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Original research paper

Swelling behavior and release properties of pH-sensitive hydrogels based on methacrylic derivatives

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The purpose of this study is to develop novel intestinal-specific drug delivery systems with pH sensitive swelling and drug release properties. Methacrylic-type polymeric prodrugs were synthesized by free radical copolymerization of methacrylic acid, poly(ethyleneglycol monomethyl ether methacrylate) and a methacrylic derivative of *N*-(4-hydroxyphenyl)-2-(4-methoxyphenyl) acetamide in the presence of ethylene glycol dimethacrylate as crosslinking agent. The effect of copolymer composition on the swelling behavior and hydrolytic degradation were studied in simulated gastric (SGF, pH 1.2) and intestinal fluids (SIF, pH 7.0). The dynamic swelling behavior of these hydrogels was investigated to determine the mechanism of water transport through these hydrogels. The mechanism of water transport through the gels was significantly affected by the pH of the swelling medium and became more relaxation-controlled in a swelling medium of pH 7.0. The swelling and hydrolytic behaviors of hydrogels were dependent on the content of methacrylic acid (MAA) groups and caused a decrease and increase in gel swelling in SGF and SIF, respectively. Drug release studies showed that the increasing content of MAA in the copolymer enhances hydrolysis in SIF. These results suggest that pH-sensitive systems could be useful for preparation of a muccoadhesive system and controlled release of *N*-(4-hydroxyphenyl)-2-(4-methoxyphenyl) acetamide.

Keywords: pH-sensitive hydrogels, swelling, controlled release, poly(ethylene glycol), poly(methacrylic acid)

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Systems based on block copolymers of ethylene oxide and methacrylic acid, poly(ethylene oxide)-block-poly(methacrylic acid), PEO-block-PMAA, are potential materials for various applications, such as drug delivery and gene therapy (1–4), emulsifiers (5), flocculants for wastewater treatment and papermaking (6), soil improvement (7), mineralization templates and crystal growth modifiers (8). In addition to the vast field of possible applications, the research on model systems of synthetic polymers provides valuable information on the mechanisms of interactions in living organisms.

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Responsive hydrogel networks consisting of polymethacrylic acid (PMAA) and poly(ethylene glycol) (PEG) are classic examples of pH-sensitive carriers that exhibit swelling transitions in response to changes in pH (9, 10). A hydrogel containing a backbone of PMAA and grafts with PEG exhibits a relatively low degree of swelling under complex-promoting conditions (low pH when acid is protonated) and a high degree of swelling when the complex is broken (high pH when the acid is neutralized) (11). A major direction in the drug delivery research concerning development of anti-inflammatory agent today is focused on how to reduce the toxicity of the existing drugs without loss of therapeutic activity. Polymer-anti-inflammatory drug conjugation has been the major approach to reducing toxicity and increasing therapeutic efficacy of the drugs (12, 13). Derivatives of phenylacetic acid are used extensively as non-steroidal anti-inflammatory agents for the treatment of edema, erythematious and the resulting tissue damage associated with inflammatory diseases (14), despite the fact that this type of compound exerts considerable hepatic toxicity, as claimed by the Food and Drugs Administration (15). In order to maintain the concentration of anti-inflammatory agent in the therapeutic range, decreasing its hepatic toxicity and protection of gastric mucus to inflammation effects, we have developed two hydrogel systems based on PEG. This paper is concerned with the synthesis of poly(methacrylic acid-co-ethyleneglycol monomethyl ether-co-*N*-(4-methacryloyloxyphenyl)-2-(4-methoxyphenyl) acetamide) (poly[MAA-co-EGMA-co-MOPA]) grafted with ethyleneglycol dimethacrylate (EGDMA). The swelling characteristics and drug release properties of the hydrogel were investigated as well.

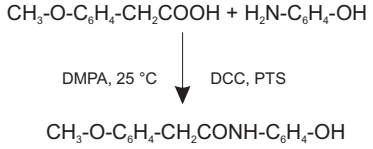
EXPERIMENTAL

Reagents

Poly(ethylene glycol) monomethyl ether methacrylate (PEGMA) was purchased from Aldrich (France) (M_r = 600, 1000, 1500, 3000). Each PEGMA sample was freeze-dried from benzene. The crosslinking agents used were EGDMA and methacrylic acid (Aldrich) which were purified by distillation under vacuum. Methacryloyl chloride (MACl, Fluka, France), 4-dimethylaminopyridine (DMAP, Fluka) and dicyclohexylcarbodiimide (DCC, Merck, France) were used as received. 4-Methoxyphenylacetic acid (MPA, Fluka), 4-aminophenol (Fluka) and 2,2'-azobisisobutyronitrile (AIBN, Aldrich) were purified by recrystallization from acetone/heptane, ethanol/heptane and methanol, respectively. *p*-Toluene sulfonic acid (PTS) was synthesized from sulfonic acid and toluene (12).

Synthesis of N-*(4-hydroxyphenyl)-2-(4-methoxy phenyl) acetamide*

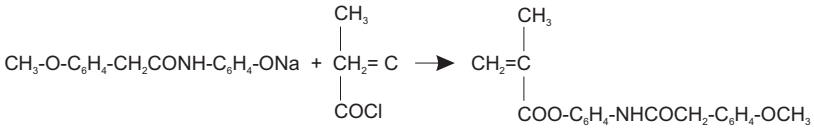
A mixture of 4-methoxy phenyl acetic acid (8.3 g, 0.05 mol), with 4-aminophenol (5.45 g, 0.05 mol), dicyclohexylcarbidiimide (10.31 g, 0.05 mol), 4-(dimethylamino) pyridine (0.61 g, 0.005 mol) and *p*-toluenesulphonic acid (0.86 g, 0.005 mol) in dichloromethane/acetone mixture (1:1, 100 mL) was stirred for 24 h at room temperature. The filtrate was concentrated until syrup formation, which was crystallized in chloroform, filtered and washed with chloroform. DCC method of the anti-inflammatory agent synthesis is given in Scheme 1.



Scheme 1.

Synthesis of N*-(4-methacryloyloxyphenyl)-2-(4-methoxyphenyl) acetamide (MOPA)*

Following the Schotten Bauman reaction (16), the methacrylic monomer was prepared by the reaction of *N*-(4-hydroxyphenyl)-2-(4-methoxy phenyl) acetamide with methacryloyl chloride. In a three-necked round-bottomed flask, the freshly distilled methacryloyl chloride (0.1 mol) was added dropwise with a syringe to a solution of anti-inflammatory agent (0.075 mol) and sodium hydroxide (5 g) in a mixture of 1:1 dioxane/water (1:1, 100 mL). The reaction was continued for further 3 hours at 0 °C. The MOPA precipitate was filtered and recrystallized twice from methanol/water, filtered and dried (Scheme 2).

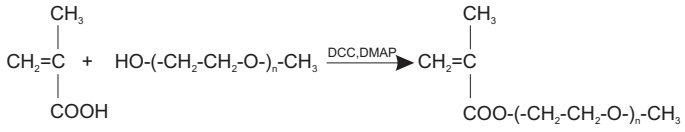


Scheme 2.

Synthesis of poly(ethylene glycol) monomethyl ether monomethacrylate (PEGME)

MAA (0.081 g, 1 mmol), poly(ethyleneglycol methylether (PEGME 600) (2 g, 1 mmol), DMAP (0.061 g, 0.5 mmol), and DCC (0.413 g, 2 mmol) were dissolved in 40 mL of dichlomethane. The reaction was left for 24 hours under stirring. The precipitated dicyclohexylurea was filtered and then the solvent was evaporated from the filtrate. Carbodiimide based reaction to synthesize PEGME (21) is presented in (Scheme 3). The synthesized product was dissolved in deionized water and extracted with heptane followed by a mixture of hexane/dichlomethane (1:1). Finally, the organic phase was evaporated and dried.

The same procedure was followed for the rest of PEGME (M_r = 1000–3000).



Scheme 3.

Characterization of products

Spectra were recorded in KBr pellets on a Perkin-Elmer spectrometer FTIR GENESIS II Shimadzu (Japan) at room temperature. ^{1}H NMR spectra were recorded in deutered dimethylsulfoxide (DMSO-d_6) solutions on a BRUKER 400 MHz spectrometer at 75 °C in 2% (*m*/*V*) solutions. The melting point was determined by DSC using Labsys^{TM} DSC16 Setaram (France). Physical and spectral data are summarized in Table I.

Table I. Melting points, yields and spectral data for synthesized compounds

Compound (name, chemical structure)	IR (ν, cm^{-1})		^{1}H NMR (δ, ppm)			Yield (%)	M.p. (°C)
N-(4-hydroxyphenyl)-2-(4-methoxy phenyl) acetamide (AA) CH_3-O-C_6H_4-CH_2CONH-C_6H_4-OH	-CH_3O- Ar-OH -CONH- -COO- -Ar-	1240 1030 3310 1735 1610, 1580	-Ar- -CH_3O- Ar-CH_2CONH- -CONH-	m s s s	6.7–7.4 3.77 3.50 9.85	58	165–168
N-(4-methacryloyloxyphenyl)-2-(4-methoxyphenyl) acetamide (MOPA) CH_2=C(CH_3)-COO-C_6H_4-NHCOCH_2-C_6H_4-OCH_3	CH_3O- -Ar- CH_2=C	1250 1610, 1500 1630	Ar-CH_2CONH- CH_3O- CH_2=C	s s s	3.56 3.8 6.36–5.70	50	126–129
Poly(ethylene glycol) monomethyl ether monomethacrylate (PEGME) CH_2=C(CH_3)COO-(-CH_2-CH_2-O-)$_n$-CH_3	C=O C=C	1717 1630	-CO-OCH_2 -OCH_3 CH_2= -(OCH_2CH_2)$_n$-	t s s s	4.2 3.3 6.10–5.60 3.6	62	104–106

Synthesis of hydrogels

Graft terpolymers were synthesized by free radical solution polymerization. To a mixture of freshly distilled methacrylic acid, poly(ethylene glycol) monomethyl ether methacrylate, and *N*-(4-methacryloyloxyphenyl-2-(4-methoxyphenyl) acetamide (MOPA) with azobisisobutyronitrile (0.025% of total monomers), ethylene glycol dimethacrylate was added as a crosslinking agent in the amount of 2% (*m*/*m*) of total monomers. The reaction mixture was diluted to 60% of total monomers with a mixture of ethanol and water 1:1 (*m*/*m*) and placed in a 500-mL three-necked flask mounted on a steam bath and equipped with a nitrogen inlet, an efficient stirrer and a reflux (the temperature was fixed at 45 °C), and the polymerization was continued for 24 h.

Hydrogel samples were dried in air and cut into 1-mm thick disks. All samples were washed in water for 1 week to remove unreacted monomer, cross-linking agent or initiator. After washing, the samples were dried in air and stored in desiccator until use.

Table II summarizes the feed composition of the prepared hydrogels.

Table. II. Monomers used for the preparation of hydrogels[a]

Code	Feed composition MAA/PEGMA/POMA					
	PEG			*w* (*m*/*m*, %)[b]	*x* (mol, %)[b]	
	M_n	*m* (mg)	*n* (mmol)			AA_{hyd}/AA_0 (%)[c]
A	600	1.44	2.40	26/60/14	70/20/10	42.3
B	600	2.16	3.60	18/71/11	60/30/10	39.2
C	600	2.88	4.80	13/78/09	50/40/10	25.1
D	600	3.60	6.00	09/83/08	40/50/10	31.7
E	1000	6.00	6.00	06/89/05	40/50/10	22.9
F	1500	9.00	6.00	04/92/04	40/50/10	10.5
G	3000	18.00	6.00	02/96/02	40/50/10	15.1

[a] Polymerization in ethanol and water 1:1 (*m*/*m*) mixture, 40 °C, 24 hours, N_2 atmosphere, initiator: AIBN, crosslinking agent: EGDMA.
[b] The mass ratio of co-monomers to solvent, initiator and crosslinking agent was 10:6:0.0025:0.2.
[c] Results obtained by UV, AA_{hyd} and AA_0 are the amount of the drug in the hydrogel and in POMA, respectively.

Dynamic swelling experiments

Hydrogels were characterized by the swelling of the network, namely by the equilibrium-swelling ratio (8). Disks (r = 1 cm, thickness 2 mm) of dried hydrogels were allowed to swell in 50 mL of enzyme-free SGF (pH 1.2) or SIF (pH 7.0) at 37 °C. SIF and SGF were prepared according to the method described in the US Pharmacopoeia (17).

At specified time intervals the disks were taken out of the buffer, blotted to remove surface water and weighed.

Hydrolysis

The slab of dried hydrogel was introduced into a flask containing 25 mL of SGF (pH 1.2) or SIF (pH 7.0) and solution was maintained at 37 °C. The external solution was continuously stirred, and 3 mL samples were removed at selected intervals. The volume removed was replaced with SGF or SIF. Triplicate samples were used. Release and concentration of *N*-(4-hydroxyphenyl)-2-(4-methoxy phenyl) acetamide was monitored continuously by recording absorbance (DU-70 spectrometer, Becknom, France). The sample showed a characteristic UV absorption band at 294 nm at pH 1.2 and at 314 nm at pH 7.0.

RESULTS AND DISCUSSION

Swelling

Figs. 1a,b and 2a,b represent the swelling curves of samples A–G (Table II) in SGF (pH 1.2) and SIF (pH 7.0) at 37 °C as a function of time. These figures show that swelling increases with time, first rapidly and then slowly, reaching maximum constant swelling (mass equilibrium swelling, MES). It was observed that the time taken to achieve swelling equilibrium of the hydrogels was at least 6–7.5 h at pH 7.0 and 5–6 h at pH 1.2. The MES values increase by increasing the molar proportion of MAA, by decreasing the molar proportion of PEGMA (Figs. 1a,b), or by decreasing the molecular mass of poly(ethylene glycol) (Figs. 2a,b).

At pH 7.0, the amount of absorbed water in the polymer network was larger than that at pH 1.2 at the same time. As the pH of the swelling medium was above 5, the ion-

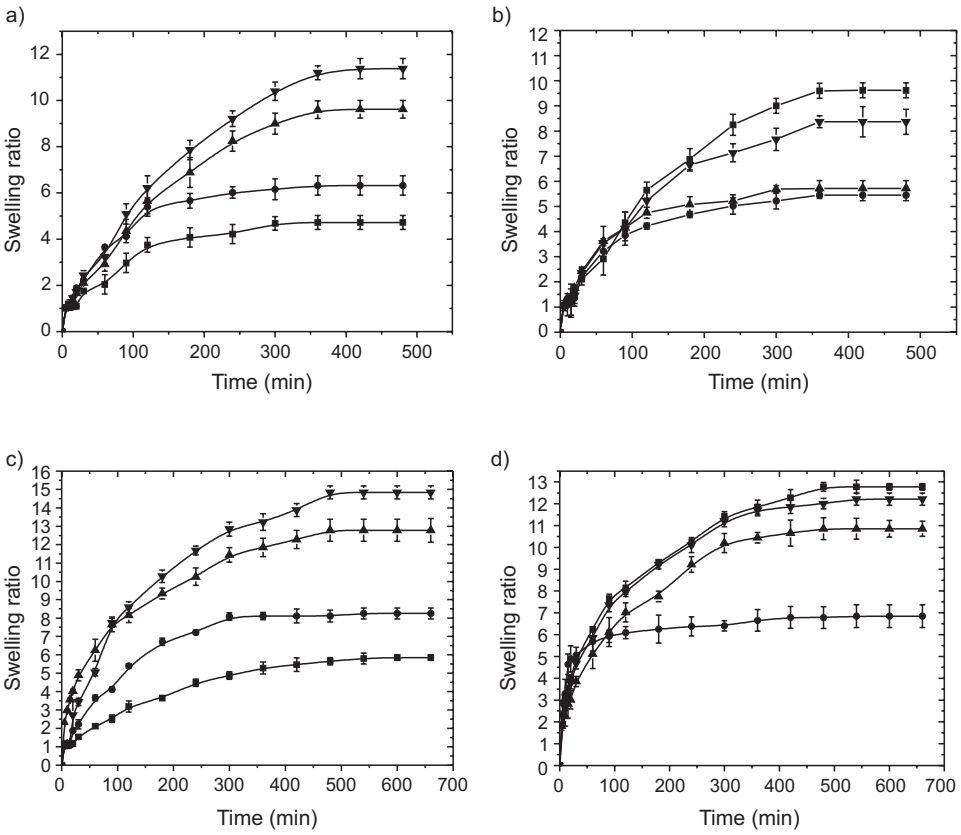


Fig. 1. Dynamic swelling behavior of samples: A(▼), B(▲), C(●), D(■) (in a and c) and B(■), E(▼), F(▲), G(●) (in b and d), swollen in buffered solution pH 1.2 (a, b) and pH 7.0 (c, d) (mean ± SD, $n = 3$).

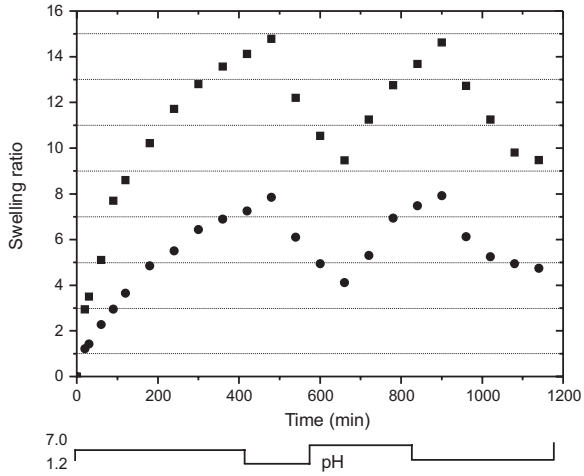


Fig. 2. Time-dependent swelling of hydrogels A(■) and C(●) in response to repeated abrupt changes in pH between 1.2 and 7.0.

ization of the carboxylic acid groups of poly(methyl methacrylate) in the gel occurred and led to ionic repulsion (18). This resulted in a more hydrophilic polymer network and contributed to higher water absorption.

In the previous study, we reported the synthesis and swelling properties of poly-(POMA-g-MAA) units (19), in which the mass percent of MAA units in the copolymer was similar to that of sample A. The swelling ratio was about 12.0 for poly(POMA-g--MAA) and it was about 11.4 for sample A at pH 1.2. In SIF (pH 7.0), the equilibrium swelling ratio of poly(POMA-g-MAA) was 12.5 compared to 14.8 for sample A. These results indicate that the incorporation of hydrophilic PEG units might increase the swelling ratio in SIF (pH 7.0) but might have an inverse effect in SGF (pH 1.2).

It seems that hydrogen-bonded complexes may form between the PEG and MAA units of the hydrogel under acidic conditions. Consequently, hydrogels exhibit a relatively low degree of swelling in SGF. The incorporation of grafted PEG chains in the PMAA polymer networks contributed to the formation of hydrogen bonds, while the presence of pendent MEG disrupted hydrogen bonding formation among the carboxylic acid groups of the PMAA in gels swollen at low pH values (20).

It was necessary for the swelling process to be reversible to ensure that the release of the solute could be initiated and stopped promptly. The pH-reversibility of the hydrogel (the reversible swelling-deswelling kinetics of hydrogels) has been studied and the reversible swelling nature of polymer networks is illustrated in Fig. 2. Hydrogel samples (A, C) swelled in buffer solution of pH 7.0, until equilibrium swelling was attained (swelling ration of 14.8 and 8.0 for samples A and C, respectively in 7.85 h. Placed in a buffer solution of pH 1.2 the hydrogels collapsed in 3 hours, showing a dynamic swelling ratio of 9.5 and 4.2 for samples A and C, respectively. They were returned to a buffer solution of pH 7.0, and finally collapsed in a buffer solution of pH 1.2. The swollen networks re-

verted to relatively collapsed networks whenever the pH decreased and the swelling time was relatively short (in the first cycle) compared to the deswelling time.

Kim and Peppas (21) synthesized a poly(methacrylic acid)-graft-poly(ethylene glycol)-based hydrogel as an oral drug delivery carrier and observed that the networks exhibited pH-responsive swelling behavior and that the carboxylic acid groups of MAA became ionized at pH values higher than pK_a of the polymer (pH ≥ 5).

The portion of the water absorption curve with fractional water uptake (M_t/M_∞) less than 0.60 was analyzed (22) using the following equation:

$$M_t / M_\infty = k_1 t^n \qquad (1)$$

where M_t is the mass of water absorbed at time t, M_∞ is the mass of water absorbed at equilibrium, k_1 (min^{-n}) is the characteristic constant of the hydrogel, and n is the characteristic exponent describing the mode of the penetrant transport mechanism. For a film, $n = 0.5$ indicates Fickian diffusion, $n > 0.5$ indicates non-Fickian or anomalous transport, and $n = 1$ implies case II (relaxation-controlled) transport. The constants n and k_1 were calculated from the slopes and intercepts of the plots of ln (M_t/ M_∞) *vs*. ln t (Figs. 3a,b and Table III). The same figures indicate the best fit of the data by the model of Eq. (*3*) (indicated by dashed lines). The values of n at pH 7.0 were around 1, which indicated that the transport mechanism was case II (relaxation control), whereas at pH 1.2, the mechanism was non-Fickian transport. The dynamic swelling behavior of crosslinked polymers is dependent on the relative contribution of penetrant diffusion and polymer relaxation. In ionic polymer networks, polymer relaxation is significantly affected by ionization of the functional groups of the polymer. An increase in the degree of ionization contributes to the electrostatic repulsion between adjacent ionized groups, leading to chain expansion, which, in turn, affects macromolecular chain relaxation. Therefore, the swelling mechanism becomes more relaxation-controlled as gel ionization becomes prominent. This explains why at pH 7.0 poly(MAA-g-MEG-g-POMA) networks swelled by a relaxation-controlled mechanism. On the other side, at pH 1.2, the ionization was

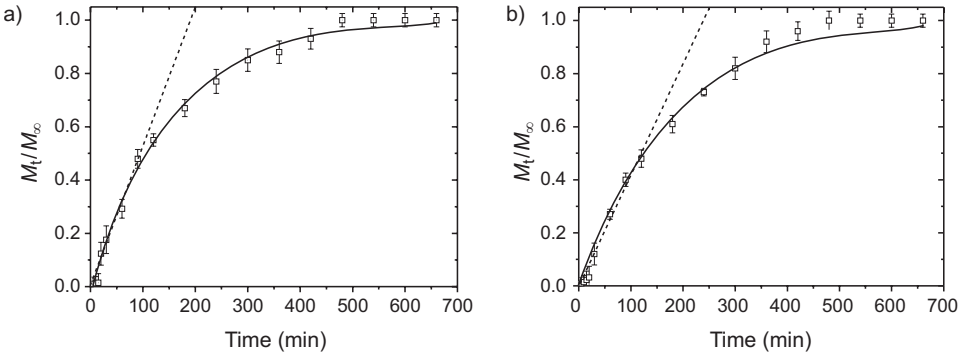


Fig. 3. M_t/M_∞ for: a) sample A and b) sample B swollen in buffer pH 7.0 at 37 °C: (□) experimental data, (—) Eq. (*3*), (- - -) Eq. (*2*) (mean ± SD, n = 3).

Table III. Parameters n, k_1 *(min^{-n}),* A *and* k_2 *(min^{-1}) for hydrogels swollen at 37 °C*

Code	*n*		$k_1 \times 10^2$ (min^{-n})		$k_2 \times 10^2$ (min^{-1})		A	
	pH 1.2	pH 7.0	pH 1.2	pH 7.0	pH 1.2	pH 7.0	pH 1.2	pH 7.0
A	0.730	0.850	9.42	4.42	1.07	1.46	0.75	1.03
B	0.567	0.888	8.87	6.26	1.70	0.52	0.65	1.03
C	0.676	0.750	7.07	5.89	1.25	1.66	0.59	1.06
D	0.890	1.083	9.82	4.99	1.15	1.66	0.61	1.06
E	0.711	0.901	10.12	5.17	0.62	2.83	0.66	0.22
F	0.521	1.083	11.89	7.08	0.84	2.56	0.62	0.20
G	0.510	1.265	8.07	5.82	1.09	1.95	0.42	0.09

not significant, and there were no interactions between ionized functional groups. Therefore, the overall transport mechanism was not affected as much by relaxation, and the result was a combined non-Fickian (anomalous) transport with *n* values approaching Fickian (diffusion-controlled) behavior.

However, the swelling mechanism of these hydrogels showed little dependence on the MAA/PEGMA ratio at pH 1.2 or pH 7.0. The previously discussed model, although adequately describing a major portion of the swelling behavior, fails to give an accurate analysis above $M_t/M_\infty = 0.60$. To obtain a better model beyond 60%, we assumed that for long periods the penetrant sorption was mainly dominated by relaxation of the polymer network and that the sorption process of the polymer by relaxation was of first-order. Then, the Berens-Hopfenberg differential equation (23) for the relaxation process could be written as follows:

$$dM_t/dt = k_2(M_\infty - M_t) \tag{2}$$

where k_2 (min^{-1}) is the relaxation rate constant. The integration of Eq. (2) leads to

$$M_t/M_\infty = (1 - A\, e^{-k_2 t}) \tag{3}$$

where *A* is a constant. In these studies, the constants *A* and k_2 were calculated from the slopes and intercepts of the plot of $\ln(1 - M_t/M_\infty)$ versus time *t* at times longer than those corresponding to $M_t/M_\infty = 0.60$.

Calculated values of *A* and k_2 are listed in Table III. Fig. 3 shows nearly the same profile as that recorded experimentally at $M_t/M_\infty < 60\%$, which provides valuable information for distinguishing between Fickian and case II transport mechanisms. The Fickian diffusion curve exhibits a monotonic inflection-free approach to equilibrium, whereas the case II curves are clearly sigmoidal.

The release profiles of hydrogels at 37 °C in SGF and SIF are shown in Figs. 4a,b, and 4c,d, respectively. The drug release proceeds more efficiently at a higher pH (SIF). Furthermore, increasing the content of the MAA units in hydrogel composition enhances the rate of drug release.

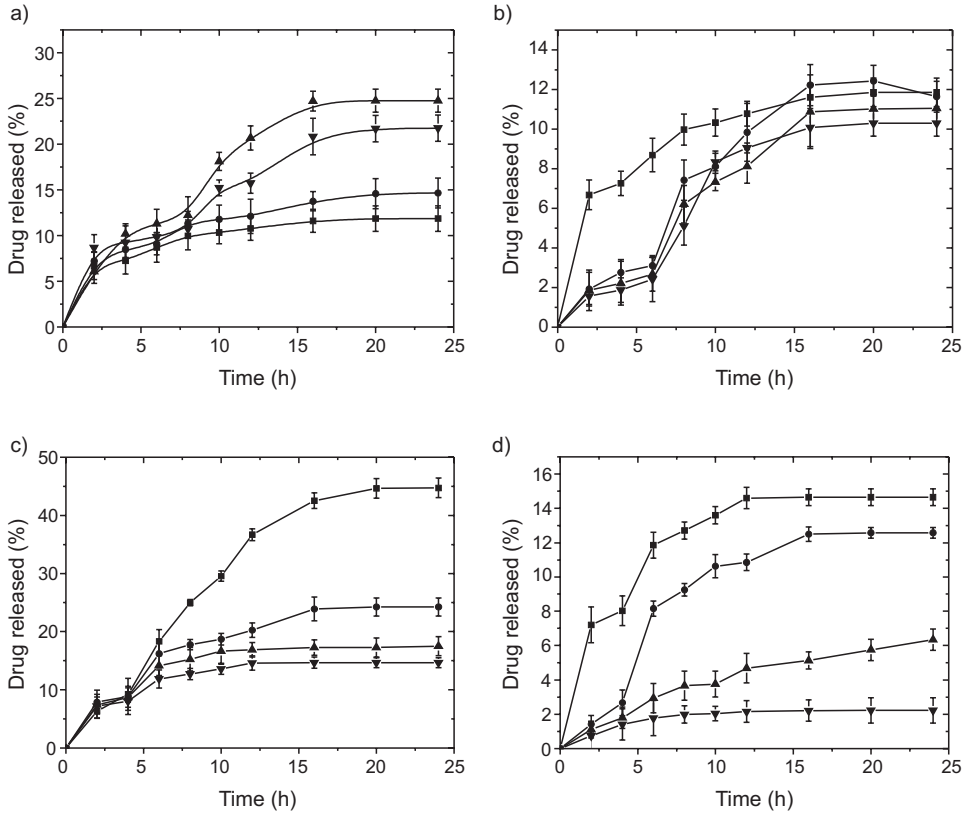


Fig. 4. Release of *N*-(4-hydroxyphenyl)-2-(4-methoxyphenyl) acetamide from PEG 600 hydrogels with various percent of MAA : A (■), B (●), C (▲), D (▼) (in a and c), and from hydrogels with PEG of different molecular mass : D (■), E (●), F (▲), G (▼) (in b and d), in simulated gastric fluid (SGF, pH 1.2) (a, b) and simulated intestinal fluid (SIF, pH 7.0) (c, d) at 37 °C.

The percentage of *N*-(4-hydroxyphenyl)-2-(4-methoxyphenyl) acetamide (AA) released from sample A was about 45%, while it was only 15% from sample D after 24 hours in SIF (Figs. 4a,b). In comparison, only 29% and 12% of the drug was released after 24 hours in SGF from samples A and D, respectively.

As shown in Fig. 4d, sample A showed about 18% release after 6 hours in SIF. This initial quick release could be related to the relaxation period of the hydrogel after 6 hours in SIF. Acids and bases catalyze the hydrolysis of ester bonds, and the ionization of COOH groups of MAA units increases with the basic conditions. Both factors (pH and MAA/PEGMA ratio) increase the swelling of hydrogel, which enhances the rate and extent of drug release in SIF. On the other hand, the higher relative molecular mass of PEG reduces the percent of drug release in SIF but has a negligible effect in SGF.

The release profile of sample A was compared with that of poly(POMA-g-MAA) (19). The amount of the drug that was released from the poly(POMA-g-MAA) was about

65% at pH 1.2 and about 18% at pH 7.0 after 24 hours of hydrolysis. It was expected that the incorporation of a water-soluble polymer such as PEGMA could enhance the extent and rate of drug release, but reverse effects were observed at pH 1.2 (29% release from sample A after 24 hours in SGF) compared to those of poly(POMA-g-MAA) with the same content of MAA units. This observation confirms the formation of a hydrogen--bonded complex between MAA and PEG in block copolymers, which leads to relative protection of the drug from hydrolytic degradation in an acidic environment such as SGF.

However, the fraction of *N*-(4-hydroxyphenyl)-2-(4-methoxy phenyl) acetamide (AA) released after 20 hours from sample D (Fig. 4c) decreases due to the hydrolysis of the anti-inflammatory agent to aminophenol and methoxyphenyl acetic acid or to the interaction between the anti-inflammatory agent and the PEGME chains which can be released at the same time.

Few papers have studied the effect of linkage cleavage on drug release (24–26). Pitt and coworkers (27) analyzed mathematically drug release from a polymeric system that combined drug cleavage and diffusion. The kinetics of cleavage and release of the therapeutic agent from solid polymer matrices are believed to be determined by a number of interdependent processes. These include diffusion of the external medium, water, protons or hydroxide ions into the hydrogel, relaxation of the polymer chains in the medium including swelling (about 6 h), hydrolytic cleavage of the conjugate linkage and diffusion of the cleaved agent from the polymer matrix (about 18 h).

The water transport mechanism through anionic hydrogels was significantly dependent on the pH of the swelling medium, hydrogel composition and PEG molecular mass. At a high pH, the water transport was controlled more by polymer relaxation (case II) than by penetrant diffusion. This resulted from the ionization of carboxylic acid groups on the PMAA of the hydrogels. Increase in the degree of ionization contributed to the electrostatic repulsion between adjacent ionized groups, leading to chain expansion, which, in turn, affected macromolecular chain relaxation.

In the acidic environment of the stomach, these hydrogels are collapsed as a result of hydrogen bonding, thus holding and protecting the incorporated drug in the hydrogel. However, under the basic and neutral conditions of the intestine, the hydrogels are swollen to a high degree, due to electrostatic repulsions, so the percent of released drug is 45%.

Kim and Peppas (28) observed that PEG-PMMA based-hydrogels could adhere more strongly to the mucosa of the intestine than to the mucosa of the stomach, and this can localize the delivery system in a site-specific manner. It is important to note that the mucoadhesivity of these hydrogels increases with the release of *N*-(4-hydroxyphenyl)--2-(4-methoxy phenyl) acetamide.

CONCLUSIONS

The experiments reported here indicate that these hydrogels can be used in controlled-release formulations of *N*-(4-hydroxyphenyl)-2-(4-methoxy phenyl) acetamide. However, balance must be found in the ratio of the drug-containing hydrophobic com-

ponent (such as POMA), which leads to an appropriate amount of drug loading, to the more hydrophilic components, which ensure good swellability and availability of the ester bond hydrolysis. The main factors influencing drug release are the molecular mass of PEG, the mass ratio of MAA/PEGMA, the drug concentration, the pH of the release medium and the kinetics of cleavage.

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S A Ž E T A K

Oslobađanje ljekovite tvari i bubrenje pH-senzitivnih hidrogelova na bazi metakrilnih derivata

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Cilj rada bio je razviti nove pH senzitivne sustave za isporuku lijekova u tankom crijevu te ispitati njihova svojstva bubrenja i oslobađanje ljekovite tvari. Metakrilni polimerni prolijekovi sintetizirani su kopolimerizacijom derivata metakrilne kiseline sa slobodnim radikalima, poli(etilenglikol monometil eter metakrilata) i metakrilnog derivata *N*-(4-hidroksifenil)-2-(4-metoksifenil) acetamida u prisutnosti etilenglikol dimetakrilata kao sredstva za umrežavanje. Učinak sastava kopolimera na svojstvo bubrenja i hidrolitički raspad proučavan je u simuliranoj želučanoj (SGF, pH 1,2) i crijevnoj tekućini (SIF, pH 7,0). Dinamičko svojstvo bubrenja hidrogelova ispitivano je da bi se odredio mehanizam transporta vode kroz hidrogelove. Mehanizam prijenosa vode značajno je ovisio o pH medija. Bubrenje i hidrolitičko ponašanje hidrogelova ovisilo je o udjelu metakrilne kiseline. U SGF se bubrenje smanjivalo, a u SIF povećavalo. Povećanje udjela metakrilne kiseline u kopolimeru povećavalo je hidrolizu u SIF. Ti rezultati sugeriraju da se pH-senzitivni sustavi mogu upotrijebiti u pripravi mukoadhezivnih sustava i za kontrolirano oslobađanje *N*-(4-hidroksifenil)-2-(4-metoksifenil) acetamida.

Ključne riječi: pH-senzitivni hidrogelovi, bubrenje, kontrolirano oslobađanje, poli(etilenglikol), poli(metakrilna kiselina)

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