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Nafcillin release from poly(acrylic acid–co–methyl methacrylate) hydrogels

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Summary

Copolymeric poly(acrylic acid-co-methyl methacrylate) hydrogels for three different compositions: (90/10), (80/20) and (60/40), have been studied. Drug release has been examined as a function of the hydrogel composition by HPLC (High Pressure Liquid Cromatography). The release experiments were carried out at 37 ºC. The fraction of available drug release was linear in $t^{1/2}$. The values of the diffusional coefficient ($0.50 < n < 1.0$) indicate that the nafcillin release mechanism from the hydrogels in study is non-Fickian. The diffusion coefficients for this drug release have been calculated. The molecular diffusion of nafcillin through hydrogels is controlled by the swelling.

Keywords. Copolymeric poly(acrylic acid–co–methyl methacrylate) hydrogels, nafcillin, drug release.

Introduction

Hydrogels are highly swollen, hydrophilic polymer networks that can absorb large amounts of water and drastically increase in volume. It is well known that the physicochemical properties of the hydrogel depend on the molecular structure, the gel structure, and the degree of crosslinking, but also on the content and state of the water in the hydrogel. Hydrogels have the inherent ability to swell in aqueous media because of their thermodynamic compatibility with water. In water they swell to an equilibrium volume, but preserve their shape. The utility of hydrogels as biomaterials lies in their permeability to small molecules, a soft consistency, and a low interfacial tension between the gel and aqueous solutions. Their physical properties are very similar to those of living tissues [1-4]. These materials can be used as contact lenses, membranes for biosensors, blood oxigenators, materials for artificial prosthesis, artificial corneas, bone cements, soft tissue substitutes, suture coatings, and have been widely used in controlled drug release systems. Of the several possible routes of introducing release medication into the body, the oral administration of single dose medicinal is one of the simplest and safest, since it does not pose the sterility problem

and the risk of damage at the site of administration is minimal. The systems developed to control drug release have been designed to maintain the concentration of the bioactive substance inside an optimum therapeutic interval. These polymers have been used as vehicles to release many substances in a controlled way [5-12].

Nafcillin is a semi-synthetic antistaphylococcal penicillin. Unlike penicillin, ampicillin, or the extended-spectrum penicillins, nafcillin resists hydrolysis by penicillinase. As a result, nafcillin, along with other agents in the same group (e.g., oxacillin, dicloxacillin), is active against penicillinase-producing Staphylococcus aureus. Nafcillin, because of its side chain, resists destruction by beta-lactamases. This makes it useful for treating bacteria that resist penicillin due to the presence of penicillinase. Nowadays, Nafcillin is employed in an invasive disease due to *Enterobacter cloacae and Serratia marcescens* [13]. The penicillin family of antibiotics have bacterial activity, low toxicity, excellent distribution throughout the body, and efficacy against infections caused by susceptible bacteria [14].

The aim of this work was to test the application of copolymeric poly(acrylic acid–co–methyl methacrylate) hydrogels to nafcillin release. Copolymers were synthesized from AA and MMA in presence of 1% wt. BIS as crosslinker and 0.1% wt. V-50 as azoinitiator. The drug release kinetics has been examined as a function of the hydrogel composition.

Materials and Methods

Materials. The monomer acrylic acid (AA; Fluka, 99%) was separated from the inhibitor. The methyl methacrylate (MMA; Polyscience, Inc.), the initiator 2,2-azobis(2-amidinopropanone) (V-50) (Wako), ethanol (Panreac, PRS), methanol (Merck, HPLC degree), acetic acid (Scharlau, HPLC degree) and nafcillin (Sigma) were used as received. The crosslinking agent N,N´-methylenebisacrylamide (BIS) (Fluka, > 98 %) was purified by recrystallization in methanol. Distilled and deionised water was used for release experiments.
Synthesis. Three hydrogels with different compositions were synthesized, MMA/AA (wt/wt): 10/90, 20/80 and 40/60. A ratio of 40/60 (wt/wt) total monomer/ethanol was used in all cases. The hydrogels were prepared with 0.1 % of 2,2-azobis(2-amidinopropanone) of total monomers. The concentration of the crosslinking agent N,N´-methylenebisacrylamide was 1% in all cases. For the synthesis, the appropriate amount of V-50 was dissolved in a small amount of water in a test tube; the crosslinking agent and the monomers were added in another tube and dissolved in the calculated amount of ethanol. The contents of both tubes were mixed, then purged with nitrogen for twenty minutes and finally introduced in the ultrasound bath for another twenty minutes to eliminate possible bubbles and to avoid any degradation. The content of the tube with the mixed components was heated in an oven at 50 ^{o}C for six hours. The products, in the shape of cylinders, were cut as disks and immersed in ethanol to remove non-reacted monomers and other soluble materials, then they were cut as disks and dried at room temperature for a week. A similar washing procedure was carried out with water. Both solvents were changed several times to optimize the extraction process. Then, the cylinders were cut in the shape of disks and dried in an oven, at 40 ^{o}C, until they reached a constant weight. The dry disks were sanded with

mild sandpaper until their thickness was approximately 1 mm ad the average diameter was 5 mm to get uniform and smooth surfaces. The dimensions of the disks were measured with a micrometer.

Loading of gels. Polymer disks were loaded with nafcillin by immersing them in an aqueous solution of the drug (2.5 mg/mL), in absence of light to avoid possible degradation, and at room temperature for a week to ensure that the equilibrium was reached. The molecular structure of nafcillin is shown in Figure 1.

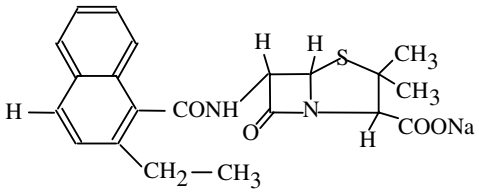

Figure 1. Molecular structure of nafcillin (molar mass = 454.5 g/mol).

Drug release. Nafcillin release experiments were performed at 37 ºC, in a constant temperature flask of 100 mL with continuous stirring, where the loaded polymer disk was introduced. The release medium was desionized water. There were taken out portions of approximately 100 μL from here. The total volume extracted by this way was considered negligible with respect to the solution total volume (100 mL). Release of nafcillin from MMA/AA disks was followed by HPLC (Perkin Elmer LC 200 pump, and Aby Applied Biosystem 785A UV detector with a Spherisorb ODS 5 μm packed Teknokroma column, 25 x 0.46 cm). The mobile phase was methanol/acetic acid (6:4). The flow rate was 1 mL/min and the detector wavelength was 280 nm. The retention time of nafcillin was 16 minutes. The concentration of released drug was monitored by taking portions of 100 μL aliquots of the media at specific time points and determining the drug concentration by HPLC, each sample showed a peak corresponding to the drug under analysis. The amount of drug released at any time (M_t) was calculated from the calibration curve obtained with aqueous solutions of nafcillin from 0.1 μg/mL to 2 mg/mL.

Results and Discussion

Diffusion from a gel phase can be considered one-dimensional process when the thickness of the disks is not very large. It has been taken into account in sodic salicilate diffusion from HEMA/sulfobetaine copolymer disks with a dry thickness between 0.9 to 2.5 mm [15], where the drug desorption was linear versus $t^{1/2}$. Moreover, with this thickness the diffusion through the edges can be despised [16]. Subsequently, the same assumption has been considered for drug diffusion from another hydrogels [17,18]. In the same way, this approach has been followed here in the determination of diffusion coefficients for nafcillin release, since the thickness of xerogel was $\pm$ 1.00 mm. Nafcillin release kinetics using MMA/AA hydrogels are presented in Figure 2, where M_t is the molar amount of drug released at time t and M_∞ is the maximum molar amount of drug released at equilibrium, which reached the values of 95, 90 and 70% of the total amount of drug loaded in the gels of 10/90, 20/80 aqnd 40/60, respectively.

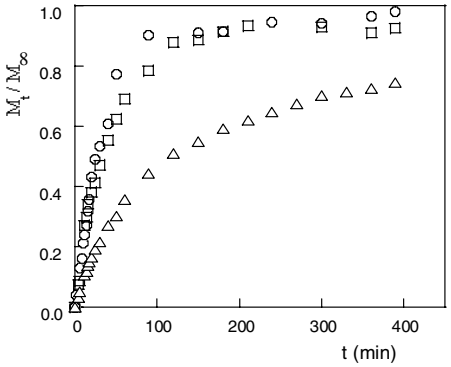

Figure 2. Kinetics of nafcillin release in water from MMA/AA hydrogels for different compositions*:* 10/90 (O), 20/80 (□) and 40/60 (Δ).

As shown, nafcillin release is slower as the percentage of methyl methacrylate in the hydrogel increases. Due to the hydrophobic character of this drug, as the content of the hydrophobic comonomer in the hydrogel (MMA) increases, the drug will be more retained inside the hydrogel structure and its release will be slower.

It is reported [19] that, generally, the diffusion of solutes from elastomeric systems in swollen equilibrium is a Fickian process. The migration is related to slow macromolecular relaxation phenomenons, which are induced by the swelling. These relaxation process depend on the finite times that the polymer chains need to answer to the osmotic swollen pressure and to arrange in order to suit the solvent molecules that go into the system [20,21]. In order to understand this behavior, is necessary to consider the Fickian diffusion of a solute through a polymer. Solving the second equation of Fick, under simple limit conditions used frequently in liberation experiments in water or biologic fluides, and for polymers with simple geometric shapes, like discs, cylinders and spheres [22], a solution (Eq. (1)) is obtained for short time intervals [10]. In general, drug release data from a polymeric disk, under countercurrent diffusion of a swelling agent, can be calculated from the following equation:

$$\frac{M_t}{M_\infty} = kt^n \qquad (\mathbf{1})$$

where k is a kinetic constant characteristic of the drug/polymer system, and n is a characteristic coefficient which depends on the solute mode of transport. These n values can be calculated from the log (M_t/M_∞) versus log t. This release rate obeys the following equation:

$$\frac{dM_t}{dt} = nc_d kt^{n-1} \qquad (\mathbf{2})$$

where c_d is the initial amount of drug in the polymer. Combining this equation with Eq. (1) allows the drug release kinetics to be described; these obey Fickian mechanisms, in which case n = 0.50, and k is expressed by:

$$k = 4 \cdot \left(\frac{D_i}{\pi h^2} \right)^{1/2} \quad (3)$$

where D_i is the apparent diffusion coefficient of the drug from the swollen polymer and h, the disk thickness. According to this, drug diffusion through swollen elastomeric polymers in the thermodynamic equilibrium with the solvent is Fickian if $n < 0.50$, while the diffusion in elastomeric polymers during continuous swelling can be Fickian or anomalous if $0.50 < n < 1.0$.

Figure 3 shows the release graphs for the release of nafcillin from swollen hydrogels with the three MMA/AA compositions as a function of $t^{1/2}$ for $(M_t / M_\infty) \leq 0.6$, following the next Equation:

$$\frac{M_t}{M_\infty} \approx 4\left(\frac{D_i t}{\pi h^2} \right)^{1/2} \quad (4)$$

As can be seen, M_t/M_∞ behavior is linear in the squared root of time for values less than 0.6 for all the studied hydrogels. However, at the shortest times of the release process, there is a slight curvature which could be caused by accommodation phenomenon of the hydrogel in the new medium. Aminophylline and nafcillin liberation studies from poli(N-isopropylacrilamide-co-itaconic acid) hydrogels [18], and theophylline and aminophylline release from poly(acrylic acid-co-n-alkyl methacrilate) hydrogels, show a global linear behavior [23] for $M_t/M_\infty < 0.6$. From the slopes of the straight zones of the representation, it is possible to obtain the values of apparent diffusion coefficients, D_i, for the three different studied systems (Table 1). The diffusion coefficient decreases with the increasing concentration of MMA (hydrophobic comonomer).

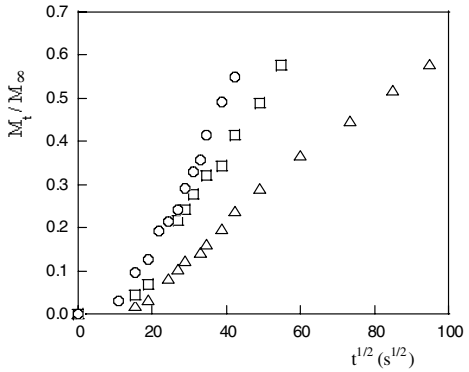

Figure 3. Fractional releases of nafcillin M_t/M_∞ versus $t^{1/2}$, from MMA/AA hydrogels with the compositions 10/90 (O), 20/80 (□) and 40/60 (Δ).

It is possible that the swelling degree affect the rate of release, because the hydrogels with low percentages of hydrophobic comonomer present higher constants of release

because of the higher mobility of the chains. The nafcillin release behavior form NIPA/IA hydrogels, in which NIPA is the hydrophobic comonomer, is very similar [18]. In those drug release experiments, the nafcillin diffusion coefficient increases as the NIPA content increases, because of the increment of water in the equilibrium.

Table 1. D_i and n values obtained from the release of nafcillin from MMA/AA hydrogels.

%MMA	10	20	40
$D_i \cdot 10^7 (cm^2/s)$	5.08 ± 0.01	4.17 ± 0.02	0.93 ± 0.02
N	0.89	0.73	0.71

The values $0.5 < n < 1.0$ presented in Table 1, indicate that the hydrogels show a non-Fickian mechanism and because of it, there is a change in their volume. The dimensional changes associated to the absorption in polymers usually show a characteristic behaviour in which the absorption of water trends to increase the dimensions of the hydrogel, and desorption of the drug trends to decrease them. In this case, the release occurs by diffusion but there is a small relaxation-controlled swelling phenomenon during the time of release. The values of n increase their proximity to Fick´s laws as the concentration of MMA increases. Nafcillin release from NIPA/IA hydrogels presents n values close to 0.5 and so, it can be considered to have a Fickian drug release behavior [18]. This difference in n values could be related to the dynamic of swelling of the hydrogels [24]. Because of the large size of the nafcillin its diffusion coefficient is very small. The voluminous molecular structure and the hydrophobic character of nafcillin could be responsible for the small diffusion coefficient of this drug. It is possible that, for this reason, the nafcillin is more retained into the hydrogel.

Conclusions

The release of nafcillin from fully swollen hydrogels made of methyl methacrylate and acrylic acid is examined here. The release mechanism of the drug depends on the initial state of the polymer. The release from hydrogels in continuous swelling deviates from Fick´s law. This is observed in the values of the diffusional exponent n, for the three different hydrogels (MMA / AA) studied: 10/90, 20/80 and 40/60.
The release of nafcillin has also been studied from fully swollen hydrogels made of poly(N-isopropyl-acrylamide-co-itaconic acid) and, in this case, the results show that the release mechanism follows the Fick´s law. The diffusion coefficients found here are smaller than those from MMA/AA, but the second ones are more hydrophilic and present different sensitivity to temperature [24,25]. We cannot forget the influence of some factors such as, the synthesis method, the crosslinking agent, the solvent and others, in the structure of the hydrogel. For this reason, it is difficult to compare the diffusion coefficients of both types of hydrogels. On the other hand, the low values of the diffusion coefficients for nafcillin from MMA/AA hydrogels, could be explained by the voluminous molecular structure and the hydrophobic character of this drug.

There have also been studied the release of theophylline and aminophylline from MMA/AA hydrogels and it is observed that they follow the Fick´s law [25,26]. These results are orientative but not comparable, because these drugs differ from the one studied here.

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