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Determination of the diffusion coefficients in the ascorbic acid delivery from nanostructured-polyacrilamide hydrogels

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Summary

In this work the diffusional behavior of water and ascorbic acid (V-C) from a new crosslinked nanostructured polyacrylamide (polyAM) hydrogels is analyzed. The process involves the synthesis of slighlty crosslinked nanoparticles of polyAM by inverse microemulsion polymerization. The dried nanoparticles are dispersed in an aqueous solution of AM and crosslinking agent (NMBA) and polymerized with V-50 as initiator at 50°C to produce the nanostructured hydrogels. Polymer disks were loaded with V-C by soaking them in an aqueous solution of the drug in absence of light for one week. The drug released into water was carried out under sink conditions and the kinetics was followed at room temperature by continuous measurement in a UV spectrophotometer. The effects on the swelling kinetics and drug release as a function of the weight ratio of particles to monomer were studied. Results indicate that the nanostructured hydrogels exhibit larger equilibrium swelling and faster release rate. A modified form of Fick´s second law that takes into account dimensional changes of the hydrogels during drug release is used here to evaluate the diffusion coefficient of the ascorbic acid into the gels.

Introduction

Hydrogels are cross-linked hydrophilic polymers that swell in water to an equilibrium volume, but preserving their shapes. The insolubility and shape stability are the result of the presence of a three-dimensional network [1]. Hydrogels are used principally in medicine as biomaterials in therapeutic devices and implants applications, and in controlled-drug delivery systems [2-5]. They can be also used for fixation of herbicides, in chromatography, as enzyme carriers, in food processing, in separations membranes, as water-retainers in sandy soils, etc. [2]. Hydrogels in the dehydrated state (or xerogels) are glassy. In the presence of water, hydrogels absorb a significant amount of water to form elastic gels. Controlled drug delivery occurs when a polymer

is combined with a drug or other active agent in such a way that the active agent is released from the material in a pre-designed manner. The network structure and the thermodynamic nature of the components play a key role in the diffusional behavior and in the associated molecular stability of the incorporated bioactive agents. The purpose behind controlling the drug delivery is to achieve more effective therapies while eliminating the potential for both under- and over-dosing [4].
The goal of many of the original controlled-release systems was to achieve a delivery profile that would yield a high blood level of the drug over a long period of time. With traditional tablets or injections, after each administration, the drug level in the blood rises beyond a maximum desired level, and then it decreases under a minimum effective level until the next administration. The key point with traditional drug administration is that the blood level of the agent should remain between a maximum value, which may be toxic, and a minimum value, below which the drug is no longer effective. In controlled drug delivery systems designed for long-term administration, the drug level in the blood follows a constant profile, between the desired maximum and minimum, for an extended period of time [5].
For many applications, hydrogels with large swelling capacity and favorable mechanical properties in the swollen state are required [3-9]. Usually, an increase in swelling is accompanied with a decrease in mechanical properties [10]; these properties, as well as others such as transparency and oxygen permeability, can be modified by: (i) changing the hydrophilic monomer, (ii) modifying the concentration and type of the crosslinking agent, (iii) varying the method of preparation or (iv) by the copolymerization of hydrophilic and hydrophobic monomers [11]. The synthesis of hydrogels is typically accomplished by free radical polymerization (although step polymerization has also been used) or by modification or functionalization of existing polymers [11]. The synthesis of nanostructured polyacrylamide and poly(N-isopropylacrylamide) hydrogels capable of larger swellings than the conventional hydrogels with similar composition and degree of cross-linking, has been reported elsewhere [12, 13]. Moreover, the nanostructured materials exhibited “better” mechanical properties at similar or even larger degrees of swelling than the conventional ones [12, 13]. Here we report the diffusion coefficient determination in the drug delivery from conventional and nanostructured polyAM hydrogels; the later were synthesized by the two-stage polymerization method described elsewhere [12]. Ascorbic acid (V-C) was selected as a convenient model drug because its solubility in water allows high loading of drug into polymer matrix from concentrated solutions and because its release into water can be followed by UV spectroscopy.

Experimental

Sodium bis (2-ethylhexyl) sulfosuccinate or AOT 98, % pure from Fluka, was dried and stored in a desiccator jar prior to use. Acrylamide (99% pure from Aldrich), AIBN (2,2´-azobisisobutyronitrile) from Dupont, V-50 (2,2´-azobis(2-amidinopropane) dihydrochloride) from Wako Chemicals, ascorbic acid, and toluene (SEALAB) were used as received. N, N´-methylenebisacrylamide or NMBA (Scientific Polymer) was recrystallized from methanol. Doubly distilled and deionized water was drawn from a Millipore purification system.
Nanostructured hydrogels were synthesized by a two-stage polymerization process. First acrylamide (AM) was polymerized at 50˚C with AIBN (m_{AIBN}/m_{AM} = 0.01) in

inverse (w/o) microemulsions to produce 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 rotatory evaporator and the surfactant was removed from the particles by washing them repetitively with toluene. To preserve the identity of the particles during drying and the following re-dispersion in water for the second-polymerization stage, 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 and NMBA (m_{NMBA}/m_{AM} = 0.01); this dispersion was polymerized at 50ºC with V-50 ($m_{V\text{-}50}/m_{AM}$ = 0.01). The concentration of particles plus monomer (AM) in the dispersions was equal to 10 wt.%. The conventional hydrogel was synthesized at 50°C by polymerizing a 10 wt.% AM aqueous solution with V-50 ($m_{V\text{-}50}/m_{AM}$ = 0.01) and NMBA (m_{NMBA}/m_{AM} = 0.01).

The size of the nanoparticles was measured with a Malvern 4700C quasielastic light scattering (QLS) apparatus. The measured diffusion coefficients were presented in terms of the apparent diameters by means of Stokes' law with the assumption that the viscosity is that of the continuous phase. Particle size in the inverse latex was 53 nm. Since the particles in the latex are swollen with water, the dried particles were re-dispersed in toluene and in water, and their sizes were measured. The diameter in toluene was 41 nm, which corresponds to the *dry* particles, and that in water was 112 nm, which corresponds to the fully hydrated particles.

The conventional and nanostructured hydrogels, obtained in the shape of rods, were cut to yield 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. In order to produce materials with similar dimensions, the dried disks were carefully sanded with mild sandpaper until its diameter and thickness were approximately 8 mm and 2 mm, respectively.

The previously weighed xerogels were loaded with V-C by immersing them in a saturated drug aqueous solution until equilibrium was obtained; then the loaded hydrogels were dried at room temperature and weighed to obtain the concentration of V-C in the xerogels. The diameters (L_x) of the xerogels with V-C were measured with a micrometer. Then the xerogel disks were weighed and immersed in pure water and the swelling kinetics was followed by removing the hydrogels from the water at given times, blotting them with a paper towel and weighing them. Also, unloaded hydrogels were immersed in water in order to obtain their swelling behavior. For both tests, the water uptake of the hydrogels (H_P) was calculated as:

$$H_p = \left(\frac{w(t) - w_0}{w_0} \right) \qquad (1)$$

Here w(t) and w_0 represent the weights of the hydrogel at time t and of the xerogel, respectively. The release of V-C from the disks, $M_S(t)$, was measured continuously with an UV spectrophotometer. A linear dependence on concentration was obtained by calibration with a standard C-V solution at 25ºC. The maximum drug weight available for release ($M_{S\infty}$) or the maximum amount of water absorbed ($M_{w\infty}$) was determined in the same way as the corresponding $M_i(t)$. The concentration of drug loaded in the different hydrogels examined here, from which $M_{S\infty}$ can be calculated from the weight of the xerogel was approximately 5.8 g V-C/g xerogel. The fractional

release (F_s) was then calculated as the ratio of species exiting (or entering in the case of water) divided by the maximum amount in the gel:

$$F_i = \frac{M_i(t)}{M_{i\infty}} \tag{2}$$

where i stands for water (w) or drug (s). The diameters of hydrogels (L_{Ht}) at any selected time (t) were determined with a video camera to follow dimensional changes during the release of V-C and water uptake.

Results and discussion

The swelling kinetics (water uptake versus time) and the fraction of water uptake (F_W) of conventional and nanostructured hydrogels made with different percentage of polyAM nanoparticles are depicted in Figure 1. The swelling rate of the nanostructured hydrogels and their maximum swelling are larger than those of the conventional gel (inset). Moreover, the equilibrium swelling increases with increasing nanoparticle content in the hydrogels. These results agree with those reported in the literature for polyAM and polyNIPA nanostructured hydrogels [12-14]. As explained elsewhere [12], the crosslinked nanoparticles, which are trapped into the polymer matrix by the chains formed in the second stage, act as reinforcement to improve the mechanical properties, whereas the loose matrix (since smaller amounts of acrylamide were used in the second stage) allows larger swellings. The value of fractional water uptake as a function of time, on the other hand, is practically independent of the nanoparticles content in the hydrogel.

Figure 2 shows the drug fractional release from the nanostructured and conventional hydrogels as a function of time. Here, in contrast to the behavior observed in water (Fig. 1), F_S depends on the nanoparticle content in the hydrogel. Clearly, the fraction of drug delivered from the nanostructured hydrogels is higher than that from the conventional hydrogel.

The diffusion from a gel phase can be considered one-dimensional when the disk thickness is much smaller than its diameter. This assumption was made for the diffusion of chloramphenicol from poly(2-hydroxyethyl methacrylate) disks, where the drug release was linear *versus* $t^{1/2}$ [15]. This 1-D assumption was also made here in the determination of diffusion coefficients for release of V-C. Two types of diffusion process were studied here: (1) the diffusion of water into the xerogel in the absence of V-C and (2) the diffusion of V-C from the charged xerogel into the swelling medium. The fractional uptake of water (F_W) and the fractional releases of drug (F_S) are the quantities related to the diffusion processes mentioned above. For a diffusion-controlled process in a thin disk with constant dimensions, the following equation can be derived from Fick's law of diffusion [17]:

$$F_i = 4\left(\frac{D_i t}{\pi h^2}\right)^{1/2} \tag{3}$$

Here D_i is apparent diffusion coefficient of V-C or water, and h is the original thickness of the disk. However, equation (3) is inadequate in our case because the

dimensions of the hydrogels studied here change appreciably with time. Figure 3 shows how the ratio L_{Ht}/L_x of the hydrogels studied here change with time during the swelling-and-drug- release process. L_{Ht} is the hydrogel diameter at any selected time and L_x is the xerogel diameter. Clearly, the dimensional changes increase with the nanoparticles content and represents the relative magnitude of the dimensional changes occurring on immersing the xerogels in the swelling medium: water diffuses from the swelling medium into the gel and V-C diffuses out of the gel to the surrounding medium.

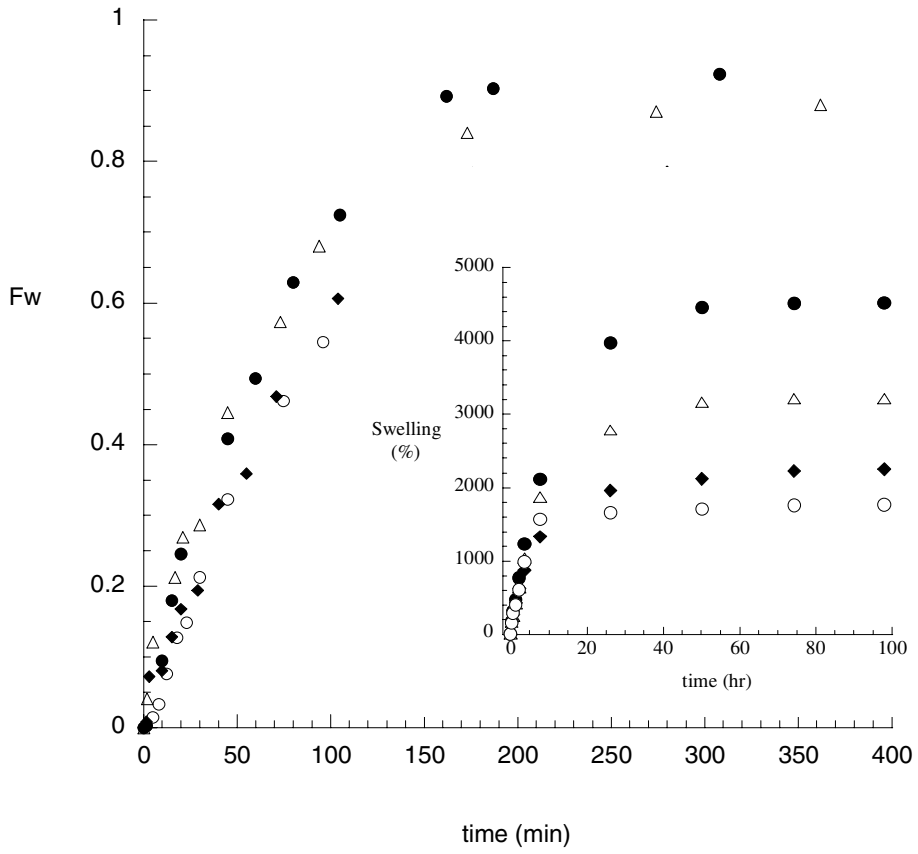

Figure 1. Plot of F_w and swelling (%) as function of time for hydrogels with different quantity of nanoparticles (● AM, △ 22.2 %, ○ 33.3%, ▲50% of nanoparticles)

To take into account dimensional variations, the starting point is the 1-D version of Fick´s second law:

$$\frac{dC}{dt} = D\frac{d^2C}{dx^2} \qquad (4)$$

where C is the solute concentration at time t and position x. A widely used approximation is that at short times, the amount released varies proportional to $t^{1/2}$. The square-root-of-time law is an exact solution to the diffusion equation in a semi-infinite medium [17, 18] and applies to an infinite medium as long as the initial concentration remains unchanged at the centerline. Application of equation (4) to a disk of thickness h (and L >> h) and a constant diffusion coefficient yields equation (3).

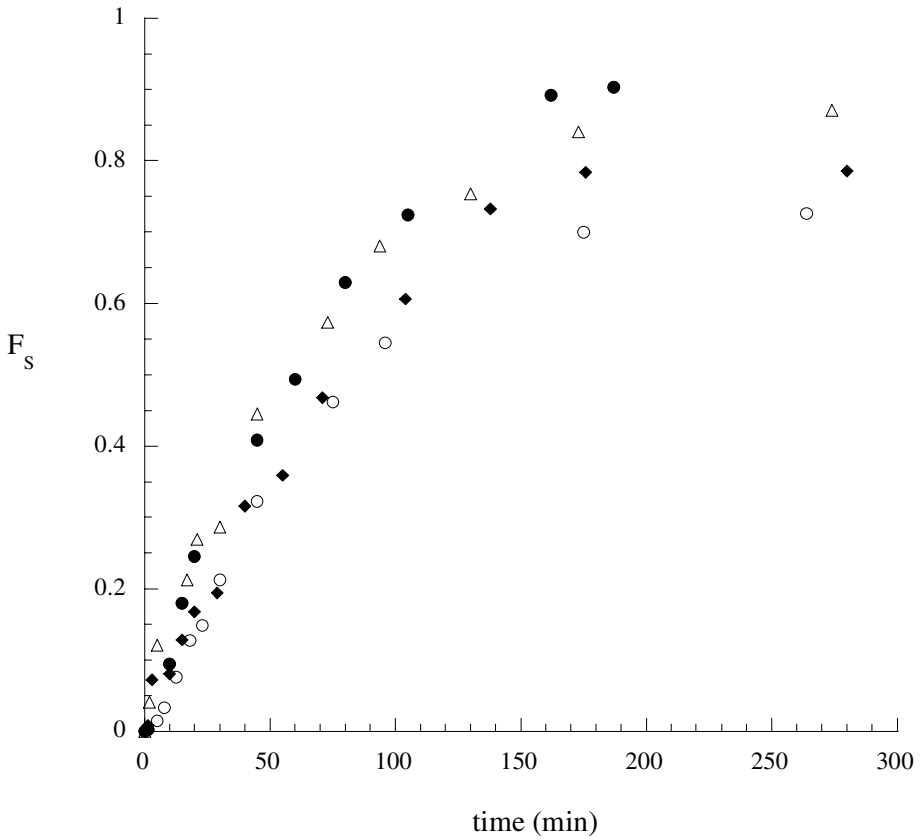

Figure 2. Plot of F_s for the ascorbic acid delivered as time function for the nanostructured hydrogels. (○ 0%, ◆ 22%, △ 33%, ● 50% of nanoparticles)

However, if D is a function of time, a procedure derived by Blanco et al. [16] is used here. First, a dimensionless time-variable function, Γ, is defined as [16]:

$$\Gamma = \int_0^t \frac{D(t)}{h_t^2} dt \tag{5}$$

where h_t is the thickness at time t. Taking the derivative of equation (5) renders:

$$\frac{d\Gamma}{dt} = \frac{D(t)}{h_t^2} \tag{6}$$

Combining equations (4) and (6) gives:

$$\frac{dC}{d\Gamma} = h_t^2 \frac{d^2C}{dx^2} \tag{7}$$

The solution of this equation at short time is:

$$F_s = \frac{M_t}{M_\infty} = 4\left(\frac{\Gamma}{\pi}\right)^{1/2} \tag{8}$$

If D(t) varies because of progressive water uptake to some equilibrium value, then, for a compound that will only diffuse out from hydrogel that hydrates very rapidly, one may assume that the following relationship is fulfilled:

$$D(t) = D_s \frac{\varnothing_{2t}}{\varnothing_{2\infty}} \tag{9}$$

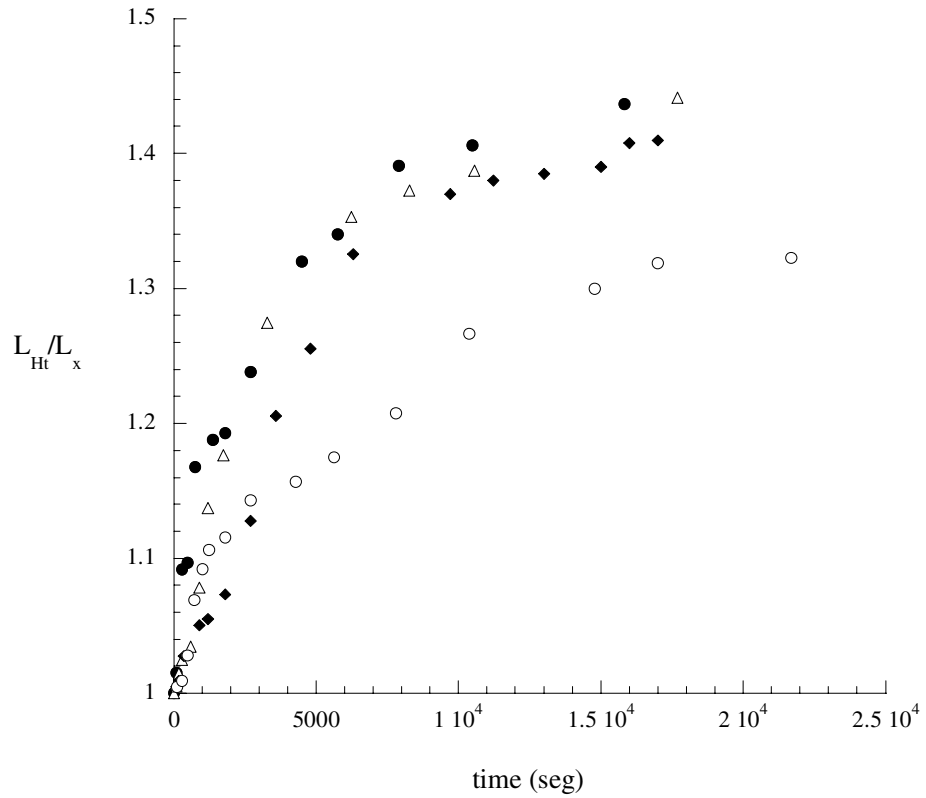

Figure 3. Variation of L_{Ht}/L_x vs. time for hydrogels with different quantity of nanoparticles. (○ 0%, ◆ 22%, △ 33%, ● 50% of nanoparticles)

Here D_s is the diffusion coefficient of the species in the fully hydrated matrix, while $Ø_{2t}$ and $Ø_{2\infty}$ are the volume fractions of polymer at a specific time and at equilibrium, given by $(L_x/L_{Ht})^3$ and $(L_x/L_{H\infty})^3$, respectively. Here, $L_{H\infty}$ is the hydrogel diameter at equilibrium [15].
The substitution of equations (8) and (9) into (5) yields:

$$F_s = \frac{M_t}{M_\infty} = \frac{4L_x}{\sqrt{\pi}h}\sqrt{D_s}\,(L_{H\infty})^{3/2}\left(\int_0^t \frac{dt}{(L_{Ht})^5}\right)^{1/2} \qquad (10)$$

Hence, a plot of F_s against the square root of the integral in the right-hand side of equation (10) should yield a linear plot and from the slope, D_s can be obtained. The integral was solved numerically for the variation of $1/(L_{Ht})^5$ for the different hydrogels examined here. Figure 4 shows representative plots according to equation (10) for the conventional and one nanostructured hydrogels. The behavior found for the other hydrogels is similar. In this figure, it is apparent that the plot is linear up to Fs $\approx$ 0.2. For higher values of Fs, there is a break and the slope of the curve increases. Blanco et al. [16] attributed this behavior to a significant erosion of the hydrogel surface due to the fast water front movement into the gel. This could produce a greater surface area for drug release, resulting in a progressive increase in release rate. Also, the state of the gel changes from glassy to rubbery upon water absorption; this gradual change in the state of the gel can also affect the behavior of the diffusing species and cause the change in the slope shown in Figure 4. However, since equation (10) takes into account only dimensional changes and not structural variations, the later effect is not further discussed.
Table 1 reports the estimated apparent diffusion coefficients V-C in the different hydrogels for F_S below and above 0.2 estimated with equations (3) and (10). As expected, the apparent diffusion coefficients for values below 0.2, where structural changes may be dominant, are smaller than those estimated for F_S larger than 0.2, where dimensional changes are more important. The release rate of V–C from the nanostructured polyacrylamide hydrogels increases as the particle content rises. Notice that for $F_S > 0.2$, the diffusion coefficients are larger than those for $F_S < 0.2$, and that they are on the order of magnitude expected for the diffusion of the drug in water. Notice also that the apparent diffusion coefficients of water, which are similar for the conventional and nanostructured hydrogels ($D_w = 3.55 \times 10^{-5}$ cm^2/s), are two to three times larger than those of the drug. Blanco et al. [16] also found that they diffusion coefficient of water were two to three time larger than those of sodium salicylate being release from copolymers hydrogels of N,N´-methacryloyloxyethyl-N-(3-sulfopropyl)ammonium betaine and 2-hydroxyethyl methacrylate).
A possible explanation of why the apparent diffusion coefficient of the ascorbic acid rises as the nanoparticle content in the hydrogel increases is related to the structure of the gels. As mentioned above and elsewhere [12, 13], the overall polymer concentration of polymer (polymer particles plus polymeric matrix) used in the synthesis (10 wt. % with respect to water), the polymer matrix becomes more open as the concentration of particles increases (as a result of the polymer content employed in the second stage), which allows a less tortuous and easier exiting route for the drug molecules.

Table 1. Values of diffusion coefficients obtained assuming a constant diffusion coefficient, Equation (3); and assuming that D is a function of time, Equation (10)

Particle content wt. %	D_s [(a)] x 10^{-5} (cm^2/s)	D_s [(b)] x 10^{-5} (cm^2/s)	D_s [(c)] x 10^{-5} (cm^2/s)
0	0.445	0.860	0.023
22.2	0.640	0.952	0.081
33.3	0.673	1.105	0.261
50.0	0.730	2.050	0.453

(a) - Estimated for Fs > 0.2 and Equation (3)
(b) - Estimated for Fs > 0.2 and Equation (10)
(c) - Estimated for Fs < 0.2 and Equation (10)

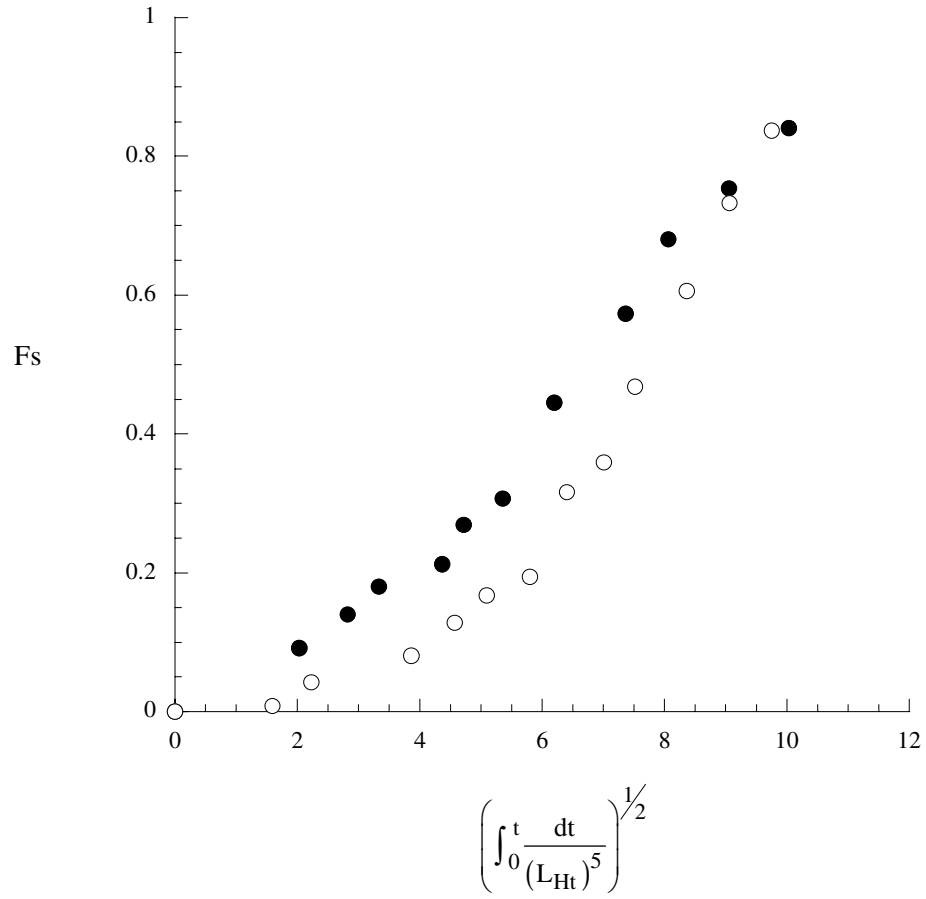

Figure 4. Plot of Equation (12) for the hydrogels with 22% of particles (○) and without particles (●)

Conclusions

The constant diffusion coefficient assumption in the Fick's equation has been used in many hydrogels systems used in drug delivery. However, in our case, because of the large dimensional changes occurring during swelling and drug release from the hydrogels formed by crosslinked polyAM nanoparticles trapped in a polyAM matrix, it is necessary using a modified form of the Fick's equation that considers dimensional changes. The diffusion coefficients obtained with this equation are larger that those obtained with the equations that do not take into account dimensional changes. Moreover, the drug delivery rate increases as the nanoparticle content in the hydrogel augments due to the formation of a more open matrix. Nevertheless, more work is required to understand the drug delivery mechanism and how the nanoparticles affect the release from these nanostructured hydrogels.

References

1. Andrade JD (1976) Hydrogels for Medical and Related Applications. In: ACS Symposium Series, 31. American Chemical Society
2. Hoffman AS (2001) Annals of the New Cork Academy of Sciences 944:62
3. Yonese M (2001) Sustained drug delivery by gels. In: Gels Handbook, Vol. 3-Applications. Chapter 4, Section 9
4. Peppas NA, Bures P, Leobandung W, Ichikawa H (2000) Eur J Pharm Biopharm 50:27
5. Peppas NA (1986) Hydrogels in medicine and pharmacy. CRC Press, Boca Raton, Florida
6. Majeti NVRK (2000) J Pharm Pharmaceut Sci 3:234
7. Peppas NA, Khare AR (1993) Adv Drug Delivery Rev 11:1
8. Jagur-Grodzinski J (1999) React Funct Polym 39:99
9. Langer R, Peppas NA (2003) AIChE Journal 49:2990
10. Madruga EL, San Román J (1987) Rev Plast Modern 377:675
11. Mathur AM, Moorjani SK Scranton AB (1996) Macromol Chem Phys C36:405
12. Puig LJ, Sánchez-Díaz JC, Villacampa M, Mandizábal E, Puig JE, Aguiar A, Katime I (2001) J Colloid Interface Sci 235:278
13. Fernández VVA, Tepale N, Sánchez-Díaz JC, Mendizábal E, Puig JE, Soltero JFA (2005) Colloid Polym. Sci. Accepted (Published Online)
14. Sánchez-Díaz JC, Martínez-Ruvalcaba A, González-Álvarez A, Ortega-Gudiño P (2005) ANTEC 2005 – Proceedings of the 63rd Annual Technical Conference, Boston, MA, May 1 -5, Society of Plastics Engineers: 2085
15. Leanirith Y, Bunel C, Vairon JP(1990) Makromol Chem 191:1119
16. Blanco MD, Rego JM, Huglin MB (1994) Polymer 35:3487
17. Crank J (1975) The mathematics of diffusion. Clarendon Press, Oxford
18. Cussler EL (1984) Diffusion- Mass transfer in fluid systems. Cambridge University Press, New York