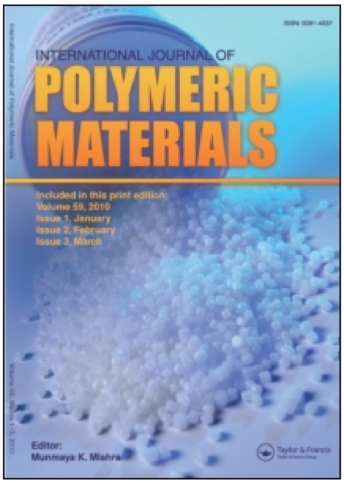

International Journal of Polymeric Materials
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713647664

A Study on the Effect of Butyl Methacrylate Content on Swelling and Controlled-Release Behavior of Poly (Acrylamide-co-Butyl-Methacrylate-co-Acrylic Acid) Environment-Responsive Hydrogels

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To cite this Article Singhal, Reena and Gupta, Indu(2010) 'A Study on the Effect of Butyl Methacrylate Content on Swelling and Controlled-Release Behavior of Poly (Acrylamide-co-Butyl-Methacrylate-co-Acrylic Acid) Environment-Responsive Hydrogels', International Journal of Polymeric Materials, 59: 10, 757 — 776

To link to this Article: DOI: 10.1080/00914037.2010.483216

URL: http://dx.doi.org/10.1080/00914037.2010.483216

International Journal of Polymeric Materials, 59:757–776, 2010
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ISSN: 0091-4037 print/1563-535X online
DOI: 10.1080/00914037.2010.483216

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A Study on the Effect of Butyl Methacrylate Content on Swelling and Controlled-Release Behavior of Poly (Acrylamide-co-Butyl-Methacrylate-co-Acrylic Acid) Environment-Responsive Hydrogels

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Poly (acrylamide-co-butyl methacrylate-co-acrylic acid) [poly (AAm-co-BMA-co-AAc)]-based environment-sensitive hydrogels were prepared by varying the butyl methacrylate (BMA) content, in the range of 20 to 66% (wt. of the total monomer) in the hydrogel. The effect of BMA content on the swelling behavior of the hydrogels was studied by keeping the other two monomers' content constant at different pH and temperatures. The synthesized hydrogels were characterized by various techniques, and release kinetics was analyzed. The application and effect of the BMA content

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Received 15 January 2010; accepted 24 March 2010.

The authors wish to acknowledge Dr. R. K. Khitoliya, Director H.B.T.I., Kanpur, for moral research support. The authors gratefully acknowledge Mr. Anil Kumar Saini and Smt. Rekha, IIC, IIT, Roorkee, for the thermal analysis and SEM analysis of the samples; and The Head, RSIC, CDRI, Lucknow, for recording the FTIR spectra.

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of these hydrogels in controlled drug release of acetaminophen and model drugs were investigated.

Keywords butyl methacrylate, controlled release, environment-sensitive, hydrogels, swelling kinetics

INTRODUCTION

Hydrogels are polymer networks swollen with a large amount of water [1]. Accordingly, hydrogels have been used as contact lenses, artificial organs, bone in growth sponge, wound dressings, and membrane materials, especially in biological science, where they are indisposable in electrophoresis [2]. Their dynamic swelling behavior can be used in the design of intelligent controlled drug delivery, or in design and analysis of artificial muscles and biosensors. Environmentally sensitive hydrogels are those materials that react to an externally applied force or stimulus, for example, stress/strain (including pressure), pH, light, temperature, solvent, and composition. Hydrogels are also "smart" or "intelligent" [2,3] in the sense that they can perceive the prevailing stimuli and respond by exhibiting changes in phases, shapes, volume, surface energies, reaction rates, and dimension. Here, the change in the external environment will act as a stimulus; whereas the response is the change in swelling properties of the network.

However, the applications of hydrogels as mechanical devices are fairly limited due to their lack of strength, especially in swollen form. It may be thought that this feature of the gels is unavoidable because of their solution-like nature, i.e., the low density of polymer chains and the low friction between the chains. Generally a hydrophilic monomer (which will ensure a higher water content in the network) is mixed with a more hydrophobic monomer to improve mechanical properties in the resulting hydrogel [4]. Emileh et al. [5] studied swelling and mechanical properties of cationic hydrogels based on poly(2-dimethyl-amino) ethyl methacrylate, and its copolymer with butyl methacrylate, and concluded that incorporation of BMA in the hydrogel structure reduces the transition pH and temperature of the pH and temperature-sensitive phase transition. Recently Ganji and Farahani [6] have reviewed the various aspects of applications of hydrogels in controlled drug release.

In our earlier investigations on hydrogels based on acrylamide, acrylic acid and butyl methacrylate, the effect of acrylamide content [7] and acrylic acid content [8] was reported.In the present study we have studied the effect of BMA content as a third monomer in the hydrogel along with acrylamide and acrylic acid as comonomers which were kept constant. BMA was used for increasing the three-dimensional strength of the poly (AAm-co-AAc-co-BMA) hydrogels in swollen form, as we have observed in our earlier studies that at a high swelling ratio, the hydrogel loses its mechanical strength, becomes difficult to handle and partially disintegrates. The effect of BMA content, which was varied from 20 to 66%, on swelling behavior of the synthesized hydrogels was investigated in order to strike a balance between hydrophobic and hydrophilic components in the hydrogel. No detailed studies on such variations in the higher range of monomers are reported in the literature on the hydrogels synthesized from the monomers employed in this work.

Detailed swelling studies such as kinetics for swelling, equilibrium swelling, transport exponent "n", diffusion coefficient "D", and the effect of pH and temperature on swelling behavior were conducted. The hydrogels were also characterized by Fourier transform infrared (FTIR) analysis, elemental analysis, differential scanning calorimetery (DSC) analysis, and scanning electron microscopy (SEM) analysis. In addition the environment-sensitive nature of these hydrogels will also be investigated at various pH and temperatures. The application of synthesized hydrogels in the controlled release of acetaminophen and model drugs as well as effect of butyl methacrylate content on controlled release will be investigated in detail.

EXPERIMENTAL

Materials

Acrylamide (AAm), butyl methacrylate (BMA), N,N′-methylenebisacrylamide (N-MBA) and benzoyl peroxide (BPO) were purchased from CDH, New Delhi, India. Dioxane and ammonium persulphate were obtained from Qualigens Fine Chem., New Delhi, India. Acrylic acid (AAc) and methyl alcohol were obtained from S.D. Fine Chem., New Delhi, India.

Acrylamide monomer was recrystallized with methyl alcohol, and butyl methacrylate was distilled with 4% aqueous sodium hydroxide solution before use. Other chemicals were used as received for the synthesis of hydrogels.

Synthesis of Poly (AAm-co-AAc) Hydrogel

In the preparation of poly (AAm-co-BMA-co-AAc) hydrogel acrylamide, butyl methacrylate, and acrylic acid are used as monomers. N,N′-methylenebisacrylamide was used as a crosslinker, while BPO and APS were used as an initiator and 50% aqueous dioxane solution were used as a solvent. A series of crosslinked poly (AAm-co-BMA-co-AAc) has been prepared in different ratios by varying butyl methacrylate content over four fold. The AAm, BMA and AAc are taken in different ratio: 1:0.5:1, 1:1:1, 1:2:1, 1:3:1, 1:4:1, and designated as $B_{0.5}$, A_1, B_2, B_3, B_4, respectively. The actual feed compositions for the synthesis of various hydrogels with respective sample designations are given in Table 1. In all feed compositions the BPO and APS were taken 0.04 g; and 20 ml of 50:50 water:dioxane mixture was taken as solvent.

Polymerization Method

To synthesize the poly (AAm-co-BMA-co-AAc) hydrogel, solution of acrylamide was prepared in 20 ml of 50% aqueous dioxane solution. In this solution NMBA (1% by weight of AAm concentration), AAc and BPO were added, respectively. The reaction mixture was mixed with the help of a mechanical stirrer for 30 min at 45°C for complete dissolution. This reaction mixture was then mixed with NMBA (1% by weight of AAc content) and APS. For homogenity the reaction mixture was again stirred under nitrogen atmosphere for 30 min at 45°C. This mixture was poured into petri dishes and kept for 2 h at temperature 60°C for polymerization. After the completion of polymerization, the firm hydrogel in the form of a thick sheet was carefully removed from the surface of the petri dishes.

To remove the unreacted monomer from the hydrogels, they were immersed into a 50% aqueous dioxane mixture for 4 h for washing, then again washed with water several times. The resultant hydrogel discs were dried in an oven at 50°C up to constant weight. The dried hydrogels were stored into an airtight container.

Swelling Measurement

The degree of swelling was measured by gravimetric measurements. In each experiment, preweighed, initially dry hydrogel ($15 \times 15\,\mathrm{mm}^2$ approximately in dimension) was immersed in 500 ml of distilled water. At different time intervals, the hydrogel was removed from water and its surface was quickly blotted free of surface water by using filter paper, then weighed and returned to the swelling medium. The swelling ratio was calculated from Eq. (1).

$$\text{Swelling ratio} = \frac{\mathrm{Ws}}{\mathrm{Wd}} \tag{1}$$

The degree of swelling was calculated from Eq. (2)

$$\text{Degree of swelling } (\%) = \frac{\mathrm{Ws} - \mathrm{Wd}}{\mathrm{Wd}} \times 100 \tag{1a}$$

where Wd is the dry weight of the hydrogel and Ws is the swollen weight of the hydrogel.

Table 1: Feed composition of poly (AAm-co-BMA-co-AAc) hydrogel prepared by varying BMA content.

Hydrogel code	Ratio AAm: BMA:AAc	Ratio in percentage AAm:BMA:AAc	Amount of AAm (gm)	Amount of BMA (ml)	Amount of AAc (ml)	Amount of NMBA 1% of AAm	Amount of NMBA 1% of AAc
$B_{0.5}$	1:0.5:1	40:20:40	1.60	0.80	1.60	0.016	0.016
A_1	1:1:1	33.33:33.33:33.33	1.33	1.33	1.33	0.013	0.013
B_2	1:2:1	25:50:25	2.00	1.00	1.00	0.020	0.010
B_3	1:3:1	20:60:20	0.80	2.40	0.80	0.008	0.008
B_4	1:4:1	17:66:17	0.68	2.64	0.68	0.006	0.006

Preparation of Swelling Medium

The buffer solutions of different pH were used as the swelling medium. Solutions were prepared by the following compositions:

pH	Compositions
2	100 ml 0.1 M potassium hydrogen phthalate + 99 ml 0.1 M HCl
5	100 ml 0.1 M potassium hydrogen phthalate + 45.2 ml 0.1 M NaOH
7.4	0.005 M NaCl solution (pH adjusted to 7.4)
10	100 ml 0.05 M $NaHCO_3$ + 21.4 ml 0.1 M NaOH

DATA ANALYSIS

Dynamic Equilibrium Swelling

The dried gel was immersed in an excess of deionized water at 25°C. The amount of water absorbed 'Mt' by the hydrogel was reported [8] as a function of time, and the equilibrium absorption at infinitely long time, designed by 'M_∞' which is given as Eq. (2). Equation (2) can be used to calculate the characteristic constant K and transport exponent 'n' for $Mt/M_\infty \leq 0.6$

$$M_t/M_\infty = K\,t^n \tag{2}$$

where 'K' is a characteristic constant of the gel, and 'n' is a characteristic exponent of the mode of transport of the penetrant. For a slab geometry when $n = 0.5$, the swelling process is diffusion-controlled and was termed as Fickian or case I transport. Transport was assumed to relaxation controlled (Case II) when $n = 1$ when the exponent n was between 0.50 and 1.0, the transport was termed anomalous. An observation of $n > 1$ is termed super case II. The rate to approach to equilibrium can be characterized by diffusion coefficient value 'D', which can be calculated for planar geometry from the Eq. (3) [9].

$$M_t/M_\infty = (4/\pi^n)(Dt/L_0^2)^n \tag{3}$$

where 't' is the time and 't_0' is the initial thickness of the dried sample. The values of 'n' and 'K' were calculated from the slope and intercept of the plot of log (M_t/M_∞) against log (t).

Fourier Transform Infrared Spectroscopy

Fourier transform spectra of various hydrogels were recorded using a Nicolet 400 D spectrophotometer in solid potassium bromide pellet after completely drying the sample in vacuum at 60°C for 8 h.

Elemental Analysis

Elemental analysis (C, H and N) was performed on an elemental analyzer (Elemental vario).

Differential Scanning Calorimetry (DSC) and Thermal Gravimetric Analyzer (TGA)

DSC was carried out using a Perkin Elmer (Pyris Diamond) differential scanning calorimeter under the nitrogen atmosphere at a heating rate of 5°C/min up to 300°C. A thermogravimetric analyzer of Perkin Elmer (Pyris Diamond) was used to study the thermal degradation pattern and thermal stabilities of the hydrogel specimens at a heating rate of $5^\circ\mathrm{C\,min^{-1}}$ in a nitrogen atmosphere.

Scanning Electron Microscopy (SEM)

The morphological behavior of synthesized poly (AAm-co-BMA-co-AAc) hydrogel surface was examined under scanning electron microscope (SEM). Dried poly (AAm-co-BMA-co-AAc) hydrogel coated with a thin layer of pure gold is 5150-sputter coated, and imaged in a SEM (LEO Electron Microscopy Ltd., England).

Controlled Release Studies

Preparation of Hydrogel Matrice Samples for Controlled Drug Release

For the drug release studies, drug-incorporated poly (AAm-co-BMA-co-AAc) discs ($10 \times 25\,\mathrm{mm^2}$) were prepared by dissolving the 20% drug (on the weight basis of the monomer) in a polymerization solution of the hydrogel. The discs were dried at room temperature for 24 h at atmospheric pressure and afterwards in an oven at 45°C for 8 h.

In Vitro Dissolution Studies of Polymer Matrices for Release Behavior

Dissolution studies were conducted by placing the matrix device in 500 ml of release medium in a conical flask without stirring. Samples of release medium (5 ml) were withdrawn at fixed time intervals (initially) for 6 h on an hourly basis and then after every 24 h, and 5 ml of fresh release medium was added simultaneously so the total volume remains 500 ml. The release medium was replaced every 24 h in order to avoid saturation with drug. The samples taken out were analyzed on an UV-vis spectrophotometer for absorbance at the corresponding λmax of that particular drug. The absorbance obtained is converted into concentration with the help of a calibration curve. The calibration curves for the three model drugs used in the study, i.e., benzoic acid ($\lambda\mathrm{max} = 232.5\,\mathrm{nm}$), salicylic acid ($\lambda\mathrm{max} = 296\,\mathrm{nm}$) and acetaminophen, ($\lambda\mathrm{max} = 381\,\mathrm{nm}$) were obtained.

RESULTS AND DISCUSSION

Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR spectra of various synthesized poly (AAm-co-BMA-co-AAc) hydrogels were recorded and were found the same for various peaks correspondingly to AAm, BMA, and AAc for all the composition of hydrogels. Figure 1 represents the FTR of (a) crosslinked polyacrylic acid, (b) crosslinked poly (AAm-co-BMA), and (c) poly (AAm-co-BMA-co-AAc) $B_{0.5}$. In Figure 1(a), the peak for C=O bond of PAAc was observed at 1724.54 cm^{-1}, and at 3600 cm^{-1} was corresponding to $-$OH group. The FTIR (Figure 1(b)) spectrum of PAAM showed a strong absorption peak at 1662.57 cm^{-1} due to C=O bond stretching, and 3424.7 cm^{-1} and 1030 cm^{-1} are corresponding to $-$NH and $-$CN stretching, respectively. In addition to the above, a strong peak was observed at 2170.14 cm^{-1} corresponding to C=O stretching of the methyl ester of BMA units. The peak at 2950 cm^{-1} corresponded to C$-$H stretching of hydrocarbon. The FTIR (Figure 1(c)) spectrum of $B_{0.5}$ hydrogels ($B_{0.5}$) showed the peak corresponding to the functional groups attached to the monomeric units. The peak for $-$OH bond of PAAc was observed at 3500 cm^{-1} and peaks were observed at 1630 cm^{-1} (amide 1-band) corresponding to C=O group of PAAm and at 1592 cm^{-1} (amide 2-band) corresponding to $-CONH_2$ group of AAm. A strong peak was also observed at 1362.50 cm^{-1} corresponding to C$-$O stretching of the methyl ester of BMA units and 720 cm^{-1} is

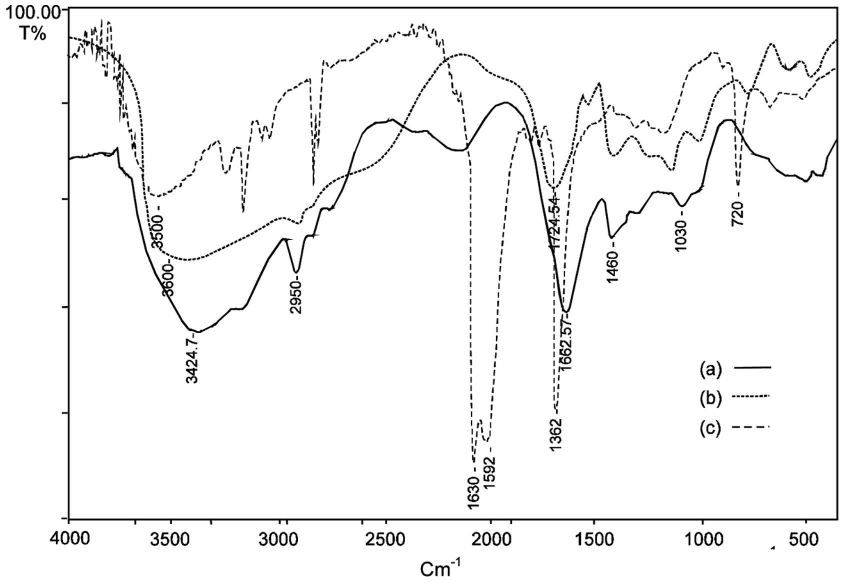


Figure 1: FTIR spectrum of (a) crosslinked poly (AAc), (b) crosslinked poly(AAm-co-BMA), (c) crosslinked poly (AAm-co-BMA-co-AAc) hydrogel ($B_{0.5}$).

corresponding to $-CH_2$ of the methyl ester of BMA units. The FTIR analysis indicates that all monomer units (AAm, BMA, AAc) were incorporated into the hydrogel.

Elemental Analysis

The nitrogen content of poly (AAm-co-BMA-co-AAc) hydrogels prepared by varying the BMA content was analyzed by elemental analysis and on the basis of the percentage of nitrogen, the percentage of acrylamide content of the hydrogels was calculated. The results are given in the Table 2. It can be seen that the nitrogen content present in the hydrogel was decreased from 8.95 to 3.32% with increasing the BMA content from 20 to 66% in feed. Through elemental analysis the total percentage of acrylic acid and BMA content was increased from 54.61 to 83.16%, which was quite near to composition taken in feed from 60 to 83%. In feed composition (Table 2) the percentage of BMA and acrylamide were the same, so we can assume (8) that the percentage of BMA and acrylamide will be approximately the same present in the various hydrogels.

DSC Analysis

The DSC scans of poly (AAm-co-BMA-co-AAc) hydrogels with different amounts of BMA content were conducted and are shown in Figure 2. The glass transition temperature (Tg) value observed by DSC scans for $B_{0.5}$, A_1, B_2, B_3 and B4 hydrogels with different amounts of BMA were 158.16, 135.38, 130.19, 123.43, and 108.58°C, respectively, which indicated clearly that when the percentage of BMA increases, the glass transition temperature reduces significantly. From Figure 2 it is clear that the Tg decreased from 158.16 to 108.58°C, with an increase in the BMA content of the hydrogel in feed from 20 to 66%. The lowering of Tg was due to an increase in BMA content as it increases the chain flexibility,but it may not result in enhanced swelling of hydrogels as BMA is hydrophobic in nature.

Effect of Butyl Methacrylate Content on Swelling Behavior

Increasing the BMA content affects the swelling properties of poly (AAm-co-BMA-co-AAc) hydrogels significantly. The plot between the equilibrium swelling ratio and BMA content of these hydrogels has been shown in Figure 3, which shows that the equilibrium swelling ratio of poly (AAm-co-BMA-co-AAc) hydrogels decreased as the BMA content increased from 20 to 66.66% in feed. The equilibrium swelling ratio decreased significantly from 84 to 62.88, with an increase in BMA content from 20 to 33.33% in feed for $B_{0.5}$ to A_1 hydrogels. Further, there was a moderate decrease in the equilibrium

Table 2: Percentage of AAm and (AAc + BMA) content present in poly (AAm-co-BMA-co-AAc) hydrogels prepared by varying BMA content, determined by elemental analysis.

Hydrogel code	Percentage of nitrogen	Percentage of AAm content taken in feed	Percentage of AAm content in hydrogel calculated by elemental analysis	Total percentage of AAc and BMA component taken in feed	Total percentage of AAc and BMA content in hydrogel calculated by elemental analysis
$B_{0.5}$	8.95	40	45.39	40 + 20 = 60	54.61
A_1	6.68	33.33	33.87	33.33 + 33.33 = 66.66	66.13
B_2	5.37	25	27.23	25 + 50 = 75	72.77
B_3	3.85	20	19.53	20 + 60 = 80	80.48
B_4	3.32	17	16.84	17 + 66 = 83	83.16

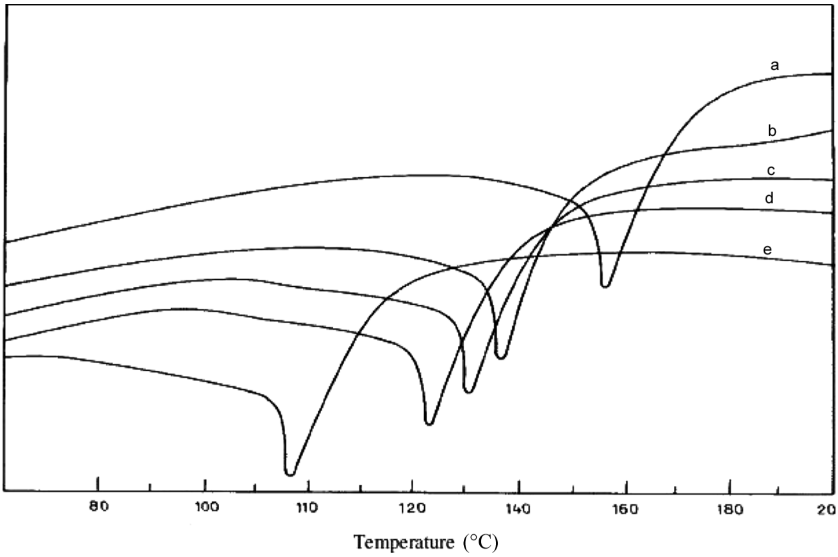


Figure 2: DSC thermograms of (a) $B_{0.5}$, (b) A_1, (c) B_2, (d) B_3, (e) B_4 hydrogels.

swelling ratio from 62.88 to 55.70 as the concentration of BMA increased from 33.33 to 50% in feed for A_1 to B_2 hydrogel. Afterwards a remarkable change in response was observed, that the equilibrium swelling ratio almost remained constant from 55.70 to 53.83, with an increase in the concentration of BMA from 50 to 60% in feed. The equilibrium swelling ratio decreased greatly again from 53.83 to 36.27 as the concentration of BMA was further increased from 60 to 66% in feed for B_3 to B_4 hydrogels. The above results indicated that although with increasing BMA content, swelling decreased (due to the increasing

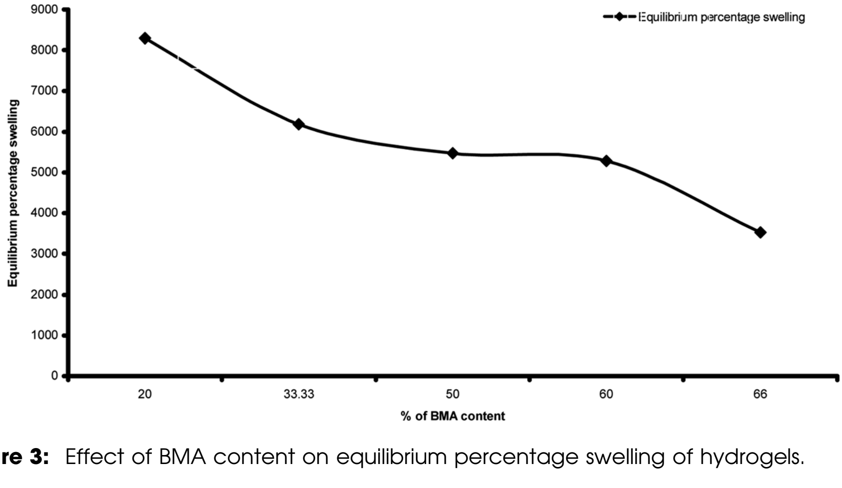


Figure 3: Effect of BMA content on equilibrium percentage swelling of hydrogels.

hydrophobic content of the hydrogel) [10], but with 50 to 60% BMA content, the swelling is nearly constant.

Katime et al. [11] had prepared hydrogels based on acrylic acid and n-alkyl methacrylate in order to find how the methacrylate group can effect the hydrophilic characteristics of the network, and therefore its influence on the swelling properties and the release of theophylline and aminophylline. They observed that swelling and release increased with the size of the side chain on the acrylate. Chandy [12] has found that the equilibrium degree of swelling for a copolymer is given by the balance of the polar and steric effects. For acrylic acid/n-alkyl methacrylate hydrogels, the polar contribution comes from the hydrophilic comonomer and the steric effects from the alkyl substituents on the methacrylate.

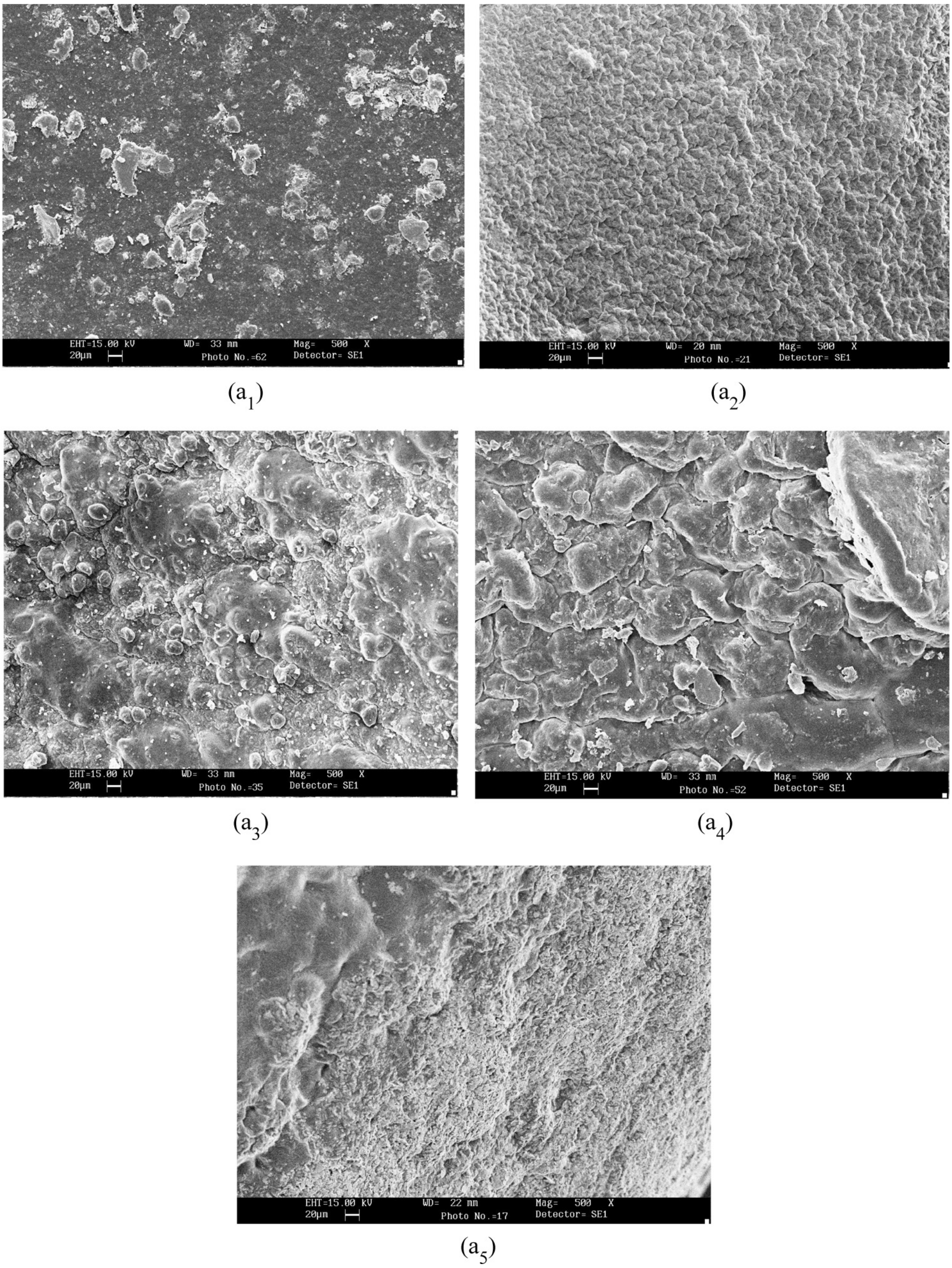
In the present study for $B_{0.5}$, A_1, B_2, B_3, and B_4 hydrogels, the dynamic water absorption experiment were performed and the data were analyzed by using Eq. (3), in terms of swelling exponent 'n', diffusion coefficient 'D' and rate constant 'K'. The results were shown in Table 3, which shows that the value of 'n' decreased from 1.09 to 0.94 as the swelling ratio decreased from 84.00 to 62.88 for $B_{0.5}$ to A_1 hydrogel, i.e., the swelling exponent changed from 'supercase' to a relaxation-controlled type mechanism. Then the value of 'n' increased from 0.94 to 1.37 as the equilibrium swelling ratio decreased from 62.88 to 36.27 for A_1 to B_4 hydrogels, i.e., swelling exponent changed from relaxation-controlled to super case. The values of diffusion coefficient 'D' lie in the range of 1.10×10^{-3} to 1.15×10^{-3} for $B_{0.5}$ to B_4 hydrogels. Bhardwaj [13] has prepared 2-hydroxyethylmethacrylate copolymerized with acrylic acid and para-sodium styrene sulfonate and observed that the values of the swelling exponent lie in the range of 0.50 to 0.80.

SEM Analysis

Equilibrium swelling ratio also depends on surface morphology of the hydrogels, therefore, SEM analysis has been conducted. Figures 4(a_1) to 4(a_5) are SEM of the poly (AAm-co-BMA-co-AAc) hydrogels before swelling have

Table 3: Swelling behavior and diffusion parameter of poly (AAm-co-BMA-co-AAc) hydrogels prepared by variation of butyl methacrylate.

Hydrogel code	Swelling ratio	Swelling exponent 'N'	K	Diffusion coefficient
$B_{0.5}$	84.00	1.09	–	1.10×10^{-3}
A_1	62.88	0.94	−1.80	1.08×10^{-3}
B_2	55.70	1.06	−2.02	6.60×10^{-3}
B_3	53.83	1.25	−2.16	6.60×10^{-2}
B_4	36.27	1.37	−1.69	1.15×10^{-3}



(a_1) (a_2)

(a_3) (a_4)

(a_5)

Figure 4: (a_1) SEM of $B_{0.5}$ poly (AAm-co-BMA-co-AAc) hydrogels (before swelling) containing 20% BMA (500 × magnification); (a_2) SEM of B_1 poly (AAm-co-BMA-co-AAc) hydrogels (before swelling) containing 33.33% BMA (500 × magnification); (a_3) SEM of B_2 poly (AAm-co-BMA-co-AAc) hydrogels (before swelling) containing 50% BMA (500 × magnification); (a_4) SEM of B_3 poly (AAm-co-BMA-co-AAc) hydrogels (before swelling) containing 60% BMA (500 × magnification); (a_5) SEM of B_4 poly (AAm-co-BMA-co-AAc) hydrogels (before swelling) containing 66% BMA (500 × magnification).

BMA content from 20 to 60%, respectively. It was observed that as the amount of BMA was increased in the poly (AAm-co-BMA-co-AAc) hydrogels from 20 to 66.66% in feed, the surface of the hydrogels became more and more heterogeneous and denser, so penetration of water molecules through them became more difficult, resulting in lowering of equilibrium swelling ratio. As in Figure 4(a_1), the plain surface had some small irregular formations of hydrogel. Figure 4(a_2) is the SEM of hydrogel (before swelling) containing 33.33% BMA in feed which shows very high shrinkage and more beads resulting in the lowering of penetration water molecule. Figure 4(a_3) is the SEM of hydrogel surface (before swelling) containing 50% BMA in feed which shows a highly uneven surface with small cracks and circular protruding formations resulting in an increase in the surface area of hydrogels for water transport. Figure 4(a_4) is the SEM of a hydrogel containing 60% BMA, which shows a highly irregular, uneven surface with intermeshing formations. In this hydrogel some cracks developed which facilitated water penetration, which explains the comparatively higher values of swelling ratios observed. Figure 4(a_5) is the SEM of the hydrogel containing 66% BMA in feed and shows comparatively less irregularity but has a porous type of small formations. The surface of the hydrogel becomes more granular and compact so the movement of water molecules became difficult, resulting in the lowering of the equilibrium swelling ratio.

Effect of pH and Temperature on Swelling

The equilibrium percentage swelling of various poly (AAm-co-BMA-co-AAc) hydrogels prepared by using various butyl methacrylate content was also studied in a buffer solution of different pH 2 to 10, and are shown in Figure 5. It is clear from Figure 5 that for $B_{0.5}$ hydrogel, when the pH was raised from 2 to 5, the percentage degree of equilibrium swelling increased more than 40 times, i.e., from 161.6 to 6641. From pH 5 to 7 the

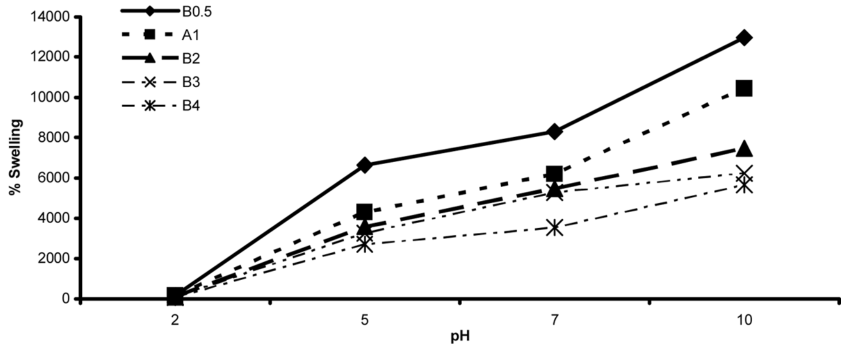


Figure 5: Effect of different pH solution (as swelling medium) on equilibrium percentage swelling of poly (AAm-co-BMA-AAc) hydrogels having different percentage of BMA content.

equilibrium percentage swelling further increased from 6641 to 8300%. When the pH was raised from 7 to 10, the equilibrium percentage swelling increased upto 12966%. For B_2 hydrogel, the percentage equilibrium swelling increased from 100 to 4340% when the pH was raised from 2 to 5 and the percentage equilibrium swelling increased from 4340 to 5470% for increasing pH 5 to 7. Moreover for increasing pH 7 to 10, the percentage equilibrium swelling increased from 5470 to 7466%.

For B_3 hydrogel, the percentage equilibrium swelling increased from 87.5 to 3275% for increasing pH 2 to 5, percentage equilibrium swelling which might be further increased from 3275 to 5283% for increasing pH 5 to 7, and when pH was beyond pH 7 to 10, the equilibrium percentage swelling increased from 5283 to 6263%. For B_4 hydrogel percentage of equilibrium swelling increased from 60 to 2700% when the pH was raised from 2 to 5; percentage equilibrium swelling further increased from 2700 to 3527% for increasing pH 5 to 7. When pH reached from 7 to 10, the percentage equilibrium swelling further increased from 3527 to 5750%.

The equilibrium percentage swelling increased gradually with increased pH of the swelling medium for all types of hydrogels. Thus the variation of swelling of hydrogels with increasing pH can be divided in three steps.

1. In the first step there was a rapid increase in the percentage equilibrium swelling (from pH 2 to 5) as the swelling increases nearly 40 times.
2. Then in the second step, there was a mild increase in the equilibrium percentage swelling as it increased nearly two times (from pH 5 to 7).
3. In the third step, there was a nominal increase in the equilibrium percentage swelling as it increased nearly one and half times as the pH was raised from pH 7 to 10.

The minimum swelling occurred in the highly acidic swelling medium having pH 3, which may be attributed to the fact that the –COOH groups present along the macromolecular chains in the hydrogel remain almost unionized (since pKa of acrylic acid is 4.7) [14], thus resulting into almost nil osmotic swelling pressure as there are no mobile/counter ions present inside the hydrogel [15]. It was observed that as the pH of the swelling medium was increased from pH 2 to 7 (i.e., above the pKa value 4.7 of acrylic acid), the degree of ionization in acrylic acid and acrylamide increased to give COO^- and NH_3^+ ions that resulted in a more hydrophilic polymer network and contributed to this higher water uptake. Moreover, hydrogen bonding interactions occurred among the carboxylic groups present within the hydrogel, thus providing a compact hydrogen-bonded structure to the hydrogel [16]. The protonation of amine and carboxylic groups takes place at pH, i.e., $2 < pH > 4.7$, and NH_2 groups are converted to NH_3^+. But at $pH < 4.7$, the carboxylic functional groups are converted to carboxylate ions. Either protonated

(NH_3^+) on deprotonated (COO^-) groups increase charge density on the polymer causing an enhancement of the osmotic pressure inside the gel particles, because of the NH_3^{+-} NH_3^+ or COO^- - COO^- electrostatic repulsion. This osmotic pressure difference between the internal and external solution of the network is balanced by the swelling of the hydrogel [14].

When the pH was changed to basic, the hydrolysis reaction of acrylamide occurs which is given as

$$\begin{array}{ccc} -CH_2-CHCONH_2 & \xrightarrow[\text{Medium}]{\text{Basic}} & -CH_2-CHCOOH \\ \text{(Acrylamide)} & & \text{(Acrylic acid)} \end{array}$$

Under a basic environment, the hydrolysis reaction of an amide group present in the hydrogel would be enhanced. This event would increase the swelling ratio higher. However, under the acidic condition, a little repulsive effect of charges would occur by hydrolysis of amide groups, so we can easily observe decreased swelling behavior.

Effect of Temperature on Swelling

Equilibrium percentage swelling of various poly (AAm-co-BMA-co-AAc) hydrogels with a BMA content of 20, 33.33, 50, 60, and 66% designated by $B_{0.5}$, A_1, B_2, B_3, and B_4 were studied at different swelling medium temperatures, i.e., 10, 20, 30, 40, 50°C, and shown in Figure 6. Figure 6 clearly indicates that equilibrium percentage swelling increases significantly with increasing the temperature of the swelling medium from 10 to 40°C for all types of hydrogels because of easy movements of the copolymeric chain.

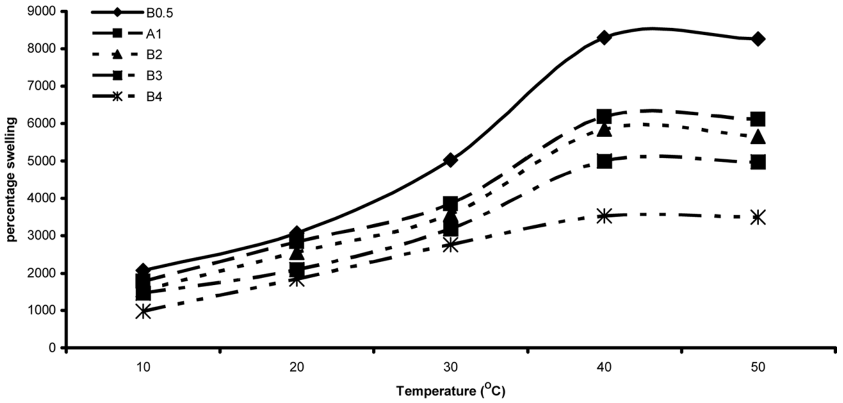


Figure 6: Effect of temperature of swelling medium on percentage swelling of poly (AAm-co-BMA-co-AAc) hydrogels having varying the BMA content.

However, when the temperature was raised above 40 to 50°C, the equilibrium swelling was nearly constant with a slight decrease for all type of hydrogel (i.e., from $B_{0.5}$ to B_4 hydrogels). The increase in equilibrium percentage swelling with an increase in temperature shows the thermosensitive nature or smart nature of hydrogels.

The lower percentage equilibrium swelling in the range of 997 to 2068% of these hydrogels at lower temperatures (10°C) is considered to result from an insolubility of PAAc and PAAm chains by formation of a hydrogen bonding AAm-AAc complex at a lower temperature. Increasing swelling ratio with increasing temperature presumably result from dissociation of the hydrogen bonding polymer complex.

Secondary bonds also exist in the hydrogel. At low temperatures (10–20°C) these bonds are unbreakable, so the swelling was low, but at a high temperature (40 to 50°C) these bonds break so intermolecular space increases; hence water molecules move very easily resulting in the increase of equilibrium percentage swelling. With further increase in temperature, the number of breakable secondary bonds remains nearly constant so equilibrium percentage swelling also remains nearly constant.

On the other hand a little decrease in equilibrium swelling percentage at 50°C elevated temperature of 50°C. X. Wei et al. [17] studied the swelling at different temperatures and found that water retention decreases at 50°C for ethylacrylamide based thermoreversible hydrogels. The synthesized hydrogels exhibited excellent dimensional stability and integrity over a wide range of temperature and pH even during very high swelling.

Study for Controlled Release of Drugs

For studying the controlled release behavior of A_1 type hydrogels, two model drugs, i.e., benzoic acid (BA), salicylic acid (SA) and one drug acetaminophen, were selected. The drug was used in 20% concentration and drug-incorporated hydrogel samples were prepared in the size of $10 \times 20\,\text{mm}^2$. All the drugs were made soluble in a crosslinking solution (50% aqueous dioxane) and had uniform drug concentrations. A plot of the percentage of cumulative drug released over time for different drugs is given in Figure 7. Figure 7 shows that 69.2% salicylic acid diffused in 24 h, 59.10% benzoic acid was released in 24 h, and 64.10% salicylic acid was released in 24 h. The results show remarkable differences in the release pattern of the three drugs when all other variables were kept constant. The dissolution of acetaminophen was fastest compared to other drugs, and may be due to the higher solubility of acetaminophen in water. The release of benzoic acid from the hydrogel matrix was slowest due to poor water solubility. After 72 h only 60% benzoic acid drug was released leaving 40% drug unreleased in the matrix.

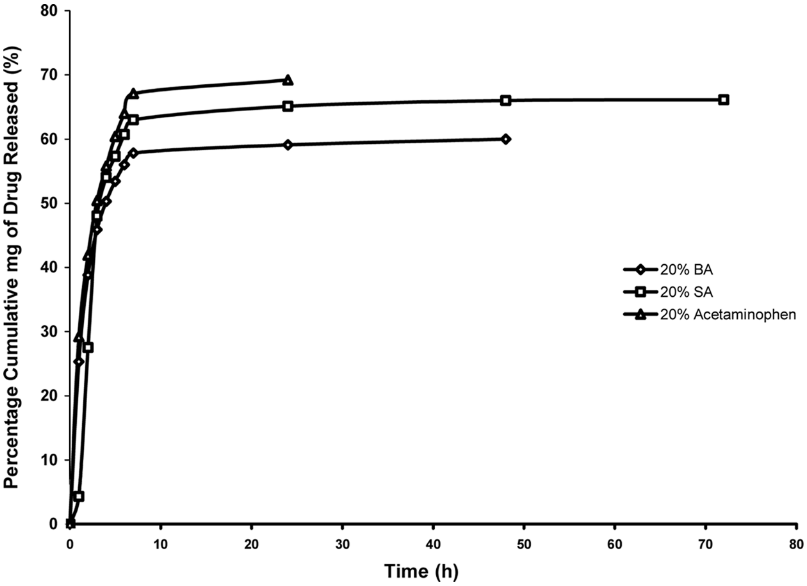


Figure 7: Controlled drug release behavior of Poly(AAm-co-BMA-co-AAc) 1:1:1 ratio at pH 7.

Acetaminophen was selected to evaluate the effect of BMA content on controlled release behavior of synthesized hydrogels. In order to investigate the effect of butyl methacrylate content on the controlled release of acetaminophen, Figure 8 was plotted in between percentage cumulative acetaminophen released with time for $B_{0.5}$, A_1, B_2, B_3, and B_4 hydrogels matrices containing

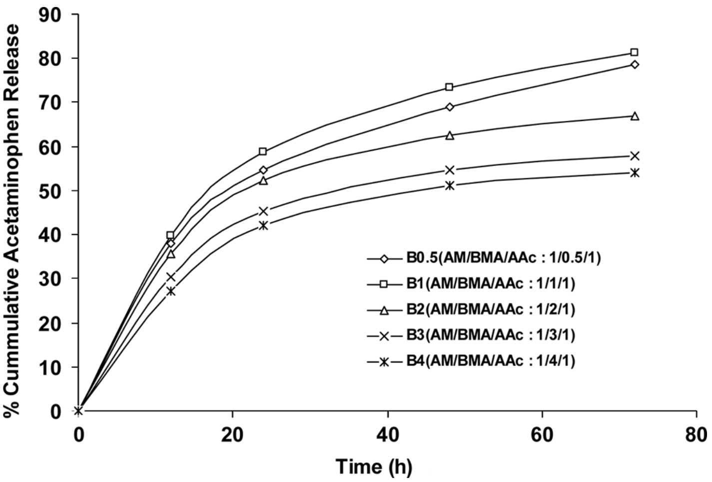


Figure 8: Controlled drug release of acetaminophen from hydrogel matrices having different butyl methacrylate content.

20% acetaminophen (by matrix weight). It is evident from Figure 8 that the release of acetaminophen was significantly slow for higher BMA (i.e., B_3 and B_4) containing matrices, as compared to low BMA containing matrices, i.e., $B_{0.5}$ and A_1. The A_1 hydrogel exhibited the highest release rates over a period of 72 h and released a total 81.46% of acetaminophen, followed closely by $B_{0.5}$ hydrogel which released nearly 78.2% acetaminophen. As BMA content increased the hydrophobicity of the hydrogel increased, leading to lower release rates.

CONCLUSION

From the study it can be concluded that the percentage equilibrium swelling decreased to less than half as the BMA content in the hydrogel was more than tripled. The transport mechanism for various hydrogels was anomalous, zero order and super case depending upon hydrogel composition. The glass transition temperature (Tg) of the synthesized hydrogels decreased with an increase in BMA content. SEM studies revealed that at higher BMA content, the hydrogel surface became more smooth and compact, resulting in a less porous nature leading to decreased swelling. The hydrogels synthesized in the study also exhibited a pH and temperature-sensitive nature, as the swelling increased drastically when the pH was raised 2 to 10, and the temperature was increased from 10 to 40°C. The synthesized hydrogels exhibited very a high level of dimensional stability and integrity over a wide range of temperature and pH even during very high swelling. The application of hydrogel for controlled drug release of the model drug and acetaminophen was also effective for 72 h. It was also observed that hydrogel matrices with a lower amount of butyl methacrylate exhibited higher release rates indicating that BMA content can be used effectively for altering the release profile of a hydrogel.

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