Synthesis of Poly(acrylamide-*co*-methyl methacrylate-*co*-vinyl amine-*co*-acrylic acid) Hydrogels by Hoffman Degradation and Their Interactions with Acetaminophen

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ABSTRACT: A modified poly(acrylamide-*co*-methyl methacrylate-*co*-vinyl amine-*co*-acrylic acid) [poly(AAm-*co*-MMA-*co*-VAm-*co*-AAc)] hydrogel was prepared by the Hofmann degradation of poly(acrylamide-*co*-methyl methacrylate) [poly(AAm-*co*-MMA)] copolymer. The hydrogel was characterized by Fourier transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC), thermogravimetric analysis, and swelling studies. Matrices of this hydrogel with acetaminophen were prepared for application in controlled release. The physical state of the drug (acetaminophen) and its interaction with the modified polymeric hydrogel were examined in hydrogel–acetaminophen matrices with DSC. The acetaminophen in the matrices (with more than 10% drug) exhibited distinct melting endotherms because of their crystalline state. The peak temperature of these endotherms was lowered and the peaks were broadened as the concentration of acetaminophen decreased. The melting enthalpy of acetaminophen in various matrices when plotted as a function of acetaminophen concentration yielded a straight line with an intercept of 142 mg/g of matrix, which was the solubility of acetaminophen in the hydrogel at its melting temperature. FTIR spectroscopy investigations confirmed that hydrogen bonding occurred between the modified polymeric hydrogel and acetaminophen. Scanning electron microscopy studies revealed the presence of acetaminophen drug crystals of various shapes, sizes, and roughness on the surface, depending on acetaminophen loading. The controlled release of acetaminophen was tested *in vitro*; 67.10 and 37.2% cumulative releases were obtained for the poly(AAm-*co*-MMA) and poly(AAm-*co*-MMA-*co*-VAm-*co*-AAc) hydrogel matrices, respectively. The acetaminophen release percentage for the modified hydrogel was low because of secondary interactions with acetaminophen. © 2004 Wiley Periodicals, Inc. J Appl Polym Sci 94: 40–52, 2004

Key words: hydrogels; degradation; differential scanning calorimetry (DSC); FT-IR

INTRODUCTION

Hydrogels are hydrophilic polymers that absorb water to an equilibrium value and are insoluble in water at physiological temperature, pH, and ionic strength because of presence of a three-dimensional network. Several articles[1–4] and reviews[5,6] have appeared on hydrogel applications as novel biomaterials, describing their use in making contact lenses, artificial organs, tissue substitutes, hemodialysis membranes, and burn wound dressing and as drug carriers. Hydrogels may also be used to control the release of drugs that are initially dissolved or trapped within the polymer phase. Polyacrylamide-based hydrogels are blood-compatible biomaterials that find application in coatings for catheters, as supports for enzyme immobilization, and as controlled release devices.[7,8]

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Hydrogels can be synthesized by the simple reaction of one or more hydrophilic monomers or by the association of bonds such as hydrogen bonds or strong van der Waal's interactions between chains. Hydrogels are generally prepared by the chemical crosslinking of the monomer and polymer with a crosslinking agent.[9] They can also be prepared with physical crosslinks, which involves the incorporation of hydrophobic monomer[10,11] segments in a limited amount in the polymer chain.

In an earlier article,[12] we reported the effect of the nature of the crosslinks on swelling behavior. In this investigation, poly(acrylamide-*co*-methyl methacrylate) [poly(AAm-*co*-MMA)] was modified further by the use of Hofmann degradation to partly convert the acrylamide (AAm) into vinyl amine (VAm). The VAm group is highly ionic and reactive and has two main advantages. First, it enhances the percentage swelling of the hydrogel; second, it may also form a complex or interact with suitable drugs. The objective of this study was to synthesize the poly(AAm-*co*-MMA) copolymer by a free-radical precipitation polymerization reaction with a benzoyl peroxide initiator and a dioxane solvent. Methyl methacrylate (MMA) units were

designed to serve as physical crosslinks, and the resulting hydrogel was expected to be thermoplastic in nature. To improve its swelling behavior, the AAm units were partly converted to VAm through Hofmann degradation. The resulting modified poly(acrylamide-*co*-methyl methacrylate-*co*-vinyl amine-*co*-acrylic acid) [poly(AAm-*co*-MMA-*co*-VAm-*co*-AAc)] hydrogel was expected to have reactive ionic functional groups that could be used for enhanced swelling. In this article, we also discuss the differential scanning calorimetry (DSC) and Fourier transform infrared (FTIR) spectroscopy studies for the determination of the occurrence of secondary interactions between acetaminophen and the modified polymeric hydrogel, as sometimes these can lead to deviations in the controlled release behavior of matrices.

The concept of the interaction of a hydrogel and drug or any other group can be extended to simpler systems such as low-molecular-weight drugs and polymers. Unanticipated contamination of drugs by organic and inorganic constituents of elastomer polymeric compounds usually involving secondary interactions has also been reported to result in serious allergic reactions.[13] Such interactions need to be identified quickly and studied in detail, especially with different polymeric materials, as many such new devices are expected to be commercialized in the near future.[14,15]

In this study, we also aimed to investigate the state of the drug in the hydrogel matrix and the occurrence of secondary interactions between acetaminophen and the poly(AAm-*co*-MMA-*co*-VAm-*co*-AAc) hydrogel. Polymeric matrix devices[16] are important controlled release devices and are finding increasing uses. Matrix-type controlled drug delivery devices contain drugs homogeneously distributed in polymers. Part of the drug is dissolved in the polymer, and the remaining fraction exists in crystal form. The determination of the amount of drug in crystalline form is crucial because it affects the rate and mechanism of drug release.[16] Theeuwes et al.[17] used DSC to determine the drug solubility in a polymer at the melting point of drug and the amount of drug present in the crystalline form. Earlier, Van Bommel[18] also used DSC to determine the percentage of crystalline drug in ethyl cellulose matrices by measuring the melting enthalpies of the pure drug and the matrix. Singhal et al.[19] used the DSC and FTIR methods to determine drug–polymer interactions that led to a reduction in the controlled release rate and the physical state of the drug between ethyl cellulose and benzoic acid. In this study, the percentage of crystalline drug present in the hydrogel matrices was evaluated by DSC because it is a simple and rapid technique.

EXPERIMENTAL

Raw materials

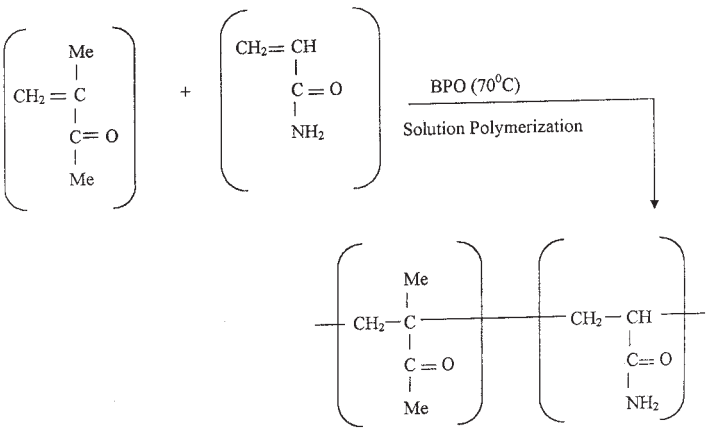
AAm (SDS, Mumbai, India) was recrystallized from methanol. MMA (CDH, New Delhi) was purified by washing with 4% sodium hydroxide to remove the inhibitor. Benzoyl peroxide (CDH) was recrystallized from a chloroform–methanol mixture. Petroleum ether (S.D. Fine, Mumbai, India); *N*,*N*′-methylene bisacrylamide (BDH, England); dioxane, sodium hydroxide (NaOH), sodium hypochloride (NaOCl), hydrochloric acid (HCl), and pyridine (Qualikems, New Delhi); and acetaminophen (Para Product Private, Ltd., Ghaziabad) were used as received. Distilled water was used for all of the experiments.

Synthesis of the poly(AAm-*co*-MMA) and poly(AAm-*co*-MMA-*co*-VAm-*co*-AAc) hydrogels

Poly(AAm-*co*-MMA) copolymer was synthesized by free-radical precipitation polymerization with a method similar to that of Sefton and Yamamoto.[10] First, 40% AAm and 60% MMA (0.12 mol total) were dissolved in 80 mL of dioxane, and polymerization was initiated by 0.3 g (1.8 mol % of the total monomer feed)[10] of benzoyl peroxide. The reaction was carried out in a controlled-temperature bath and with continuous stirring by a mechanical stirrer in a sealed, three-necked flask under a nitrogen atmosphere at 70°C. After some time, turbidity developed and a white precipitate started collecting in the flask, and the reaction was carried out for 4 h. The resulting hydrogel was precipitated with petroleum ether. To remove the traces of homopolymers, the precipitate was continuously stirred for 6 h in toluene and water [solvents of poly(methyl methacrylate) and polyacrylamide, respectively] and was then dried in oven at 45°C. There was a weight loss in the range of 22.73 to 25.50%. The synthesis of hydrogel is given in Scheme 1. The yield of copolymer was 74.29%

Hofmann degradation

The (AAm-*co*-MMA) copolymer was further modified by Hofmann degradation. The polymer (10 g) was dissolved in 80 mL of 50% aqueous dioxane and cooled to 0°C; 18.7 mL of ice-cooled sodium hypochlorite (0.67*M*) was added to the polymer solution and stirred. After 5 min, 36 mL of ice-cooled, aqueous NaOH solution (7.6*M*) was added to the mixture. After 30 min, the reaction mixture was transferred to an ice bath and allowed to stand for 12 h. After the reaction, excess sodium hydrogen sulfate ($NaHSO_4$) was added to the polymer solution to reduce residual chlorine followed by the addition of 2*M* HCl solution for neutralization. The polymer was separated and washed with distilled water. The yield was about 64.31%



Scheme 1 Synthesis of the poly(AAm-*co*-MMA) copolymer.

Preparation of the matrices

The solvent casting technique, which is a standard technique for producing homogeneous matrices with good reproducibility on a laboratory scale, was used for preparing the matrices.[20] The casting solutions were prepared in 50% aqueous pyridine and contained 0, 5, 10, 20, 25, 30, 35, 40, 50, and 60% acetaminophen. For preparation of the matrices, 50% aqueous dioxane was also used, but the matrices were nonuniform in consistency and color, so it was not used. A leveled glass plate clamped with metal strips on both sides was used as the mold. The film was dried for 24 h at room temperature and then for 24 h *in vacuo* to complete solvent evaporation, which can be toxic in the case of pyridine. To determine the solvent residue in the matrices, dynamic DSC thermograms were taken from 50 to 300°C, and an absence of an endothermic peak near 115°C (the boiling point of pyridine) confirmed complete removal of solvent. The matrices were cut to the size 10 × 20 mm from the dried film (thickness = 1.60 mm) and stored in desiccators.

Characterization

Viscosity measurements

The solution viscosity of the synthesized copolymer was obtained with an Ubbelohde viscometer (Per fit India Ambala cantt. India) at 25°C in aqueous dioxane, as it is an indirect measure of molecular weight. However, the viscosity-average molecular weight could not be determined because the k and α values were not available.

FTIR spectra

The FTIR spectra of copolymeric and modified hydrogels were recorded with an MB-100 FTIR spectrometer (BOMEM, Japan) in solid potassium bromide pellet form after the sample was dried. For the FTIR spectra, 16 scans were taken and averaged to improve the signal-to-noise ratio. The resolution in wave number was 4 cm^{-1}.

Thermogravimetric analysis (TGA)

The TGA studies were carried out with 2 ± 0.5-mg samples in platinum crucibles with a TG-750 thermogravimetric analyzer (Stanton-Rederoft, London) under a nitrogen atmosphere (flow rate = 40–60 mL/min) at a heating rate of 20°C/min.

DSC

DSC was carried out with a differential scanning calorimeter (TA Instruments, model 2910, New Castle, Delaware, USA) under a nitrogen atmosphere (flow rate = 100 mL/min) at a heating rate of 10°C/min up to 250°C.

Scanning electron microscopy (SEM)

The matrix surfaces were studied with SEM (Phillips 151 and JEOL 35 CF). The matrices were mounted on specimen stubs and coated with gold at a vacuum pressure of 1×10^{-3} Torr by the ion-sputtering method.

Measurement of the swelling of the hydrogels

The degree of swelling was measured by gravimetric measurement. The hydrogel samples were suspended in 500 mL of distilled water at 25°C in a beaker.[12] The sample was removed from the beaker at different time intervals. It was quickly blotted free of surface water with filter paper, weighed on analytical balance (accuracy = ±.0002), and then returned to the swelling medium. The degree of swelling was calculated from the following equation:

TABLE I
$\eta_{sp/c}$ of the Poly(AAm-*co*-MMA) Copolymer at Various Concentrations

Concentration of poly(AAm-*co*-MMA) (%)	$\eta_{sp/c}$
0.1	0.107
0.2	0.113
0.4	0.169
0.8	0.338

$$\text{Degree of swelling (\%)} = W_s - W_d/W_d \times 100 \quad (1)$$

where W_d is weight of the dry hydrogel and W_s is the weight of the swollen hydrogel.

Release rate measurements

The release rates were measured by the placement of the matrix devices in 500 mL of a 0.005*M* saline solution (with the pH adjusted to 7.40) under stirred conditions in a conical flask at room temperature. Samples (5 mL) were with drawn to estimate released acetaminophen at hourly intervals for the initial 8 h, after which samples for analysis were withdrawn at 24-h intervals. Acetaminophen concentration was determined by a double-beam ultraviolet–visible spectrophotometer (PerkinElmer 522) at its λ_{max} of 244 nm at different time intervals.

RESULTS AND DISCUSSION

Viscosity

The $\eta_{sp/c}$ values of poly(AAm-*co*-MMA) in 50% aqueous dioxane were determined in the range 0.107–0.338% and are listed in Table I.

Synthesis of poly(AAm-*co*-MMA)

The copolymer of poly(AAm-*co*-MMA) was synthesized by the free-radical precipitation polymerization method.[1] The synthesis of the copolymer is shown in Scheme 1. After polymerization, the resulting copolymer was precipitated with petroleum ether. The precipitate of the copolymer was continuously stirred for 6 h in toluene and then in water to separate the homopolymer of PMMA and PAAm, respectively. After extraction, there was no possibility of the homopolymers of AAm and MMA in the copolymer. Soxhlet extraction is the standard method for purification of polymers.[21] The FTIR spectrum of poly(AAm-*co*-MMA) hydrogel is shown in Figure 1. The absorption band near 1729 cm^{-1} was assigned to the C═O stretching of methyl ester in MMA units. The absorp-

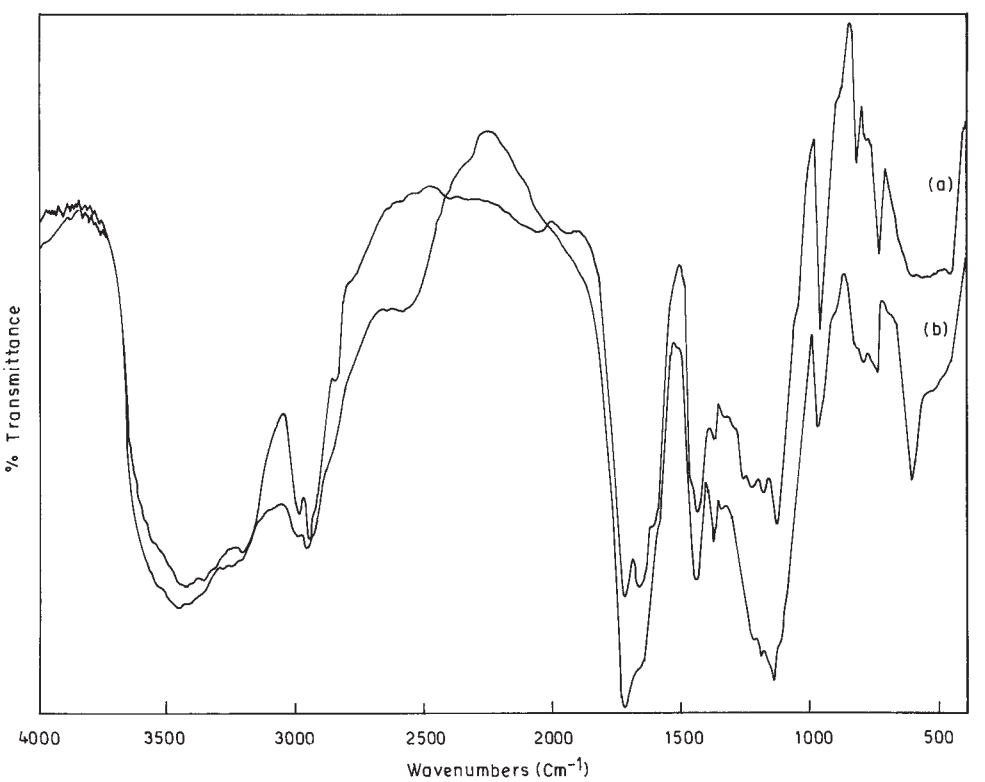
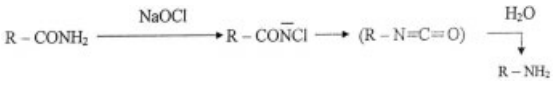


Figure 1 FTIR spectra of the (a) poly(AAm-*co*-MMA) and (b) poly(AAm-*co*-MMA-*co*-VAm-*co*-AAc) hydrogels.



Scheme 2 Reaction mechanism of Hoffman degradation.

tion band near 1650 cm^{-1} was assigned to the C═O stretching of the amide group of AAm units. Similar FTIR results were obtained by Sefton and Yamamoto.[10] A strong band at 2993 cm^{-1} from C—H stretching was observed for the AAm–MMA copolymeric gel.

Synthesis of the modified poly(AAm-*co*-MMA-*co*-VAm-*co*-AAc) hydrogels

To prepare a hydrogel with a high water content and reactive side groups, the poly(AAm-*co*-MMA) copolymer was used for further modification of the hydrogel. VAm is the simplest polymer structure conceivable, but so far, there are no reports of a successful direct polymerization method.[10] Rather, it has been synthesized indirectly by various polymer reactions.[22,23] Among them, Hofmann degradation of polyacrylamide is one of the simplest methods; it uses a readily available monomer and can result in a high amine content.[24]

The Hofmann degradation reaction mechanism is shown in Scheme 2. The modified polymer consisted of four monomeric units: acrylic acid, VAm, MMA, and AAm. The initial step in the reaction was the chlorination of the amide (Scheme 2). Once the amide was chlorinated, it was not expected to hydrolyze to produce carboxylic acid.[25] The nonchlorinated amides were considered to be the source of carboxyl groups. Hofmann degradation of a poly(acrylamide–styrene) copolymer has been done on the surfaces of latex particles, and this reaction was able to introduce a sufficient amount of primary amines.[26]

After modification, the spectrum of the copolymeric gel was compared with the spectrum of the original copolymer, as shown in Figure 1(a). It is obvious that the absorption band near 1650 cm^{-1} assigned to C═O stretching of the amide group partly disappeared; only a small shoulder of this peak remained in the spectrum in Figure 1(b) compared to the spectrum in Figure 1(a). This was due to the fact that after Hofmann degradation, the amide group of AAm was partly converted to VAm groups. Another distinct change was the decrease of the absorption band near 1452 cm^{-1} (C—N stretching of the primary amide), and the absorption band near 1146 cm^{-1} also decreased, but both AAm and MMA units had absorption bands near this region. It was difficult to find an increase in the absorption band characteristic of the primary amine group because the absorption bands (e.g., C—N stretch at 1040–1250 cm^{-1} or N—H stretch at 3400–3500 cm^{-1}) were similar to those of AAm or MMA. Our findings were supported by the results of Sefton and Yamamoto,[10] where they synthesized a copolymer of poly(AAm-*co*-MMA) and a poly(AAm-*co*-MMA-*co*-VAm) thermoplastic hydrogel. They observed similar positions of the peaks and shifts in FTIR peaks, 1664 cm^{-1} (C═O stretch of the amide group) and 1456 cm^{-1} (C—N stretch of the primary amide group).

Study of thermal degradation behavior by TGA

The TGA curve in Figure 2(a,b) shows the weight loss versus temperature of the poly(AAm-*co*-MMA) copolymer and its modified poly(AAm-*co*-MMA-*co*-VAm-*co*-AAc) hydrogel. The thermal behavior results are summarized in Table II. As shown in Figure 2(a), the thermogram of poly(AAm-*co*-MMA) copolymer exhibited three-step degradation. The initial decomposition temperature was 130°C, and this decomposition completed around 190°C. The second-step decomposition temperature was 225°C, and decomposition completed at 440°C. A sharp percentage weight loss was observed in this step. Further, the third step

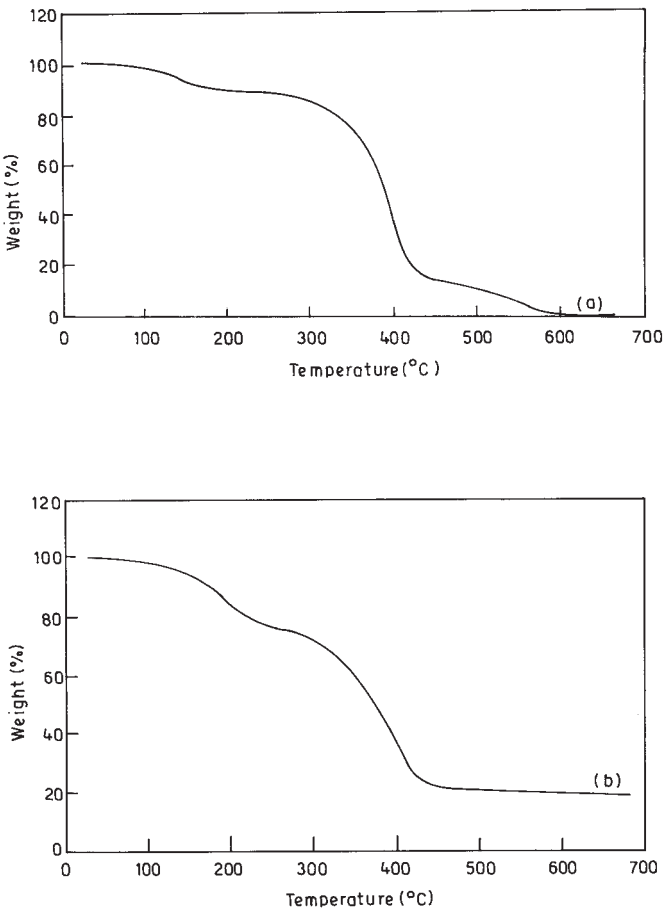


Figure 2 TGAs of the (a) poly(AAm-*co*-MMA) and (b) poly(AAm-*co*-MMA-*co*-VAm-*co*-AAc) hydrogels.

TABLE II
Thermal Degradation Characteristics of the Poly(AAm-*co*-MMA) and Modified Poly(AAm-*co*-MMA-*co*-VAm-*co*-AAc) Hydrogels

Hydrogel type	Temperature (°C) for weight loss				Initial decomposition temperature (°C)	Peak temperature maximum rate of decomposition (°C)		Fractional char yield (%) at 500°C
	20%	40%	60%	80%		1st peak	2nd peak	
Poly(AAm-*co*-MMA) copolymer	325	375	395	415	130	135	390	9.30
Poly(AAm-*co*-MMA-*co*-VAm-*co*-AAc) hydrogel	205	340	382	435	105	198	396	20.20

showed a slow rate of weight loss from 450 to 580°C. In poly(methyl methacrylate) prepared by free-radical polymerization, a three-step decomposition has been reported in literature.[27,28]

Figure 2(b) shows the thermogram of the modified poly(AAm-*co*-MMA-*co*-VAm-*co*-AAc) hydrogel. A two-step degradation was observed in modified hydrogel. The initial decomposition temperature was 105°C, and the first step was completed around 225°C. The second-step decomposition temperature was 270°C, and decomposition completed around 455°C. A major weight loss was observed above 270°C (Table II). The results indicated that the poly(AAm-*co*-MMA) copolymer and poly(AAm-*co*-MMA-*co*-VAm-*co*-AAc) hydrogels had different thermal degradation behaviors, further confirming an alteration in the chemical structure due to the modification reaction.

The glass-transition temperature of the copolymer was 134°C as determined by DSC for the dry form. The glass-transition temperature of the modified polymeric hydrogel could not be obtained because the DSC thermogram failed to show a clear transition.

Swelling properties

The swelling percentage of the poly(AAm-co-MMA) copolymer and the modified poly(AAm-*co*-MMA-*co*-VAm-*co*-AAc) hydrogel are shown in Figure 3. Figure 3 shows the degree of swelling of the hydrogel at 25°C in distilled water[12] plotted as a function of time; the swelling percentage was calculated by eq. (1). The copolymer reached equilibrium in 28 h. The equilibrium swelling percentage of copolymer was 103.98%. The detailed swelling kinetics of the copolymer were studied in an earlier investigation.[12] Figure 3 shows the swelling behavior of the modified hydrogel prepared by the Hofmann degradation of poly(AAm-*co*-MMA) copolymer. After Hofmann degradation, the amide groups formed carboxylic acid and VAm groups, enhancing the hydrophilicity of the polymeric gels and causing the gels to absorb more water.

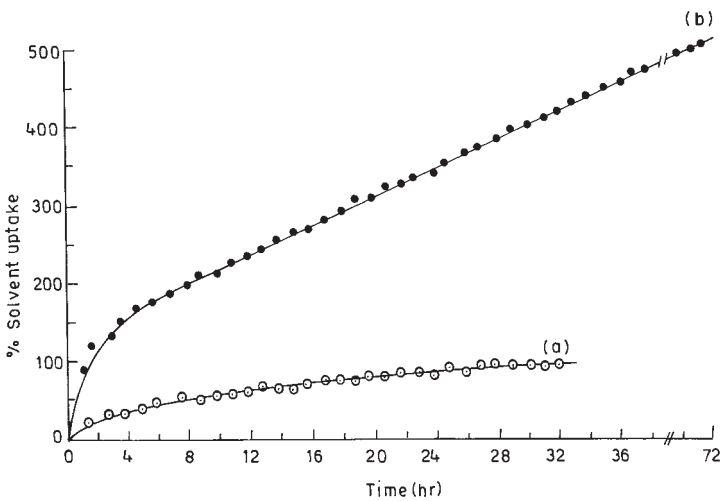


Figure 3 Degree of swelling as a function of time for the (a) poly(AAm-*co*-MMA) and (b) poly(AAm-*co*-MMA-*co*-VAm-*co*-AAc) hydrogels.

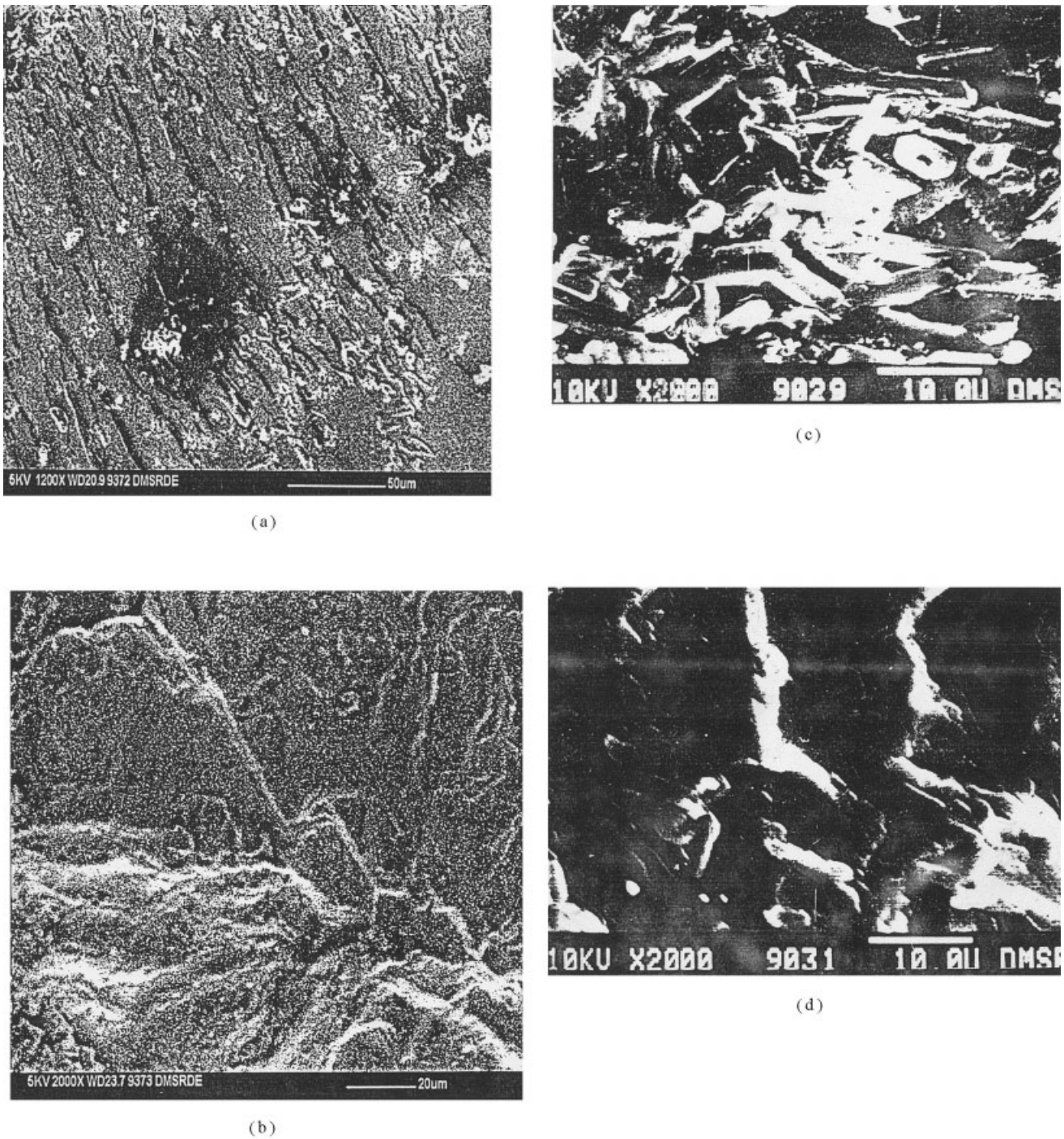


Figure 4 Scanning electron micrographs for the modified polymeric hydrogel matrices containing (a) 25, (b) 30, (c) 35, and (d) 40% acetaminophen.

The modified polymer reached equilibrium after 3 days. The initial swelling rate of the modified hydrogel was very slow in the initial 24 h. It absorbed only 342% water, but after 2 days, the swelling rate increased, and it absorbed 515% water in 3 days. After 3 days, some degradation was observed in the hydrogel, and it had difficultly maintaining its shape.

Interaction of the modified poly(AAm-*co*-MMA-*co*-VAm-*co*-AAc) hydrogel with acetaminophen

The physical appearance of the polymeric hydrogel matrices prepared with 5, 10, 20, 25, 30, 35, 40, 50, and 60% acetaminophen differed remarkably. The matrices with 5 and 10% acetaminophen loadings were clear and colorless in the appearance. The matrices

with 20% acetaminophen loading were nearly transparent and homogeneous. The matrices with 25% acetaminophen changed to white and was quite plain in nature [Fig. 4(a)]. However, a number of small crystals were also visible, indicating small amount of crystallization of acetaminophen at this level. Roughness was observed in the matrix containing 30% acetaminophen, along with drug crystals bigger and longer in size [Fig. 4(b)]. Clear and big crystals of acetaminophen were observed in the matrix containing 35% acetaminophen [Fig. 4(c)]. Crystal size increased, and crystals became narrow and straight in the matrix containing 40% acetaminophen, and minor surface roughness was observed [Fig. 4(d)]. The SEM study revealed the presence of acetaminophen drug crystals of various shapes, sizes, and roughness on the surface, depending on the drug concentration. The results of the DSC investigations of matrices containing 5–60% acetaminophen follow.

Melting endotherm corresponding to the drug crystals

The melting point of pure acetaminophen was determined by DSC as 177.7°C, and the melting enthalpy was 120.4 J/g, as shown in Figure 5. The melting point of the polymeric hydrogel was 180.9°C. Figure 5 also shows the DSC run of the physical mixture of acetaminophen and the polymeric hydrogel in 50:50 ratios with melting enthalpies of 43.3 J/g. It is also clear from Figure 5, from the DSC scan of matrix containing same ratio of acetaminophen (i.e., 50%), that a further lowering of the melting enthalpy and melting point was accompanied by a considerable broadening of the peak. These observations clearly indicate some sort of interaction between acetaminophen and the polymeric hydrogel in various matrices. Earlier, Donbrow and Friedman[29] observed some kind of secondary interaction, such as hydrogen bonding, between ethyl cellulose and benzoic acid during sorption and permeability studies. Recently, the synthesis of a polymer biomolecular conjugate received significant attention.[30] One of the futuristic applications of such interaction may be made with glucose-containing polymers and glucose receptor molecules to prepare glucose-sensitive hydrogel systems.

The DSC analyses of the matrices containing 5, 10, 20, 25, 30, 35, 40, 50, and 60% acetaminophen were carried out. The DSC thermograms of matrices containing 5 and 10% acetaminophen did not exhibit melting endotherms. This indicated that acetaminophen dissolved in matrices with up to 10% loading in the polymeric hydrogels. Matrices containing 20–60% acetaminophen showed distinct melting endotherms. The DSC thermograms showed a separate fusion peak of acetaminophen in matrices containing acetaminophen at levels of 20% and higher (Fig. 6). This was

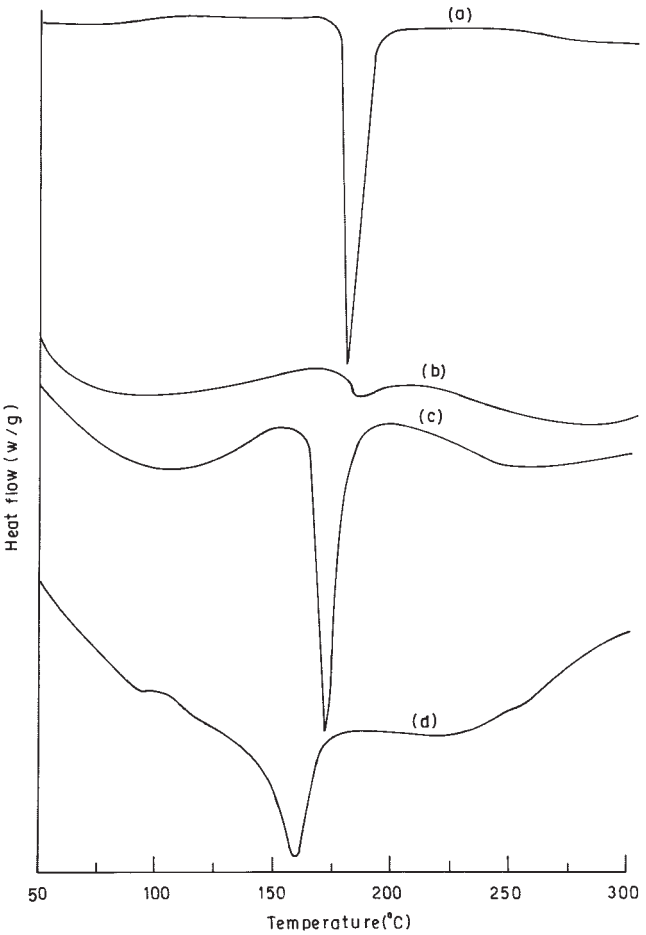


Figure 5 DSC scans of (a) pure acetaminophen, (b) the plain polymeric hydrogel, (c) a physical mixture of the polymeric hydrogel and acetaminophen in equal ratios, and (d) a matrix containing equal amounts of the polymeric hydrogel and acetaminophen.

similar to the values observed by van Bommel[18] and Abdul Razzak,[31] who reported 25 to 30 and 20% loading for acetaminophen/xylitol and salicylic acid, respectively, for ethyl cellulose matrices.

Table III lists the results of DSC scans of various matrices and pure acetaminophen. From Table III, it is clear that melting point of acetaminophen decreased because of the incorporation of the polymeric hydrogel. Figure 6 also shows that the shift in melting point increased with decreased drug loading. A similar phenomenon of the broadening of the melting peak and the lowering of the melting point was observed by Bacon[32] for case of polyethylene and low-molecular-weight diluents, such as waxes. The depression of melting temperature in polymer–diluent systems is well established and is related to the volume fraction of diluent. A large shift of 56.8°C observed in the melting point of acetaminophen indicated that acetaminophen had very good solubility in the modified hydrogel and acted as a diluent.

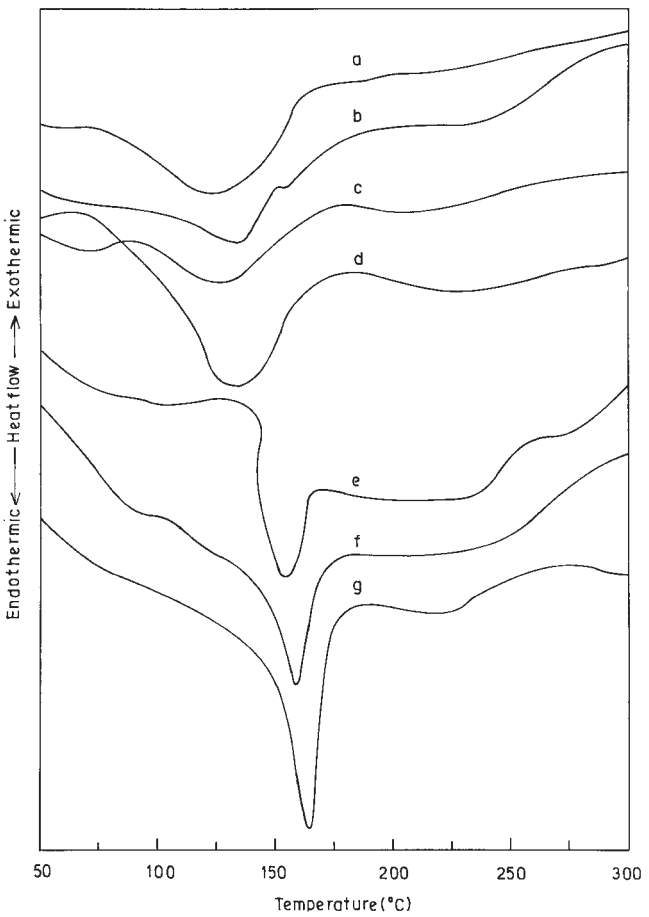


Figure 6 Dynamic DSC scans of polymeric hydrogels containing (a) 20, (b) 25, (c) 30, (d) 35, (e) 40, (f) 50, and (g) 60% acetaminophen.

We obtained the depression in melting point by subtracting the melting point of the matrix from the melting point of pure acetaminophen and plotted it against the drug content. A linear plot was obtained (Fig. 7), which was used to determine the drug content of the hydrogel matrix by the measurement of the shift in melting temperature by a simple dynamic DSC scan. Kimura et al.[33] and Nadkarni et al.[34] reported similar depressions in melting points for blends of polyesters with polyacrylates and poly(ethylene terephthalate), respectively.

The drug content (mg of acetaminophen/g of matrix) versus the melting enthalpy of various acetaminophen-containing matrices is plotted in Figure 8. A straight line plot was obtained, which on extrapolation, gave an intercept value of 142 mg/g of matrix. This could be considered the solubility in the polymer at the melting temperature of the drug.[18] This value was equivalent to 14.2% drug in the matrix, so it could be assumed that up to 14.2% acetaminophen remained in its dissolved form in the matrix at its melting temperature. This was quite low in comparison to 330 mg/g of matrix observed for ethyl cellulose and benzoic acid matrices.[19] This indicated some possibility of the occurrence of secondary interactions between acetaminophen and the polymeric hydrogel. This may have resulted in the enhanced solubility of the drug in the polymer, as observed by Singhal et al.[19] Acetaminophen above a concentration of 14.2% existed in crystalline form in the matrices and was responsible for the melting corresponding to the melting of the acetaminophen crystals.

The heat required to melt the crystalline portion of the acetaminophen in the matrix (qt) could be calculated with the acetaminophen solubility in the matrix obtained with Figure 8. The following simple relation-

TABLE III
Summarized Results for DSC Investigations Conducted on Acetaminophen Polymeric Hydrogel Matrices

Drug concentration based on total solid content		Observed enthalpy of the melting endotherms (J/g)	Calculated enthalpy of the melting endotherms (J/g)	Concentration acetaminophen in dissolved form (%)	Concentration of acetaminophen in crystalline form (%)[b]	Peak maximum (°C)
%	mg of drug/mg of matrix[a]					
0.0	0.0	—	—	0.0	0.0	—
5.0	50	—	—	5.0	0.0	—
10.0	100	—	—	10.0	0.0	—
20.0	200	9.50	6.98	14.2	5.8	121.91
25.0	250	15.00	13.00	14.2	10.8	133.25
30.0	300	22.56	19.02	14.2	15.8	126.24
35.0	350	27.00	25.04	14.2	20.8	142.66
40.0	400	34.50	31.06	14.2	25.8	154.92
50.0	500	46.00	43.10	14.2	35.8	159.19
60.0	600	57.60	55.14	14.2	45.8	169.61
100	—	120.40	—	—	—	177.66

[a] mg of acetaminophen/g of matrix = (Acetaminophen %/100) × 100
[b] Concentration of Acetaminophen in crystalline form = Total percentage of acetaminophen − 14.2.

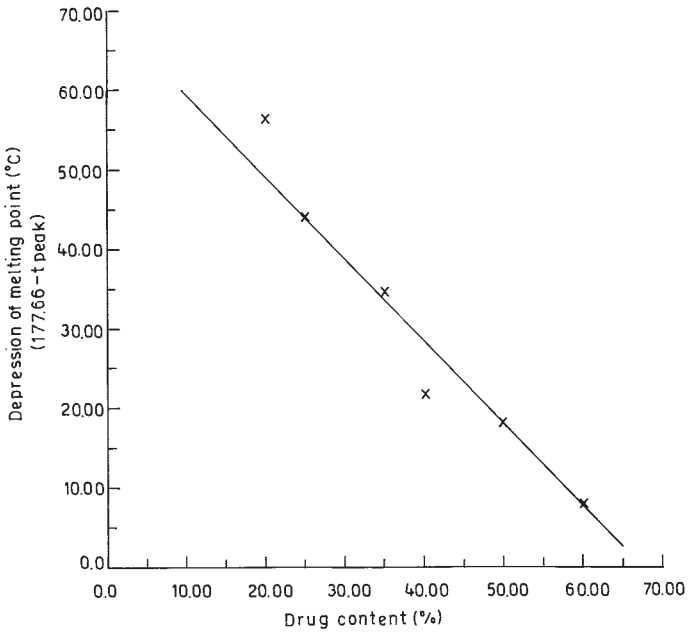


Figure 7 Depression in melting point versus drug content of modified hydrogel matrices containing various amounts of acetaminophen.

ship is proposed and tested to qt with the heat of mixing considered to be zero or negligible:

$$qt = (m_t - m_s)qd$$

where qd is the melting enthalpy of the pure drug (J/g), m_t is the total drug concentration (g of drug/g of matrix), m_s is the solubility of the drug in the polymer at the melting point of the drug (g of drug/g of matrix; here, m_s was 142 mg/g of matrix).

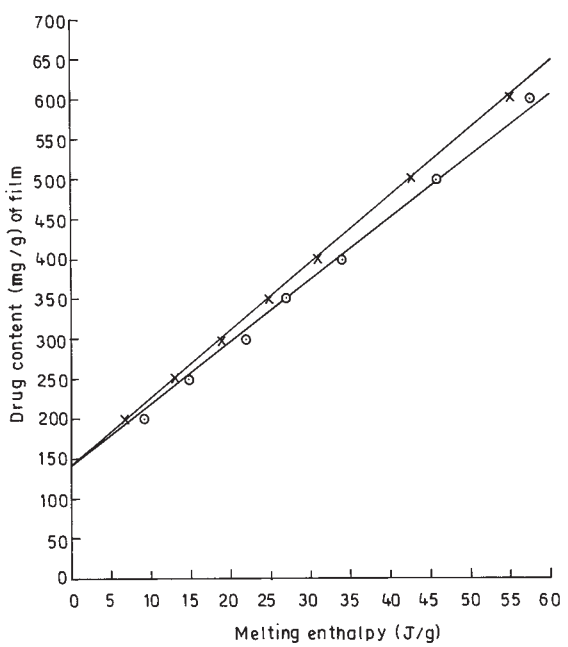


Figure 8 Melting enthalpy [(ò) observed and (×) calculated] versus drug content for hydrogel and acetaminophen matrices.

To verify the validity of the previous equation, the values were calculated and plotted, as shown in Figure 8 by the dotted line. The values of the melting enthalpies obtained experimentally and calculated by this equation confirmed its validity. The differences between the observed and calculated values of qt were in the range 2.56–2.60 and were due to heat of mixing or other thermal effects. It has also been reported that the heat of mixing should be zero or negative in case of the occurrence of secondary interactions between two components,[35] which affirmed our suspicion of secondary interactions between acetaminophen and the modified hydrogel.

As mentioned earlier, DSC analysis clearly indicated interactions between acetaminophen and the modified hydrogel. Das et al.[36] synthesized poly(vinyl amine) complexes with f-block salts from the lanthanide series. Their results showed interactions between the amino nitrogen lone pair in poly(vinyl amine) and the lanthanide metal center, as proved by IR spectroscopy. To exactly determine the nature of our interactions, FTIR spectroscopy of matrices having 20, 25, 40, and 45% acetaminophen was performed. Hydrogen bonding is characterized by the broadening and lowering of peak positions of corresponding functional groups in IR spectra. On analysis of the spectra, changes in the peak positions of only hydroxyl, carboxyl, and N—H groups were observed (Figs. 9 and 10). Figure 9 shows that the

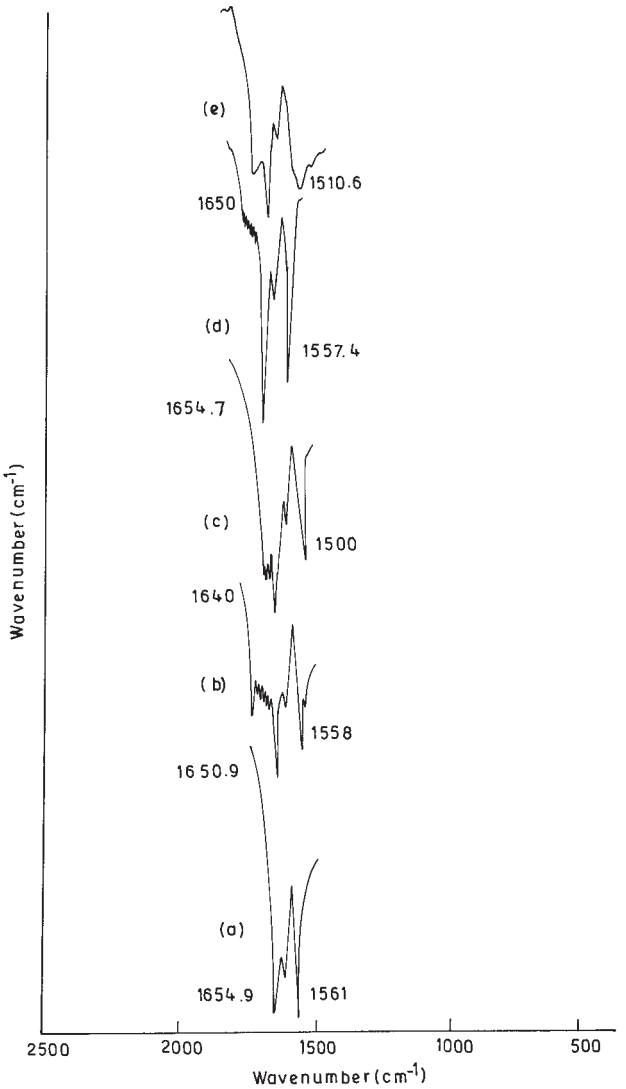


Figure 9 Peak positions of C═O and N—H graphs in (a) pure acetaminophen and modified polymeric hydrogel matrices containing (b) 20, (c) 25, (d), 40, and (e) 45% acetaminophen.

band position for the C═O group shifted toward the lower side compared to pure acetaminophen. The band positions were reduced from 1650.9 to 1650 cm^{-1} for matrices containing 20 to 45% acetaminophen, respectively. The band position of the N—H groups of pure acetaminophen[37] was 1561 cm^{-1}, which decreased from 1558 to 1510.7 cm^{-1} as the drug concentration increased from 20 to 45%, respectively. The considerable shifting in the peak position indicated the formation of intermolecular hydrogen bonding.

Figure 10 shows that the peak position of the hydroxyl group of pure acetaminophen was 3443.9 cm^{-1}; and for the hydrogel matrix with 20% acetaminophen, it was 3396.4 cm^{-1}. It is clear from Figure 10 that there was shift in the peak position toward the lower side for the hydroxyl group on incorporation of acetaminophen in the matrix, which indicated hydrogen bond formation. The hydroxyl peak position for 20% acetaminophen was 3396.38 cm^{-1}, which decreased from 3328 to 3325 cm^{-1} as acetaminophen concentration increased from 25 to 50%, respectively. There was a shift of 71.4 cm^{-1} (3396.4 to 3325 cm^{-1}), which was significant, indicating hydrogen bonding of reasonable high strength. The absorption bands corresponding to various other functional groups present in the system did not exhibit any shifting. Therefore, the results indicated that only C═O, O—H and N—H groups were possibly involved in the hydrogen bonding.

Controlled release behavior of the poly(AAm-*co*-MMA) and poly(AAm-*co*-MMA-*co*-VAm-*co*-AAc) hydrogels

To study the effects of interactions on the controlled release behavior of the copolymeric and modified hydrogels, acetaminophen as a drug at 20% loading was used. Figure 11 shows the plot of percentage cumulative drug released as function of time. It shows that a

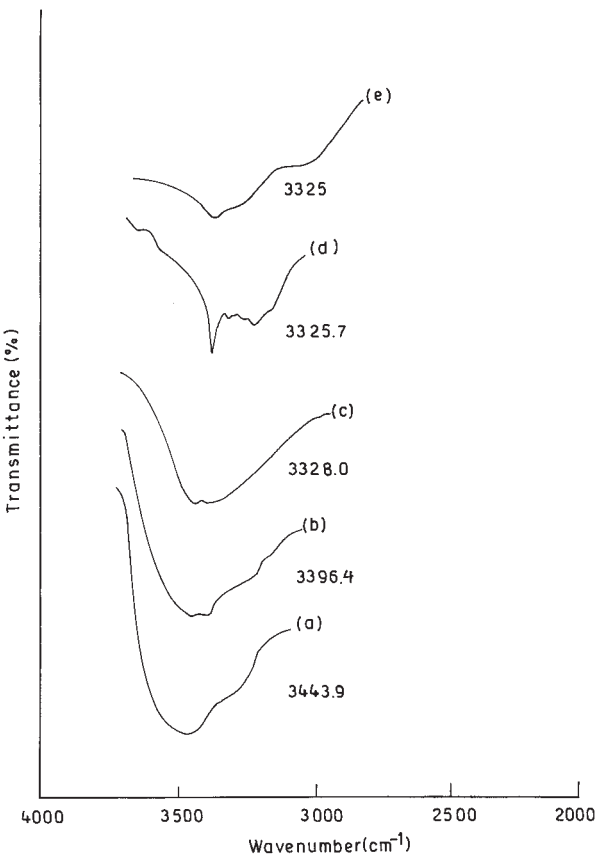


Figure 10 Peak positions of the O—H group in (a) pure acetaminophen and modified polymeric hydrogel matrices containing (b) 20, (c) 25, (d), 40, and (e) 45% acetaminophen.

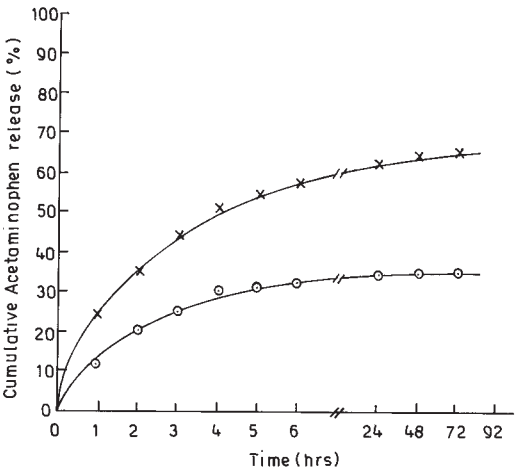


Figure 11 Release behavior of the (×) poly(AAm-*co*-MMA) copolymer and (ȯ) poly(AAm-*co*-MMA-*co*-VAm-*co*-AAc) hydrogel matrices containing 20% acetaminophen.

66.5% release was obtained for the acetaminophen-loaded poly(AAm-*co*-MMA) copolymer matrix (shown by dotted lines). A large amount of acetaminophen, that is, 63.8%, was released during the first 24 h. Figure 11 shows that 66.5% acetaminophen was released in 72 h, after which the release rate declined. Acetaminophen (33.5%) was left unreleased for the copolymer matrix of poly(AAm-*co*-MMA) containing 20% acetaminophen.

Figure 11 also shows that a release of 37.2% acetaminophen was obtained for the poly(AAm-*co*-MMA-*co*-VAm-*co*-AAc) hydrogel matrix loaded with 20% acetaminophen. Here, only 33.5% acetaminophen was released during the first 24 h, and 37.2% acetaminophen was released in 72 h. Figure 11 shows that 62.8% acetaminophen was left unreleased in the 20% acetaminophen hydrogel matrix. Figure 11 indicates a similar release pattern with higher release rates for poly(AAm-*co*-MMA) compared to the poly(AAm-*co*-MMA-*co*-VAm-*co*-AAc) hydrogel. More detailed investigations are required to correlate the occurrence of interactions and the controlled release behavior of the modified hydrogel with various other interacting and noninteracting drugs.

CONCLUSIONS

From the study, the following conclusions were drawn:

1. Synthesis of the poly(AAm-*co*-MMA-*co*-VAm-*co*-AAc) hydrogel was achieved by Hofmann degradation of poly(AAm-*co*-MMA) copolymer, with reactive side groups and improved swelling. After Hofmann degradation, the modified poly(AAm-*co*-MMA-*co*-VAm-*co*-AAc) hydrogel absorbed nearly fivefold more water than the copolymer.
2. The melting of acetaminophen in the modified polymeric hydrogel matrix was characterized by a decrease in the melting point and a considerable broadening of peak. The drug solubility at the melting point of the drug was determined to be 142 mg/g of matrix by the measurement of the melting endotherm of acetaminophen for matrices containing various drug levels. Good miscibility of acetaminophen in the polymeric hydrogel was evident from the decrease in the acetaminophen melting point, and a high solubility of polymeric hydrogel indicated secondary interactions, such as hydrogen bonding, was confirmed by FTIR studies.
3. Acetaminophen (66.5%) release was obtained for the poly(AAm-*co*-MMA) copolymer loaded with 20% acetaminophen. A 37.2% acetaminophen release was obtained for the poly(AAm-*co*-MMA-*co*-VAm-*co*-AAc) hydrogel loaded with 20% acetaminophen.

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