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Swelling and Aspirin Release Study: Cross-Linked pH-Sensitive Vinyl Acetate-co-Acrylic Acid (VAC-co-AA) Hydrogels

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The objective of this work was to develop new pH-sensitive hydrogels to deliver gastric mucosal irritating drugs to the lower part of the gastrointestinal tract. For this purpose, cross-linked vinyl acetate-co-acrylic acid (VAC-co-AA) hydrogels were synthesized by using *N, N,* methylene bisacrylamide (MBAAm) as a cross-linking agent. Different ratios of 90:10, 70:30, 50:50, 30:70, and 10:90 of VAC-co-AA were synthesized. All of the compositions were cross-linked using 0.15, 0.30, 0.45, and 0.60 mol percent MBAAm. Swelling and aspirin release were studied for 8 hour period. The drug release data were fitted into various kinetic models like the zero-order, first-order, Higuchi, and Peppas. Hydrogels were characterized by Fourier transform infrared spectroscopy and scanning electron microscopy. In addition to the above, these hydrogels were loaded with 2%, 8% and 14% w/v aspirin solutions, keeping the monomeric composition and degree of cross-linking constant. In conclusion, it can be said that aspirin can be successfully incorporated into cross-linked VAC/AA hydrogels and its swelling and drug release can be modulated by changing the mole fraction of the acid component in the gels.

Keywords pH-sensitive hydrogels; cross-linked; acrylic polymers; aspirin

INTRODUCTION

Hydrogels based on acrylic acid (AA) and its copolymers have been used in order to develop pH-sensitive drug release systems (Dimitron, Lambov, Shenkov, Dosseva, & Baranovski, 2003). There are a number of copolymers that show pH-sensitive swelling and drug release behavior (Tasdelen, Kayaman-Apohan, Guven, & Baysal, 2005; Tasdelen, Kayaman-Apohan, Guven, & Baysal, 2004). Carboxylic acid containing pH-sensitive gels would be very useful for the delivery of gastric irritating drugs to the small intestine or the colon; therefore, pH-sensitive hydrogels are an attractive alternative system for enteric coating (Wen-Fu & Yu-Hung, 2001). Peppas and Peppas (1990) found that the degree of ionization and the nature of the medium surrounding the polymers of acrylic acid are extremely important, and polymers containing acrylic acid show sensitivity to the pH of their surroundings. pH sensitivity, swelling, and drug release behavior is also influenced by the degree of cross-linking. In addition, cross-linking protects the gels from disintegration during swelling, and these cross-linked gels may be used for studying swelling kinetics (Ranjha & Rashid, 2001). Cross-linked polymers studied are much less acidic than the linear ones; the acidity decreases with increasing networks density (Prandy & Kopcek, 1990).

In this article, a pH-sensitive hydrogel consisting of vinyl acetate (VAC) and AA have been developed. These swell in a higher pH while collapsing in an acidic pH. Both components of the gels are hydrophobic in acidic media. On arrival in a basic or neutral environment, the carboxyl-containing component changes from hydrophobic to hydrophilic and drug is released due to swelling of the hydrogels.

Aspirin (acetylsalicylic acid) has been shown to give occult gastrointestinal bleeding in most persons who take a normal therapeutic dose of aspirin 3 to 4 g/day (Croft & Wood, 1967; Pierson, Holt, Watson, & Keating, 1961). This seems to be due to a local irritant effect (Edmer, 1975; Thorson, Western, Tanaka, & Morrissey, 1968). For patients who must take large doses of aspirin continuously, for example, patients with rheumatoid arthritis, this constitutes a significant clinical problem.

The traditional way to reduce gastric irritation has been to administer aspirin as enteric-coated tablets (Scott, Porter, Lewis, & Dixon, 1961; Stubbe, Pietersen, & Van Heulen, 1962). Enteric-coated tablets however have a variable onset of action (Day, Paul, Champion, & Graham, 1976), and sometimes incomplete absorption (Clark & Lasagna, 1965). These pH-sensitive hydrogels may prevent gastric distress or nausea due to aspirin irritation.

The aim of this work was to investigate the effect of pH and the effect of the molar ratio of both component and that of the cross-linking ratio on the dynamic equilibrium swelling and on the drug release in order to find hydrogels that could exhibit Case II or constant drug release.

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MATERIALS AND METHODS

Materials

The comonomers used were VAC and AA (Merck, Darmstadt, Germany). *N, N,* methylene bisacrylamide (MBAAm, Merck) was used as cross-linking agent, while benzoyl peroxide (Merck) was used as catalyst.

Synthesis of Cross-Linked VAC-co-AA Hydrogels

A series of cross-linked samples of VAC/AA were synthesized with varying monomeric compositions and degrees of cross-linking using MBAAm as a cross-linking agent. Synthesis was carried out after the modification of the procedure reported earlier (Ranjha & Doelker, 1999a). The procedure used is briefly described here. Benzoyl peroxide was dissolved in vinyl acetate at a concentration of 1% w/v of the total monomers as catalyst. The second monomer, AA, was added, and the cross-linking agent was dissolved in ethanol and mixed in monomeric solution. The ratio of ethanol and monomers was 1:1 by volume. The cross-linking ratio of MBAAm was calculated as:

$$\text{Cross-linking ratio} = \frac{\text{Mole of EGDMA} \times 100}{\text{Mole of bifunctional monomers}} \qquad (1)$$

After mixing thoroughly, the final solution was introduced into glass tubes (Pyrex), each with internal diameters of 20 mm and snugly fitted with a lid. These tubes were placed in a water bath. The temperature was gradually increased in all samples to avoid auto acceleration and bubble formation. The reaction temperature of solution polymerization was 45°C for 1 hour, 50°C for 2 hours, 55°C for 3 hours, 60°C for 4 hours, and 65°C for 24 hours. After this period, tubes were cooled to room temperature and the cylinders were removed from the tubes. In all trials, cylinders were cut into small disks (10 mm in length). These disks were washed with 40% v/v ethanol water for complete removal of the unreacted monomers. The solvent was changed daily. The washing of the gels was completed until the pH of the washing solution and freshly prepared solution (40% v/v ethanol water) were the same. The disks were then dried, at first at room temperature and then in a vacuum oven at 40°C to 45°C, for one week. Copolymerization and cross-linking reaction occured simultaneously. Table 1 shows the various hydrogels used for this study. The results shown in graphs and in tables are the average of two experimental runs.

TABLE 1
Hydrogels Prepared for Swelling Sudies with Different Monomeric Composition and MBAAm as a Cross-Linking Agent

No. of Samples	Monomeric Composition (VAC/AA)	Degree of Cross-Linking (mol %)
1.	10:90	0.15
2.	30:70	0.15
3.	50:50	0.15
4.	70:30	0.15
5.	90:10	0.15
6.	10:90	0.30
7.	30:70	0.30
8.	50:50	0.30
9.	70:30	0.30
10.	90:10	0.30
11.	10:90	0.45
12.	30:70	0.45
13.	50:50	0.45
14.	70:30	0.45
15.	90:10	0.45
16.	10:90	0.60
17.	30:70	0.60
18.	50:50	0.60
19.	70:30	0.60
20.	90:10	0.60

Scanning Electron Microscopy (SEM)

The morphology of the hydrogel samples was investigated using JOEL 5910 scanning electron microscope. The secondary imaging techniques were used. The surface was scanned using two magnifications, that is, 1,000 and 2,000, for investigating the structure formed by using a cross-linking agent. In order to keep the pores of hydrogels intact for imaging, the hydrogels were left in liquid nitrogen and then broken. Before SEM observation, specimens were fixed on stubs and hydrogels were coated with gold/platinum alloys (15:85) under vacuum using JOEL JEE-SS vacuum evaporator and observed at 5 KV.

Swelling Behavior of VAC/AA Hydrogel

The dynamic and equilibrium swelling experiments were carried out in 100 ml of solution at 37°C. Two types of solutions were used for the swelling experiments; 0.1 M HCl as simulated gastric fluid (pH 1.2) and United States Pharmacopeia (USP) phosphate buffer solutions. Dry discs were weighed and immersed in United States Pharmacopeia (USP) phosphate buffer solutions of varying pH. The concentration of the buffering agent was 0.05 M. The pH of these solutions was adjusted by adding HCl or NaOH solution. Samples were taken out at regular intervals of time and weighed after removing the excess surface water by blotting using laboratory tissue. The equilibrium swelling was attained after 3 to 4 weeks and after 2 to 3 weeks at higher pH values. The swelling coefficient was calculated as (Peppas & Barr-Howell, 1987):

$$q = W_h / W_d \tag{2}$$

where W_h and W_d are the weights of the hydrated and of the dry gel, respectively.

Preparation of Drug-Loaded Hydrogels

Synthesized dry hydrogels discs were loaded by swelling to equilibrium in different concentrations (2%, 8%, and 14% w/v) of aspirin solution. Solvent selected for drug loading was 80:20% v/v ethanol water mixtures. To avoid hydrolysis, the pH of the drug-loading solutions was kept acidic. In this solution, the polymers showed moderate swelling without breaking. These disks were placed in the drug solution until they attained a swelling equilibrium value (constant weight; Ranjha & Doelker, 1999b). Polymers were removed from the solutions and were first dried at room temperature and then in an oven at 40°C to 50°C. The amount of drug loaded into the disks was determined from the volume of drug solution absorbed by the disks (Changez, Burugapalli, Koul, & Chaudhary, 2003).

Aspirin Release from Cross-Linked VAC/AA Hydrogels

Aspirin release profiles were obtained using the USP paddle apparatus at 37°C and were stirred at the rate of 100 rpm. A freshly prepared mixture of 0.1 N HCl and 0.20 M tribasic sodium phosphate (3:1) was used and pH was adjusted if necessary with 2 N HCl or 2 N NaOH. One thousand ml of dissolution medium was used for maintaining the sink conditions. The analysis of the aspirin release was carried out by taking the readings every 15 minutes. The amount of aspirin released at time *t* was determined spectrophotometrically. Absorbance was taken at the wavelength of the isosbestic point of aspirin and salicylic acid (about 280 nm in the acidic stage and about 265 nm in the buffer stage), and each time a filtered portion of the solution was used for analysis. For comparison, a reagent solution having a known concentration of USP aspirin RS in the same medium was prepared. The drug release profiles of aspirin were determined in solutions of different pH values like 1.2, 4.5, 5.0, 5.5, 6.0, 6.5, and 7.0. However, the release kinetics were calculated at higher pH values like 5.0, 5.5, 6.5, and 7.0.

Analysis of Release Pattern

Zero-order, first-order, Higuchi, and Korsmeyer-Peppas models are used for analysis of drug release mechanism. These models are generally used to analyze the release mechanism when more than one type of release phenomenon is involved.

The obtained release data were subjected to different drug release models in order to establish the drug release mechanism. The drug release patterns from various samples with different monomeric compositions and degree of cross-linking of VAC/AA hydrogels were determined as a function of pH of external media. Equations used for the zero-order release model (Najib & Suleman, 1985), first-order model (Desai, Singh, Simonelli, & Higuchi, 1966), Higuchi model (1963), and Peppas model (1985) are as follows:

$$\text{Zero-order kinetics:} \quad F_t = K_0 t \tag{3}$$

where F_t represents the fraction of drug released in time *t* and K_0 is the apparent rate constant of zero-order release constant.

$$\text{First-order kinetics:} \quad \ln(1-F) = -K_1 t \tag{4}$$

where *F* represents the fraction of drug released in time *t* and K_1 is the first-order release constant.

$$\text{Higuchi model:} \quad F = K_2 t^{1/2} \tag{5}$$

where *F* represents the fraction of drug released in time *t* and K_2 is the Higuchi constant.

$$\text{Korsmeyer-Peppas model:} \quad \frac{M_t}{M_\infty} = K_3 t^n \tag{6}$$

where K_3 is a constant incorporating the structural and geometric characteristics of the gels and *n* is the release exponent. When $n = 0.45$ order of release is Fickian, $n = 0.89$ corresponds to Case II transport, while $0.45 < n < 0.89$, the diffusional mechanism, is non-Fickian. No kinetic data or *n* values were calculated when swelling and drug release was not significant.

RESULTS AND DISCUSSION

SEM

To investigate the morphology of the hydrogels, SEM analysis was performed. Figure 1 shows the SEM micrographs of VAC/AA at two different magnifications. Since the SEM analysis was done with dry hydrogels, pores are not clearly visible. Therefore, pore size cannot be absolutely determined, nor does it reflect the magnitude of drug diffusion from completely dried hydrogels at 40°C to 45°C in their swollen state. The effective pore size of the hydrogel in the swollen state would also depend on the hydrodynamic properties of the polymer chains.

Fourier Transform Infrared (FTIR) Spectroscopic Studies

An FTIR spectrum was prepared for confirmation of the structure of the hydrogel. FTIR spectrum of VAC/AA is presented in Figure 2. Results of Table 2 show the characteristic vibrations and functional groups of VAC/AA copolymers.

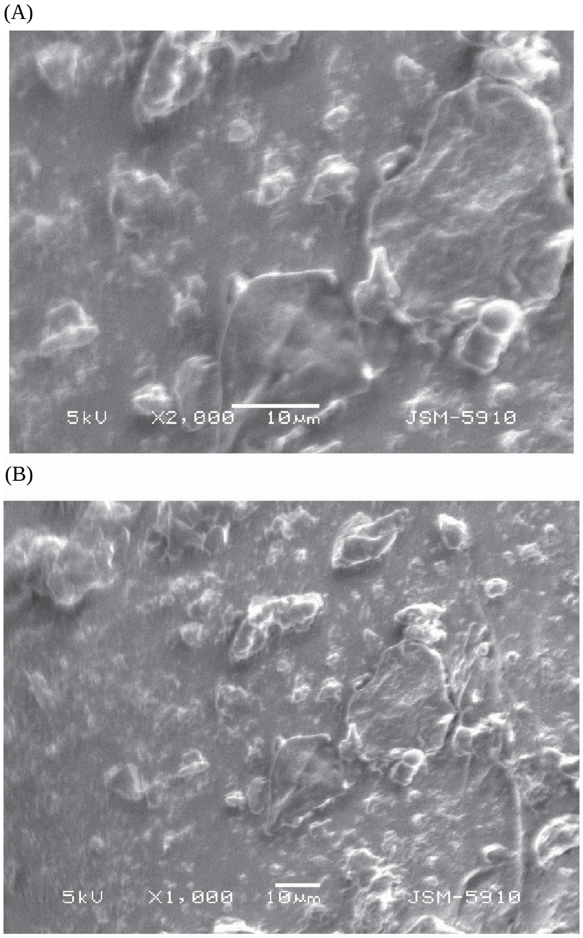

FIGURE 1. SEM micrograph of the VAC/AA hydrogels at two different magnifications: (A) × 1,000 and (B) × 2,000.

Effect of pH and Acrylic Acid Contents on Swelling and on Drug Release

For pH-dependent polymers, the pH of the medium and pKa values of the acidic component of the polymer play a key role in the swelling of the polymer. To investigate the effect of the AA content on the dynamic and equilibrium swelling, four series of copolymers were synthesized. Results of Table 3 show the equilibrium swelling coefficient of VAC/AA at a fixed cross-linking ratio, that is, x = 0.30 mol percent as a function of monomer ratio and pH. Figure 3 shows the effect of AA content on dynamic swelling at x = 0.15 mol percent. The monomeric composition of the sample which showed maximum dynamic swelling after 8 hours is different to that of the sample that showed maximum equilibrium swelling, for dynamic swelling hydrogels containing 50 mol percent AA showed maximum swelling, while for equilibrium swelling hydrogels containing 70 mol percent AA showed maximum swelling. This might be due to difference in glass transition temperatures of the samples 50:50 and 70:30. The results of Table 4 show the dynamic swelling study (q values up to 8 hours) for all the samples synthesized for this study as a function of AA content and degree of cross-linking at various pH. In anionic polyelectrolyte polymers, after the ionization of the carboxyl groups, an electrostatic repulsion along the chains takes place that causes an expansion of the originally coiled molecules (Ranjha & Doelker, 1999a). Shin and colleagues (1997) report that there was a similar expansion of the polymeric chains when there was an increase of ionic groups in the formulations. As the pH of medium increases above the pKa of the acidic component of the polymer, it starts swelling due to ionization of carboxylic groups. In anionic polyelectrolyte polymers, after the ionization of the carboxyl groups, an electrostatic

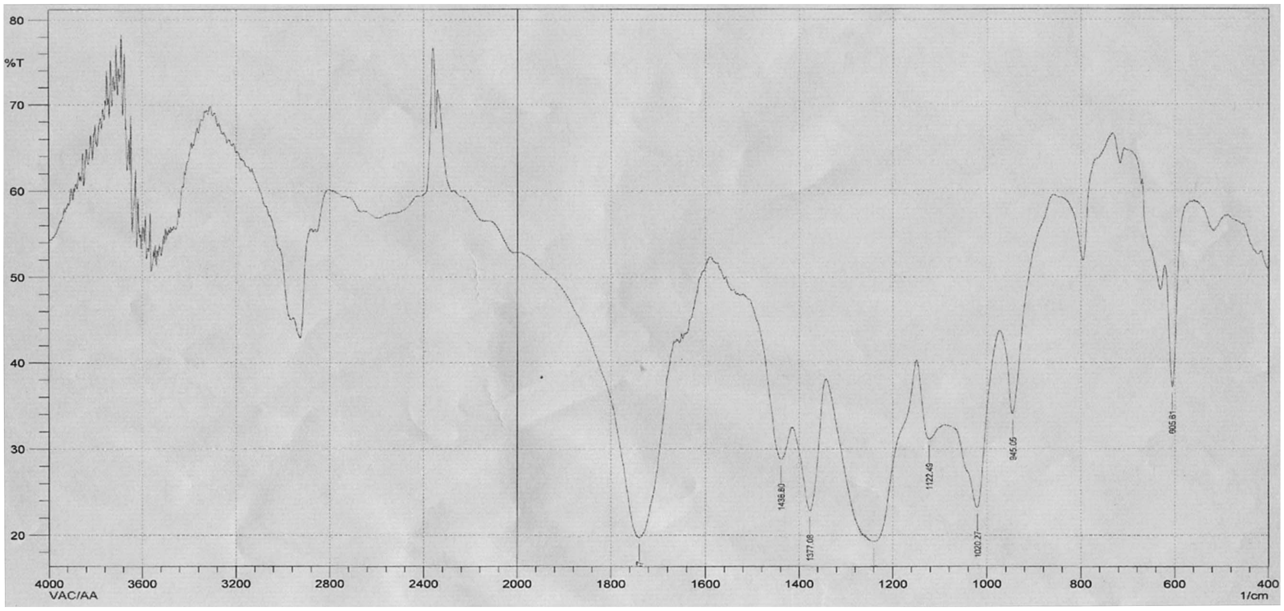

FIGURE 2. FTIR spectra of a VAC/AA hydrogel.

TABLE 2
Characteristic Vibrations and Functional Groups of Cross-Linked VAC/AA Hydrogel

Wave Number (cm^{-1})	Bond Causing Absorption
1452	C–H bending
1735–1768	–C=O (acid, ester stretching)
2953	$-CH_3$, $-CH_2$ (C–H stretching)

TABLE 3
Equilibrium Swelling Coefficient of VAC-co-AA x = 0.30 mol Percent as a Function of Monomer Ratio and pH

pH of Solution	AA content (mol %)				
	10	30	50	70	90
1.2	1.29	1.83	1.44	2.33	2.38
4.5	1.49	1.88	2.20	2.76	2.80
5.5	3.05	4.09	4.61	8.08	7.50
6.5	19.22	24.00	28.80	31.44	15.79
7.0	23.05	38.72	41.11	46.85	25.31

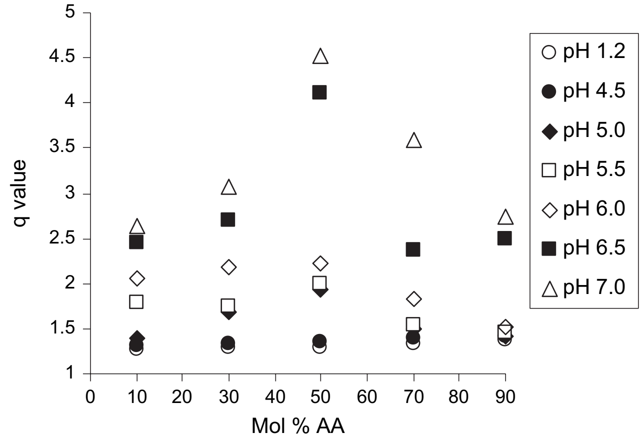

FIGURE 3. Dynamic swelling behavior of VAC/AA copolymers at x = 0.15 mol percent MBAAm in various solutions of different pH as a function of mol percent of AA in the copolymer.

repulsion along the chains takes place that causes an expansion of the originally coiled molecules. The ionization in turn stretches the coiled molecules to an extent that depends on the percent ionization of the carboxylic groups.

TABLE 4
Dynamic Swelling (q Values) for an 8 Hour Period of VAC/AA Hydrogels as a Function of Monomeric Composition and Degree of Cross-Linking in Various Solutions of Different pH

Monomeric Composition (VAC/AA)	pH of the Solution	Degree of Cross-Linking (x = mol % MBAAm)			
		0.15	0.30	0.45	0.60
90:10	1.2	1.26	NA	1.18	NA
	4.5	1.31	NA	1.26	NA
	5.0	1.40	1.58	1.39	1.37
	5.5	1.79	1.94	1.42	1.40
	6.0	2.06	2.22	1.49	1.47
	6.5	2.46	2.57	1.70	1.56
	7.0	2.64	2.71	2.00	1.79
70:30	1.2	1.28	NA	1.20	NA
	4.5	1.33	NA	1.28	NA
	5.0	1.68	1.89	1.44	1.38
	5.5	1.74	1.93	1.65	1.57
	6.0	2.18	2.22	1.83	1.69
	6.5	2.70	2.51	2.19	1.94
	7.0	3.07	2.96	2.32	2.25
50:50	1.2	1.30	1.28	1.26	1.22
	4.5	1.36	2.21	1.30	1.25
	5.0	1.93	1.28	1.60	1.46
	5.5	1.99	2.21	1.69	1.60
	6.0	3.23	3.31	2.89	2.39
	6.5	4.11	4.24	3.55	3.18
	7.0	4.52	4.45	3.67	3.33
30:70	1.2	1.33	1.26	NA	1.25
	4.5	1.39	1.31	NA	1.28
	5.0	1.50	1.51	1.36	1.33
	5.5	1.53	1.88	1.41	1.36
	6.0	1.82	2.02	1.48	1.43
	6.5	2.36	2.55	1.84	1.76
	7.0	3.60	3.45	3.14	3.02
10:90	1.2	1.37	1.30	1.31	NA
	4.5	1.42	1.34	1.34	NA
	5.0	1.41	1.66	1.35	1.30
	5.5	1.45	1.81	1.47	1.42
	6.0	1.52	2.00	1.55	1.51
	6.5	2.50	2.50	1.83	1.69
	7.0	2.75	2.69	2.25	2.02

NA = not available.

Selected samples were loaded with aspirin as a model drug and are shown in Table 5. To study the effect of monomeric composition on drug release, the degree of cross-linking was kept constant, that is, 0.30 mol percent. Maximum drug release was observed in sample VAC/AA; 50:50 (Figure 4) at higher pH values. It was also observed that increasing the AA content in polymers shifts the increase in drug release to lower pH values. The drug release results can be correlated with the results of Khanna and Speiser (Khanna & Speiser, 1970) who prepared beads from noncross-linked methyl methacrylate/methacrylic acid copolymer with various proportions in the

TABLE 5
Various Hydrogels Selected for Aspirin Release Studies

No. of Samples	Different Monomeric Compositions at Fixed Degrees of Cross-Linking x = 0.30 mol %	No. of Samples	Different Degrees of Cross-Linking with a Fixed Monomeric Composition of 50:50
1.	10:90	5.	0.15
2.	30:70	6.	0.30
3.	50:50	7.	0.45
4.	70:30	8.	0.60
5.	90:10		

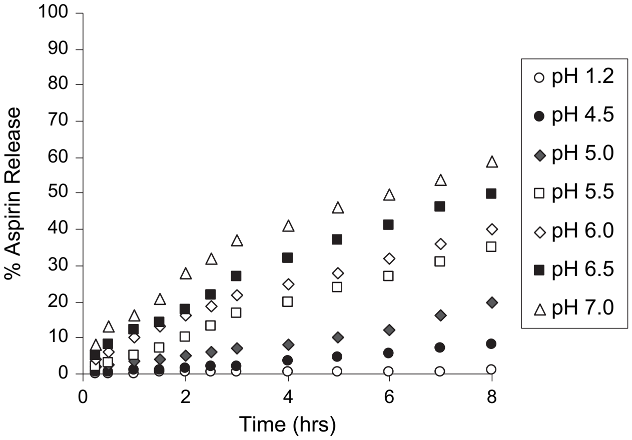

FIGURE 4. Aspirin release from VAC/AA (50:50) copolymer cross-linked using 0.30 mol percent MBAAm at 37°C in solutions of different pH. pH 1.2 (○), pH 4.5 (●), pH 5.0 (♦), pH 5.5 (□), pH 6.0 (◇), pH 6.5 (■), and pH 7.0 (△). (Loading 2.65% w/w.)

presence of chloramphenicol as a model drug. They reported that the higher the acidic content in the polymeric beads, the lower the pH at which the release of the drug starts.

By increasing the acidic fraction (AA) in the copolymer, two types of drug release behaviors are observed. Firstly, when increasing the AA fraction in the copolymer, drug release shifts to lower pH values. Secondly, an increase in the AA fraction in the copolymer decreases the drug release at higher pH values. The shifting of the drug release to lower pH values might be due to a decrease of the apparent pKa values of those samples (Ranjha & Doelker, 1999a).

Three different reasons may be put forward to explain the drug release behavior. Firstly, there may be an increase in glass transition temperature of the polymer as it was observed that increasing the methacrylic acid fraction in Styrene/methacrylic acid copolymer glass transition temperature increases (Greenwald & Luskin, 1980). In fact, it has been observed that as the AA fraction was increased in VAC/AA, the hardness of the samples was increased. This reason gets further support from the fact that the 90:10 proportion in the polymer conferred elasticity. Secondly, it can be suggested that by increasing AA proportion in the polymer, this may lead to the formation of acrylic anhydride during cross-linked polymer synthesis due to the vicinity of COOH groups in the chain. This dense network would thus decrease the extent of drug release from the samples.

Effect of Degree of Cross-Linking on Swelling and on Drug Release

Mechanistically, the effect of increasing cross-linking can be explained by the decreased mesh size of the polymer network. Furthermore, highly cross-linked polymers are less acidic because as the mesh size is reduced, the carboxylic groups are concealed and higher cross-linking ratios hinder the ionization process.

To study the effect of the degree of cross-linking, four series of samples of VAC/AA were synthesized with varying degrees of cross-linking while keeping the monomeric composition constant. Each series of four samples was cross-linked at x = 0.15, 0.30, 0.45, and 0.60 mol percent. Results of Table 4 show the dynamic swelling behavior of VAC/AA copolymers as a function of degree of cross-linking. It was found that swelling order was as x = 0.15 > x = 0.3 > x = 0.45 > x = 0.60 at higher pH values, but the effect of degree of cross-linking on swelling was not significant.

Figure 5 shows the effect of degree of cross-linking on aspirin release after 8 hours from VAC/AA copolymers with fixed monomeric composition 50:50 in solution of pH 7. The results show that maximum drug release was from samples cross-linked at 0.15 mol percent. However, like swelling from these gels, no marked difference in drug release was noticed between the various samples with different cross-linking ratios.

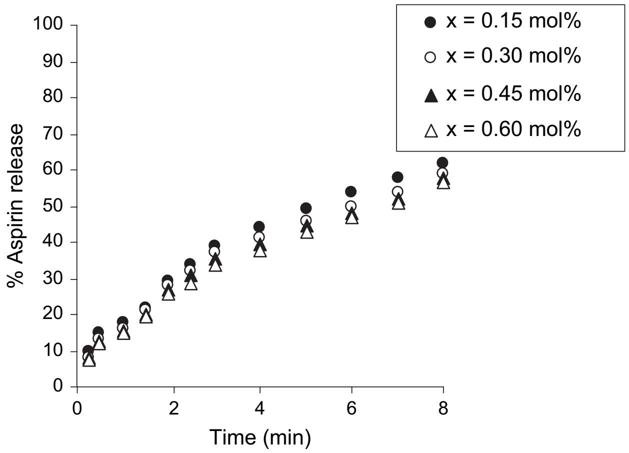

FIGURE 5. Effect of the degree of cross-linking on aspirin release after 8 hours from VAC/AA copolymers with a fixed monomeric composition of 50:50 in solution of pH 7.0. (Loading: x = 0.15, 3.0% w/w; x = 0.30, 2.65% w/w; x = 0.45, 2.45% w/w; and x = 0.60, 2.36% w/w.)

Effect of Drug Loading on Drug Release

The results of Figure 6 show the effect of amount of drug loaded on release behavior. Various samples of VAC/AA with the same monomeric composition (50:50) with x = 0.3 mol percent were loaded with different amount of drug by using 2%, 8%, and 14% w/w drug loading solution. It was observed that the greater the amount of drug loaded in the gels, the greater the drug release. The presence of drugs in the hydrogels affects its swelling behavior due to osmotic pressure, thus facilitating the greater drug release (Kim & Lee, 1992; Lee, 1984). Zhang and colleagues (1996) report the effect of the presence of drug on the swelling of the hydrogels. They suggest that the presence of osmotic agent in the swellable polymers exert a turger pressure that ruptures the septa between adjacent particles, creating microchannels, and thus facilitate the escape of the drug molecules into the surrounding media by diffusion or convective flow.

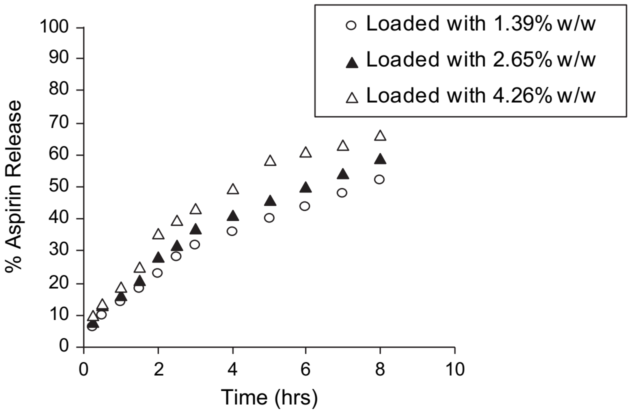

FIGURE 6. Effect of aspirin concentration on its release from VAC/AA 50:50 x = 0.30 mol percent in a phosphate buffer solution of pH 7.0.

Analysis of Release Pattern

The model that best fits the release data was evaluated by the correlation coefficient (*r*). A criterion for selecting the most appropriate model was based on of the most ideal fit indicated by the values of regression coefficients (*r*) nearer to 1.

The correlation coefficient (*r*) obtained for VAC/AA at varying content of AA from 10 to 90 mol percent are given in Table 6. The value of r obtained for zero-order release rate constants were found to be slightly higher (*r* = 0.8918–0.9983) compared with those of first-order release rates (*r* = 0.8058–0.9462) indicating that drug release from most of the samples of monomeric composition was according to zero-order kinetics.

TABLE 6
Effect of Monomeric Composition on Release Kinetics of VAC/AA in the Solutions of Different pH at a Fixed Cross-Linking Ratio, x = 0.30 mol Percent

		Zero-Order Kinetics		First-Order Kinetics		Higuchi Model	
AA content	pH	$K_0(h^{-1})$	*r*	$K_1(h^{-1})$	*r*	$K_2(h^{-1/2})$	*r*
10	5.0	1.5318	0.9725	0.4541	0.9065	5.0265	0.8930
	5.5	2.2636	0.9799	0.3262	0.9091	7.4683	0.9092
	6.5	4.0727	0.9876	0.3239	0.9158	13.635	0.9437
	7.0	4.6113	0.9974	0.3060	0.8821	15.573	0.9697
30	5.0	1.2819	0.9186	0.3813	0.9384	4.1354	0.8158
	5.5	2.1774	0.9919	0.3753	0.8748	7.2604	0.9546
	6.5	3.7583	0.8918	0.3146	0.8665	12.746	0.9704
	7.0	4.1357	0.9919	0.3184	0.8715	14.034	0.9737
50	5.0	2.1250	0.9657	0.2764	0.9462	6.9803	0.8883
	5.5	4.3154	0.9903	0.3318	0.8372	14.683	0.9773
	6.5	5.8006	0.9844	0.2582	0.8453	19.907	0.9883
	7.0	6.3371	0.9543	0.2170	0.8058	22.145	0.9934
70	5.0	1.2819	0.9196	0.3768	0.8228	4.1354	0.8158
	5.5	2.1774	0.9919	0.3753	0.8748	7.2604	0.9401
	6.5	3.7583	0.9898	0.3146	0.8665	12.746	0.9704
	7.0	4.1357	0.9919	0.3076	0.8715	14.034	0.9737
90	5.0	1.7985	0.9845	0.4541	0.9065	5.9133	0.9073
	5.5	1.9792	0.9914	0.4066	0.817	6.6226	0.9462
	6.5	2.9476	0.9905	0.3473	0.8065	10.042	0.9801
	7.0	3.5771	0.9983	0.3184	0.8918	11.980	0.9546

TABLE 7
Effect of Degree of Cross-Linking on Release Kinetics of VAC/AA 50:50 in Solutions of Different pH

		Zero-Order Kinetics		First-Order Kinetics		Higuchi Model	
MBAAm mol %	pH	$K_0(h^{-1})$	r	$K_1(h^{-1})$	r	$K_2(h^{-1/2})$	r
0.15	5.0	2.6095	0.9719	0.2704	0.9627	8.5587	0.8912
	5.5	5.1325	0.9906	0.3357	0.8741	17.353	0.9652
	6.5	5.6710	0.9847	0.2069	0.8562	19.498	0.9922
	7.0	6.6397	0.9607	0.2065	0.8366	23.114	0.9931
0.30	5.0	2.1250	0.9657	0.2964	0.9462	6.9803	0.8863
	5.5	6.0577	0.9903	0.3318	0.8372	14.386	0.9772
	6.5	5.8006	0.9844	0.2583	0.8453	19.907	0.9883
	7.0	6.3371	0.9660	0.2198	0.8053	22.147	0.9934
0.45	5.0	1.8011	0.9723	0.3191	0.9272	5.9080	0.8918
	5.5	3.8795	0.9883	0.3367	0.8250	13.215	0.9775
	6.5	5.8451	0.9787	0.3038	0.7898	21.030	0.9926
	7.0	6.1518	0.9567	0.2175	0.8103	21.468	0.9931
0.60	5.0	1.7359	0.9599	0.3748	0.9539	5.6382	0.8632
	5.5	3.5830	0.9932	0.3939	0.8743	12.051	0.9578
	6.5	5.6433	0.9748	0.3282	0.7513	19.508	0.9930
	7.0	4.3154	0.9543	0.2170	0.8364	20.161	0.9925

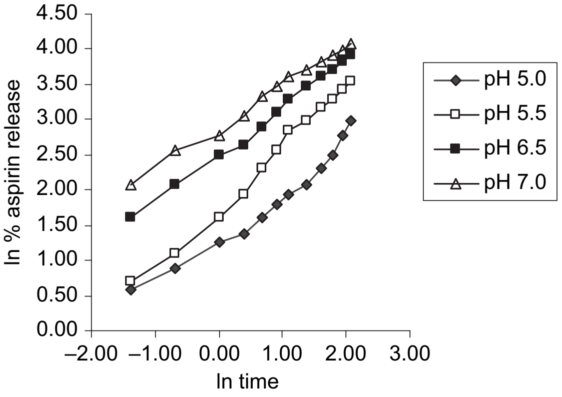

FIGURE 7. Aspirin release curve from VAC/AA (50:50) x = 0.30 mol percent MBAAm at 37°C in solutions of different pH. pH 5.0 (♦), pH 5.5 (□), pH 6.5 (■), and pH 7.0 (△). (Loading 2.65% w/w.)

The correlation coefficients obtained for VAC/AA at different degrees of cross-linking are shown in Table 7. Here again correlation coefficients obtained for zero-order were found to be slightly higher (r = 0.9543–0.9932) compared with those of first-order release rates (r = 0.7513–0.9627), indicating that the drug release from most of the samples of varying degree of cross-linking was according to zero-order kinetics.

The r values for the Higuchi model at differet monomeric composition (r = 0.8158–0.9934) and at different degrees of cross-linking (r = 0.8632–0.9934) indicated that the drug release mechanism was diffusion controlled.

The values of diffusion exponent n for VAC/AA 50:50, x = 0.30 mol percent were calculated by plotting drug release data as given in Figure 7. The effect of monomeric composition on n and r values is given in Table 8 and the effect of degree of cross-linking on release kinetics of aspirin is given in Table 9. In all buffer solutions non-Fickian behavior is observed, and as the pH of the media is increased, n value progressively increased. Results indicate that at almost all investigated monomeric compositions and degrees of cross-linking, hydrogels followed the non-Fickian release mechanism, while in some cases the n value exceeds 0.89, indicating Case II transport.

CONCLUSION

pH-sensitive hydrogels composed of VAC and AA in the presence of MBAAm as cross-linking agent have been synthesized by free radical polymerization. These pH-sensitive gels respond to small changes of pH to a much sharper extent than other pH-sensitive gels. Hydrogels with high contents of AA, up to 50 mol percent, showed more drug release than those gels with a low content of AA. However, the drug release was not significantly affected by changing the degree of cross-linking.

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TABLE 8
Effect of Monomeric Composition on the Drug Release Mechanism of VAC/AA in Solutions of Different pH at a Fixed Cross-Linking Ratio, x = 0.30 mol Percent

AA Content	pH	Release Exponent (*n*)	*r*	Order of Release
10	5.0	0.7832	0.9684	Non-Fickian
	5.5	0.8143	0.9777	Non-Fickian
	6.5	0.7819	0.9210	Non-Fickian
	7.0	0.7777	0.9830	Non-Fickian
30	5.0	0.9275	0.9581	Case II transport
	5.5	0.9555	0.9785	Case II transport
	6.5	0.7992	0.9653	Non-Fickian
	7.0	0.7832	0.9751	Non-Fickian
50	5.0	0.6678	0.9535	Non-Fickian
	5.5	0.8688	0.9908	Non-Fickian
	6.5	0.6740	0.9942	Non-Fickian
	7.0	0.5794	0.9911	Non-Fickian
70	5.0	0.9275	0.9785	Case II transport
	5.5	0.9555	0.9785	Case II transport
	6.5	0.7992	0.9653	Non-Fickian
	7.0	0.7832	0.9750	Non-Fickian
90	5.0	1.1134	0.9406	Case II transport
	5.5	1.0679	0.9716	Case II transport
	6.5	0.9282	0.9943	Case II transport
	7.0	0.8044	0.9829	Non-Fickian

TABLE 9
Effect of the Degree of Cross-Linking on the Drug Release Mechanism of VAC/AA in the Solutions of Different pH at a Fixed Monomeric Composition of 50:50

MBAAm mol %	pH	Release Exponent (*n*)	*r*	Order of Release
0.15	5.0	0.8460	0.9581	Non-Fickian
	5.5	0.8460	0.9581	Non-Fickian
	6.5	0.5365	0.9934	Non-Fickian
	7.0	0.5403	0.9880	Non-Fickian
0.30	5.0	0.6688	0.9535	Non-Fickian
	5.5	0.8688	0.9905	Non-Fickian
	6.5	0.5798	0.9942	Non-Fickian
	7.0	0.5794	0.9911	Non-Fickian
0.45	5.0	0.7853	0.9692	Non-Fickian
	5.5	0.8800	0.9862	Non-Fickian
	6.5	0.8213	0.9963	Non-Fickian
	7.0	0.5789	0.9914	Non-Fickian
0.60	5.0	0.8838	0.9156	Non-Fickian
	5.5	0.5795	0.9658	Non-Fickian
	6.5	0.9075	0.9914	Case II transport
	7.0	0.6740	0.9908	Non-Fickian

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