Delivery of Bupivacaine Included in Poly(acrylamide-co-monomethyl itaconate) Hydrogels as a Function of the pH Swelling Medium

M. V. Bernardo, M. D. Blanco, R. Olmo, J. M. Teijón

Departamento de Bioquímica y Biología Molecular, Facultad de Medicina, Universidad Complutense de Madrid, 28040 Madrid, Spain

Received 8 March 2001; accepted 2 November 2001

ABSTRACT: Copolymeric hydrogels of poly(acrylamide-co-monomethyl itaconate) (A/MMI) crosslinked with *N,N′*-methylenbisacrylamide (NBA) were synthesized as devices for the controlled release of bupivacaine (Bp). Two compositions of the copolymer, 60A/40MMI and 75A/25MMI, were studied. A local anesthetic was included in the feed mixture of polymerization (2–8 mg Bp/tablet) and by immersion of the copolymeric tablets in an aqueous solution of the drug. A very large amount of Bp (36–38 mg Bp/tablet) was included in the gels by sorption due to interactions between the drug and the side groups of the hydrogels. Swelling and drug release were in accordance with the second Fick's law at the first stages of the processes. The swelling behavior of these copolymers depended on the pH of the medium. The equilibrium swelling degree (W_∞) was larger at pH 7.5 ($W_\infty \approx 90$ wt %) than at pH 1.5 ($W_\infty \approx 52$–64 wt %) due to the ionization of the side groups of the copolymer. Release of the drug also depended on the pH of the swelling medium; at pH 7.5, about 60% of the included drug was released, and at pH 1.5, about 80% was released. Bp release was controlled by the comonomer composition of the gels, their drug-load, and the pH of the swelling medium. © 2002 Wiley Periodicals, Inc. J Appl Polym Sci 86: 327–334, 2002

Key words: drug delivery systems; high performance liquid chromatography (HPLC); hydrogels; stimuli-sensitive polymers; swelling

INTRODUCTION

Hydrogels are three-dimensional hydrophilic networks capable of absorbing large amounts of water or aqueous solutions. They are insoluble because of the presence of physical or chemical crosslinks.[1,2] Hydrogel characteristics depend on their monomer composition, and they can be homopolymers or copolymers.[3–5]

Some hydrogels are stimuli sensitive; they exhibit significant changes in their swelling and mechanical properties in response to changes in pH, ionic strength, or temperature of the external environment.[1] All the pH-sensitive hydrogels contain ionizable groups on polymer chains.[6,7] These acid or basic pedant groups accept or release protons in response to changes in the environmental pH; when pedant groups of the hydrogel are charged, electrostatic repulsions are originated, and the uptake of solvent in the polymeric matrix is increased. The swelling of hydrogels with acid pedant groups (e.g., carboxylic or sulfonic acid) increases when the pH of the swelling solution is above the pK_a of the ionizable pedant group. The extent of swelling depends on the amount of ionized acidic groups; thus, swelling increases with the pH of the swelling solution. On the other hand, when the pedant groups are basic (e.g., amines), the swelling of hydrogels increases in solutions whose pH is below the pK_b of the ionizable groups. Different polymeric and copolymeric pH-sensitive hydrogels have been synthesized with monomers of methacrylic acid,[8] *N*-isopropylacrylamide,[9] and acrylamide (A).[10]

Because of these characteristics, pH-sensitive hydrogels have been studied to develop drug-delivery systems.[11] They are mainly interesting for oral administration because they can swell at acidic pH,[12] and thus, drug release takes place in the stomach; they can also swell at neutral or basic pH,[13] in which case drug would be released in the intestine.

Our aim in this study was to prepare hydrogels of high swelling capability in simulated biological fluids, in which bupivacaine (Bp) could be incorporated and released in its pharmacologically active form. Bp is one of the local anesthetics usually used for regional anesthesia; it exhibits a long action and high therapeutic power. Bp is a lidocaine-like drug. Lidocaine has been applied as a cream to burn wounds with significant pain relief for a long duration without associated systemic side effects.[14] Local anesthetics such as lidocaine have potent anti-inflammatory effects, which may partly explain their analgesic effects in an in-

Correspondence to: J. M. Teijón (jmt77255@eucmax.sim.ucm.es).

Contract grant sponsor: CICYT; contract grant number: MAT2000-0768-CO2-01.

© 2002 Wiley Periodicals, Inc.

flamed burn wounds. These drugs can also significantly reduce experimental edema formation in burns.[15] On the other hand, hydrogels have been used as dressings,[16,17] which can deliver different drugs as antimicrobial agents[18] or local anaesthetics.[19] Thus, this Bp formulation could be applied as a dressing against burn wound pain. In gastroduodenal ulcers, an increase of acid in the stomach and intestines takes place, and benzodiacepins (oxazepam) or benzamides (sulpiride) are used for treatment due to their sedative effects.[20] These pH-sensitive hydrogels could release Bp in the stomach, where it could produce analgesic effects.

EXPERIMENTAL

Materials

Itaconic acid (methylene succinic acid; Merck, Darmstadt, Germany), acrylamide (A; Merck), *N*,*N*′-methylenbisacrylamide (NBA; Merck), ammonium peroxodisulfate [$(NH_4)_2\ S_2O_8$; Merck), sodium disulfite ($Na_2S_2O_5$; Merck), sodium chloride (Panreac, Barcelona, Spain), hydrochloric acid (Panreac), methanol (Panreac), acetyl chloride (Merck), dichloromethane (Panreac), sodium hydroxide (Panreac), anhydrous sodium sulfate (Merck), toluene (Panreac), dipotassium monohydrogen phosphate (K_2HPO_4; Panreac), and potassium dihydrogen phosphate (KH_2PO_4; Panreac) were used as received.

Bp ($C_{18}H_{28}N_20$) was supplied by Sigma-Aldrich (Madrid, Spain); Milli-Q (Millipore, Madrid, Spain) water was used.

Synthesis of poly(acrylamide-co-monomethyl itaconate) (A/MMI) hydrogels

Monomethyl itaconate (MMI) was obtained by esterification of itaconic acid with methanol.[21,22] Two different A/MMI compositions were studied: 75A/25MMI and 60A/40MMI (wt/wt). In the feed mixture, the monomer-to-water ratio was 60/40 (wt %). The crosslinking agent was NBA (2 wt %), and the initiator was the redox pair $(NH_4)_2S_2O_8$ (1 wt %)/$Na_2S_2O_5$ (0.4 wt %); their contents were based on the total mass of the monomers. The mixture was weighted out and degassed with nitrogen. Teflon molds were sealed and placed in an oven at 313 K; the temperature was increased slowly up to 333 K and then maintained for 2 h.

To obtain thin gel pieces, we adjusted the amount of the feed mixture of the components by diluting with 0.5 mL of water in each Teflon mold (1.3 × 1.6 cm). After polymerization, the samples were maintained in the molds for 15 h, and then they were removed and cut into four rectangular tablets, whose dimensions were determined with a micrometer.

The conversion was 45–52 wt %. These small values were caused by the synthesis of the gels with water in the polymerization feed mixture; therefore, the loss of freezing water during the dehydration of the gels was the main cause of the loss in weight after polymerization and drying of the tablets.

Bp inclusion in the copolymers

To include Bp in the gels, we used two different methods. In the first one, we included Bp in the feed mixture of polymerization by dissolving it in the aqueous solution of the initiator. Tablets loaded with 2, 4, 6, and 8 mg of Bp (0.54, 1.08, 1.63, and 2.17 wt %, respectively, of the total formulation) for each copolymer composition were synthesized. After polymerization, the samples were optically transparent, showing complete solubility of Bp in the copolymer matrices. The maximum amount of Bp in the tablets (8 mg) was determined by the water amount in the feed mixture of polymerization.

For the second method, we loaded copolymer tablets with Bp by immersing them in an aqueous solution of the drug (10 mg/mL) at 37°C until equilibrium was obtained. Then, the hydrogel tablets containing the drug were dried at ambient temperature until a constant weight was reached. The Bp included was determined by difference in weight.

Swelling of the copolymers

We used two different pH solutions to study the swelling of the 60A/40MMI and 75A/25MMI tablets. pH 7.5 phosphate buffer (1 m*M*) was used because this pH is that of the mainly physiological fluids. pH 1.5 simulated gastric fluid [NaCl (2 g), HCl (7 mL), H_2O up to 1 L)][23] was also used.

The swelling of the tablets in phosphate buffer or simulated gastric fluid was carried out for the two copolymeric compositions at 310 K. The gel tablets (without the drug) were placed into a bath with each one of the solutions at a constant temperature, and we obtained the swelling degree (W_t) by withdrawing the tablets, lightly drying with filter paper, and weighing quickly in a tared sample bottle by means of an electronic balance ($\pm\ 10^{-4}$ g). W_t was calculated by use of the expression[24,25]

$$W_t = \frac{\text{Weight of Swollen Tablet} - \text{Weight of Dry Tablet}}{\text{Weight of Swollen Tablet}} \times 100 \qquad (1)$$

The extent of the equilibrium swelling degree (W_∞) of the hydrogel was reached when the weight of the swollen tablet was constant. All experiments were performed in triplicate.

The swelling of the tablets in water up to equilibrium allowed us to obtain the ultraviolet–visible (UV–vis) spectrum of the medium (Unicam 8700 spectrophotometer, Madrid, Spain). The UV–vis spectra of aqueous solutions of known concentrations of A (33 μg/mL), MMI (100 μg/mL), and NBA (10 μg/mL) were also determined. The wavelength of maximum absorbance was 218.0 nm for A, 221.6 nm for MMI, and 224.8 nm for NBA. The spectra of samples were almost the same as those of A with a maximum of 218–220 nm. If the released compound was A, the absorbance of which at 218–220 nm is much larger than that of MMI, the maximum amount would be 2.43 μg from 75A/25MMI and 7.35 μg from 60A/40MMI, which means a very small amount of total A in the feed mixture.

Bp stability

The effect of pH on drug degradation at 37°C was studied. Bp (25 mg) was dissolved in 20 mL of phosphate buffer (1 m*M*, pH 7.5) or simulated gastric fluid (pH 1.5). The solution was maintained at a constant rate at 37°C for 21 days. At intervals, we withdrew 100 μL samples from the solution to follow the change in Bp concentration. The concentration of Bp was determined by HPLC (Spectra-Physics SP 8800 HPLC pump, SP 100 ultraviolet detector, and SP 4400 computing integrator). The stationary phase was Lichrosorb RP8 5μ (15 $\times$ 0.46 μm; Teknokroma, Barcelona, Spain). The eluent was 0.01*M* dihydrogen sodium phosphate with acetonitrile (70:30 v/v) at pH 2.1.[26] The flow rate was set at 1.5 mL/min, and the detector wavelength was 205 nm. Bp standards of 0.1–5.0 mg/mL were run for external standardization, and linear curves with a correlation coefficient of 0.999 were generated from the area under the peak measurements. The Bp retention time was 5.5 $\pm$ 0.2 min.

Bp release experiments

We performed release experiments by placing a gel tablet in a highly perforated glass holder in a double-walled vessel (7 $\times$ 5.5 cm inner diameter) connected to a water recirculating thermostat, so that the position of the tablet in the vessel was at the same height in all experiments. The release medium (75 mL) was phosphate buffer or simulated gastric fluid. The vessel was covered with laboratory film (Parafilm). The stirring rate was constant at approximately 500 rev/min (Velt multiposition electromagnetic stirrer; Gomensoro, S.A., Madrid, Spain). At different times, we withdrew samples (100 μL) from the medium to monitor Bp release; this volume was replaced with phosphate buffer or simulated gastric fluid. The concentration of Bp in the release medium was always less than 10% of the maximum solubility of Bp (45 mg/mL in both phosphate buffer and simulated gastric fluid; sink conditions).[27,28]

TABLE I
W_∞ of the 75A/25MMI and 60A/40MMI Copolymers at pH 7.5 (Phosphate Buffer) and pH 1.5 (Simulated Gastric Fluid) and the Time Needed to Reach It

	pH 7.5	pH 1.5
W_∞ (wt %)		
75A/25MMI	89.6 $\pm$ 1.4	51.9 $\pm$ 4.5
60A/40MMI	90.4 $\pm$ 0.6	63.9 $\pm$ 2.3
Time (h)		
75A/25MMI	89 $\pm$ 12	19 $\pm$ 9
60A/40MMI	122 $\pm$ 2	25 $\pm$ 1

RESULTS AND DISCUSSION

The copolymer hydrogels of A/MMI crosslinked with NBA were synthesized in rectangular tablets whose dimensions were (8.7 $\pm$ 0.2) $\times$ (7.6 $\pm$ 0.6) $\times$ (3.1 $\pm$ 0.3) mm for 75A/25MMI and (8.7 $\pm$ 0.8) $\times$ (7.8 $\pm$ 0.5) $\times$ (3.1 $\pm$ 0.2) mm for 60A/40MMI.

We conducted the swelling of crosslinked A/MMI copolymers in phosphate buffer (pH 7.5) and also in simulated gastric fluid (pH 1.5) at a constant temperature of 37°C to study hydrogel behavior in two different pH conditions similar to *in vivo* systems. W_∞ and the time needed to obtain it for both copolymers is shown in Table I. The W_∞ value was significantly lower for gels immersed in simulated gastric fluid (pH 1.5) for both copolymeric compositions; so this kind of hydrogel was pH sensitive. At pH 7.5, the swelling process is favored due to the side groups that are ionized increasing the repulsion forces among them and, therefore, the expansion process, which involves a larger W_t.[10,29]

When pH decreased, with the corresponding acidification of the medium, H^+ prevented the ionization of the side groups of the hydrogels, and as a consequence, they tended to interact among them, decreasing the expansion and, therefore, the W_t. In this sense, swelling studies of these copolymers in saline solution (NaCl 0.9 wt %),[22] whose pH was 6.0, showed W_∞ values of 78 $\pm$ 1 wt % for 75A/25MMI and 76 $\pm$ 2 wt % for 60A/40MMI, which means W_∞ was lower than that at pH 7.5 as a consequence of a lower ionization degree of the side groups.

On the other hand, the ionic strength of the medium influenced the swelling process. Thus, the ionic strength of the simulated gastric fluid was much larger than that of the phosphate buffer. When the ionic strength was low, the concentration of charged groups in the hydrogel surpassed the salt concentration in the external solution; this induced the gel to expand, decreasing the ion concentration inside the gel. Also, the repulsion forces were high, and the hydrogel tended to expand to minimize repulsion,

favoring the swelling process. If the external salt concentration increased and so did the ionic strength, the difference between external and internal ion concentration decreased, restraining the swelling process. At high ionic strength values, the carboxylic groups of the copolymer are protected by the cations, avoiding the repulsive forces.[10,29] Thus the swelling of A/MMI hydrogels in phosphate buffer medium at pH 7.5 was favored by the very low ionic strength, whereas in simulated gastric fluid at pH 1.5, when the ionic strength was very much higher, the swelling was not favored.

The time required for the gels to attain their equilibrium swelling depended not only on the pH of the swelling medium but also on their monomeric composition; thus larger amounts of MMI required larger times for equilibrium swelling in both swelling mediums.

Attempts have made to interpret the kinetics of swelling and drug release from hydrogels, utilizing the concept that absorption of water into glassy hydrogels generally exhibits anomalous behavior ranging from Fickian to Case II diffusion. Variations were found to be dependent on the experimental conditions in relation to the glass-transition temperature and the thermodynamic parameters between the solvent and the hydrogels.[30] Fickian and non-Fickian behavior of drug release depends on the rate of polymer relaxation at the glassy–rubbery transition at the swelling interface. For a polymer slab, Fickian diffusion is proportional to the square root of time, whereas Case II diffusion, which is determined by the rate of polymer relaxation and the diffusional rate, exhibits a linear time dependence of solute release.[31,32]

To characterize the various types of solute diffusion in polymers, the following equation can be used:[25,32]

$$Mt/M_\infty = Kt^n \qquad (2)$$

where M_t and M_∞ are the mass of water or aqueous solution taken up at t and at infinite time, respectively, in sorption experiments. In drug-release experiments, M_t and M_∞ are the amount of drug released at time t and the maximum amount of drug released, respectively; K is a constant incorporating characteristics of the macromolecular network system and the drug; and n is the diffusional exponent, which is indicative of the transport mechanism. Equation (2) is valid for the first 60% of the fractional swelling (F_s) or release. For $n > 0.5$, non-Fickian diffusion is observed, whereas $n = 0.5$ represents the Fickian diffusion mechanism. The case $n = 1$ provides the Case II transport mechanism in which drug release from a hydrogel having a slab geometry will be of zero order.

In its logarithmic form, eq. (2) was used to determine n (Table II). For the swelling process, n values were very close to 0.5, so that Fickian diffusion could be considered.

TABLE II
Values of the n of eq. (2) for Swelling and also for Bp Release from A/MMI Copolymers

	Swelling	Bp release 1[a]	Bp release 2[b]
pH 7.5 phosphate buffer			
75A/25MMI	0.50 ± 0.01	0.52 ± 0.02	0.53 ± 0.01
60A/40MMI	0.53 ± 0.01	0.52 ± 0.01	0.52 ± 0.02
pH 1.5 simulated gastric fluid			
75A/25MMI	0.47 ± 0.01	0.48 ± 0.03	0.48 ± 0.02
60A/40MMI	0.43 ± 0.01	0.49 ± 0.02	0.48 ± 0.03

[a] Bp was included in the feed mixture of polymerization.
[b] Bp was included by sorption.

The solution of the differential form of the second Fick's law, considering one-dimensional diffusion from a thin sheet and a constant diffusion coefficient (D),[33] can be approached for early and moderate times of diffusion through the reduced expression[25,34]

$$Mt/M_\infty = 2(Dt/\pi l^2)^{1/2} \qquad M_t/M_\infty \leq 0.6 \qquad (3)$$

where l is the sheet half-thickness. Thus, for a diffusion-controlled process, F_s due to aqueous solution ($F_s = W_t/W_\infty$) may be expressed as

$$F_s = Wt/W_\infty = 2(D_s t/\pi l^2)^{1/2} \qquad (4)$$

where D_s is the diffusion coefficient for transport of a multicomponent species (i.e., phosphate buffer or simulated gastric fluid) into the hydrogel. One criterion of Fickian behavior[25,35,36] holds that the plot of F_s versus $t^{1/2}$ should be linear up to 60% of reduced sorption. When F_s values were plotted against $t^{1/2}$ for both polymers in phosphate buffer and simulated gastric fluid for first states of swelling ($F_s \leq 0.6$), a linear relationship was observed between F_s and $t^{1/2}$ (Fig. 1); thus, D_s could be obtained directly from the corresponding slopes (Table III). Although significant differences of D_s as a function of comonomer composition were not observed, the swelling process seemed slower as the amount of MMI increased in the gel.

Release of Bp included in the polymerization feed mixture from hydrogels

The effect of pH on Bp stability at 37°C is shown in Figure 2. At pH 7.5 (1 m*M* phosphate buffer), the drug was slowly degraded, and the degradation became significant after 30 h. However, at pH 1.5, Bp did not change as a function of time.

The Bp release experiments from 75A/25MMI and 60A/40MMI gels were carried out in phosphate buffer (pH 7.5) and simulated gastric fluid (pH 1.5) at 310 K. Each gel, in the shape of thin sheet, was prepared with four different Bp quantities: 2, 4, 6, and 8 mg Bp/tablet

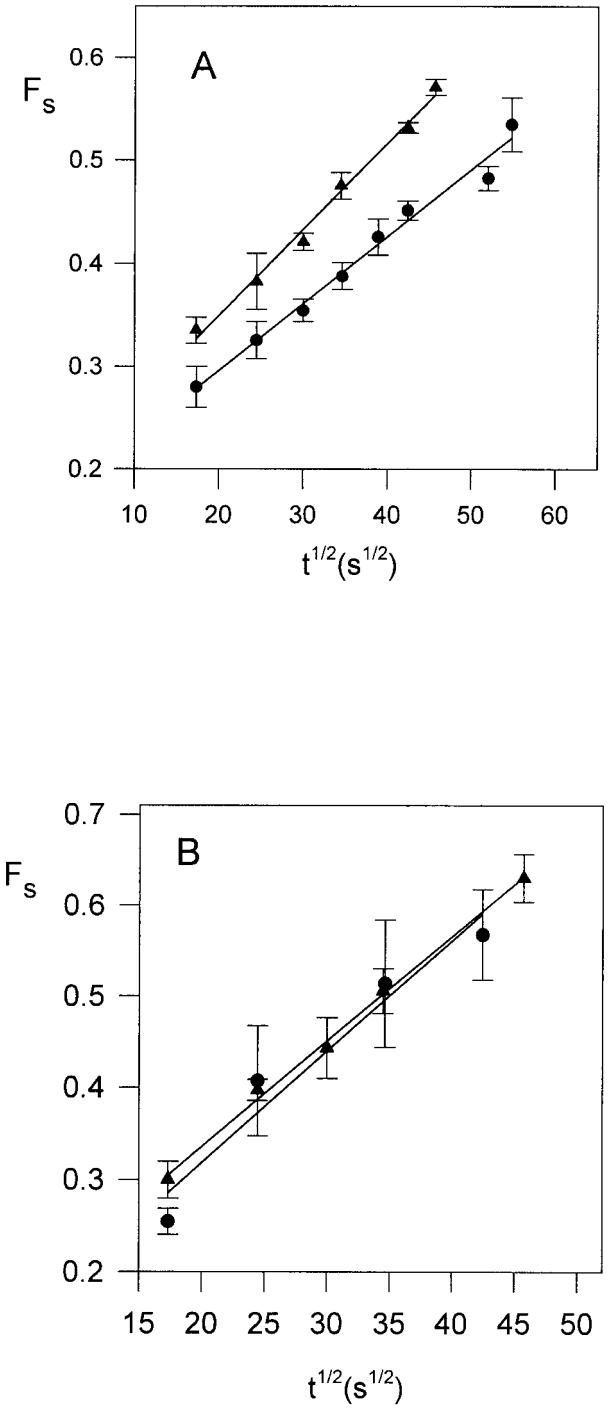

Figure 1 F_s versus $t^{1/2}$ for (▲) 75A/25MMI and (●) 60A/40MMI in (A) phosphate buffer (1 m*M*, pH 7.5) and (B) simulated gastric fluid (pH 1.5).

(0.54–2.17 wt % of the total formulation). The release of Bp from 75A/25MMI and 60A/40MMI in both swelling mediums showed a hyperbolic kinetic; an example for 60A/40MMI is shown in Figure 3. In phosphate buffer, maximum drug release took place at 5.8 ± 1 h. In any case, the maximum amount of Bp released was higher than 60% of the drug load (*A*), with an average value of 52.21 ± 6.38%. However, in simulated gastric fluid, 84 ± 7% of the drug was

TABLE III
Values of the D_s for Phosphate Buffer (pH 7.5) or Simulated Gastric Fluid (pH 1.5) Uptake into A/MMI Hydrogels Crosslinked with 2 wt % NBA ($D_s \times 10^{10} m^2/s$)

	pH 7.5 (phosphate buffer)	pH 1.5 (simulated gastric fluid)
75A/25MMI	1.2 ± 0.3	1.4 ± 0.3
60A/40MMI	1.1 ± 0.1	1.3 ± 0.2

released; the maximum amount of Bp released took place at 24 ± 5 h. Thus, at pH 7.5, the strong interactions among the drug and the components of the polymer matrix were maintained, and a large amount of drug was not released from the hydrogels; the acidity increase of the medium favored the drug-delivery process, although there were very strong interactions that were not broken. At neutral pH (7.5), the side groups of the monomers of the hydrogels were ionized, so repulsion among them was favored. The pK_a of Bp (pK_a = 8.16) was larger than pH of the medium, and the drug is a cation;[37] therefore, the drug could establish interactions with the ionized side groups of the hydrogels, which prevented Bp release.[10,29] On the other hand, in acid pH (1.5), Bp was much more ionized because the pH was very much lower than the pK_a of the drug. In this case, the side groups of the hydrogels were not ionized because there was a large amount of H^+ in the medium; thus, the side groups of the hydrogels tended to interact among them, and these interactions gained importance to the detriment of the drug–polymer interactions. Therefore, the Bp release was favored at pH 1.5.[10,20]

For drug-release experiments, the *n* value of eq. (2) (Table II) was 0.52 in phosphate buffer and 0.48–0.49

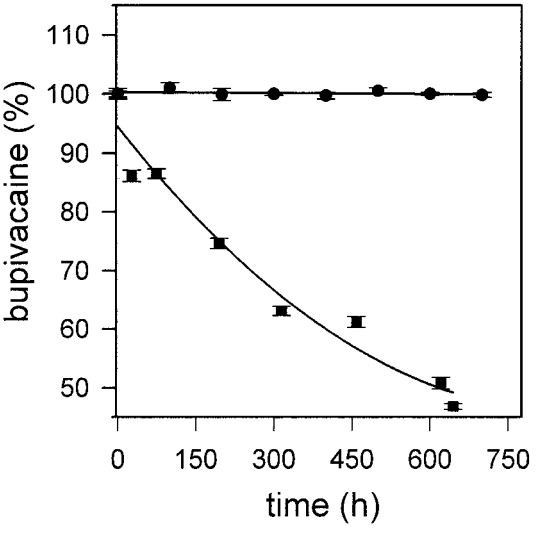

Figure 2 Percentage of Bp as a function of time of incubation in (●) simulated gastric fluid (pH 1.5) and (■) phosphate buffer (1 m*M*, pH 7.5) at 37°C.

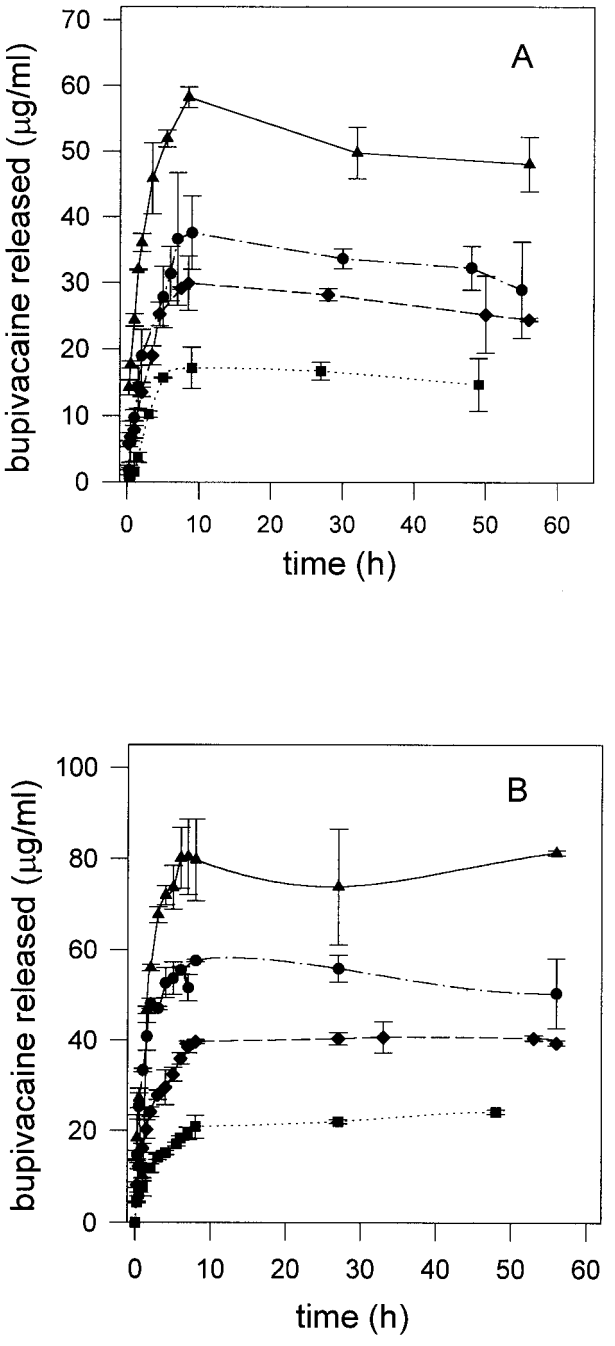

Figure 3 Bp released (μg/mL) as a function of time (h) from 60A/40MMI hydrogels in (A) phosphate buffer (1 m*M*, pH 7.5) and (B) simulated gastric fluid (pH 1.5). Drug-load of gel tablets: (■) 2, (♦) 4, (●) 6, and (▲) 8 mg.

in simulated gastric fluid; thus, a Fickian behavior of the desorption process could be considered for all Bp loads used in the experiments.

Therefore, eq. (3) could be used to determine the diffusion coefficient of Bp from the hydrogels because in all cases, a linear relationship between the fractional release of Bp ($F_{Bp} = M_t/M_\infty$) and $t^{1/2}$ was observed for $F_{Bp} \leq 0.6$. An example for release experiments in phosphate buffer (pH 7.5) and simulated gastric fluid (pH 1.5) is shown in Figure 4. In Table IV, the diffusion coefficients for Bp release are shown.

The A increase in the hydrogel made Bp release easier in both media, probably due to a lower amount of ionized side groups. The drug release in pH 1.5 medium was slower at the first stage of the process, which was in relationship to the lower W_t of the hydrogels in this medium.

The influence of loading on Bp release in both media was reflected in the values of the diffusion coeffi-

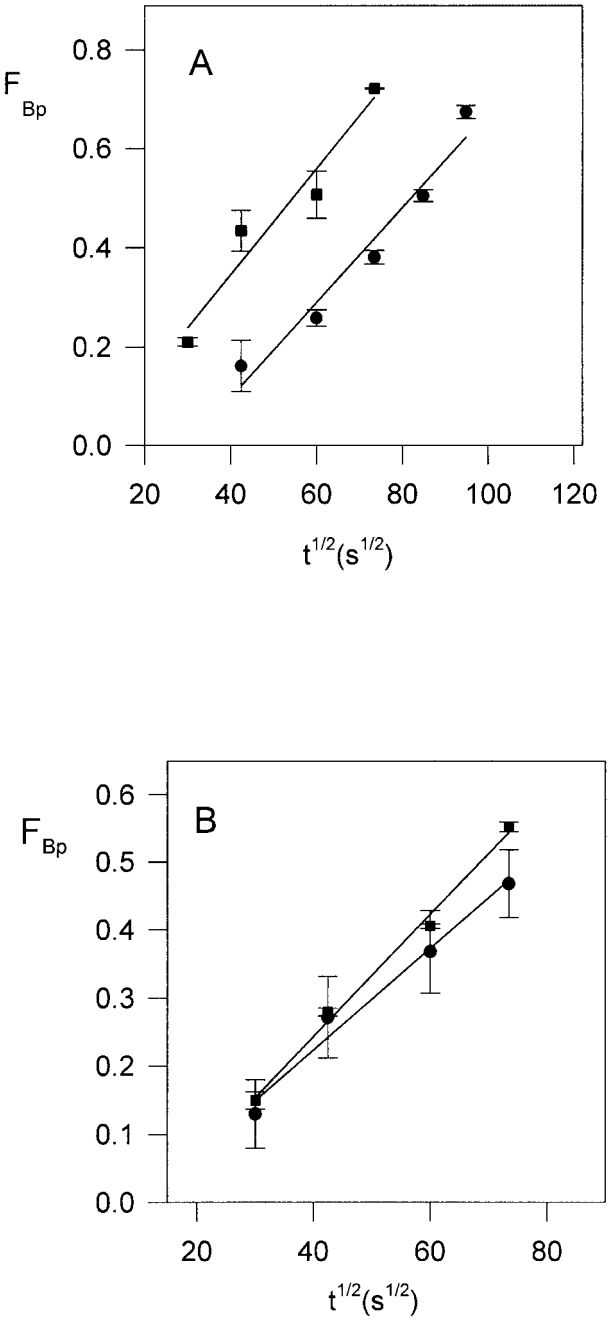

Figure 4 F_{Bp} versus $t^{1/2}$ of (■) 75A/25MMI and (●) 60A/40MMI hydrogel tablets loaded with (A) 6 mg of the drug in phosphate buffer (pH 7.5) and (B) 8 mg of the drug in simulated gastric fluid (pH 1.5). Bp was included in the feed mixture of polymerization.

TABLE IV
Values of the Diffusion Coefficient ($D_{Bp} \times 10^{10}$ m^2s^{-1}) for Release of Bupivacaine from Poly(acrylamide-co-monomethyl itaconate) Hydrogels as a Function of the Drug Load, in Phosphate Buffer (pH 7.5) and Simulated Gastric Fluid (pH 1.5) Bp Included in the Feed Mixture of Polymerization.

75A/25MMI		pH 7.5	pH 1.5	60A/40MMI		pH 7.5	pH 1.5
Bupivacaine (mg)	8	1.56 ± 0.40	1.08 ± 0.06	Bupivacaine (mg)	8	1.01 ± 0.01	0.90 ± 0.10
	6	1.54 ± 0.60	0.81 ± 0.01		6	0.91 ± 0.01	0.76 ± 0.06
	4	0.84 ± 0.10	0.66 ± 0.02		4	0.70 ± 0.06	0.66 ± 0.03
	2	0.65 ± 0.10	0.60 ± 0.04		2	0.46 ± 0.04	0.46 ± 0.07

cient (Table IV), which increased with Bp load. Thus, for each gel drug release became more favorable as the Bp load increased. The drug concentration in the polymeric matrix generated a driving force for the diffusion of the drug. Therefore, it was necessary to calculate a diffusion coefficient that did not depend on the tablet load. For this, if eq. (3) was used and we took into account that $M_\infty = AV = AS2l$; where V is the gel tablet-loaded volume and S is its surface, another expression could be obtained:[38]

$$\left(\frac{M_t}{t^{1/2}}\right)\frac{1}{S} = 4\left(\frac{D_{Bp}}{\pi}\right)^{1/2} \qquad A = \left(\frac{F_{Bp}}{t^{1/2}}\right)A2l \qquad (5)$$

where $M_t t^{-1/2} S^{-1}$ is the release rate per unit of gel area. The plot of this parameter rate versus A yielded a straight line for each hydrogel composition; thus, in phosphate buffer (pH 7.5): (1) 75A/25MMI, $M_t t^{-1/2} S^{-1} = -1.29 \times 10^{-4} + 0.26 \times 10^{-4}\, A$, $r = 0.99$; (2) 60A/40MMI, $M_t t^{-1/2} S^{-1} = -1.33 \times 10^{-4} + 0.24 \times 10^{-4}\, A$, $r = 0.99$; in simulated gastric fluid (pH 1.5): (3) 75A/25MMI, $M_t t^{-1/2} S^{-1} = -0.89 \times 10^{-4} + 0.28 \times 10^{-4}\, A$, $r = 0.99$; (4) 60A/40MMI, $M_t t^{-1/2} S^{-1} = -1.74 \times 10^{-4} + 0.26 \times 10^{-4}\, A$, $r = 0.99$. From the slope, a diffusion coefficient was obtained that was independent of the tablet load. The diffusion coefficients for each gel were as follows: in phosphate buffer (pH 7.5), (1) 75A/25MMI, $1.53 \times 10^{-10} \pm 0.05 \times 10^{-10}$ m^2/s and (2) 60A/40MMI, $1.38 \times 10^{-10} \pm 0.06 \times 10^{-10}$ m^2/s; in simulated gastric fluid (pH 1.5), (3) 75A/25MMI, $1.30 \times 10^{-10} \pm 0.06 \times 10^{-10}$ m^2/s and (4) 60A/40MMI, $1.04 \times 10^{-10} \pm 0.01 \times 10^{-10}$ m^2/s. These values again indicated the influence of the comonomeric gel composition and the delivery medium on Bp release.

Release of Bp included by immersion of copolymeric tablets in an aqueous solution of the drug

The Bp loaded xerogel tablets obtained after immersion of the copolymers in an aqueous solution of the drug were used for drug-release experiments in phosphate buffer (pH 7.5) and simulated gastric fluid (pH 1.5).

The amount of Bp included in the polymeric matrix by this method was 38.7 ± 3 mg (23 wt % of the tablet) for 60A/40MMI and 36.1 ± 4 mg (22% wt of the tablet) for 75A/25MMI. This large amount of Bp included in the gels only can be explained by interactions between the drug and the polymer matrices. Thus, the Bp solution concentration used for loading the gels was 10 mg/mL, and we determined that the W_∞ of A/MMI

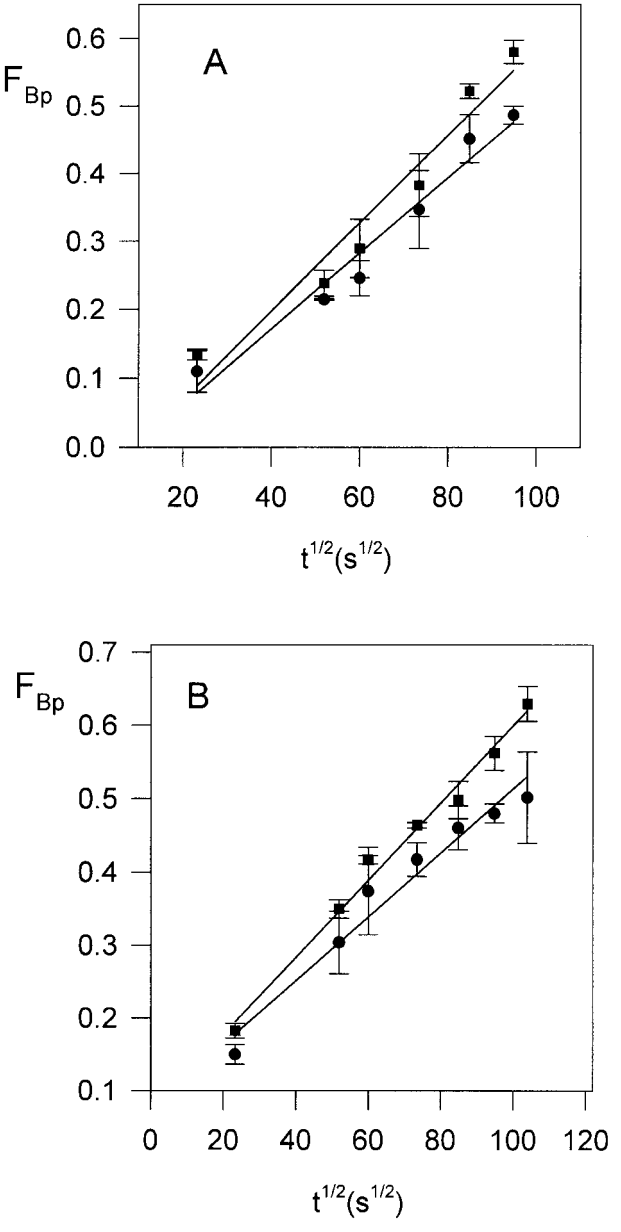

Figure 5 F_{Bp} versus $t^{1/2}$ for (■) 75A/25MMI and (●) 60A/40MMI hydrogels in (A) phosphate buffer (1 m*M*, pH 7.5) and (B) simulated gastric fluid (pH 1.5). Bp was included by sorption.

hydrogels was 90 ± 5%; the weight of the xerogels was 0.14 ± 0.02 g, and that of the hydrogels was 1.4 ± 0.01 g; so the amount of water inside the hydrogels was 1.26 g ≈ 1.26 mL. If Bp load in the hydrogel was caused only by W_∞, the amount of the drug would be only 12.6 mg and not almost 40 mg as was determined; this fact indicates that interactions between the drug and the hydrogels determined the amount of loaded Bp.

Drug-release experiments showed that the maximum amount of Bp released from 60A/40MMI was 60 ± 4% of that included at pH 7.5 and 80 ± 1% at pH 1.5; for 75A/25MMI, this amount was 52 ± 1% at pH 7.5 and 60 ± 5% at pH 1.5. Thus, Bp interacted with the side groups of the polymeric matrices, and some amount of the drug included was not released.

Release kinetics of Bp from these gels were in accordance with the second Fick's law. Thus, n (Table II) was very close to 0.5, and in accordance with eq. (3), a linear relationship between F_{Bp} and $t^{1/2}$ was observed (Fig. 5). The diffusion coefficients for Bp release were $0.70 \times 10^{-10} \pm 0.29 \times 10^{-10}$ m^2/s and $0.49 \times 10^{-10} \pm 0.02 \times 10^{-10}$ m^2/s for 75A/25MMI in phosphate buffer (pH 7.5) and simulated gastric fluid (pH 1.5), respectively, and $0.69 \times 10^{-10} \pm 0.14 \times 10^{-10}$ m^2/s and $0.31 \times 10^{-10} \pm 0.16 \times 10^{-10}$ m^2/s for 60A/40MMI in pH 7.5 and 1.5 solvent media, respectively. Thus, Bp release at the first stages of the process was slower at pH 1.5, although the total amount of drug released was larger.

Thus, the A/MMI hydrogels were pH sensitive, and they could load a very large amount of Bp by sorption, which was favored due to the interactions between the drug and the side groups of the copolymer. At pH 7.5, the W_∞ of these hydrogels was very high (≈ 90 wt %), and 52% of the Bp load was released. These hydrogels could absorb exudates of wounds and enhance wound healing because they could provide a moist wound environment. Thus, these Bp-loaded hydrogels would be suitable to be used as dressings with analgesic action. On the other hand, at pH 1.5, A/MMI hydrogels released more than 80% of the Bp load, and they would be suitable for Bp release in the stomach.

CONCLUSIONS

The results indicate that A/MMI hydrogels, due to the presence of ionizable carboxylic groups, are pH sensitive, and their W_∞ increases at higher pH, above the pK_a of carboxylic groups (pK_a = 4.6). The release of Bp from these hydrogels depends not only on the pH sensitivity of the polymeric matrices but on the ionized groups of this drug, which causes a larger amount of Bp to be released at acid pH. Analgesic effects of these devices must be confirmed through *in vivo* experiments with laboratory animals.

References

1. Peppas, N. A.; Bures, P.; Leobondung, W.; Ichikawa, H. Eur J Pharm Biopharm 2000, 50, 27.
2. García, O.; Blanco, M. D.; Martín, J. A.; Teijón, J. M. Eur Polym J 2000, 36, 111.
3. García, O.; Trigo, R. M.; Blanco, M. D.; Teijón, J. M. Biomaterials 1994, 15, 689.
4. Sastre, R. L.; Blanco, M. D.; Gómez, C.; del Socorro, J. M.; Teijón, J. M. Polym Int 1999, 48, 843.
5. Blanco, M. D.; Trigo, R. M.; García, O.; Teijón, J. M. J Biomater Sci Polym Ed 1997, 9, 709.
6. Brannon-Peppas, L.; Peppas, N. A. Chem Eng Sci 1991, 46, 715.
7. Scranton, M. B.; Rangaragan, B.; Klier, J. Adv Polym Sci 1995, 120, 1.
8. Khore, N. R.; Peppas, N. A. Biomaterials 1995, 16, 559.
9. Yoo, M. K.; Sung, Y. K.; Lee, Y. M.; Cho, C. S. Polymer 2000, 41, 5713.
10. Dhara, D.; Nisha, C. K.; Chatterji, P. R. Pure Appl Chem A 1999, 36, 197.
11. Vakkalanka, S. K.; Brazel, C. S.; Peppas, N. A. J Biomed Mater Sci Polym Ed 1996, 8, 119.
12. Varshosaz, J.; Falamarzian, M. J Pharm Biopharm 2001, 51, 235.
13. Soppimath, K. S.; Kulkarni, A. R.; Aminabhavi, T. M. J Control Rel 2001, 75, 331.
14. Brofeldt, B.T.; Cornwell, P.; Doherty, D.; Batra, K.; Gunther, R. A. J Burn Care Rehab 1989, 10, 63.
15. Cassuto, J.; Nellgard, P.; Stage, L.; Jönsson, A. Anesthesiology 1990, 75, 302.
16. Eaglstein, W. H. J Am Acad Dermatol 1985, 12, 434.
17. Fulton, J. E. J Dermatol Surg Oncol 1990, 16, 460.
18. Fang, C. H.; Nathan, P.; Robb, E. C. J Burn Care Rehab 1987, 8, 206.
19. Koren, G. Clin Dermatol 1989, 7, 136.
20. Harvey, S. C. In Las Bases Farmacológicas de la Terapéutica;. Gilman, A. G.; Goodman, L. S.; Rall, T. W.; Murad. F., Eds.; Médica Panamericana: Madrid, Spain, 1986; Chapter 17, p 335.
21. Katime, I.; Madoz, A.; Velada, J. L. Rev Iberoam Polim 1993, 2, 73.
22. Blanco, M. D.; García, O.; Trigo, R. M.; Teijón, J. M.; Katime, I. Biomaterials 1996, 17, 1061.
23. Patel, V. R.; Amiji, M. Pharm Res 1996, 13, 588.
24. Kou, J. H.; Amidon, J. L.; Lee, P. I. Pharm Res 1988, 5, 592.
25. Allen, P. E. M.; Bennet, D. J.; Williams, D. R. Eur Polym J 1992, 28, 347.
26. Le Guévello, P.; Le Corre, P.; Chevanne, F.; Le Verge, R. J Chromatogr 1993, 622, 284.
27. Lee, P. I. Polym Commun 1983, 24, 45.
28. Song, S. Z.; Cardinal, J. R.; Kim, S. H.; Kim, S. W. J Pharm Sci 1981, 70, 216.
29. Kiatkamjornwong, S.; Phunchareon, P. J Appl Polym Sci 1999, 72, 1349.
30. Lee, P. I. J Control Rel 1985, 2, 227.
31. Krosmeyer, R. W.; Peppas, N. A. In Controlled Release Delivery Systems; Roseman, T. J.; Monsdarf, S. Z., Eds.; Marcel Dekker: New York, 1983; p 77.
32. Kim, S. W.; Bae, Y. H.; Okano, T. Pharm Res 1992, 9, 283.
33. Carnk, J., Ed. The Mathematics of Diffusion; Clarendon: Oxford, 1975.
34. Lusting, S. R.; Peppas, N. A. J Appl Polym Sci 1988, 36, 735.
35. Fujita, D. In Diffusion in Polymers; Cranck, J.; Park, G. S. Academic: London, 1968; Chapter 3.
36. Yean, L.; Bunel, C.; Vairon, J. P. Makromol Chem 1990, 191, 1119.
37. Skidmore, R.; Patterson, J.; Tomsick, R. Dermatol Surg 1996, 22, 511.
38. Huglin, M. B.; Sloam, D. J. Br Polym J 1983, 15, 165.