Release Study of Alfuzosin Hydrochloride Loaded to Novel Hydrogel P(HEMA-*co*-AA)

R. Mohapatra,[1] D. Ray,[2] A. K. Swain,[3] T. K. Pal,[4] P. K. Sahoo[5]

[1]*University Department of Pharmaceutical Sciences, Utkal University, Vani Vihar, Bhubaneswar 751004, India*
[2]*Department of Pharmaceutics, Sri Jayedev College of Pharmaceutical Sciences, Bhubaneswar 751004, India*
[3]*Department of Pharmacy, Hitech Medical College, Pandara, Bhubaneswar, India*
[4]*Department of Pharmacy, Jadavpur University, Jadavpur, Kolkata, India*
[5]*Department of Chemistry, Utkal University, Vani Vihar, Bhubaneswar 751004, Orissa, India*

Received 22 September 2006; accepted 6 February 2007
DOI 10.1002/app.27089
Published online 28 December 2007 in Wiley InterScience (www.interscience.wiley.com).

ABSTRACT: Hydrogels are of great interest in delivering drugs through their polymeric network. Hydrogels of macroporous copolymer 2-hydroxy ethyl methacrylate (HEMA) with acrylic acid (AA) were prepared in the presence of *N*,*N*′-methylene-bis-acrylamide as crosslinker and benzoyl peroxide as initiator. The structure of the copolymer, hydrogel character, and biodegradability have already been discussed in our previous article (Mohapatra et al., Polym Polym Compos 2005, 13, 807) entitled P(HEMA-*co*-AA) as Novel Biodegradable Macroporous Hydrogel. The current study involves the *in vitro* and *in vivo* release of alfuzosin hydrochloride at pH 7.0 and 9.2, taking different concentrations of drug and hydrogel. The percentage of drug entrapment study was done and the stability study was also performed according to I.C.H. guidelines for a period of 6 months giving satisfactory results. J Appl Polym Sci 108: 380–386, 2008

Key words: copolymer; hydrogels; drug delivery system; drug stability; swelling

INTRODUCTION

In the recent years, an ever-increasing interest has been focused on the use of hydrogels in modified release dosage forms[1–3] in relation to their physicochemical properties, properties of drug molecules that can be loaded in polymeric network, the mechanism and rate of drug delivery. Sol–gel technology has the most promising applications in drug delivering system as well as in industries.[4] Hydrogels preformed by chemical or physical crosslinking form three-dimensional hydrophilic polymeric networks capable of imbibing large amount of water or biological fluid.[2] Their on–off drug release with on at low temperature and off at high temperature helps in following pulsatile drug release. When the pH sensitive polymers containing acidic or basic groups are used to prepare hydrogel, the swelling of hydrogel increases as the external pH increases (in case of weakly acidic group) or decreases[5] (in case of weakly basic group). Hydrogels have drawn attention because of their versatile uses in various fields such as in controlled delivery of drugs,[6] in ophthalmic delivery of drugs,[7] and in rectal delivery of drugs.[8] Hydrogels also show gastroprotective property[9] during release of prednisolone in the gastric medium. Biodegradable hydrogels have two major advantages of delivery: first, surgical removal of the drug-depleted device is not necessary, and second, the drug release kinetics can be controlled. Poly(2-hydroxyethyl-methacrylate) [P(HEMA)] is used as a biomaterial because of its nontoxic and biological compatibility in various biomedical applications. P(HEMA) is neutral (nonionic) with water content of $\sim$ 40%. The swelling of P(HEMA) can be regulated by copolymerization with hydrophobic or hydrophilic monomers. Swelling property of polymers is regulated by external environmental conditions such as pH changes,[10–12] magnetic field,[13] temperature changes,[14,15] etc. It is known that polyacrylic acid (PAA) is a pH and electrically sensitive material because of its ionic repulsion between anionic charged groups forming polymer complexes with polybases such as P(HEMA).[16] As the equilibrium water content can be increased by copolymerization with a monomer of more hydrophilic nature, AA is chosen for copolymerization reaction with HEMA. Ease of purification, adjustable mechanical properties, and equilibrium water content contribute to the applications of P(HEMA) and PAA. The main objective of the present work is to deliver alfuzosin hydrochloride (ALF), which is a functionally uroselective alpha-adrenergic blocking agent, indicated for management of benign prostatic hyperplasia[17] and hypertension[18] in a controlled manner through the prepared copolymer hydrogel, P(HEMA-*co*-AA).[19]

Correspondence to: P. K. Sahoo (psahoochemuu@satyam.net.in).

EXPERIMENT

Materials

HEMA and AA were purchased from E. Merck, Germany, and were used after distillation under reduced pressure. Benzoyl peroxide (E. Merck) was recrystallized from benzene and a stock solution was prepared in acetone and *N*,*N*′-methylene-bis-acrylamide (MBA; AR grade) were used as purchased. ALF was a gift sample from Dr. Reddy's Laboratories, India. All other reagents were used after purification by standard techniques.

Drug loading to hydrogel

Drug ALF solution was prepared with distilled water, pH 7.0, and with phosphate buffer solution pH 9.2. The hydrogels prepared as per our previous report[19] were allowed to soak in the drug solution at different ratio as per Tables I and II, stirred in magnetic stirrer (Remi, 1MLH, India) for 24 h. The drug-loaded swollen hydrogel was lyophilized (FTS, Dura-Dry FD-14-84 apparatus) for 24 h at −30°C and at a pressure of 0.05 mmHg. All the batches were prepared in triplicate. The samples were stored at room temperature in amber glass containers.

Yield calculation

The prepared hydrogels from each batch were assessed for the yield value and % yield was calculated using the formula given below.

$$\%\,\text{Yield} = \frac{W_{\text{MF}}}{W_{\text{C}}} \times 100$$

where W_{MF} = weight of the prepared hydrogel and W_{C} = change in weight.

Mean % yield of hydrogels of each batch with standard deviation are illustrated in Table II.

Drug entrapment efficiency (%)

ALF-loaded hydrogels (20 mg) from each batch were dispersed separately in pH 7.4 phosphate buffer and kept for 24 h; filtered through 0.45-μm microfilter and absorbance was measured using UV–vis spectrophotometer (Elice SL159 Spectro, Japan) at 242 nm. ALF contents were determined in triplicate and expressed in terms of weight of ALF per weight of hydrogels, thus determining the actual entrapment ratio (AER) defined by the following expression.

$$\text{AER} = \frac{\text{Measured drug weight}}{\text{Hydrogel weight}}$$

The theoretical entrapment ratios (TER) were also calculated to determine the entrapment efficiency.

$$\text{TER} = \frac{\text{Drug weight}}{\text{Drug weight} + \text{polymer weight}}$$

$$\%\,\text{Entrapment efficiency} = \frac{\text{AER}}{\text{TER}} \times 100$$

TABLE I
Formulation of ALF-Loaded P(HEMA-*co*-AA) Hydrogel in Distilled Water, pH 7.0

Batch	ALF : P(HEMA-*co*-AA)	% Yield (mean ± SD)	% Drug entrapped
A	1 : 1	81 ± 1.47	56 (1.8)
B	1 : 2	73 ± 2.61	49 (1.2)
C	1 : 3	80 ± 1.80	58 (1.6)
D	1 : 5	84 ± 1.12	64 (2.1)

Values in parentheses indicate coefficient of variance.

TABLE II
Formulation of ALF-Loaded P(HEMA-*co*-AA) Hydrogel in Phosphate Buffer, pH 9.2

Batch	ALF : P(HEMA-*co*-AA)	% Yield (mean ± SD)	% Drug entrapped
A_1	1 : 1	74 ± 2.1	64 (2.1)
B_1	1 : 2	75 ± 1.8	63 (1.8)
C_1	1 : 3	70 ± 2.6	70 (2.2)
D_1	1 : 5	87 ± 1.9	71 (1.2)

Values in parentheses indicate coefficient of variance.

In vitro drug release study

The *in vitro* drug release of ALF-loaded hydrogel from each batch was filled in capsule (Size 2) and was analyzed using USP Type-I basket dissolution apparatus (Labindia Disso 2000). Fixed amounts of ALF-loaded hydrogels (20 mg) from each batch were suspended in 500 mL of pH 7.4 phosphate buffer at 37°C. The dissolution medium was kept on stirring at 75 rev/min. Aliquots of the dissolution medium were withdrawn at predetermined time intervals, filtered through 0.45-μm microfilter, and analyzed in UV spectrophotometer at 242 nm.

In vitro drug release kinetics and mechanism

The kinetics of ALF release from hydrogel formulations was studied by finding the best fit of the dissolution data (drug release vs. time) to distinct models: first-order and Higuchi[20,21]

$$Q_t = Q_\infty \left(1 - e^{-k_1 t}\right) \quad (1)$$

where Q_∞ being the total amount of drug in the matrix and k_1 the first-order kinetic constant.

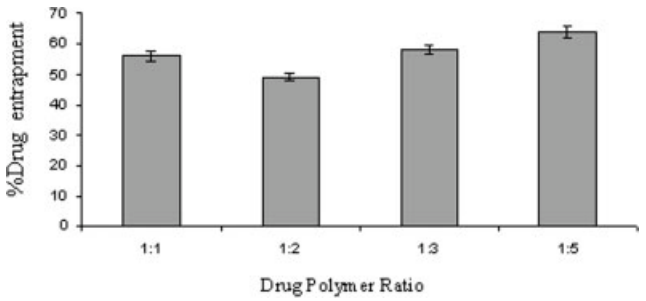

Figure 1 % Drug entrapment of ALF-loaded P(HEMA-*co*-AA) hydrogel prepared in distilled water, pH 7.0.

$$Q_t = k_H t^{1/2} \quad (2)$$

where k_H represents the Higuchi rate constant.

Furthermore, to better characterize the drug release behavior of the polymeric systems studied, namely to understand the corresponding mechanism, the Korsmeyer–Peppas Eq. (3) semiempirical model was applied.[22]

$$\frac{Q_t}{Q_\infty} = kt^n \quad (3)$$

where Q_t/Q_∞ is the fraction of drug released at time t, k is a constant comprising the structural and geometric characteristics of the tablet, and n the release exponent is a parameter that depends on the release mechanism for which it is characterized.[23]

In vivo study

For *in vivo* studies of the hydrogel system, 36 male albino rats (8 weeks old; 220–260 g) were supplied by Institutional Central Animal House Facility and kept under standard laboratory conditions in 12-h light/dark cycle at 25°C. Animals were provided with standard diet and water. They were marked with picric acid solution for easy identification.

For conducting the blood pressure (BP) measurement studies, the animals were kept in a restrainer (rat holder), which had only one side open with proper ventilation at all other sides. The rats were trained for their stay in the restrainer as slight movement would have led to variation in BP reading.

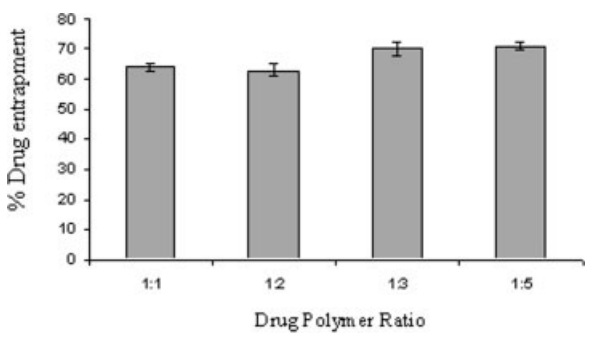

Figure 2 % Drug entrapment of ALF-loaded P(HEMA-*co*-AA) hydrogel prepared in phosphate buffer, pH 9.2.

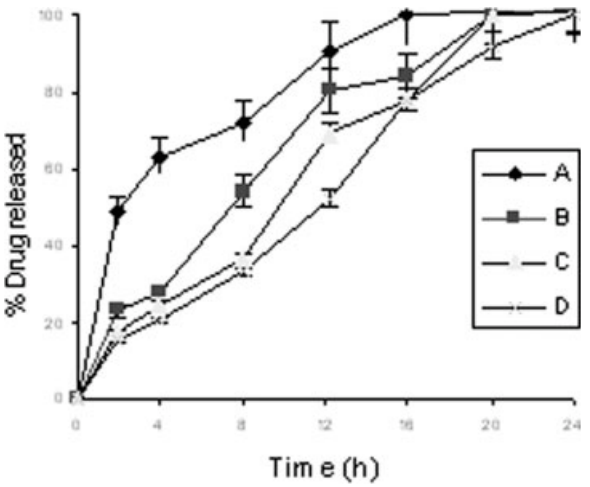

Figure 3 Comparison of *in vitro* release study of ALF-loaded P(HEMA-*co*-AA) hydrogel prepared in distilled water, pH 7.0, with release medium phosphate buffer, pH 7.4.

The initial BP of all the rats was recorded using BP measuring instrument (Digital 1500 controller, Stoctling). The restrainer carrying the rat was placed in the BP instrument, with tail protruding out. The tail of rat was connected to the transducer membrane of the instrument. The instrument was then turned on and allowed to stabilize until steady pulse rate was observed. After stabilizing the steady pulse rate, the mean arterial BP was recorded.

For induction of hypertension, the rats were divided into six groups of six animals each. Group 1 was taken as control. Hypertension was induced in the remaining five groups by subcutaneous injection of methyl prednisolone acetate (MPA, 20 mg/kg/week) for 2 weeks as per the method reported by Krakoff et al.[24] After MPA treatment, Groups 3, 4, 5,

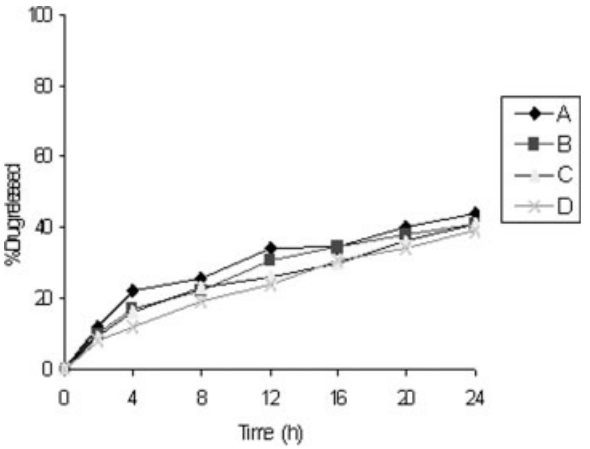

Figure 4 Comparison of *in vitro* release study of ALF-loaded P(HEMA-*co*-AA) hydrogel prepared in distilled water, pH 7.0, with release medium 0.1*N* HCl.

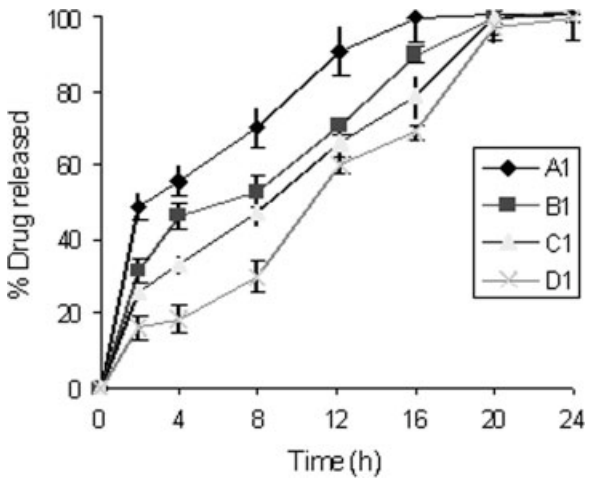

Figure 5 Comparison of *in vitro* release study of ALF-loaded P(HEMA-*co*-AA) hydrogel prepared in phosphate buffer, pH 9.2, with release medium phosphate buffer, pH 7.4.

and 6 were subjected to copolymeric hydrogel formulations (A_1, B_1, C_1, and D_1, respectively) orally, containing identical dose of ALF. Group 2 served as toxic control and received no further treatment. The rat was placed in the restrainer and BP was recorded at regular time intervals up to 48 h.

Statistical analysis

The statistical analysis was performed in INSTAT software and results were expressed as arithmetic mean ± SEM. The pre- and post-treatment values within a group were compared using paired *t*-test. The comparison between various groups was performed by one-way analysis of variance. The percentage reduction in BP for all the treatment groups was also compared.

Stability study

The physical stability of the prepared drug-loaded hydrogel of different batches was evaluated after storing for 6 months under different temperature and humidity conditions. Particular amount of freeze-dried hydrogel from each batch was packed in amber glass vials and stored in the stability chamber at 40°C and 75% relative humidity condition as per I.C.H. guidelines.[25] Samples of definite amount from each batch were withdrawn after 6 months to see the effect of ALF release from the polymers on storage.

Swelling behavior of P(HEMA-*co*-AA)[19]

Dried hydrogels were immersed in vials (200 mL) filled with distilled deionized water at different pH conditions, such as buffer solution of pH 4.0, saline water of pH 6.33, distilled water of pH 7.0, and buffer solution of pH 9.2. The vials were set in a temperature-controlled bath at (25 ± 0.1)°C. To reach the equilibrium degree of swelling, the copolymers were immersed in the aforementioned solutions up to a period of 6 months. Each swelling ratio reported in this work is an average of three separate measurements.

The swelling behavior of the copolymer was computed by calculating the percentage swelling (%*S*).

$$\%S = \frac{M_t - M_o}{M_o} \times 100$$

where, M_t is the mass of the swollen sample at time t and M_o is the mass of the dry sample.

RESULTS AND DISCUSSION

Drug loading and entrapment studies

ALF entrapment in the P(HEMA-*co*-AA) hydrogel prepared with distilled water of pH 7.0 (shown in Table I and Fig. 1) and phosphate buffer solution of pH 9.2 (shown in Table II and Fig. 2) was studied. ALF entrapment was found to be more in pH 9.2 phosphate buffer than in distilled water of pH 7.0. This might be more due to swelling properties of ALF-loaded copolymer in the particular medium. Low coefficient of variance (<2.2%) in % ALF entrapment indicated uniformity of drug entrapment in different batches of hydrogel as per Tables II and III. Percentage yield from all the batches of hydrogel was found to be in the range of 70–88%.

In vitro drug release study

ALF release from ALF-loaded hydrogel was evaluated in pH 7.4 phosphate buffer (Fig. 3) as well as in 0.1*N* HCl (Fig. 4) as the dissolution medium to see the release behavior in different pH conditions. The applied formulate varies, i.e., the changes in concen-

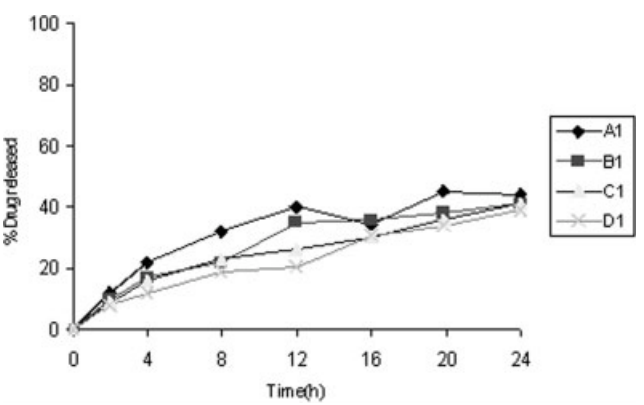

Figure 6 Comparison of *in vitro* release study of ALF-loaded P(HEMA-*co*-AA) hydrogel prepared in phosphate buffer, pH 9.2, with release medium 0.1*N* HCl.

TABLE III
Fitting Results of Experimental ALF Release Data of Formulation A_1–D_1 to Different Kinetic Equations

	First order		Higuchi		Korsemeyer-Peppas		
Formulation	k_1 (h^{-1})	R^2	k_H (% h^{-1})	R^2	k_{KP} (% h^{-n})	N	R^2
A_1	0.391 (0.041)	0.9921 (0.0068)	51.676 (1.249)	**0.9941 (0.0004)**	25.453 (1.114)	0.841 (0.011)	0.9979 (0.0051)
B_1	0.057 (0.078)	0.9958 (0.0003)	18.582 (1.461)	**0.9990 (0.0004)**	12.098 (1.161)	0.674 (0.012)	0.9992 (0.0011)
C_1	0.056 (0.035)	0.9947 (0.0014)	19.081 (0.974)	**0.9989 (0.0002)**	9.881 (0.015)	0.624 (0.009)	0.9974 (0.0003)
D_1	0.040 (0.132)	0.9918 (0.0010)	15.461 (0.989)	**0.9980 (0.0006)**	9.926 (0.168)	0.621 (0.010)	0.9978 (0.0005)

Values in parentheses indicate mean ± SD, R^2 is the coefficient of determination. Best results in bold.

tration of crosslinked polymer were compared for their influence on drug release rate. By increasing the drug and copolymer ratio, the release rate of ALF is reduced in both pH 7.4 phosphate buffer and 0.1*N* HCl. Formulation D_1 prepared in pH 9.2 phosphate buffer (Figs. 5 and 6) medium containing drug to copolymer ratio 1 : 5 showed slowest drug release profile in both the medium than other formulations. Formulation A_1 showed relatively more release in both pH 7.4 phosphate buffer and 0.1*N* HCl. Such behavior would suggest more homogeneous dispersion of drug molecule in the polymer matrix, allowing better penetration of dissolution medium through the hydrogel. *In vitro* release from all batches of hydrogel showed an interesting biphasic release with initial burst release due to the release of drug loaded on hydrogel surface and the second part of drug release may be due to the slow diffusion of drug as matrix erodes slowly. The dispersion of ALF in the polymeric matrix led to a gradual dissolution and release of the drug, which became complete within 24 h; however, over 30% of the drug was released after 2 h in pH 7.4 phosphate buffer medium. ALF releases from hydrogel in two different pH conditions were compared to know whether the drug releases at different pH conditions were showing similar kind of release profile. ALF release from hydrogel at pH 7.4 phosphate buffer was showing much higher release in comparison with 0.1*N* HCl. This type of behavior might be due to solubility of drug in the particular medium, but similar fashion of drug release was observed from different formulations in both the media.

In vitro drug release kinetic mechanism

The drug release mechanism from swellable hydrogel matrices is complex. Although some processes may be classified as either purely diffusion or purely erosion controlled, many others can only be interpreted as being governed by both. The analysis of experimental data in the light of the Korsmeyer–Peppas Eq. (3) as well as the interpretation of the corresponding release exponent values n leads to a better understanding of the balance between these mechanisms. For A_1 formulation, n was determined to be 0.841. Notwithstanding, this value is pointing to an anomalous (non-Fickian) diffusion mechanism; both Higuchi's model (Fickian) and first-order kinetics yielded similarly good quality adjustments.

For formulations B_1–D_1, the diffusion exponent value n ranged from 0.674 to 0.621, shown in Table III, indicating that the release mechanism of ALF from these hydrogel matrices is an anomalous (non-Fickian) transport, which suggests that both diffusion of the drug in the hydrated matrix and its own erosion modulate drug release. For these systems, the Higuchi's kinetic model yielded remarkably good adjustment ($R^2 > 0.999$).

TABLE IV
Effect of Hydrogel System (A_1, B_1, C_1, D_1) of ALF on Mean BP in Control and MPA-Induced Hypertensive Rats

		Mean BP (mmHg) ± SEM			% BP
Group	Treatment	Before treatment	After MPA treatment	After hydrogel treatment	reduction
1	Control[a]	96.8 ± 4.3	–	95.3 ± 5.6 (ns)	–
2	MPA + Placebo Hydrogel[b]	93.5 ± 6.1	162.5 ± 5.2 (s)	163.6 ± 6.8 (ns)	–
3	MPA + A1 Hydrogel[c]	96.7 ± 3.6	156.4 ± 2.9 (s)	106.1 ± 3.3 (s)	32.1
4	MPA + B1 Hydrogel[c]	94.9 ± 3.7	163.7 ± 4.6 (s)	115.3 ± 5.3 (s)	29.5
5	MPA + C1 Hydrogel[c]	91.6 ± 6.8	161.8 ± 3.8 (s)	121.7 ± 4.1 (s)	24.7
6	MPA + D1 Hydrogel[c]	92.5 ± 5.1	159.7 ± 7.1 (s)	130.1 ± 4.7 (s)	18.5

ns, not significant; s, significant ($P < 0.01$).
[a] Control group: received no treatment. After treatment value represents final pressure at 48 h.
[b] Toxic control group: received MPA followed by placebo hydrogel for 48 h.
[c] Treatment groups: received methyl prednisolone acetate followed by hydrogel formulations for 48 h.

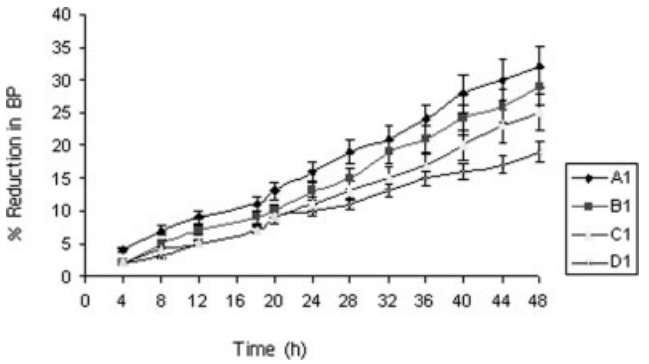

Figure 7 BP reduction profile of ALF hydrogel formulations A_1, B_1, C_1, and D_1 (treatment groups 3, 4, 5, and 6, respectively).

In vivo studies

Hypertension was successfully induced in the normotensive rats by MPA administration as highly significant difference (paired *t*-test, $P < 0.005$) was found in the pre and post treatment values (Group 2, Table IV). The rats remained hypertensive (with a minimum mean BP of 150 mmHg) for 3 days. On treating ALF copolymeric hydrogel system, a significant fall in BP ($P < 0.01$) was observed in the treatment Groups 4–6 (Table IV). The effect in Group 3 was even more pronounced ($P < 0.005$). However, post treatment BP values in control and treatment Group 3 were comparable and not significant ($P > 0.01$). On comparing the effects of all the systems, the percentage reduction of mean BP in rat by formulations, formulation A_1 prepared with HEMA : AA ratio 25 : 75 was found to be more effective in reducing BP to 32.1% (Fig. 7). Although there was significant fall in BP by formulations B_1, C_1, and D_1, these formulations failed to restore the normotensive BP values. The results of *in vivo* studies were in conformity with *in vitro* drug release data.

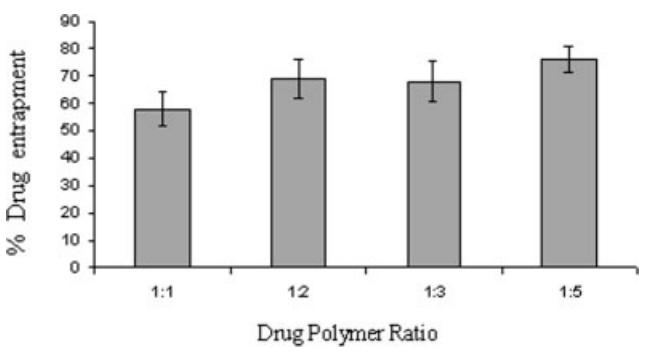

Figure 8 % Drug entrapment of ALF-loaded P(HEMA-*co*-AA) hydrogel prepared in phosphate buffer, pH 9.2, after storing for 6 months at accelerated stability condition.

Stability studies

After storing the formulations for six months at accelerated stability condition, i.e., 40°C and 75% relative humidity as per I.C.H. guidelines, the ALF-loaded hydrogels showed similar type of ALF release profile in both the media and retained the % ALF entrapment with minor deviations (Figs. 8 and 9).

Swelling behavior

In the presence of an aqueous solution, the polymer chains absorb water and the association, dissociation, and binding of various ions to polymer chains cause the hydrogel to swell. Ionic polymer gels are composed of a solid and a liquid phase. In the present polymer gel, the solid portion of the gel consists of a crosslinked polymer network with acidic or basic groups bound to the polymer chains. Crosslinking prevents complete mixing of the polymer chains and the solvent provides an elastic restoring force that counters the expansion of the network. As the prepared polymer is made up of P(HEMA-*co*-AA), the acidic groups bound to their polymer chains, from where the H^+ comes off and combines with OH^- to form H_2O. The charge is compensated by cations that enter the gel together with another OH, thus charge neutrality is maintained. The increased cation concentration gives rise to an osmotic pressure that causes the gel to swell/deswell. An equilibrium ionic gel occurs when the elastic restoring force of the network balances the osmotic forces. It has been marked that gels swell faster in the presence of buffered solutions. In the hydrogel formed by the homogenous copolymer of AA and HEMA with MBA as crosslinker, the acidic groups bound to the polymer chains are carboxyl groups, which made the gels pH sensitive. The

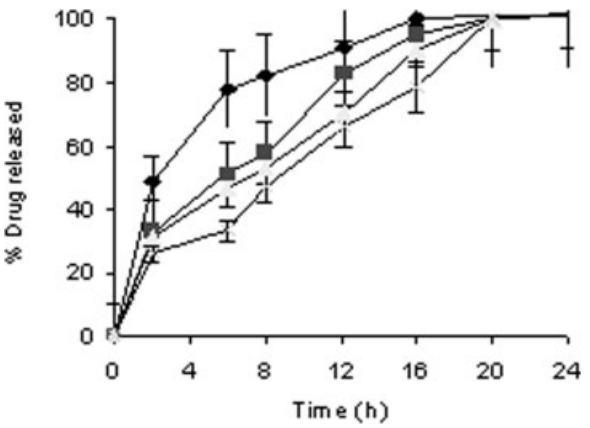

Figure 9 Comparison of *in vitro* release study of ALF-loaded P(HEMA-*co*-AA) hydrogel prepared in phosphate buffer, pH 9.2, with release medium phosphate buffer, pH 7.4, after storing for 6 months at accelerated stability condition.

TABLE V
Percentage Swelling of Copolymer Samples (Initial Weight = 1 g)

S. No.	Distilled water, pH = 7	Saline water, pH = 6.33	Buffer solution	
			pH = 4	pH = 9.2
1 h	796	685	456	929
2 h	857	750	592	1135
3 h	1235	935	733	1498
24 h	3250	2405	1848	4162
48 h	5460	3385	2472	6438
1 month	7650	6283	3883	9135
3 months	8848	7345	4668	11,091
6 months	9982	8225	4896	12,368

water intake or the swelling responses of the P(HEMA-*co*-AA) at intervals were shown in Table V; in distilled water, saline water (NaCl = 1%, ionic conductivity = 11.2 μm S, pH = 6.01), and buffer solutions of pH 4 and 9.2. It has been marked that the hydrogel swells more in buffer pH = 9.2.

CONCLUSION

The prepared copolymer is biodegradable in nature, thus it is ecofriendly. The copolymer showed comparatively higher swelling properties as well as higher % ALF entrapment in pH 9.2 phosphate buffer solutions. ALF release mechanism from the copolymer hydrogel was fitted to different kinetic models, and Higuchi's kinetic model yielded remarkably good adjustment. On comparing the percentage of BP reduction by the prepared hydrogel formulations, formulation A_1 prepared with HEMA : AA ratio 25 : 75 was found to be more effective in reducing BP to 32.1% in rats. The stability studies of the hydrogel was conducted and found to retain their % drug entrapment as well as release profile. A single use of the prepared hydrogel system of ALF can effectively control hypertension in rats for 2 days. The system holds promise for clinical studies.

The authors acknowledge Dr. Reddy's Laboratories, India, for supplying the gift sample of Alfuzosin Hydrochloride.

References

1. Hoffman, A. S. Adv Drug Deliv Rev 2002, 43, 3.
2. Peppas, N. A.; Bures, P.; Leobandung, W.; Ichikawa, H. Eur J Pharm Biopharm 2000, 50, 27.
3. Kikuchi, A.; Okano, T. Adv Drug Deliv Rev 2002, 43, 53.
4. Habsuda, J.; Simon, G. P.; Cheng, Y. B.; Hewitt, D. G.; Toh, H. D. R. J Polym Sci Part A: Polym Chem 2001, 39, 1342.
5. Qiu, Y.; Park, K. Adv Drug Deliv Rev 2001, 53, 321.
6. Mastschke, C.; Isele, U.; Van Hoogevest, P.; Fahr, A. J Controlled Release 2002, 85, 1.
7. Wei, G.; Xu, H.; Ding, P. T.; Li, S. M.; Zheng, J. M. J Controlled Release 2002, 8, 365.
8. Miyazaki, S.; Suisha, F.; Kawasaki, A.; Shirakawa, M.; Yamatoya, K.; Attwood, D. J Controlled Release 1998, 56, 75.
9. Carelli, V.; Coltelli, S.; Di Colo, G.; Nannipieri, E.; Serafini, M. F. Int J Pharm 1999, 179, 73.
10. Sen, M.; Uzun, C.; Guven, O. Int J Pharm 2000, 203, 149.
11. Negishi, M.; Hiroki, A.; Miyakojima, Y.; Asano, M.; Kalakai, R.; Yoshida, M. Drug Dev Ind Pharm 1999, 25, 437.
12. Ganorkar, C. R.; Liu, F.; Baudys, M.; Kim, V. J Controlled Release 1999, 59, 287.
13. Viroonchatapam, E.; Sato, H.; Ueno, M.; Adachi, I.; Tazawa, K.; Horikhosi, I. J Controlled Release 1997, 46, 263.
14. Dinarvand, R.; D'Emaniele, A. Int J Pharm 1995, 118, 237.
15. D'Emanuele, A.; Dinarvand, R. J Controlled Release 1995, 36, 221.
16. Nicolic, L.; Skal, D.; Nicolic, V.; Stamen, S. J.; Babic, D.; Stojanovic, S. J Appl Polym Sci 2004, 91, 387.
17. Lee, M. Am J Health Syst Pharm 2003, 60, 1426.
18. Joneil, M.; Smith, A. The Merk Index: An Encyclopedia of Chemicals, Drugs and Biologicals, 12th ed.; Merck Research Laboratories: White House Station, NJ, 1996; p 235.
19. Mohapatra, R.; Swain, A.; Mohapatra, R.; Rana, P. K.; Sahoo, P. K. Polym Polym Compos 2005, 13, 807.
20. Higuchi, T. J Pharm Sci 1961, 61, 874.
21. Higuchi, T. J Pharm Sci 1963, 52, 1145.
22. Korsmeyer, R. W.; Gurny, R.; Doelker, E. M.; Buri, P.; Peppas, N. A. Int J Pharm 1983, 15, 25.
23. Peppas, N. A. Pharm Acta Helv 1985, 60, 110.
24. Krakoff, L. R.; Selvadurai, R.; Sytter, E. Am J Physiol 1975, 228, 613.
25. Carstensen, J. T.; Rhodes, C. T. In Drug Stability, Principles and Practices, 3rd ed.; Swarbrick, J., Ed.; Marcel Dekker: New York, 2000; Vol. 107, p 649.