; for these hydrogels, the relationship between the diameter and thickness ranged from 5 to 8.

Equation (2) is inadequate to determine the diffusion coefficients because the dimensions of the hydrogels change considerably as a function of time. Figure 3 shows how the ratio of the hydrogels (L_{Ht}/L_x) changes with time during the release process.

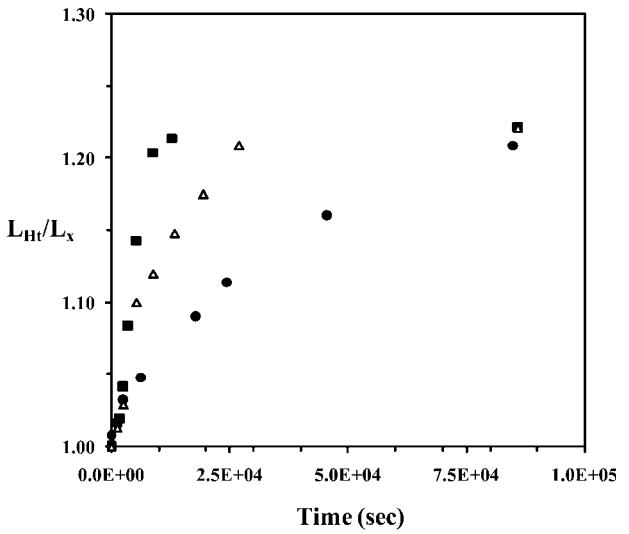

Figure 3 Variation of L_{Ht}/L_x versus the time for hydrogels with different concentrations of nanoparticles: (■) 50, (△) 30, and (●) 0 wt %.

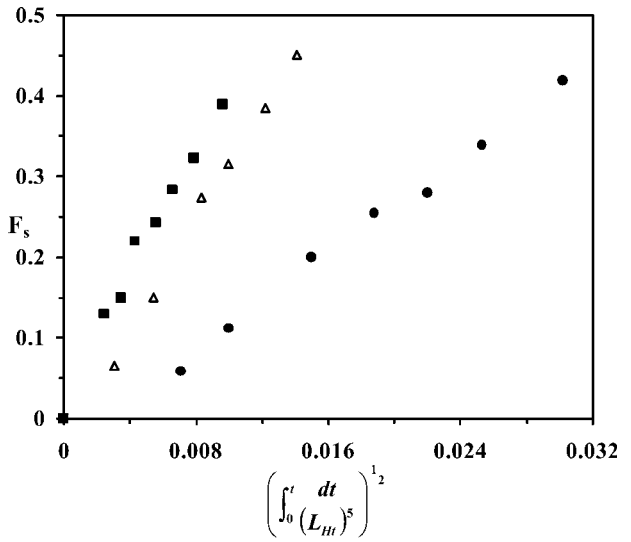

Figure 4 Plot of eq. (3) for hydrogels with different concentrations of polyacrylamide nanoparticles: (■) 50, (△) 30, and (●) 0 wt %.

The observed behavior demonstrates that the V-C release depends on the nanoparticle concentration. A high content of nanoparticles results in increased dimensional changes; these changes occur during the immersion of the hydrogels in the swelling medium: water diffuses from the swelling medium into the gel, and V-C diffuses out of the gel into the surrounding medium.

To consider the influence of the dimensional changes in the disks during the V-C release, we used an equation developed by Blanco et al.[23,24] The equation was elaborated from Fick's second law:

$$F_s = \frac{M_t}{M_\infty} = \frac{4}{\sqrt{\pi}} \frac{L_x}{h} \sqrt{D_i} (L_{H\infty})^{3/2} \left(\int_0^t \frac{dt}{(L_{Ht})^5} \right)^{1/2} \quad (3)$$

where F_s is the drug fraction released (calculated as a function of the dimensional changes) and $L_{H\infty}$ is the hydrogel diameter at equilibrium. A plot of F_s against the square root of the integral in the right-hand side of eq. (3) should yield a linear plot, and from the slope, D_i can be obtained; the integral was solved numerically for the variation of $1/(L_{Ht})^5$ for the different hydrogels. Figure 4 shows a plot of F_s versus the integral of eq. (3) for three of the samples. The plot is linear up to $F_s \approx 0.4$; for higher values of F_s, there is a break, and the slope of the curve increases. This behavior could be due to a decrease in the release rate and a consequent increase in the water penetration rate from the surroundings to the polymeric matrix. For these reasons, the diffusion coefficients were determined from the F_s values below 0.4, and the obtained coefficients are listed in Table II and plotted in Figure 5. The diffusion coefficients are directly proportional to the nanoparticle content, so the release rate of V-C from the nanostructured polyacrylamide hydrogels increases as the particle content rises; as mentioned previously, the polymer matrix becomes more open as the concentration of the particles increases.

TABLE II
Diffusion Coefficients at 25°C

Polyacrylamide nanoparticle concentration (wt %)	Diffusion coefficient (m^2/s)
0	1.63×10^{-10}
10	2.39×10^{-10}
20	3.40×10^{-10}
30	4.05×10^{-10}
40	4.58×10^{-10}
50	5.90×10^{-10}

The diffusion coefficients were assumed to be a function of time.

The diffusion coefficients reported by Sánchez-Diáz et al.[23] are significantly lower than the coefficients reported here. Figure 5 compares the values reported for the hydrogels without chitosan and for the hydrogels that contain chitosan and form an AM/acrylic acid copolymer. The presence of chitosan chains and the copolymer formation in the system allow the formation of a more open polymeric network, and this situation creates larger spaces through which the charged substances can pass. For biomedical applications, with these systems, it is possible to control the drug delivery by means of three mechanisms: varying the nanoparticle concentration, forming a copolymer with AM, and adding chitosan chains.

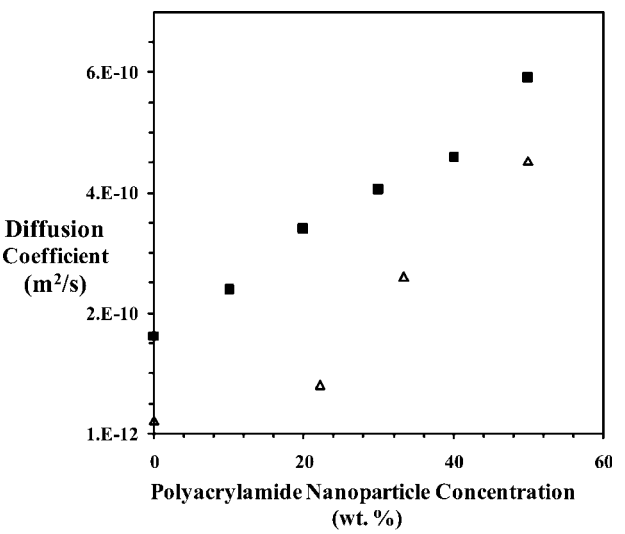

Figure 5 Diffusion coefficients at 25°C as a function of the quantity of polyacrylamide nanoparticles for the hydrogels (■) with and (△) without chitosan.[23]

CONCLUSIONS

The drug kinetic release process in nanostructured hydrogels of poly(acrylamide-*co*-acrylic acid)/chitosan cannot be studied with Fick's equation because of the large dimensional changes occurring during drug release. Exponent n (>0.5) and kinetic constant k from Fick's second law suggest an anomalous delivery process; however, the release is a linear function of the polyacrylamide nanoparticle concentration. The diffusion coefficients obtained with this equation are larger that those obtained with systems without nanoparticles, chitosan chains, and copolymer formation. The data indicate that V-C has more difficulty diffusing through the hydrogel in the absence of these three factors, which help the formation of a more open polymeric network.

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