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# An Investigation into the Influence of Hydrogel Composition on Swelling Behavior and Drug Release from Poly(Acrylamide-co-Itaconic Acid) Hydrogels in Various Media

**Marija Stanojević**
*Department of Pharmaceutical Technology and Cosmetology, Faculty of Pharmacy, University of Belgrade, Serbia and Montenegro*

**Melina Kalagasidis Krušić and Jovanka Filipović**
*Department of Organic Chemical Technology, Faculty of Technology and Metallurgy, University of Belgrade, Serbia and Montenegro*

**Jelena Parojčić and Mirjana Stupar**
*Department of Pharmaceutical Technology and Cosmetology, Faculty of Pharmacy, University of Belgrade, Serbia and Montenegro*

**The hydrogels prepared by free radical copolymerization of acrylamide and itaconic acid were investigated with regard to their composition and crosslinking degree to find materials with satisfactory swelling and drug release properties. Samples were characterized by measuring the swelling behavior and in vitro release of paracetamol as a model drug in aqueous media with different pH values. The two-factor, three-level experimental design and response surface methodology were applied to statistically evaluate the influence of investigated factors.**

**Keywords** Experimental Design, Hydrogels, Paracetamol Release, Swelling

Hydrogels are hydrophilic, crosslinked polymers made of homo- or copolymers that can absorb significant amounts of water or biological fluids but do not dissolve owing to the presence of chemical or physical cross-links. In chemically crosslinked hydrogels, covalent bonds are present between different polymer chains, while in physically crosslinked hydrogels, dissolution is prevented by ionic interactions, hydrophobic associations, or hydrogen bonds. In general, hydrogels exhibit good biocompatibility. Their hydrophilic surface is characterized by a low interfacial free energy in contact with body fluids, which results in a low tendency for proteins and cells to adhere to these surfaces. Due to their high water content, hydrogels also possess a degree of flexibility similar to natural tissues, which minimizes potential irritation to surrounding membranes and tissues (Hennink and van Nostrum 2002; Peppas et al. 2000). Thus, hydrogels have found widespread biomedical and pharmaceutical applications. They have been increasingly studied for uses such as matrices for tissue engineering, materials for immobilization of enzymes and cells, contact lenses, and drug delivery devices. The ability of molecules of different sizes to diffuse into and out of hydrogels allows their possible use as drug delivery systems for oral, nasal, ocular, rectal, vaginal, and transdermal routes of administration (Gupta, Vermani, and Garg 2002; Hoffman 2002; Qui and Park 2001).

Recently, there has been an increased interest for preparation and characterization of environmentally sensitive or stimuli-sensitive hydrogels that can control drug release by changing the gel structure in response to some environmental stimuli. These hydrogels are called "intelligent" or "smart" because of their ability to change the swelling behavior, permeability, and mechanical strength in response to changes in the pH, ionic strength, temperature, or composition of the surrounding fluid. Due to the large variations in physiological pH values, as well as the pH variations in pathological conditions, pH-responsive polymeric networks have been studied extensively (Gupta et al. 2002; Peppas et al. 2000; Qui and Park 2001).

pH-sensitive hydrogels contain ionizable pendant groups that can release or accept protons in response to the changes in environmental pH. When the pendant groups of the hydrogel are ionized, the gel hydrophilicity increases, and electrostatic repulsion

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Address correspondence to Marija Stanojević, Department of Pharmaceutical Technology and Cosmetology, Faculty of Pharmacy, Vojvode Stepe 450, 11221 Belgrade, Serbia and Montenegro. E-mail: marija@pharmacy.bg.ac.yu

between the equally charged pendant groups causes enhancement in the chain relaxation process along the macromolecular chains, both leading to an increase of solvent uptake in the polymeric matrix. The swelling of hydrogels with anionic pendant groups (i.e., carboxylic acid) increases when the pH of the external medium is above the $pK_a$ of the ionizable group. When the pendant groups are basic (i.e., amines), the swelling of hydrogels increases in media with pH below the $pK_b$ of the ionizable group. The extent of swelling can be controlled by the amount of ionic groups. Therefore, pH-sensitive hydrogels have been used most frequently to develop controlled release formulations for oral administration (Alvarez-Lorenzo and Concheiro 2002; Bernardo et al. 2002).

During the past decade, pH-sensitive hydrogels based on polyacrylamide copolymers with acrylic and maleic acid have been studied extensively (Isik 2004; Katime et al. 1999; Bajpai 2001; Saraydin et al. 2001; Sen, Uzun, and Guven 2000). Some research has dealt with hydrogels based on polyacrylamide and itaconic acid or its esters (Karadag, Saraydin, and Guven 2001; Kayaman et al. 1999; Blanco et al. 1996, 2003; Karadag et al. 1996). It was reported that hydrogels of acrylamide and itaconic acid exhibit very high capability to absorb water and have good biocompatibility (Blanco et al. 1996; Karadag et al. 1996).

However, the hydrogels of acrylamide and itaconic acid synthesized by free radical copolymerization with different amounts of crosslinking agent and monomer ratio have not been studied extensively. Itaconic acid has two ionizable groups, with different $pK_a$ values, which can form hydrogen bonds. The potential for substitution of acrylic and methacrylic acid in polymers with itaconic acid is high. Its outstanding properties in polymer chemistry, pharmacy, and agriculture open up new applications. It also is interesting that itaconic acid is obtained by fermentation from renewable resources using carbohydrate materials containing sucrose and glucose, such as molasses and hydrolyzed starch (Kirimura et al. 1997; Willke and Vorlop 2001).

The aim of our present work was to investigate the swelling properties of the hydrogels based on acrylamide and itaconic acid with different crosslinking agent concentrations and itaconic acid contents as a response to the changes of pH, as well as their potential use as drug delivery systems. Paracetamol, classified as highly permeable and highly soluble drug according to the Biopharmaceutics Classification System (Amidon and Lobenberg 2000), and present in a nonionized form throughout the gastrointestinal pH range ($pK_a$9.5), was selected as a model drug. Hydrogels were loaded with paracetamol by immersing the dry discs in the aqueous drug solution (Bettini, Colombo, and Peppas, 1995; Quaglia et al. 2001; Rodriguez, Alvarez-Lorenzo, and Concheiro 2003; Sen et al. 2000; Sen and Yakar 2001).

To statistically evaluate the effect of crosslinking agent concentration and itaconic acid content, factorially designed experiments were conducted, followed by multiple regression analysis and response surface methodology (Box, Hunter, and Hunter 1978; Montgomery 1997).

## MATERIALS AND METHODS

The monomers used in this study, acrylamide (AAm) and itaconic acid (IA), were obtained from Merck (Germany) and Fluka (Switzerland), respectively. The crosslinking agent N,N′-methylenebisacrylamide (MBA) was obtained from Serva (Germany). Potassium persulphate (PPS) and potassium pyrosulphate (PyPS), as the initiator and the accelerator, respectively, were obtained from Merck (Germany). All materials were used as received, without purification. Distilled water was used in copolymerizations. Paracetamol (Merck, Germany) was used as a model drug. Aqueous media with different pH values were prepared using hydrochloric acid (Lachema, Czech Republic), potassium chloride (Alkaloid, Macedonia), potassium dihydrogenphosphate (Lachema, Czech Republic), and sodium hydroxide (Zorka Pharma, Serbia).

### Hydrogel Preparation

The copolymer hydrogels of AAm and IA were obtained by free radical crosslinking copolymerization at 60°C during 24 hr. All 9 samples were prepared with different AAm/IA weight ratios and MBA concentrations according to the two-factor, three-level experimental design. One part by weight of the monomer mixture was dissolved in 9 parts by weight of water, and the initiator redox couple PPS/PyPS (1.0 wt% with respect to the monomers) was added. The reaction mixture was purged with $N_2$ and poured between two glass plates sealed with a rubber spacer. After completion of the reaction, gels were cut into discs and repeatedly washed with distilled water for 1 week to remove the unreacted materials. After washing, the discs were dried at room temperature to xerogels (1 mm thick and 5 mm in diameter). By weighing the unreacted materials, it was found that the conversion was practically complete (∼99%).

### Swelling Studies

The equilibrium swelling behavior of the prepared PAAm/IA hydrogels as a function of pH was monitored gravimetrically at 37°C. Three aqueous media with different pH values were used, namely: USP hydrochloric acid buffer (pH 2.2), 0.05 M $KH_2PO_4$ (pH 4.5), and USP phosphate buffer (pH 6.8). The swelling degree (q) was calculated from the following:

$$q = \frac{W_t}{W_0} \quad [1]$$

where $W_0$ and $W_t$ are the weights of the xerogel at time 0 and swollen hydrogel at time t, respectively. The equilibrium swelling degree ($q_e$) was calculated as follows:

$$q_e = \frac{W_e}{W_0} \quad [2]$$

where $W_e$ is the weight of swollen hydrogel at equilibrium state.

Water transport in polymer networks, i.e., swelling-time curves, may be described by the following equation (Khare and Peppas 1995):

$$\frac{M_t}{M_e} = kt^n \quad [3]$$

In this expression, k is a proportionality constant related to the structure of the network, n is a diffusion exponent, $M_t$ and $M_e$ are the amounts of water absorbed at time t and at equilibrium, respectively. This equation was applied to the first 60% of the total amount of absorbed water. The parameters n and k were calculated using the power fitting function (MS Excel 97).

## Experimental Design

The two-factor, three-level factorial design was applied to investigate the influence of selected independent variables on the swelling behavior of PAAm/IA hydrogels. The two independent variables were $X_1$—crosslinking agent concentration (2.0, 2.5 and 3.0 wt%); $X_2$—itaconic acid content (10, 5, and 1 wt% with respect to the monomers). Prepared hydrogels were designated as samples H1–H9. The selected response variables (Y) were the equilibrium swelling degrees obtained in aqueous media pH 2.2, 4.5, and 6.8. The experimental matrix and the response variables, for 3 different pH values, are presented in Table 1.

Multiple linear regression was applied to the experimental results to calculate the regression coefficients ($b_0 - b_5$) of the mathematical model, which includes the linear and quadratic terms of the investigated factors, as well as the interaction factor (Equation 4).

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_1^2 + b_4X_2^2 + b_5X_1X_2 \quad [4]$$

Student's *t*-test was applied to each term of the quadratic model to evaluate their significance. Only the significant terms were included in the final model ($p < 0.05$). After estimation of the regression coefficients, the experimental matrix was used to present the results as a response surface and contour plots.

## Loading of Drug

Hydrogels were loaded with paracetamol by immersing the dry discs in the aqueous drug solution (10 mg/ml) at room temperature for 2 days. Preliminary tests revealed that 2 days was the minimum time to ensure maximal drug loading. After that time the hydrogels were removed from the drug solution and left to dry to the constant weight. To assess the amount of loaded drug, the paracetamol content in reference hydrogel sample was determined both spectrophotometrically and calculated as a weight difference of sample before swelling in drug solution and after drying to the constant weight. As the obtained results were in accordance, the amount of loaded drug in hydrogels was attained by difference in weight, also reported by Bernardo et al. 2002.

## Release Studies

The release studies were performed using the rotating basket apparatus (Erweka DT 70, Germany), in 500 ml of selected media at 37°C at 50 rpm. The aqueous media pH 2.2, 4.5, and 6.8 were used as drug release media. At predetermined times, 3-ml samples were removed, filtered, properly diluted, and assayed for paracetamol at 243 nm using a Varian Cary UV-VIS spectrophotometer. The amount of paracetamol was determined using the validated calibration curve. All data points were determined as the average value of 3 independent measurements. The amount of drug released was expressed as the percent of drug load in the hydrogel sample.

Drug release kinetics were evaluated using the following equation (Peppas 1985):

$$\frac{M_t}{M_e} = kt^n \quad [5]$$

where $M_t$ and $M_e$ are the amounts of drug released at any time t and at equilibrium, respectively; k is the kinetic constant and the exponent n characterizes the mechanism of drug release. The experimental data were fitted to the proposed equation using the power function (MS Excel 97).

The dissolution profiles of different hydrogel compositions were compared using the similarity factor ($f_2$) as proposed by FDA Guidance (1997):

$$f_2 = 50 \log \left\{ \left[ 1 + \frac{1}{n} \sum_{n=1}^{t} (R_t - T_t)^2 \right]^{-0.5} \cdot 100 \right\} \quad [6]$$

where $R_t$ and $T_t$ are percent dissolved at each time point for the reference sample and the test sample, respectively. Using the $f_2$ values dissolution profiles are considered dissimilar if these values are less than 50.

## RESULTS AND DISCUSSION

The equilibrium swelling degrees of the investigated hydrogels obtained in 3 different media, selected as the response variables in the $3^2$ experimental design, are listed in Table 1. Multiple regression analysis revealed that both crosslinking agent concentration and monomer ratio significantly influence the hydrogel swelling behavior. At pH 2.2 and pH 6.8, the effect of crosslinking agent concentration was linear and quadratic, whereas IA content exhibited only linear effect. When swelling experiments were monitored at pH 4.5, the most significant was the linear effect of IA content. The interaction factor also was significant in all cases studied. The summary of the multiple regression analysis is reported in Table 2. The mathematical models obtained from these results could be useful for prediction of the swelling behavior with respect to the IA content and crosslinking density of the investigated hydrogels.

The response surface and contour plots of equilibrium swelling degree versus crosslinking agent concentration versus

TABLE 1
Experimental matrix and the obtained response variables

| Sample | $X_1$ MBA wt% | $X_2$ IA content | Y $q_e$ (pH 2.2) | Y $q_e$ (pH 4.5) | Y $q_e$ (pH 6.8) |
|---|---|---|---|---|---|
| H1 | 2.0 | 10 | 14.1 | 35.3 | 55.2 |
| H2 | 2.5 | 10 | 12.2 | 29.0 | 50.5 |
| H3 | 3.0 | 10 | 7.5 | 28.0 | 40.8 |
| H4 | 2.0 | 5 | 13.0 | 25.6 | 34.8 |
| H5 | 2.5 | 5 | 14.3 | 26.0 | 32.5 |
| H6 | 3.0 | 5 | 13.3 | 23.1 | 27.1 |
| H7 | 2.0 | 1 | 14.9 | 17.4 | 18.8 |
| H8 | 2.5 | 1 | 17.6 | 19.2 | 19.6 |
| H9 | 3.0 | 1 | 14.8 | 16.2 | 17.2 |

IA content in aqueous media pH 2.2, 4.5 and 6.8 are given in Figures 1a, 1b, and 1c, respectively.

It is obvious that an increase of IA content would favor the swelling, which is highly pH dependent due to complexation, via hydrogen bonding, between the PIA carboxylic groups and PAAm amide groups. This complexation occurs at low pH and results in increased hydrophobicity of the network and lower $q_e$ values. At higher pH values carboxylic groups ionize and the complexes are broken. As the degree of ionization increases in media with pH above the nominal $pK_a$ values of IA, 3.85 and 5.44 (Wheast 1975), the swelling degree increases for three reasons: most of H-bonds are broken, carboxylate groups are more hydrophilic than carboxylic groups, and the electrostatic repulsion between the carboxylate groups pushes the network chains apart. The most pronounced pH sensitivity was observed for samples with high IA content (10 wt%), whereas it was less noticeable for hydrogels containing lower amounts of IA (5 and 1 wt%). As expected, higher values of $q_e$ were observed at lower crosslinking ratios.

The kinetic parameters of the swelling process are summarized in Table 3. The diffusion exponent n was used to determine

TABLE 2
Summary of the multiple regression analysis

| Regression coefficient | pH 2.2 | pH 4.5 | pH 6.8 |
|---|---|---|---|
| $b_0$ | −31.6989* | 16.6831 | −30.0302 |
| $b_1$ | 37.3762* | — | 37.3339 |
| $b_2$ | 1.3873* | 3.1713 | 6.9182 |
| $b_3$ | −7.1000* | — | −7.5333 |
| $b_4$ | — | — | — |
| $b_5$ | −0.7549 | −0.6881 | −1.4189 |
| $R^2$ | 0.9214 | 0.9497 | 0.9993 |

*$p < 0.1$.

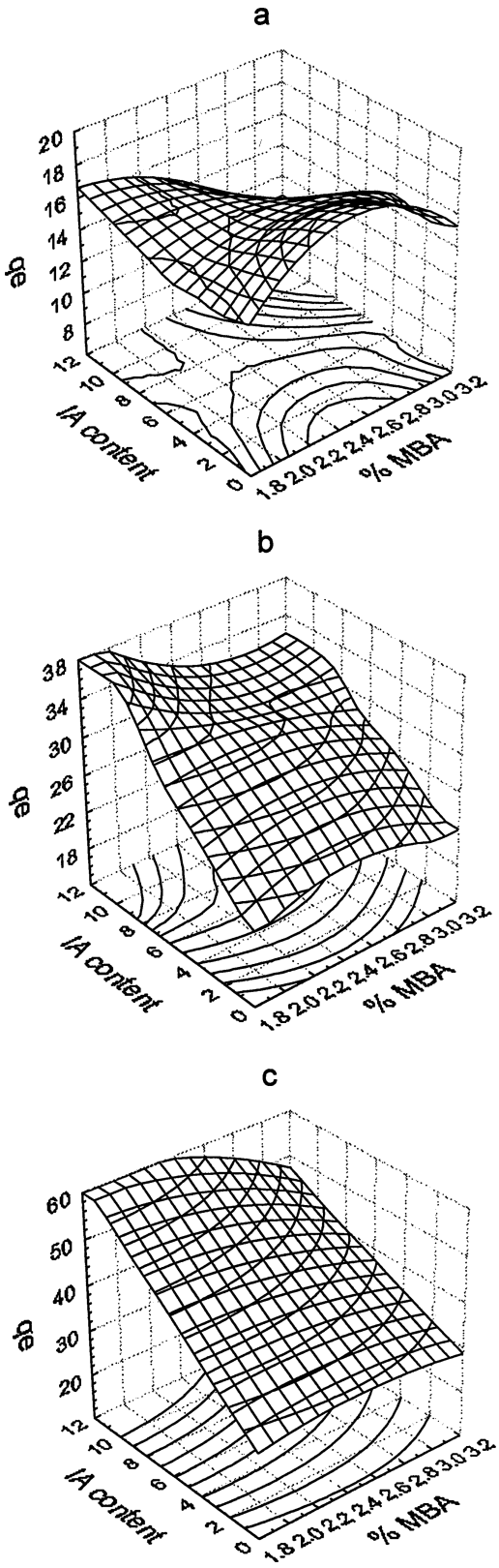


FIG. 1. Response surface and contour plot of equilibrium swelling degree ($q_e$) versus crosslinking agent concentration (% MBA) versus IA content for PAAm/IA hydrogels in aqueous media pH 2.2 (a), pH 4.5 (b), and pH 6.8 (c).

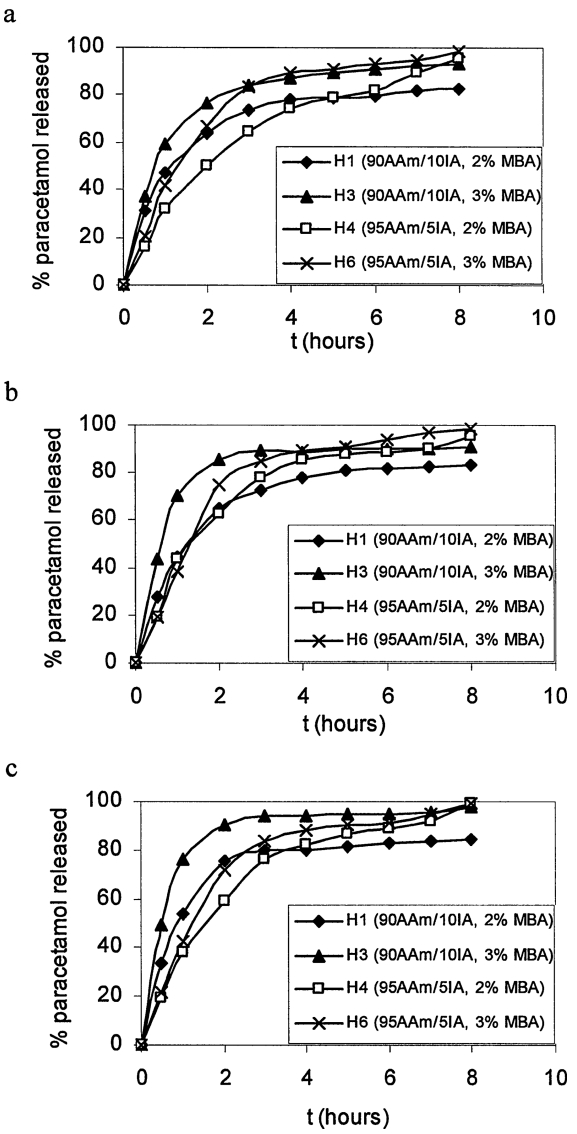


FIG. 2. Drug release profiles obtained in aqueous media pH 2.2 (a), pH 4.5 (b), and pH 6.8 (c) for PAAm/IA hydrogels with varying IA content and crosslinking agent concentration (standard deviation error bars were omitted because they overlap symbols).

the mechanism of the swelling process. In Case I the value of n = 0.5 signifies a Fickian water diffusion mechanism, where water diffusion controls the process, while in Case II the value of n = 1.0 signifies a mechanism in which macromolecular relaxations predominate. For $0.5 < n < 1.0$ the mechanism is non-Fickian, where both diffusion and polymer relaxation control the process of water uptake. The n values for all the samples were higher than 0.5 and increased at pH 4.5 and 6.8 (Table 3). These results indicate that at higher pH values (above the IA $pK_a$ value 3.85) chain relaxation is favored in the swelling process. As IA ionization proceeds, the osmotic swelling pressure increases as well as macromolecular relaxation, as explained earlier, and a non-Fickian water transport mechanism is observed.

TABLE 3
Kinetic swelling parameters for water transport into the PAAm/IA hydrogels obtained in different media

| | pH 2.2 | | | pH 4.5 | | | pH 6.8 | | |
|---|---|---|---|---|---|---|---|---|---|
| Sample | k | n | $R^2$ | k | n | $R^2$ | k | n | $R^2$ |
| H1 | 0.24 | 0.45 | 0.945 | 0.19 | 0.69 | 0.995 | 0.17 | 0.78 | 0.989 |
| H2 | 0.38 | 0.58 | 0.945 | 0.32 | 0.76 | 0.975 | 0.25 | 0.88 | 0.988 |
| H3 | 0.46 | 0.62 | 0.982 | 0.29 | 0.76 | 0.942 | 0.30 | 0.82 | 0.938 |
| H4 | 0.35 | 0.52 | 0.974 | 0.35 | 0.62 | 0.975 | 0.27 | 0.80 | 0.988 |
| H5 | 0.29 | 0.61 | 0.979 | 0.26 | 0.69 | 0.983 | 0.27 | 0.73 | 0.980 |
| H6 | 0.34 | 0.58 | 0.994 | 0.32 | 0.60 | 0.991 | 0.35 | 0.59 | 0.981 |
| H7 | 0.37 | 0.48 | 0.972 | 0.26 | 0.70 | 0.993 | 0.31 | 0.59 | 0.984 |
| H8 | 0.25 | 0.63 | 0.992 | 0.24 | 0.71 | 0.981 | 0.29 | 0.72 | 0.995 |
| H9 | 0.29 | 0.78 | 0.984 | 0.32 | 0.61 | 0.991 | 0.35 | 0.59 | 0.981 |

To evaluate the potential of the prepared hydrogels as drug delivery systems, drug release from paracetamol loaded hydrogel samples was investigated. Hydrogel samples with high and medium IA content and the MBA concentration 2.0 wt% (H1 and H4) and 3.0 wt% (H3 and H6) were selected for this investigation. The amount of paracetamol loaded into the samples H3 and H6 prepared with 3.0 wt% of MBA was substantially lower (24 and 14 mg per disc, respectively) then in samples H1 and H4 (48 and 30 mg per disc, respectively). As expected, drug loading correlated with the swelling behavior, as it was increased with IA content and at lower crosslinking agent concentrations.

The release profiles obtained for samples H1, H3, H4 and H6 in aqueous media pH 2.2, 4.5, and 6.8 are presented in Figures 2a, 2b, and 2c, respectively. We can see that the increase in IA content, as well as in crosslinking agent concentration, led to the higher drug release rate. This effect was more pronounced at pH 6.8 than at lower pH values, which was in accordance with the results of swelling studies. The effect of the IA content could be explained on the basis of the swelling behavior of hydrogels, as a function of IA ionization. A highly swollen hydrogel released a greater amount of loaded drug, as expected.

On the other hand, the effect of crosslinking agent concentration on drug release does not completely correlate with the swelling behavior, where the increase of the proportion of crosslinking agent led to decrease of the equilibrium swelling degree. The reason for higher drug release rate from samples H3 and H6 may be in a higher network density and small available free volume between the chains. Therefore, small capacity for drug loading, located near the surface, caused rapid drug release. Furthermore, for samples with higher MBA concentration the equilibrium swelling is attained earlier than for those containing lower amounts of MBA, also reported by Bajpai and Giri 2003. At higher crosslink density the network chains are quite inflexible and, therefore, even at lower water uptake the hydrogel appears to have equilibrated. Therefore, the possible explanation for faster drug release from densely crosslinked hydrogels may

TABLE 4
Kinetic parameters of drug release profiles obtained in different media

| | pH 2.2 | | | pH 4.5 | | | pH 6.8 | | |
|---|---|---|---|---|---|---|---|---|---|
| Sample | k | n | $R^2$ | k | n | $R^2$ | k | n | $R^2$ |
| H1 | 0.45 | 0.51 | 0.990 | 0.42 | 0.63 | 0.996 | 0.51 | 0.59 | 0.987 |
| H3 | 0.55 | 0.53 | 0.976 | 0.63 | 0.49 | 0.952 | 0.69 | 0.44 | 0.949 |
| H4 | 0.29 | 0.76 | 0.985 | 0.37 | 0.85 | 0.954 | 0.35 | 0.82 | 0.984 |
| H6 | 0.38 | 0.87 | 0.983 | 0.38 | 0.99 | 1.000 | 0.40 | 0.85 | 0.997 |

be the shorter time needed for swelling and, hence, quick release of small amounts of a solute, probably entrapped toward the surface of the gel matrix.

To establish a link between drug release and molecular transport parameters, the dissolution data were evaluated by applying the Peppas kinetic model (Equation 5). The release kinetic parameters of four hydrogels, obtained at various pH values, are given in Table 4. The values of release exponent n for samples H4 and H6 were higher than 0.5 in all media, indicating non-Fickian drug release kinetics. These results are consistent with the swelling behavior, meaning that both diffusion and polymer relaxation control the overall rate of water uptake and consequently drug release kinetics. For sample H3 the value of n was below 0.5 at pH 4.5 and 6.8, in contrast with the swelling results. This suggests that hydrogels with higher IA content and crosslinking agent concentration, at higher pH values, exhibit drug release mechanisms determined by Fickian diffusion. Possible explanation for this effect could be that in a densely crosslinked hydrogel the chain relaxation is suppressed and the water diffusion process predominates.

However, this phenomenon was not observed in hydrogels with lower IA content where both chain relaxation and Fickian diffusion affect drug transport nevertheless of proportion of MBA. The obtained differences in the release exponent values indicate the influence of hydrogel composition on drug release kinetics. These differences were additionally documented with the calculated values of the similarity factor $f_2$, reported in Table 5. The most pronounced differences were found for H3 sample in comparison to the other three formulations, where $f_2$ values were less than 50 in all the media investigated.

Hydrogel sample prepared with high levels of both investigated factors exhibited the highest drug release rate, where mechanism of drug release was Fickian diffusion. Decrease of both investigated factors led to slower drug release followed by non-Fickian kinetics.

TABLE 5
Values of similarity factor ($f_2$) for investigated dissolution profiles

| | H1–H3 | H1–H4 | H1–H6 | H3–H4 | H3–H6 | H4–H6 |
|---|---|---|---|---|---|---|
| pH 2.2 | 48.57 | 49.95 | 53.08 | 32.66 | 46.55 | 42.60 |
| pH 4.5 | 34.77 | 61.69 | 50.83 | 32.61 | 33.87 | 58.16 |
| pH 6.8 | 37.33 | 47.42 | 53.71 | 23.99 | 28.28 | 56.37 |

## CONCLUSION

The results of the present study revealed that both the IA content and crosslinking agent concentration significantly influence swelling behavior of PAAm/IA hydrogels synthesized by free radical copolymerization. Water uptake was favored by the increase of IA content and at lower crosslinking agent concentrations. The investigated hydrogels exhibited pH-dependent swelling behavior with the restricted swelling and lower equilibrium swelling degrees at lower pH values (pH 2.2). The mechanism of water uptake was non-Fickian with increased macromolecular relaxation at higher pH values. By applying multiple regression analysis, the mathematical models predictable of hydrogel swelling behavior with respect to the applied IA content and crosslinking agent concentration were developed.

The investigated factors also influenced the drug uptake into the hydrogels, as it was increased with IA content and at lower crosslinking agent concentrations. However, drug release from densely crosslinked hydrogels was faster. The hydrogel sample prepared with high levels of both investigated factors exhibited the fastest drug release, governed by Fickian diffusion at higher pH values. This indicates that the drug-loading capacity, as well as the rate and mechanism of drug release, could be controlled by hydrogel composition and crosslinking density, which is important for application of the investigated hydrogels as drug delivery systems.

## REFERENCES

Alvarez-Lorenzo, C., and Concheiro, A. 2002. Reversible adsorption by a pH- and temperature-sensitive acrylic hydrogel. *J. Control. Rel.* 80:247–257.

Amidon, L. G., and Lobenberg, R. 2000. Modern bioavailability, bioequivalence and biopharmaceutics classification system. New scientific approaches to international regulatory standards. *Eur. J. Pharm. Biopharm.* 50:3–12.

Bajpai, S. K. 2001. Swelling-deswelling behavior of poly(acrylamide-co-maleic acid) hydrogels. *J. Appl. Polym. Sci.* 80:2782–2789.

Bajpai, A. K., and Giri, A. 2003. Water sorption behaviour of highly swelling (carboxymethylcellulose-g-polyacrylamide) hydrogels and release of potassium nitrate as agrochemical. *Carbo. Polym.* 53:271–279.

Bernardo, M. V., Blanco, M. D., Olmo, R., and Teijon, J. M. 2002. Delivery of Bupivacaine included in poly(acrylamide-co-monomethyl itaconate) hydrogels as a function of the pH swelling medium. *J. Appl. Polym. Sci.* 86:327–334.

Bettini, R., Colombo, P., and Peppas, N. A. 1995. Solubility effects on drug transport through pH-sensitive, swelling-controlled release systems: transport of theophylline and metoclopramide monohydrochloride. *J. Control. Rel.*37:105–111.

Blanco, M. D., Garcia, O., Trigo, R. M., Teijon, J. M., and Katime, I. 1996. 5-Fluorouracil release from copolymeric hydrogels of itaconic acid monoester. *Biomaterials* 17:1061–1067.

Blanco, M. D., Bernardo, M. V., Teijon, C., Sastre, R. L., and Teijon, J. M. 2003. Transdermal application of bupivacaine-loaded poly(acrylamide-co-monomethyl itaconate) hydrogels. *Int. J. Pharm.* 255:99–107.

Box, G. E. P., Hunter, W. G., and Hunter, J. S. 1978. *Statistic for Experimenters. An Introduction to Design, Data Analysis and Model Building*. New York: John Wiley & Sons.

FDA Guidance for Industry 1997. *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*. Rockville, MD: Center for Drug Evaluation and Research.

Gupta, P., Vermani, K., and Garg, S. 2002. Hydrogels: from controlled release to pH- responsive drug delivery. *Drug Dis. Today*7:569–579.

Hennink, W. E., and van Nostrum, C. F. 2002. Novel crosslinking methods to design hydrogels. *Adv. Drug Del. Rev.* 54:13–36.

Hoffman, A. S. 2002. Hydrogels for biomedical applications. *Adv. Drug Del. Rev.* 54:3–12.

Isik, B. 2004. Swelling behavior and determination of diffusion characteristics of acrylamide-acrylic acid hydrogels. *J. Appl. Polym. Sci.* 91:1289–1293.

Karadag, E., Saraydin, D., and Cetinkaya, S., and Guven, O. 1996. In vitro swelling studies and preliminary biocompatibility evaluation of acrylamide-based hydrogels. *Biomaterials* 17:67–70.

Karadag, E., Saraydin, D., and Guven, O. 2001. Radiation induced superabsorbent hydrogels. Acrylamide/Itaconic acid copolymers. *Macromol. Mater. Eng.* 286:34–42.

Katime, I., Novoa, R., Diaz de Apodaca, E., Mendizabal, E., and Puig, J. 1999. Theophylline release from poly(acrylic acid-co-acrylamide) hydrogels. *Polym. Test.* 18: 559–566.

Kayaman, N., Hamurcu, E. E. G., Uyanik, N., and Baysal, B. M. 1999. Interpenetrating hydrogel networks based on polyacrylamide and poly(itaconic acid): synthesis and characterization. *Macromol. Chem. Phys.* 200:231–238.

Khare, A. R., and Peppas, N. A. 1995. Swelling/deswelling of anionic copolymer gels. *Biomaterials* 16:559–567.

Kirimura, K., Sato, T., Nakanishi, N., Terada, M., and Usami, S. 1997. Breeding of starch-utilizing and itaconic-acid-producing koji molds by interspecific protoplast fusion between Aspergillus terreus and Aspergillus usamii. *Appl. Microbiol. Biotechnol.* 47:127–131.

Montgomery, D. 1997. *Design and Analysis of Experiments*, 4th ed. New York: John Wiley & Sons.

Peppas, N. A. 1985. Analysis of Fickian and non-Fickian drug release from polymers. *Pharm. Acta Helv.*60:110–111.

Peppas, N. A., Bures, P., Leobandung, W., and Ichikawa, H. 2000. Hydrogels in pharmaceutical formulations. *Eur. J. Pharm. Biopharm.* 50:27–46.

Qiu, Y., and Park, K. 2001. Environment-sensitive hydrogels for drug delivery. *Adv. Drug Deliv. Rev.* 53:321–339.

Quaglia, F., Varricchio, G., Miro, A., La Rotonda, M. I., Larobina, D., and Mensitieri, G. 2001. Modulation of drug release from hydrogels by using cyclodextrins: the case of nicardipine/$\beta$-cyclodextrin system in crosslinked polyethylenglycol. *J. Control. Rel.* 71:329–337.

Rodriguez, R., Alvarez-Lorenzo, C., and Concheiro, A. 2003. Interactions of ibuprofen with cationic polysaccharides in aqueous dispersions and hydrogels. Rheological and diffusional implications. *Eur. J. Pharm. Sci.* 20:429–438.

Saraydin, D., Karadag, E., Caldiran, Y., and Guven, O. 2001. Nicotine-selective radiation-induced poly(acrylamide/maleic acid) hydrogels. *Radiat. Phys. Chem.* 60:203–210.

Sen, M., Uzun, C., and Guven, O. 2000. Controlled release of terbinafine hydrochloride from pH sensitive poly(acrylamide/maleic acid) hydrogels. *Int. J. Pharm.* 203: 149–157.

Sen, M., and Yakar, A. 2001. Controlled release of antifungal drug terbinafine hydrochloride from poly(N-vinyl 2-pyrrolidone/itaconic acid) hydrogels. *Int. J. Pharm.* 228:33–41.

Wheast, R. C. 1975. *Handbook of Chemistry and Physics*, 53rd ed. Cleveland, OH: CRC Press.

Willke, T., and Vorlop, K. D. 2001. Biotechnological production of itaconic acid. *Appl. Microbiol. Biotechnol.* 56:289–295.