Journal of Applied Polymer Science

Synthesis and characterization of cetirizine-containing, pH-sensitive acrylic acid/poly(vinyl alcohol) hydrogels

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ABSTRACT: In this study, interpenetrated acrylic acid (AA)/poly(vinyl alcohol) (PVA) hydrogels were prepared by free-radical polymerization with *N,N*-methylene bisacrylamide (MBAAm) as a crosslinker. The basic structural parameters, such as the molecular weight between crosslinks, volume interaction parameter, number of crosslinks, Flory–Huggins solvent interaction parameter, and diffusion coefficient, were calculated. Cetirizine dihydrochloride was loaded as a model drug in selected samples. The prepared hydrogels were evaluated for swelling, sol–gel fraction, and porosity. The swelling of the AA/PVA hydrogels was found to be directly proportional to the pH, that is, 1.2–7.5, depending on composition. The percentage of cetirizine hydrochloride was found to be directly proportional to the buffer pH and was at its maximum at pH 7.5, that is, 90–95%, and its lowest at pH 1.2, that is, 20–30%. The gel fraction increased with increasing concentration of AA and MBAAm, whereas the porosity showed the same response with AA, but an inverse relationship was observed with MBAAm. The drug-release data were fitted into various kinetics models, including the zero-order, first-order, Higuchi, and Peppas models, which showed non-Fickian diffusion. The prepared hydrogels were characterized by Fourier transform infrared spectroscopy and scanning electron microscopy, and no interaction was found among the polymer ratio and the drug. © 2016 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2016**, *133*, 43407.

KEYWORDS: crosslinking; drug-delivery systems; kinetics; manufacturing; swelling

Received 17 May 2015; accepted 2 January 2016
DOI: 10.1002/app.43407

INTRODUCTION

Hydrogels are an interesting class of materials that have achieved importance as biomaterials, drug-delivery systems, and novel controlled release formulations. These are hydrophilic, three-dimensional polymeric networks that do not dissolve in water but are capable of absorbing a large volume of water. Their ability to absorb water is mainly related to different properties, such as the elasticity of the network, the presence of hydrophilic functional groups (e.g., —OH, —CONH—, —$CONH_2$, —COOH, and —SO_3H) in the polymer chains, the extent of crosslinking, and the porosity of the polymer.[1] Hydrogels have physical properties similar to those of living tissue because of their high water content, soft and rubbery consistency, and low interfacial tension with water or biological fluids.[2] For instance, hydrogels are used for delivering drugs, artificially dressing burns, cell encapsulation, and constructing scaffolds for use in tissue engineering.[3–6]

The preparation of interpenetrating polymeric networks (IPNs) is a useful tool for controlling drug release; this can be easily achieved by changes in the components of the hydrogels. The use of poly(vinyl alcohol) (PVA)-based hydrogels as biomaterials has increased because of PVA's low toxicity, noncarcinogenic nature, and high biocompatibility.[7] It is a hydrophilic, semicrystalline, synthetic polymer that has been widely used in the biomedical and pharmaceutical industries because of its good biocompatibility and physical properties.[8]pH-sensitive poly(vinyl alcohol) hydrogels were prepared by γ-ray irradiation for the controlled release of insulin. The *in vitro* release of insulin was observed in simulated intestinal fluid (pH 6.8), and an *in vivo* rat model confirmed the effectiveness of the oral delivery of insulin.[9] Fechine *et al.*[10] prepared poly(*N*-vinyl-2-pyrrolidone) hydrogels with high-energy radiation. This explained the crosslinking of poly(*N*-vinyl-2-pyrrolidone) based on hydrogen peroxide photolysis.

Acrylic acid (AA) is a monomer that is used for pH-dependent response.[11] Hydrogels networks formed from poly(acrylic acid) can absorb amounts of water many times greater than the weight used in preparation. These polymers are used in many applications, including diapers and personal hygiene products,

Table I. Different Compositions of Crosslinked AA/PVA Preparations

Sample code	AA (g/100 g of solution)	PVA (g/100 g of solution)	MBAAm (g/100 g of solution)	AA/MBAAm
S_1	22.90	5.72	0.115	80:20
S_2	22.90	6.44	0.115	78:22
S_3	22.90	7.64	0.115	75:25
S_4	15.02	6.44	0.075	70:30
S_5	20.40	6.44	0.102	76:24
S_6	27.44	6.44	0.137	81:19
S_7	27.44	6.44	0.096	81:19
S_8	27.44	6.44	0.178	81:19
S_9	27.44	6.44	0.233	81:19

ion-exchange resins, membranes for hemodialysis, ultrafiltration, and controlled release devices.[12,13] The swelling of hydrogels based on AA is facilitated by the presence of carboxylic acid groups in the polymer chain; these are strongly associated with water molecules. These groups are readily ionizable and sensitive to the effects of the pH and ionic strength. Thus, the equilibrium swelling of the AA copolymers are affected by the solution pH and the ionic strength of the solution in which they are swollen.[14]

The crosslinking ratio is another important factor in the swelling nature of hydrogels. The mesh size of the polymer network decreases as the degree of crosslinking increases. Highly crosslinked hydrogels hold a tighter structure and will swell less than identical hydrogels with a lower crosslinking ratio. Hence, the ultimate objective in such delivery systems is to attain the best possible degree of crosslinking to have relatively strong and yet elastic hydrogels.[15] *N,N*-Methylene bisacrylamide (MBAAm) has been used as a crosslinking agent in many polymeric networks and showed good biocompatibility without any deleterious effects on the cell viability and functionality.[16]

In this study, a novel interpenetrated AA/PVA hydrogel was prepared by a free-radical polymerization method at various polymeric, monomeric, and crosslinking compositions. Swelling studies were performed in United State Pharmacopoeia (USP) phosphate buffer solutions at pHs of 1.2, 5.5, 6.5, and 7.5, whereas release studies were performed in the same medium except the USP buffer at pH 6.5. The sol–gel fraction and porosity were calculated, whereas simple equations were used to calculate the average molecular weight between crosslinks (M_c), volume fraction of the polymer ($V_{2,s}$), solvent interaction parameters (χ), crosslinked density, and diffusion coefficient (D). Cetirizine dihydrochloride was loaded as a model drug. Hydrogels characteristics were studied by Fourier transform infrared (FTIR) spectroscopy and scanning electron microscopy (SEM) to investigate their structure, surface morphology, and crystallinity.

EXPERIMENTAL

Materials

AA was used as a monomer. PVA (weight-average molecular weight ≈ 72,000), with a hydrolysis degree of 98%, was used as the polymer, and MBAAm, which was used as the crosslinking agent, were purchased from Merck Chemical Co. (FR, Germany). Benzoyl peroxide, which was used as the initiator, was purchased from Sigma-Aldrich. Cetirizine dihydrochloride was gifted by Novartis (Pakistan) and was used as a model drug.

Preparation of the Crosslinked AA/PVA Polymeric Networks

A series of crosslinked polymeric networks were synthesized after the slight modification of a procedure reported elsewhere,[17] as mentioned in Table I. A PVA solution (10%) was prepared with distilled water; it was first stirred at room temperature for 2 h and then stirred at 80 °C for 30 min. Various amounts of MBAAm and benzyl peroxide (BP) (1% w/v of AA) were dissolved in AA. Both solutions were mixed well for up to 30 min. The final weight of all of the samples was 100 g with distilled water, and the reaction mixture was once again stirred rapidly to ensure the homogeneity of the reaction mixture. The final solution was introduced into glass tubes having an internal diameter of 16 mm and a length of 150 mm. These test tubes were deoxygenated with nitrogen-gas bubbling for 10–20 min and then snugly fitted with a lid. The capped tubes were placed in a water bath at a temperature of 45 °C for 1 h, 50 °C for 2 h, 55 °C for 3 h, 60 °C for 4 h, and 65 °C for 12 h. The temperature was gradually increased from 45 to 65 °C to prevent autoacceleration and bubble formation. After this period, the tubes were cooled to room temperature, and cylinders of the prepared hydrogels were removed from the tubes and cut into 7-mm lengths. These cylindrical discs were washed with distilled water for 1–2 weeks for complete removal of the unreacted monomers. During this period, the solvent was changed daily. The washing process of the gels was continued until the pH of the washing was the same as that of distilled water before washing. The disks were dried, first at room temperature and then in an oven at 40–45 °C until a constant weight was reached. The obtained products were stored in vacuum desiccators for further use.

Swelling Studies

Dynamic and equilibrium swelling ratios (qs) were studied in 100 mL of USP buffer solutions at pHs of 1.2, 5.5, 6.5, and 7.5 at 37 °C. A dynamic study was performed up to 12 h, whereas an equilibrium study was continued until the samples reached a constant mass; this took almost 2–3 weeks. The q of each disc was calculated from the following relation:[18]

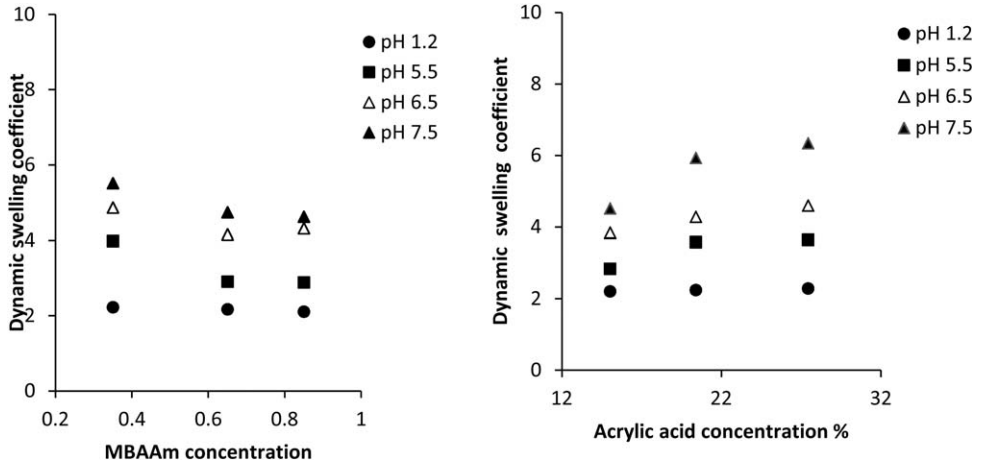

Figure 1. Dynamic swelling coefficient after 8 h of the AA/PVA copolymer with (A) different MBAAm concentrations and various pHs at 37 °C and (B) different AA concentrations and various pHs at 37 °C.

$$p_l q = W_h / W_d \tag{1}$$

where W_h is the weight of the swollen hydrogels at time t and W_d is the initial weight of the dry hydrogels.

D

D is the amount of a particular solvent that diffuses across a unit area through a unit concentration gradient in unit time. It is an important parameter and is indicative of the diffusion mobility. It was calculated by the following relation[19]:

$$D = \pi \left(\frac{h\theta}{4 q_{eq}} \right)^2 \tag{2}$$

where q_{eq} is volume fraction of the swollen gel, θ is the slope of the linear part of the swelling curves, and h is the initial thickness of the gel before the swelling.

Characterization of the AA/PVA IPN

The Flory–Huggins theory was used to find χ.[20] According to this theory:

$$\chi = \frac{\ln(1 - V_{2,s}) + V_{2,s}}{V_{2,s}^2} \tag{3}$$

where $V_{2,s}$ is the volume fraction of the swollen gel in the equilibrium state (mL/mol). Average molecular weight between two adjacent crosslinks represents the degree of crosslinking of hydrogel, M_c was determined with equilibrium swelling data through this equation[21]:

$$M_c = \frac{d_p V_s (V_{2,s}^{1/3} - V_{2,s}/2)}{\ln(1 - V_{2,s}) + V_{2,s} + \chi V_{2,s}^2} \tag{4}$$

where d_p and d_s are the densities of the polymer and solvent (g/mL), respectively, whereas χ is the Flory–Huggins polymer solvent interaction parameter.

The crosslinked hydrogels were characterized by their crosslinking densities. The equation used for the crosslinked density is as follows[15]:

$$N = \frac{2M_c}{M_r} \tag{5}$$

where M_c is the average molecular weight between crosslinks and M_r is the molar mass of the repeating unit and was calculated by the following equation:

$$M_r = \frac{m_{AA} M_{AA} + m_{MBAAm} M_{MBAAm}}{m_{AA}} \tag{6}$$

where m_{AA} and m_{MBAAm} are the masses of AA and MBAAm, respectively, and M_{AA} and M_{MBAAm} are the molar masses of AA and MBAAm, respectively.

Sol–Gel Fraction

For sol–gel analysis, nonwashed discs were used. Fresh discs were cut into pieces 3–4 mm in length, dried in a vacuum oven at 45 °C to a constant mass, and then subjected to Soxhlet extraction for 4 h with deionized water with zero electrical conductivity. Uncrosslinked polymers were removed from the gel structure during this extraction procedure. The extracted gels were dried again in a vacuum oven at 45 °C to a constant weight. The gel fraction was calculated with the initial weight of the dry gel (W_0) and the weight of the extracting dry gel (W_1) according to the following equation[19]:

$$\text{Sol fraction } (\%) = \left(\frac{W_0 - W_1}{W_0} \right) \times 100 \tag{7}$$

$$\text{Gel fraction} (\%) = 100 - \text{sol fraction} \tag{8}$$

Porosity Measurement

The solvent replacement method was used to determine the porosity. The dried hydrogels were immersed in absolute ethanol overnight and weighed after we blotted the excess ethanol on the surface. The porosity was calculated from the following equation:

$$\text{Porosity} = \frac{M_2 - M_1}{\rho V} \times 100 \tag{9}$$

where M_1 and M_2 are the masses of the samples before and after immersion in ethanol, respectively; ρ is the density of absolute ethanol; and V is the volume of the hydrogel.

Cetirizine Dihydrochloride Loading and Release Analysis

For drug loading, six samples were selected in such a way that three of them had different concentrations of AA (e.g., S_4–S_6 had AA/PVA concentration ratios of 15.02:6.44, 20.4:6.44, and 27.44:6.44, respectively), and three had different crosslinking agent ratios (i.e., crosslinking ratio of S_7–S_9 = 0.096, 0.178, and 0.233, % w/w MBAAm, respectively), as shown later in Table

Table II. Flory–Huggins Network Parameters of AA/PVA Hydrogels

Sample code	$V_{2,s}$	χ	M_c	M_r	N	$D \times 10^{-6}$ (cm^2/s)
S_1	0.086559	−0.51088	2755.450	37938.39	0.191479	0.054698
S_2	0.117253	−0.52288	1484.989	20446.06	0.093995	0.088103
S_3	0.122352	−0.53493	1441.612	19848.82	0.080096	0.104876
S_4	0.159163	−0.53032	800.8135	11026.53	0.037105	0.144362
S_5	0.090789	−0.54245	1914.110	26355.40	0.110863	0.063928
S_6	0.056561	−0.54969	1535.453	21141.93	0.404357	0.031064
S_7	0.111830	−0.55071	1627.784	22471.01	0.118766	0.125833
S_8	0.149568	−0.55621	938.8674	12894.39	0.068665	0.139110
S_9	0.145036	−0.56431	911.1152	12470.63	0.066741	0.107413

N, number of crosslinks.

IV. Cetirizine dihydrochloride 1% w/v was dissolved in distilled water, and selected samples were immersed in this solution until equilibrium was achieved. Fully swelled hydrogels were removed from the drug solution and blotted with filter paper to remove the surface drug solution. The drug-loaded samples were first dried at room temperature and then dried in an oven at 40–45 °C until a constant weight was obtained. To determine the percentage drug loading, the drug-loaded samples were extracted repeatedly with the same solvent used for drug loading up to exhaustion, and the concentration of drug was determined spectrophotometrically at 230 nm. We used a dissolution apparatus (USP II, paddle apparatus) associated with a spectrophotometer (IRMECO, ultraviolet–visible U2020) by placing a polymer sample in 500 mL of dissolution medium at 37 °C with constant stirring at a rate of 100 rpm. An aliquot of 5 mL was withdrawn, replaced by fresh medium, and filtered through a 0.45-µm syringe filter, and the concentration of cetirizine dihydrochloride observed at 230 nm.

In Vitro Kinetics

Model-dependent *in vitro* kinetic parameters, including the zero-order kinetics [eq. (10)], first-order kinetics [eq. (11)], Higuchi model [eq. (12)], and Korsmeyer–Peppas model [eq. (13)], were used to analyze the drug-release pattern[22]:

$$F_t = K_0 t \tag{10}$$

$$\ln(1-F) = -K_1 t \tag{11}$$

$$F_r = K_2 t^{1/2} \tag{12}$$

where F_r is the fraction of drug release.

$$M_t / M_\infty = K_3 t_n \tag{13}$$

where F_t is the fraction of drug release at time t, K_0 is the apparent rate constant for zero-order release constant, F is the fraction of drug release at time t, K_1 is the first-order release rate constant that represents the fraction of drug release at time t, K_2 is the Higuchi constant, K_3 is the constant incorporating the structural and geometric characteristics of the hydrogels, and n is the release exponent. M_t is amount of drug release at time T, M_∞ is amount of drug release at infinity, T is time and n is diffusion constant. When n is 0.5, the order of release is Fickian. A value of n of 1 corresponds to case II transport, and at $0.5 < n < 1$, the diffusion mechanism is non-Fickian. No kinetic data or n values were calculated when the swelling and drug release were not significant.

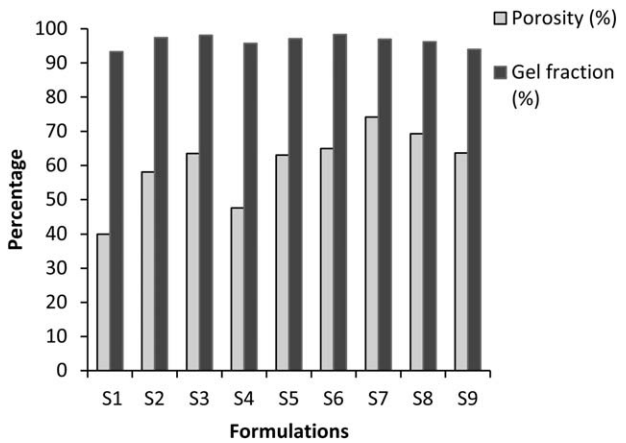

Figure 2. Porosity percentages and gel fractions of the different formulations: S_1–S_3 (22.9/5.72, 22.9/6.44, and 22.9/7.64 AA/PVA), S_4–S_6 (15.02/6.44, 20.4/6.44, and 27.44/6.44 AA/PVA), and S_7–S_9 (0.096, 0.178, and 0.233% w/w MBAAm) at pHs 1.2, 5.5, and 7.5.

FTIR Spectroscopy

Crosslinked discs were crushed with a pestle in an agate mortar and mixed with potassium bromide (IR spectroscopy grade, Merck) at a ratio of 1:100. The powder mixture was dried at 40 °C and compressed to a 12-mm semitransparent disk through the application of a pressure of 65 kN (pressure gauge, Shimadzu) for 2 min. The FTIR spectrum (shown later in

Table III. Amount of Cetirizine Dihydrochloride Loaded (g/g of Dry Gel)

Sample code	By swelling	By extraction	By weight
S_4	0.0163	0.0155	0.0132
S_5	0.0170	0.0164	0.0136
S_6	0.0174	0.0169	0.0141
S_7	0.0181	0.0177	0.0137
S_8	0.0175	0.0173	0.0134
S_9	0.0169	0.0162	0.0133

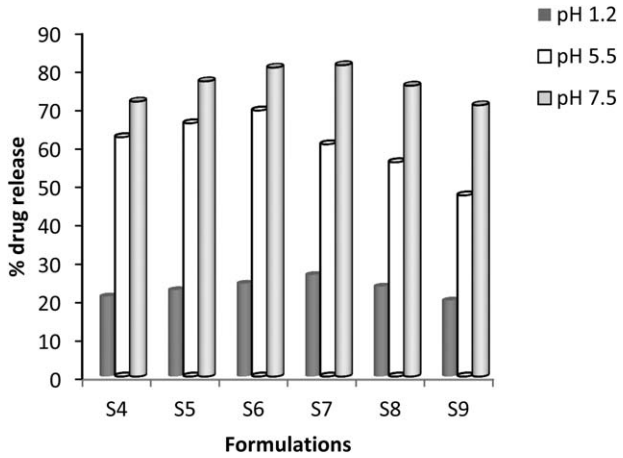

Figure 3. Percentage drug release of different formulations: S_4–S_6 (15.02/6.44, 20.4/6.44, and 27.44/6.44 AA/PVA) and S_7–S_9 (0.096, 0.178, and 0.233% w/w MBAAm) at pHs 1.2, 5.5, and 7.5.

Figure 4) over the wavelength range 4500–400 cm^{-1} were recorded with an FTIR spectrophotometer (FTIR 8400 S, Shimadzu).

SEM

The morphology of the selected hydrogels was observed with SEM (JEOL SEM instrument, model JSM 5910). Hydrogel samples with the drug (shown later in Figure 5) and without the drug were randomly selected, and their combined structures were observed.

RESULTS

Dynamic swelling studies of the prepared hydrogels were observed to be pH dependent. An increase in the percentage swelling was observed when the concentrations of AA were increased, as shown in Figure 1. The crosslinking agent had an inverse effect on the dynamic swelling, as shown in Figure 1.

Observational parameters, such as D, solvent interaction parameter (χ), M_c, and volume fraction, were calculated and are shown in Table II with the names of the Flory–Huggins parameters. Figure 2 shows that the sole gel fraction was between 90 and 95% and the porosity was between 40 and 70% of that of the prepared hydrogels. The amounts of cetirizine loaded by swelling, extraction, and hydration calculated successfully were observed to be quite up to the mark, and the maximum cetirizine loaded was found by swelling to be 0.0181, as expressed in Table III. The percentage of cetirizine hydrochloride release at

Table IV. Effects of the AA and MBAAm Contents on the Release Kinetics (Zero-Order, First-Order, and Higuchi Models) from the AA/PVA Hydrogels in Solutions at Different pHs

Composition and experimental conditions			Zero-order		First-order		Higuchi	
Sample code	AA (%)	pH	K_0 (h^{-1})	r	K_1 (h^{-1})	r	K_2 (h^{-1})	r
S_4	15.02	1.2	1.6099	0.996	0.0182	0.998	0.0683	0.990
		5.5	5.1824	0.982	0.0822	0.996	0.2247	0.997
		7.5	6.1127	0.980	0.1094	0.998	0.2646	0.9915
S_5	20.4	1.2	1.7252	0.992	0.0797	0.994	0.0738	0.9936
		5.5	5.4936	0.986	0.0891	0.997	0.2366	0.995
		7.5	6.4407	0.992	0.1196	0.995	0.2751	0.913
S_6	27.44	1.2	1.8663	0.980	0.0216	0.985	0.0808	0.995
		5.5	5.778	0.973	0.1002	0.996	0.2522	0.989
		7.5	6.4121	0.968	0.1319	0.997	0.2815	0.988

Composition and experimental conditions			Zero-order		First-order		Higuchi	
Sample code	MBAAm (%)	pH	K_0 (h^{-1})	r	K_1 (h^{-1})	r	K_2 (h^{-1})	r
S_7	0.35	1.2	1.974	0.979	0.0230	0.986	0.0868	0.998
		5.5	4.7876	0.966	0.077	0.989	0.2105	0.9957
		7.5	6.3415	0.959	0.135	0.995	0.2801	0.9927
S_8	0.65	1.2	1.81	0.983	0.021	0.989	0.0784	0.9988
		5.5	4.338	0.945	0.0662	0.9726	0.1933	0.987
		7.5	6.0465	0.976	0.1168	0.9974	0.2642	0.9958
S_9	0.85	1.2	0.14319	0.9821	0.0162	0.9865	0.0621	0.9984
		5.5	3.4369	0.9537	0.0479	0.9729	0.1521	0.9895
		7.5	5.7024	0.9677	0.1041	0.9937	0.2502	0.995

Table V. Effect of the AA and MBAAm Contents on the Release Mechanism with the Application of the Peppas Model to the AA/PVA IPNs in Solutions at Different pHs

Sample code	AA (%)	pH	*n*	Regression, *R*	Order of release
S_4	25.45	1.2	0.7299	0.9971	Non-Fickian
		5.5	0.9281	0.9921	Non-Fickian
		7.5	0.8969	0.9951	Non-Fickian
S_5	32.72	1.2	0.7505	0.9971	Non-Fickian
		5.5	0.9544	0.9951	Non-Fickian
		7.5	0.9245	0.9911	Non-Fickian
S_6	27.44	1.2	0.7371	0.9851	Non-Fickian
		5.5	0.9118	0.9891	Non-Fickian
		7.5	0.8610	0.9881	Non-Fickian

Sample code	MBAAm (%)	pH	*n*	Regression, *R*	Order of release
S_7	0.35	1.2	0.7117	0.9951	Non-Fickian
		5.5	0.8033	0.9835	Non-Fickian
		7.5	0.7801	0.9866	Non-Fickian
S_8	0.65	1.2	0.6931	0.9971	Non-Fickian
		5.5	0.7986	0.9771	Non-Fickian
		7.5	0.7815	0.9931	Non-Fickian
S_9	0.85	1.2	0.6572	0.9809	Non-Fickian
		5.5	0.7294	0.9683	Non-Fickian
		7.5	0.7836	0.9885	Non-Fickian

different pH buffers (1.2, 5.5, and 7.5) for 12 h were observed, and the maximum release was observed at pH 7.5. Different release patterns at different concentrations of AA and crosslinking agent are shown in Figure 3.

The first-order release rate was observed in almost all of the formulations either with a difference in the AA concentration or the crosslinking agent concentration. Table IV provides detailed values of the release rate of the different kinetic models and the regression values of the respective kinetic models, whereas in Table V, those of the Peppas model with its non-Fickian order of release were reported.

There were no interactions between the peaks of the reactants and the crosslinking agent, as shown in the FTIR chromatograms of the simple AA, MBAAm, and PVA alone and in hydrogel form in Figure 4. Morphological structures of the prepared hydrogels loaded with cetirizine and without the drug are shown in Figure 5. The results of SEM of the drug-loaded hydrogel show that the drug was uniformly distributed in the hydrogels.

DISCUSSION

A direct increasing effect of the pH on the swelling nature of the hydrogels was observed. pH sensitivity was observed because of the presence of the carboxylic group, which is a weak acid with an intrinsic pK_a of about 4.26. Efficient swelling was obtained in the buffer solution having a higher pH because of the acceptance of the proton by a carboxylic group, which ionized it. As a result of this ionization, electrostatic repulsion along the chain may have resulted in the expansion of the

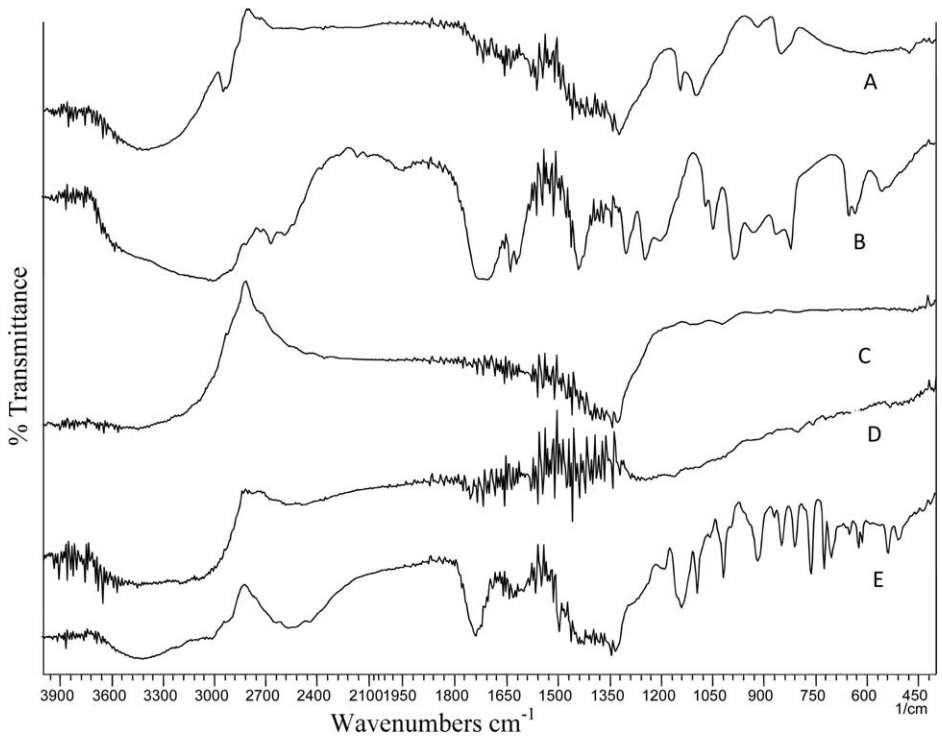

Figure 4. FTIR spectra: (A) pure PVA, (B) AA, (C) AA/PVA hydrogel, (D) AA/PVA hydrogel with cetirizine hydrochloride, and (E) cetirizine dihydrochloride.

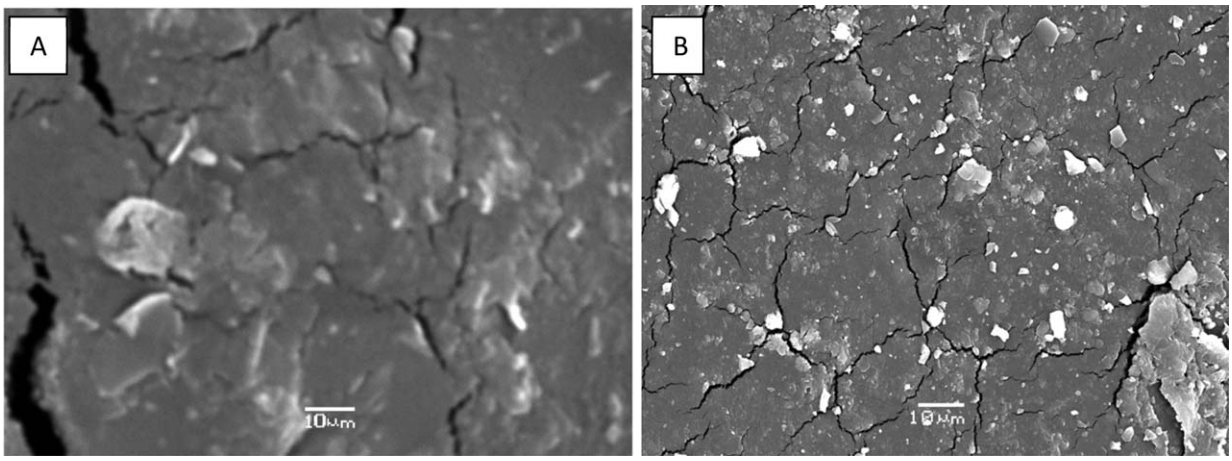

Figure 5. SEM results: (A) drug-unloaded hydrogel and (B) drug-loaded hydrogel.

originally coiled molecule. The ionic swelling pressure increased and showed more swelling. The increase in the degree of ionization converted the polymeric network into a more hydrophilic one; this further supported the swelling behavior. A similar attitude was reported by Sadeghi and Yarahmadi,[23] who observed that when the pH was increased, the swelling and drug-release increased in the chitosan-*g*-poly(acrylic acid-*co*-acrylonitrile) hydrogel.

The incorporation of the AA contents during hydrogel formation made it pH dependent. Figure 1 shows the dynamic swelling behavior of hydrogels having a pH-dependency date with different AA concentrations (15.02, 20.40, and 27.44%) in solution as a function of the pH of the swelling medium and with the crosslinker concentrations kept constant at 0.5% AA. The dynamic and equilibrium swelling coefficients did not increase considerably at low pH because the carboxyl groups remained associated and formed hydrogen bonding with PVA chains, but at higher pHs, that is, 5.5, 6.5, and 7.5, there was a significant increase in the swelling because of the availability of a large number of carboxylate ions.[24]

Three samples of AA/PVA hydrogels having different concentrations of crosslinking agent, that is, 0.35, 0.65, and 0.85% AA, were selected to investigate the effect of MBAAm on swelling. Figure 1 reveals that the swelling of the gel decreased with increasing MBAAm concentration because of the presence of more physical entanglements between the hydrogels. Mechanistically, the influence of the increasing crosslinking concentration decreased the mesh size of the network. Moreover, highly crosslinked polymers were less acidic because of the conciliation of carboxylate groups; this resulted in a reduction in the process of ionization.[25]

The values of M_c and χ are shown in Table II. It was reported that values of M_c increased with increasing concentration of AA. This higher swelling was due to the impartment of hydrophilicity in the polymer by ionization of the carboxylic groups of AA.[26] A critical overview of these results clearly depicted that those values of χ decreased with increasing concentration of AA. This elaborated the hydrophilic nature of the chains and the strong interaction with the solvent. The values of N were directly proportional to the concentration of AA and inversely proportional to the concentration of PVA. When the sol–gel fractions of the different formulations of PVA/AA were calculated, we noticed that the gel fraction increased with increasing concentration of AA, PVA, and MBAAm, whereas the sol fraction decreased, as shown in Figure 2. As with increasing concentration of the polymer, monomer, and crosslinker, there was more crosslinking between the monomer and crosslinker, and this ultimately increased the gel strength and M_c.[27] Figure 2 shows the porosity of different AA/PVA formulations. We noticed that porosity increased as the PVA and AA concentrations (S_1–S_6) increased. This could be explained by the increase in the concentrations of the polymer and monomer; the viscosity of the solution increased the prevention of the bubbles escaping from the solution. This resulted in the formation of interconnected channels, and thus, the porosity increased. When the concentration of MBAAm increased (S_7–S_9), the porosity showed an inverse relationship because of increases in the entanglement between the monomer and polymer; this resulted in a decreased porosity.[28]

Table IV shows the correlation coefficients (rs) obtained from the AA/PVA hydrogels at various contents of AA and MBAAm. The best fit release model was evaluated by r, which should have been nearer to 1. The values of r obtained for the zero-order release rate constants were found to be higher compared with those of the first-order rates; this showed that the drug-release rate was definitely zero order. The r values of the Higuchi model showed a diffusion-controlled, drug-release mechanism, whereas the values of the release exponent (n) and r for various samples of AA/PVA hydrogels were calculated with the Peppas equation and are given in Table V. The r values obtained for the Peppas model were found to be very close to 1; this indicated good linearity, so we concluded that the drug release from these samples followed non-Fickian behavior at all pH values.

Figure 4 shows the spectra of the AA, pure PVA, AA/PVA hydrogel, and drug-loaded AA/PVA hydrogel and cetirizine dihydrochloride. The FTIR spectra of the pure PVA showed a broad peak at 3425 cm^{-1}; this indicated stretching of the hydroxyl groups (—OH). The peaks at 2923 and 2850 cm^{-1} were due to —C—H stretching vibrations. The peaks at 1485

and 1342 cm^{-1} were assigned to —CH_2 scissoring and —OH bending vibrations, respectively. The peak at 1150 cm^{-1} suggested the presence of —CH—OH groups. The peaks at 1090 and 917 cm^{-1} showed C—O stretching vibrations of secondary alcohol and O—H bending, respectively. The FTIR spectra of AA showed a broad peak at 3000 cm^{-1} for —OH stretching and at 2922 cm^{-1} for —CH groups.

The FTIR spectra of the AA/PVA hydrogel indicated the main changes in the region 1300–1800 cm^{-1}; this evidence of interactions between them were also attributed to overlapping bonds. The incorporation of AA was confirmed by the formation of an extra peak at 1732 cm^{-1} for the carbonyl group of AA units. In this study, a band appeared at 1721 cm^{-1} showing a negative shift; this indicated the formation of hydrogen bonding. Carbonyl bands in the complex were broader than PVA and AA; this was also evidence of strong interactions. N—H stretching between 3330 and 3060 cm^{-1}, and C—N stretching at 1650 cm^{-1} indicated the presence of the MBAAm crosslinker.

The results of SEM showed that the drug was uniformly distributed in the hydrogels, as is clear in Figure 5. In comparison with the nonloaded gel, the hydrogel loaded with drug showed a compact structure; this was attributed to the filling of pores with the drug and the removal of the solvent from the hydrogel when it was dried after swelling.

CONCLUSIONS

The AA/PVA hydrogels were synthesized in the presence of MBAAm as the crosslinking agent. Moreover, various parameters, such as the gel fraction, porosity, and q, proved to be linked to the concentration of various variables, such as the AA, PVA, and crosslinker concentrations. The results of swelling kinetic and drug-release data showed zero-order kinetics and non-Fickian diffusion behavior. FTIR spectroscopy studies exposed the presence of hydrogen bonding between PVA and AA in the hydrogels, whereas SEM revealed the spongelike porous structure. So, we concluded that the prepared pH-sensitive hydrogels are an appropriate applications for oral-modified drug-delivery systems.

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