Journal of Applied Polymer Science

# Preparation and characterization of pH responsive poly(methacrylic acid-acrylamide-N-hydroxyethyl acrylamide) hydrogels for drug delivery systems

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**ABSTRACT:** In this study, pH responsive polymers composed of methacrylic acid, acrylamide, and N-hydroxyethyl acrylamide were synthesized by free radical polymerization technique. The characterization was done with Fourier transform infrared spectroscopy and scanning electron microscopy. The swelling and drug release behavior of the hydrogels was determined as a function of time at 37°C in pH 2.1 and 7.4. The swelling and drug release studies showed that increased methacrylic acid amount caused a higher increase in swelling and drug release values at pH 7.4 than those at pH 2.1. In addition, the drug release data were applied to kinetic models such as zero order, first order, and Higuchi equations, and it fit well in the Higuchi model of the hydrogel. © 2015 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2016**, *133*, 43226.

**KEYWORDS:** adsorption; copolymers; drug delivery systems; gels; kinetics

Received 14 August 2015; accepted 13 November 2015
**DOI: 10.1002/app.43226**

## INTRODUCTION

Hydrogels are cross-linked hydrophilic polymer networks with the ability to retain large amounts of water or biological fluids, and resemble natural living tissue more than any other synthetic biomaterials making them an ideal class of materials for biological applications.[1,2] Especially, stimulus-responsive polymeric hydrogels that can undergo reversible phase transition in their physical nature by the environmental stimulus changes (i.e. pH, ionic strength, temperature, electric field, solvent, or magnetic field) are favorite in drug delivery applications.[1–3]

The pH sensitive hydrogels are ideal candidates for delivery of therapeutic agents because of the pH changes of the human body. These polymers have weak acidic and weak basic pendant groups in their polymeric structure and their response to the external pH changes with the ionization state. Anionic hydrogels with carboxylic or sulphonic pendant groups are ionized when the pH of the surrounding environment is above the $pK_a$ of the ionizable group. This leads to an increased swelling ratio because of the electrostatic repulsion. On the other hand, cationic hydrogels with amine pendant groups are protonated at the pH below the $pK_b$ of the ionizable group, and the swelling occurred at lower pH. The most studied synthetic and natural ionic polymers are poly(acrylic acid) (PAA), poly(methacrylic acid) (PMAA), poly(N,N-dimethylaminoethyl methacrylate) (PDMAEMA), poly(2-diethylaminoethyl methacrylate) (PDEAEMA), albumin, gelatin, and chitosan.[1,4,5]

Thermosensitive hydrogels are also used in drug delivery and administration systems. These hydrogels exhibit volume phase transitions or sol-gel phase transitions at critical temperatures. Hydrogels, which become swelling to shrinking (or sol to gels) transition upon heating have a lower critical solution temperature (LCST), while hydrogels, which undergo the opposite transitions have an upper critical solution temperature (UCST).[6,7] N-isopropylacrylamide and N-vinyl caprolactam are the preferred monomers in biological applications because of their LCST values being close to the body temperature.[5,8,9]

Nadolol is a hydrophilic, nonselective, beta adrenoceptor blocking drug used clinically for the treatment of hypertension,[10,11] and have a plasma half-life of 14–24 h.[12] In the literature, drug release studies from sensitive hydrogels are very limited for beta blockers. Meng *et al.* prepared alginate-chitosan hydrogel beads for a beta blocker, carvedilol delivery to be used as a controlled pH sensitive drug delivery system. The beads showed high swelling and drug release percentage at high pH, and the percentage

**Table I.** The Feed Composition of the Gels

| Polymer Code | MA (mole) | AAm (mole) | HEAA (mole) | NMBA (%mole) | APS (%mole) | TEMED (g) |
|---|---|---|---|---|---|---|
| C0-AH | - | 0.01 | 0.01 | 1 | 1 | $M_{APS}$ |
| T1-MAH | 0.004 | 0.008 | 0.008 | 1 | 1 | $M_{APS}$ |
| T2-MAH | 0.008 | 0.006 | 0.006 | 1 | 1 | $M_{APS}$ |

of carvedilol released from the beads was 22.83% within 2 h at pH 1.5; however, the amount of carvedilol released increased significantly at pH 7.4 (approximately 81.28%) within 15 h. To conclude, the investigators suggested this system as a promising vehicle for oral drug delivery.[13] Vihola *et al.* studied the release of the beta blocking agents, nadolol and propranolol, and a choline-esterase inhibitor tacrine from thermosensitive PVCL nanoparticles. The release of nadolol and propranolol from the collapsed PVCL particles at 40°C was less than the amount released at 20°C, where PVCL particles were in a swollen state, in 6 h.[8] In another study by Vihola *et al.*, thermosensitive polymer particles of PVCL and PVCL grafted with poly(ethylene oxide) macromonomer were prepared to investigate the drug release properties for three model drugs, nadolol, propranolol, and ketoprofen. All the drugs were released in 6 h more efficiently from the PVCL particles than from the PEO-macromonomer grafted particles because of the weaker interactions and the more gel-like structure of the PVCL. In addition, drug concentration and pH affected clearly the rate and extent of drug release in physiological buffer (pH adjusted to 7.4 or 3.0).[9] In our best knowledge, nadolol release studies on pH sensitive hydrogels have not been reported previously.

The aim of this work is investigating the usage of pH-sensitive poly(methacrylic acid-acrylamide-N-hydroxyethyl acrylamide) poly(MAA-AAm-HEAA) hydrogels as a significant drug delivery device to examine the release characteristic of model drug, nadolol. For this purpose, the terpolymeric gels were synthesized from MAA, AAm, and HEAA monomers in the presence of cross-linking agent, N,N′-methylene bisacrylamide (NMBA), and initiating system, ammonium persulphate/N,N,N′,N′-tetramehylethylene diamine (APS/TEMED) by varying the MAA amount. The characterization of the obtained gels by swelling studies, at pH 2.1 and 7.4 at 37°C, acid group content, FTIR spectroscopy, and SEM analysis (before and after drug loading) was performed. Additionally, the release kinetics and mechanism of nadolol loaded hydrogels was investigated in pH 2.1 and 7.4 as a function of time.

## EXPERIMENTAL

### Materials

Acrylamide (AAm), methacrylic acid (MAA), N-hydroxyethyl acrylamide (HEAA), nadolol were purchased from Sigma-Aldrich (St. Louis, MO). Ammonium persulphate (APS), N,N,N′,N′-tetramehylethylene diamine (TEMED), and N,N′-methylene bisacrylamide (NMBA) were Riedel-de Haen (Seelze, Germany) products. Sodium chloride, potassium chloride, potassium dihydrogen phosphate, sodium hydroxide, potassium hydrogen phtalate, sodium bicarbonate, and hydrochloric acid were used for the preparation of buffer solutions and all were obtained from Merck Chemicals (Hohenbrunn, Germany).

### Synthesis of Hydrogels

Poly(AAm-HEAA) copolymer and poly(MAA-AAm-HEAA) terpolymers were prepared by free radical chain polymerization in aqueous solution using APS as initiator and TEMED as accelerator in the presence of the cross-linker, NMBA. The polymerizations were done in the glass tubes with inner diameters of 1.3 cm and lengths of 15 cm. Firstly, the monomers and NMBA were dissolved in distilled water. Then, the solution was bubbled by nitrogen gas, and APS and TEMED were added before sealing the tubes. The amount of NMBA and APS were in the amount of 1 mol % of total monomer content in the feed, and the TEMED amount was in the equal weight of APS. Then, the tubes were immersed in a water bath at 60°C and held there for 24 h. At the end of the polymerization, the tubes were broken carefully and the gels cut into small pieces. The gels were immersed in distilled water and the water was replaced periodically over one week to remove the unreacted monomers. The swollen gels were dried in air and then in a vacuum oven until attaining a constant weight. The feed composition was given in Table I.

### Characterization Studies

The gels were characterized by potassium bromide (KBr) pellet technique between the range of 650–4000 $cm^{-1}$ by a Cary 630 FTIR spectrometer (Agilent Technologies, USA). The SEM images of drug-loaded and unloaded gels were taken by a JEOL JSM-7001F Scanning electron microscope. The acid group content was determined as reported in the literature.[14,15]

### Swelling Studies

The swelling characteristics of the gels were determined by gravimetric method in various buffer solutions, pH 2.1 (KCl-HCl), pH 4 (KHphtalate-NaOH), pH 5.5 (KHphtalate-NaOH), pH 7.4 ($Na_2HPO_4$-$KH_2PO_4$), pH 10 ($NaHCO_3$-NaOH), and pH 12 ($Na_2HPO_4$-NaOH). The buffer solutions were prepared according to the recipes given by Perrin and Dempsey.[16] The dry gels were immersed in these mediums at 37°C (±0.1°C) in a circulating water bath (Polyscience, USA) and they were taken out from the swelling medium and weighted after the excess water was wiped off from the gel surface at regular intervals until equilibrium was attained. The swelling value ($S$) was determined from the following equation:

$$S\ (g\ H_2O/g\ polymer) = (W_s - W_d/W_d) \quad (1)$$

where $W_s$ and $W_d$ are the weights of the swollen gels at equilibrium and dry gels, respectively.

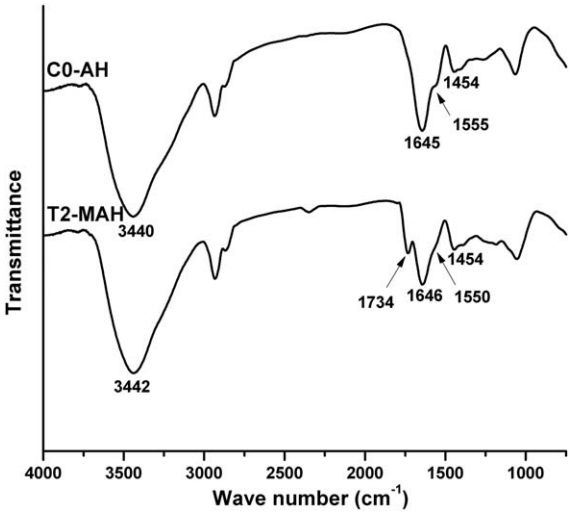


**Figure 1.** FTIR spectra of C0-AH and T2-MAH.

The ionic strength of each buffer solution was adjusted to 0.09*M* by adding sodium chloride to the solution. All experiments were carried out in duplicate, and the mean values were given.

### Drug Loading and Release Studies

Nadolol was used for the release studies as the model drug which has the hydroxyl and amino groups in its chemical structure. The aim of this study is to investigate the interaction of the hydroxyl and amino groups of nadolol with the synthesized polymer on its release behavior and kinetics.

A known amount of the dry gels were immersed in the drug solution (0.2 g Nadolol/10 mL distilled water) at room temperature for one week. During the process, the drug in the distilled water will absorb into the surface as well as adsorbed onto the gels. The amount of nadolol loaded into the discs was calculated as the difference between the initial amount of the drug to incubate in and the amount that was found in the supernatant. The amount of nadolol loaded was determined using T80+ UV/VIS Spectrometer (PG Instruments) at 271 nm and a standard nadolol calibration curve.

*In vitro* release experiments were carried out in a test tube containing 10 mL buffer solutions with pH 2.1 and 7.4 as the release mediums at 37°C. At specific time aliquots of 3 mL were withdrawn from the release medium and replaced with fresh buffer solutions to keep the volume constant. The amount of nadolol in the aliquot was determined spectrophotometrically at 271 nm by using a T80+ UV/VIS Spectrometer. The amount of drug released from the drug-loaded gels was calculated with aid of calibration curves for pH 2.1 and pH 7.4. All experiments were carried out in triplicate, and the mean values were given.

## RESULT AND DISCUSSION

### FTIR Studies

The FTIR spectra of C0-AH and T2-MAH were shown in Figure 1. As can be seen from Figure 1, the characteristic bands around at 3440 $cm^{-1}$ (N-H and O-H stretching vibrations), 1645 $cm^{-1}$ (C=O stretching vibration, amid I), 1555 $cm^{-1}$ (N-H bending vibration, amid II), and 1450 $cm^{-1}$ (C-N stretching vibration) were observed for all of the hydrogels.[17–19] In case of the terpolymeric hydrogel (T2-MAH), the distinctive peak around 1734 $cm^{-1}$ was attributed to the carbonyl stretching vibration from carboxylic groups of methacrylic acid. That peak provided the evidence for the incorporation of MAA into the copolymer structure.

### SEM Observation

Figure 2 shows SEM images of drug-unloaded (a and b) and drug-loaded (c) T2-MAH gel (magnification, ×2000). As it is seen from Figure 2(a,b), the T2-MAH gel has a porous surface morphology. After the adsorption of Nadolol on the gel, the morphology has changed and became more smooth [Figure 2(c)] that indicates the drug adsorption on the gel surface.

### Swelling Studies

The swelling values of the gels in the buffer solutions at 37°C as a function of pH are given in Figure 3 to observe the swelling behavior. It is seen from the figure that the swelling values of terpolymers (T1-MAH and T2-MAH) increased in alkaline pH values because of their responsive behavior, whereas the copolymer (C0-AH) did not show any changes according to pH. Figure 4(a,b) shows the swelling values of the gels as a function of time in the buffer solution of pH 2.1 and 7.4. The C0-AH gel exhibited equilibrium swelling values of 13.1 and 13.5 g $H_2O$/g polymer at pH 2.1 and 7.4, respectively. Although, acrylamide-based gels have high swelling values,[20] the presence of HEAA did not significantly increase the swelling values. According to the literature,[17] the swelling of poly(HEAA) nanogels were found to be independent of pH, and suggesting that the poly(-HEAA) nanogels are not swollen. For this reason, it has been thought that an increase in the amount of HEAA caused a decrease in swelling values of the gels. In addition, poly(HEAA) and poly(AAm) are independent of pH because of the nonionic nature of the polymers,[17,21] and pH did not affect the swelling values noticeably. On the other hand, in case of terpolymers, the swelling value at different pH's changed with the acid group content of MAA. The acid values were 0.36 and 0.77 mmol/g, for T1-MAH and T2-MAH gels, respectively. The acid group content increased with MAA amount as expected. For the gel with low MAA amount (T1-MAH), the equilibrium swelling values were 14.8 and 16.7 g $H_2O$/g polymer at pH 2.1 and 7.4, respectively; while the T2-MAH gel with higher MAA amount were swollen to 17.6 and 21.9 g $H_2O$/g polymer at equilibrium at pH 2.1 and 7.4, respectively. As the pH of the swelling medium increased through the $pK_a$ of MAA, the degree of ionization in the gel increased. T2-MAH gel with the highest acid group content had the highest swelling value at pH 7.4. This responsive swelling behavior can be attributed to the electrostatic repulsion between these carboxylic acid charge groups of anionic MAA.[22]

### Drug Loading and Release Studies

**Drug Loading Capacity.** The effect of different MAA amount on the drug loading capacity was investigated. The increased MAA amount caused an increase in the drug loading capacity of the hydrogels as determined 101.9, 136.6, and 200.2 mg drug/g polymer for C0-AH, T1-MAH, and T2-MAH gels, respectively. The interaction between the carboxylic acid (T1-

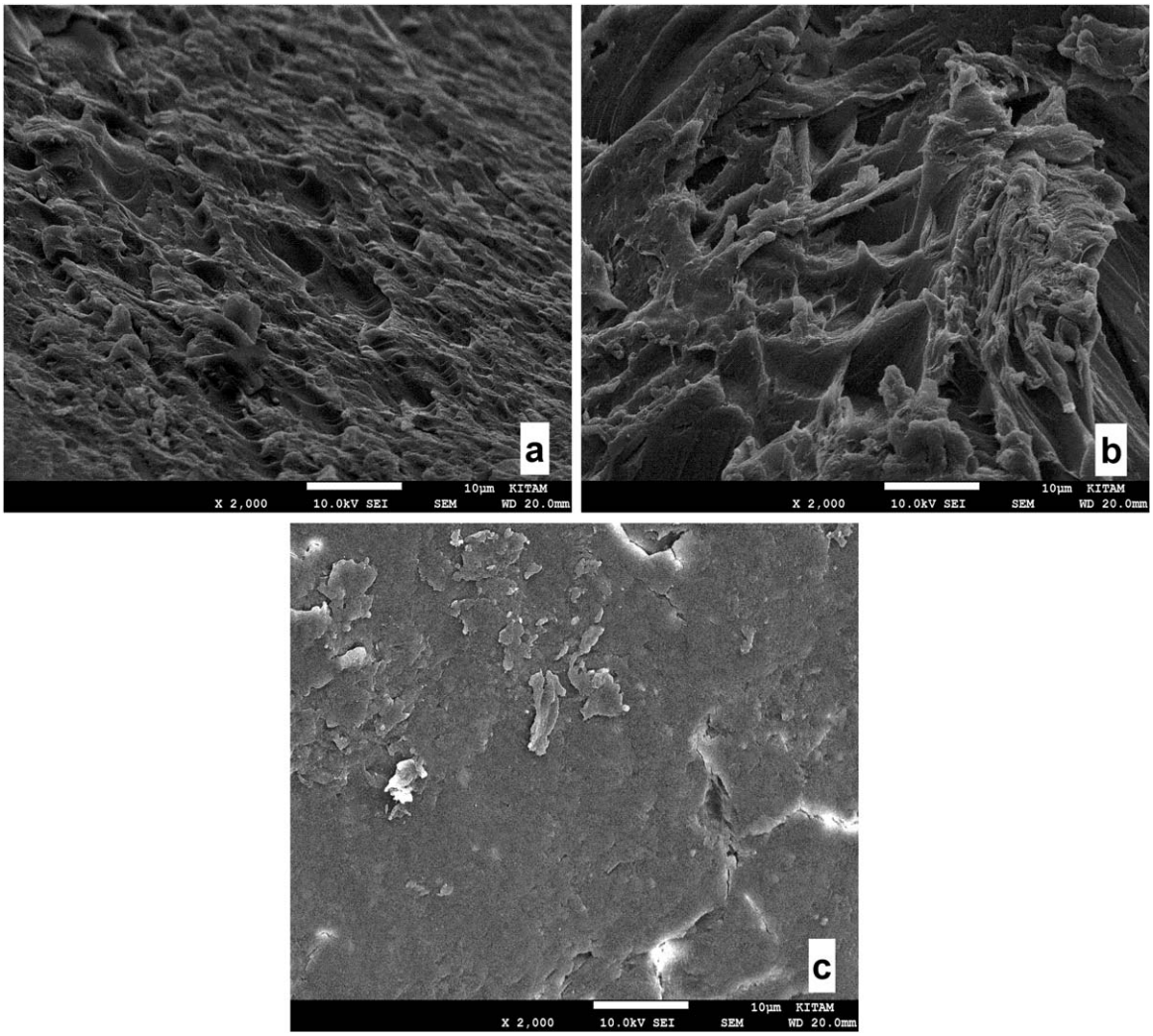


**Figure 2.** SEM images of (a and b) drug-unloaded and (c) drug-loaded T2-MAH gel.

MAH and T2-MAH) and amine groups (Nadolol) led to an increase in the drug loading.

***In Vitro* Release Studies.** The influence of pH on the drug release rate was investigated for C0-AH, T1-MAH, and T2-MAH gels at 37°C. The cumulative released (%) was given as a function of time at pH 2.1 and 7.4 in Figure 5(a,b), respectively. Although any significant increase in the cumulative release percentage was observed for C0-AH gel, the release percentages of the terpolymeric gels (T1-MAH and T2-MAH) were increased by increasing the pH from 2.1 to 7.4. The hydrogel with high MAA content had a positive effect on the release percentages. In addition, the terpolymeric gels had a slower and higher drug release rate at pH 7.4 compared to pH 2.1. Under acidic conditions (pH 2.1), the interaction between the carboxylic groups on the matrix surface and the drug disappeared because of the decrease in the ionization degree of MAA, and the hydrogen ions compete with the interactions which cause to decrease in the release rate. On the other side, under higher pH medium (pH 7.4), the carboxylic groups are ionized, and the electrostatic repulsion between these carboxylic acid charge groups and the drug are dominated.

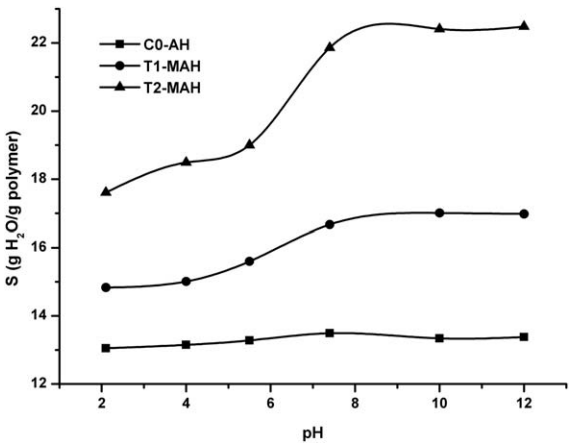


**Figure 3.** The swelling values of the gels as a function of pH.

Park *et al.*[23] prepared pH-sensitive poly(vinyl alcohol-g-methacrylic acid) and poly(vinyl alcohol-g-acrylic acid) hydrogels and their insulin release behavior were investigated. It was found that the graft copolymer containing the highest amount

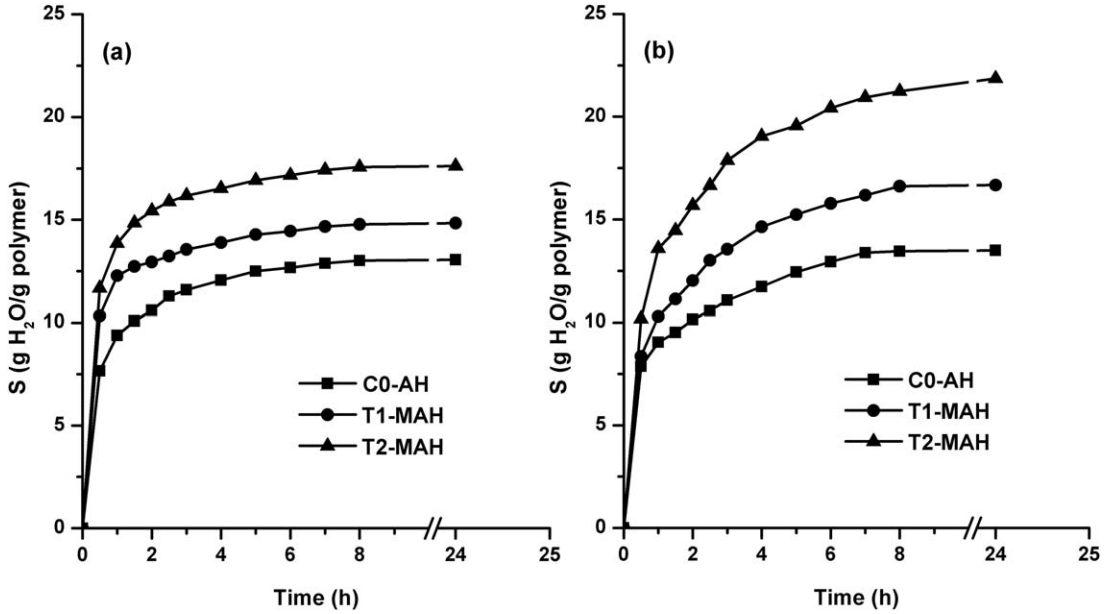


**Figure 4.** Swelling behavior of the gels at 37°C as a function of time in the buffer solutions with (a) pH 2.1 and (b) pH 7.4.

of MAA or AA gave rise to higher swelling ratio because of the larger electrostatic repulsion between ionized carboxylate groups. Also, the insulin release behavior of the hydrogels showed that these hydrogels could be applied for oral drug delivery to the gastrointestinal tract. 2-hydroxyethyl methacrylate and methacrylic acid hydrogels were synthesized by Garcia *et al.*,[24] and the effect of hydrogel composition and pH on the swelling and timolol maleate release were studied. The higher MAA content in the hydrogel increased its swelling value because of the hydrophilic character of MAA. The pH increased supposed a higher ionization of the polymer network and, a higher swelling and a faster release from the hydrogel. Diez-Pena *et al.*[25] studied the diltiazem hydrochloride release from a series of pH sensitive poly[(N-isopropylacrylamide)-*co*-(methacrylic acid)] hydrogels. Copolymers presenting the highest equilibrium of swelling, also exhibited the fastest diltiazem hydrochloride release.

**Mathematical Modeling.** Different mathematical models such as zero-order [eq. (2)], first-order [eq. (3)], and Higuchi [eq. (4)] models were applied to the drug release data at pH 7.4 in order to evaluate the drug release kinetics.[26–28]

The zero-order model is presented as

$$q_t = q_0 + k_0 t \tag{2}$$

where $q_t$ is the amount of drug dissolved in time $t$, $q_0$ is the initial amount of drug in the solution (usually $q_0 = 0$), $k_0$ is the zero-order release rate constant, and $t$ is the release time.

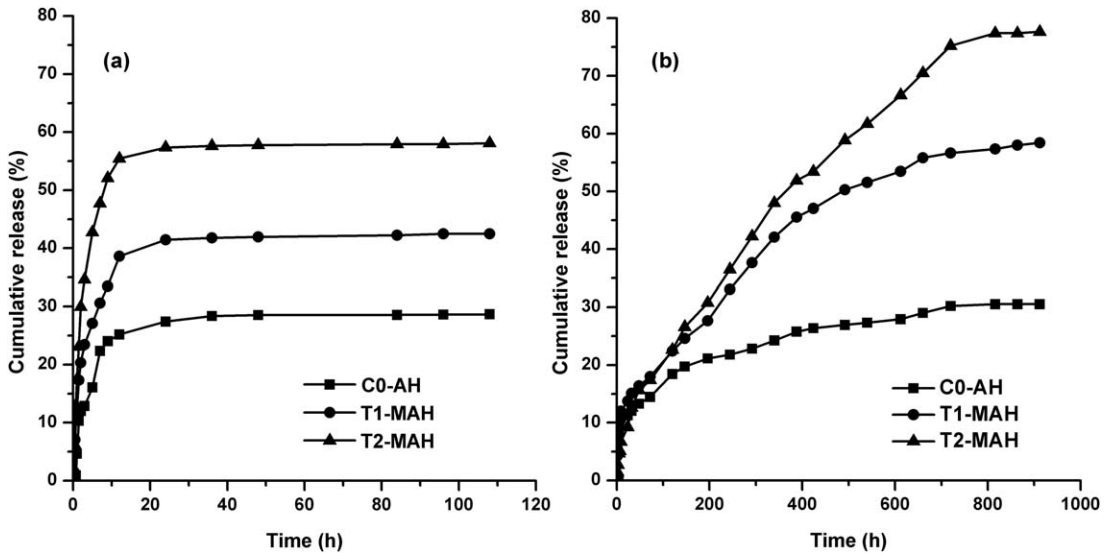


**Figure 5.** Drug release behavior from the hydrogels in (a) pH 2.1 and (b) 7.4.

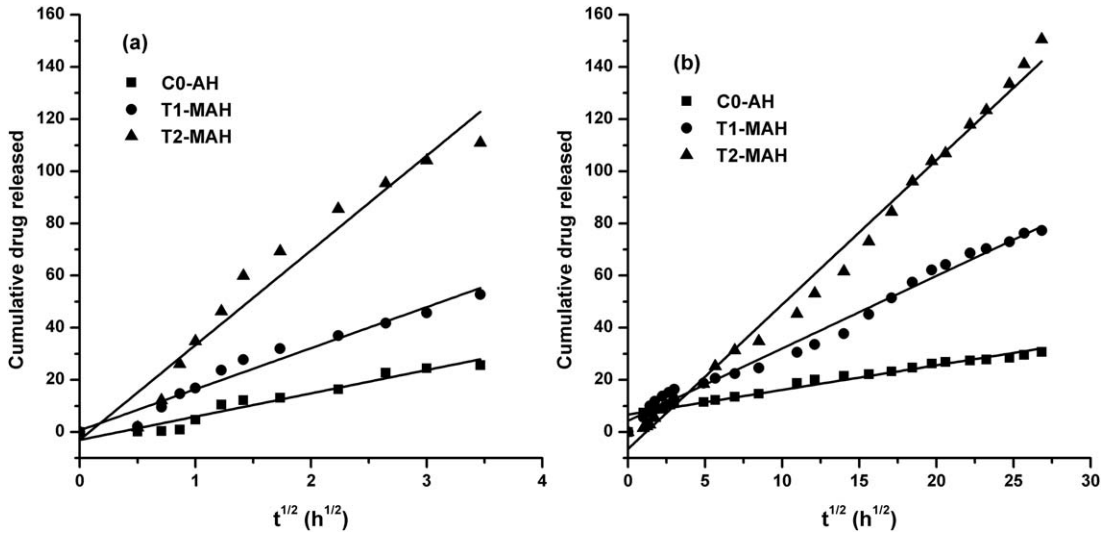


**Figure 6.** Higuchi model release kinetic at (a) pH 2.1 and (b) 7.4.

The first-order model is expressed as

$$In(q_t) = In(q_0) - k_1 t \quad (3)$$

where $q_t$ is the amount of drug dissolved in time $t$, $q_0$ is the initial amount of drug in the solution, and $k_1$ is the first-order release rate constant.

The Higuchi model is formulated as

$$q_t = k_H \sqrt{t} \quad (4)$$

where $q_t$ is the amount of drug dissolved in time $t$, and $k_H$ is the Higuchi rate constant.

The rate constants and correlation coefficients were calculated from the plots of $q_t$ against $t$, In($q_t$) against $t$ and $q_t$ against $t^{1/2}$, for the zero-order, first–order, and Higuchi models, respectively. The kinetic parameters of nadolol release from the gels for each model were given in Tables II and III at different pH values. From the tables, it can be concluded that the gels were more fitted to Higuchi model than the other mathematical models at pH 2.1 and 7.4. Higuchi model drug release profile of the hydrogels was given at different pH values in Figure 6.

Higuchi's model describes the release of drugs from an insoluble matrix as a square root of a time-dependent process based on Fickian model. Higuchi model is based on the hypotheses that (i) initial drug concentration in the matrix is much higher than the solubility of the drug; (ii) drug diffusion takes place only in one dimension (edge effect must be negligible); (iii) drug particles are much smaller than the thickness of the system; (iv) matrix swelling and dissolution are negligible; (v) drug diffusivity of the drug is constant.[29,30] This is the reason why the drug diffuses at a comparatively slower rate as the distance for diffusion increases, which is referred to Higuchi's kinetics.[31]

**Table II.** Kinetic Parameters of Nadolol Release from the Gels at pH 2.1

| | Zero-order equation | | First-order equation | | Higuchi equation | |
|---|---|---|---|---|---|---|
| Polymer code | $k_0$ | $R^2$ | $k_1$ | $R^2$ | $k_H$ | $R^2$ |
| C0-AH | 2.2657 | 0.8606 | 0.3119 | 0.5007 | 8.9221 | 0.9444 |
| T1-MAH | 3.7326 | 0.8544 | 0.1659 | 0.4963 | 15.764 | 0.9564 |
| T2-MAH | 8.6986 | 0.8307 | 0.2072 | 0.4399 | 36.327 | 0.9649 |

**Table III.** Kinetic Parameters of Nadolol Release from the Gels at pH 7.4

| | Zero order equation | | First order equation | | Higuchi equation | |
|---|---|---|---|---|---|---|
| Polymer code | $k_0$ | $R^2$ | $k_1$ | $R^2$ | $k_H$ | $R^2$ |
| C0-AH | 0.0296 | 0.8911 | 0.0016 | 0.7776 | 0.9247 | 0.9691 |
| T1-MAH | 0.0950 | 0.9478 | 0.0026 | 0.7769 | 2.7879 | 0.9891 |
| T2-MAH | 0.1984 | 0.9729 | 0.0042 | 0.6620 | 5.6508 | 0.9909 |

## CONCLUSIONS

The presence of MAA to AAm and HMAA hydrogel systems influenced the swelling and drug release behavior because of the anionic carboxylate groups of MAA. The swelling behavior of the prepared hydrogels with MAA was investigated in pH 2.1 and 7.4, and the results showed pH responsive nature of these terpolymeric hydrogels. At high pH, the carboxylic groups on the polymer (T1-MAH and T2-MAH) are ionized and the polymer swelled more because of the electrostatic repulsion between the ionized acid groups. Whereas, at low pH carboxylic groups are less ionized, the repulsion between carboxylic groups and the interaction of water with carboxylic groups are lower. Therefore swelling is lower, and drug release is faster and controlled by diffusion.[32]

The *in vitro* release profile of nadolol was observed in pH 2.1 and 7.4. The release percentage of nadolol by the terpolymeric hydrogel matrices was higher at pH 7.4 than 2.1, but the drug release reached equilibrium more rapidly at pH 2.2 than at pH 7.4. At pH 7.4, the carboxylic groups on the polymer (T1-MAH and T2-MAH) are ionized and can interact with the amino group on the Nadolol through ionic bond formation or hydrogen bonding. When pH was decreased, the ionized carboxylic groups were turned to protonated form, and the interaction has disappeared. The release time of the drug is greatly extended at pH 7.4. From the results, it is seen that the drug with hydroxyl and amino groups can be used for the systems to be given at a low dose, and this pH responsive terpolymeric hydrogel system can be employed for drug delivery application in the intestinal tract.

## ACKNOWLEDGMENTS

The authors would like to thank Prof. Dr. Gamze Güçlü, Assoc. Prof. Dr. Işıl Acar and Assoc. Prof. Dr. Serkan Emik for their support.

## REFERENCES

1. Peppas, N. A.; Bures, P.; Leobandung, W.; Ichikawa, H. *Eur. J. Pharm. Biopharm.* **2000**, *50*, 27.
2. Himi, M.; Maurya, S. D. *J. Drug Deliv. Therap.* **2013**, *3*, 131.
3. El-Sherbiny, I. M.; Lins, R. J.; Abdel-Bary, E. M.; Harding, D. R. K. *Eur. Polym. J.* **2005**, *41*, 2584.
4. Gupta, P.; Vermani, K.; Garg, S. *Drug Discov. Today* **2002**, *7*, 569.
5. Almeida, H.; Amaral, M. H.; Lobão, P. *J. Appl. Pharm. Sci.* **2012**, *02*, 01.
6. Schmaljohann, D. *Adv. Drug Deliv. Rev.* **2006**, *58*, 1655.
7. Lee, D. S.; He, C. Biomedical applications of hydrogels handbook; Raphael M. Ottenbrite (Editor-in-Chief); Springer: New York, **2010**; Part II, p 123.
8. Vihola, H.; Laukkanen, A.; Hirvonen, J.; Tenhu, H. *Eur. J. Pharm. Sci.* **2002**, *16*, 69.
9. Vihola, H.; Laukkanen, A.; Tenhu, H.; Hirvonen, J. *J. Pharm. Sci.* **2008**, *97*, 4783.
10. Srinivas, N. R.; Barr, W. H.; Shyu, W. C.; Mohandoss, E.; Chow, S.; Staggers, J.; Balan, G.; Belas, F. J.; Blair, I. A.; Barbhaiya, R. H. *J. Pharm. Sci.* **1996**, *85*, 299.
11. Mehvar, R.; Brocks, D. R. *J. Pharm. Pharmaceut. Sci.* **2001**, *4*, 185.
12. Borchard, U. *J. Clin. Basic Cardiol.* **1998**, *1*, 5.
13. Meng, X.; Li, P.; Wei, Q.; Zhang, H. X. *Pharm. Dev. Technol.* **2011**, *16*, 22.
14. Pramanik, S.; Dhara, P. K.; Chattopadhyay, P. *Talanta* **2004**, *63*, 485.
15. Emik, S. *React. Funct. Polym.* **2014**, *75*, 63.
16. Perrin, D. D.; Dempsey, B. Buffers for pH and Metal Ion Control; Chapman and Hall: London, **1974**.
17. Zhao, C.; Chen, Q.; Patel, K.; Li, L.; Li, X.; Wang, Q.; Zhang, G.; Zheng, J. *Soft Matter* **2012**, *8*, 7848.
18. Bayramoglu, G.; Yılmaz, M.; Senel, A. U.; Arıca, M. Y. *Biochem. Eng. J.* **2008**, *40*, 262.
19. Berger, A.; Frezet, L.; Israëli, Y. *J. Phys. Chem. B* **2009**, *113*, 14218.
20. Kaşgöz, H.; Aydın, İ.; Kaşgöz, A. *Polym. Bull.* **2005**, *54*, 387.
21. Ozbas, Z.; Gurdag, G. *J. Appl. Polym. Sci.* **2015**, *132*, 41886.
22. Garcia, D. M.; Escobar, J. L.; Bada, N.; Casquero, J.; Hernaez, E.; Katime, I. *Eur. Polym. J.* **2004**, *40*, 1637.
23. Park, S. E.; Nho, Y. C.; Lim, Y. M.; Kim, H. I. *J. Appl. Polym. Sci.* **2004**, *91*, 636.
24. Garcia, D. M.; Escobar, J. L.; Noa, Y.; Bada, N.; Hernaez, E.; Katime, I. *Eur. Polym. J.* **2004**, *40*, 1683.
25. Díez-Peña, E.; Frutos, P.; Frutos, G.; Quijada-Garrido, I.; Barrales-Rienda, J. M. *AAPS PharmSciTech* **2004**, *5*, 1.
26. Gibaldi, M.; Feldman, S. *J. Pharm. Sci.* **1967**, *56*, 1238.
27. Wagner, J. G. *J. Pharm. Sci.* **1969**, *58*, 1253.
28. Higuchi, T. *J. Pharm. Sci.* **1963**, *52*, 1145.
29. Siepmann, J.; Peppas, N. A. *Adv. Drug Deliv. Rev.* **2012**, *64*, 163.
30. Dash, S.; Murthy, P. N.; Nath, L.; Chowdhury, P. *Acta Pol. Pharm.* **2010**, *67*, 217.
31. Merchant, H. A.; Shoaib, H. M.; Tazeen, J.; Yousuf, R. I. *AAPS PharmSciTech* **2006**, *7*, E178.
32. Baumgartner, S.; Pavli, M.; Kristl, J. *Eur. J. Pharm. Biopharm.* **2008**, *69*, 698.