

# Designing of superporous cross-linked hydrogels containing acrylic-based polymer network

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**B**iodegradable cross-linked polymer, 2-hydroxyethyl methacrylate-co-acrylic acid was synthesized by free radical polymerization technique using N,N'-methylene-bis-acrylamide as cross-linker and benzoyl peroxide as reaction initiator. FT-IR, <sup>1</sup>H-NMR, scanning electron microscopy (SEM), and thermogravimetric analysis (TGA) studies of the copolymer along with homopolymers were carried out. FT-IR studies showed no interactions on copolymerization. SEM studies of the copolymer were carried out and mean particle size was found to be 50 μm. TGA analysis indicated an increase in thermal stability by cross-linking the polymer network. Swelling behavior of the copolymer showed more swelling by increasing pH of the medium and the prepared polymer was found to be biodegradable. The prepared cross-linked polymer system holds good for further drug delivery studies in connection to its super swelling and biodegradability.

**Key words:** *Biodegradability, copolymer hydrogel, free radical polymerization, super swellability*

## INTRODUCTION

In the recent years, an ever-increasing interest has been focused on the use of hydrogels in modified release dosage forms<sup>[1-3]</sup> in relation to their physicochemical properties, to the properties of drug molecules that can be loaded in polymeric network, to the mechanism and rate of drug delivery. In the present era, sol-gel technology has the most promising applications in drug delivering system as well as in industries.<sup>[4]</sup> Hydrogels prepared by chemical or physical cross-linking form three-dimensional hydrophilic polymeric networks capable of imbibing large amount of water or biological fluid.<sup>[2]</sup> The pH sensitive polymers containing acidic or basic groups when used to prepare hydrogel, the swelling of hydrogel increases as the external pH increases (in case of weakly acidic group), but decreases<sup>[5]</sup> (in case of weakly basic group). Hydrogels have drawn attention due to their versatile uses in various fields such as in controlled delivery of drugs,<sup>[6]</sup> in ophthalmic delivery of drugs,<sup>[7]</sup> and in rectal delivery of drugs.<sup>[8]</sup> Hydrogels also show gastroprotective property<sup>[9]</sup> during release of prednisolone in the gastric medium. Biodegradable hydrogels have two major advantages of delivery: first surgical removal of the drug-depleted device is not necessary and second, the drug releases kinetics can be controlled. Poly 2-hydroxy ethyl methacrylate-co-acrylic acid [P(HEMA)-co-AA] was

used as biomaterial due to its non-toxic and biologically compatibility for various biomedical applications.<sup>[10]</sup> P(HEMA) are neutral (non-ionic) with water content of approximately 40%. The swelling of P(HEMA) can be regulated by copolymerization with hydrophobic or hydrophilic monomers. Swelling properties of polymers is regulated by external environmental conditions such as pH changes,<sup>[11-13]</sup> magnetic field,<sup>[14]</sup> temperature changes,<sup>[15-16]</sup> etc. It is known that acrylic acid is a pH and electrically sensitive material due to its ionic repulsion between anionic charged groups forms polymer complexes with polybases.<sup>[17]</sup> As the equilibrium water content can be increased by copolymerization with a monomer of more hydrophilic nature, AA is chosen for copolymerization reaction with HEMA. Ease of purification, adjustable mechanical properties, and equilibrium water content contribute to the applications of P(HEMA) and PAA. The main objective of the present work is to develop newly synthesized copolymer hydrogel, P(HEMA-co-AA) with a cross-linker MBA and initiator benzoyl peroxide (BPO) that could be used as a drug delivery device in future.

## MATERIALS AND METHODS

HEMA and AA were purchased from E. Merck, Germany and were used after distillation under reduced pressure. BPO purchased from E. Merck, Germany was recrystallized from benzene and a stock solution was prepared in acetone, MBA (AR grade) was purchased from Sisco Research Laboratories, Mumbai. All other reagents used were of analytical grade.

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### Synthesis of P(HEMA-co-AA) cross-linked polymer

The polymerization experiments were carried out in a three-necked round bottom reaction vessel taking HEMA (0.405 mol/dm<sup>3</sup>), AA (0.229 mol/dm<sup>3</sup>), MBA (0.01 mol/dm<sup>3</sup>), and distilled water in nitrogen atmosphere and sealed by a rubber septum. The solutions were stirred at 400-500 rpm. The requisite amount of BPO (0.01 mol/dm<sup>3</sup>) in acetone was carefully injected to the reaction mixture. The temperature was maintained at 80°C. The pH of the medium at beginning of the polymerization reaction was found to be 3.12 and at the end it was found to increase to 6.33. After 6 h, the reaction was ceased by keeping the flask in ice-cold water and by addition of 5% ferrous ammonium sulfate. The precipitated polymers were filtered and purified by washing repeatedly with distilled water and methanol. Then the polymers were dried at 40°C and stored.

### Biodegradation by cultured media and quantitative estimation of CO<sub>2</sub>

A cultured medium was prepared by taking agar nutrient broth. The nutrient broth so prepared was sterilized maintaining at a pressure of 15 lb/inch<sup>2</sup> at 121°C for 20 min in autoclave. Then to 10 ml of sterilized broth 0.1 g each of the samples, i.e., P(HEMA-co-AA), was taken in test tubes under aseptic conditions. To the medium two types of bacteria, i.e., *E. coli* and *S. viridae*, were inoculated. The biodegradation through these microbes was studied by weight loss and the amount of CO<sub>2</sub> evolved during the incubation periods of 7, 14, 21 and 28 days.

**Swelling behavior of P(HEMA-co-AA) cross-linked polymer**  
Dried hydrogels were immersed in vials (100 ml) filled with distilled deionized water at different pH conditions such as buffer solution of pH 4.0, saline water of pH 6.33, distilled water of pH 7.0, and buffer solution of pH 9.2. The vials were set in a temperature-controlled bath at 25°C. To reach the equilibrium degree of swelling, the copolymers were immersed in the above-mentioned solutions up to a period of 1 month. Each swelling ratio reported in this work is an average of three separate measurements [Table 1]. The swelling behavior of the copolymer was computed by calculating the percentage swelling (%S).

$$\%S = [(M_t - M_0)/M_0] \times 100$$

**Table 1: Percentage swelling of copolymer samples (initial weight = 1 g)**

S. No.	Distilled water (pH = 7)	Saline water (pH = 6.33)	Buffer solution (pH = 4)	Buffer solution (pH = 9.2)
1 h	796	685	456	929
2 h	857	750	592	1135
3 h	1235	935	733	1498
24 h	3250	2405	1848	4162
48 h	5460	3385	2472	6438
1 month	7650	6283	3883	9135

where  $M_t$  is the mass of the swollen sample at time 't' and  $M_0$  is the mass of the dry sample.

### FT-IR spectra studies

FT-IR spectra of the cross-linked polymer along with homopolymers were recorded on a Perkin Elmer Paragon 500 FT-IR spectrophotometer using KBr pellets in the range 400-4000/cm.

### <sup>1</sup>H-NMR studies

The <sup>1</sup>H-NMR of the samples was recorded on a Jeol, GSX 400 at 25°C using DMSO-d<sub>6</sub> as the solvent.

### Scanning electron microscopy studies

The scanning electron microscopy (SEM) of the gold-coated samples before and after biodegradation was obtained using a Jeol Ltd., Japan model 5200 SEM at a magnification of ×5000.

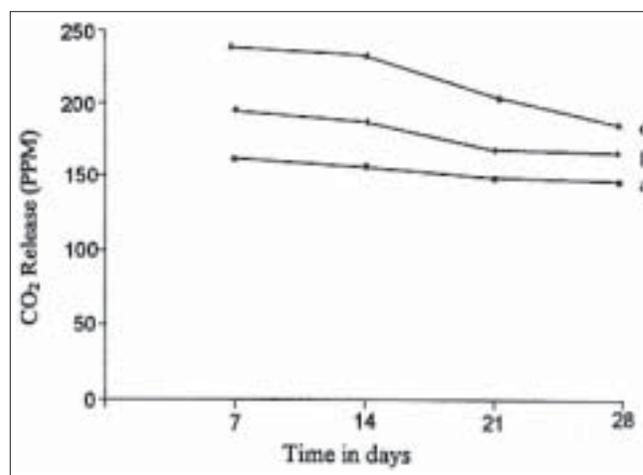
### Thermogravimetric analysis

The thermogravimetric analysis (TGA) data were recorded with a Shimadzu DTG-50 thermal analyzer. The samples were heated from room temperature to 600°C at a heating rate of 10°C/min.

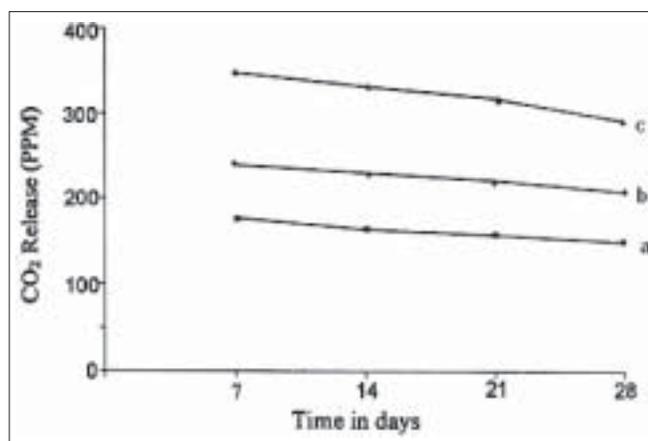
## RESULTS AND DISCUSSION

### Biodegradation studies

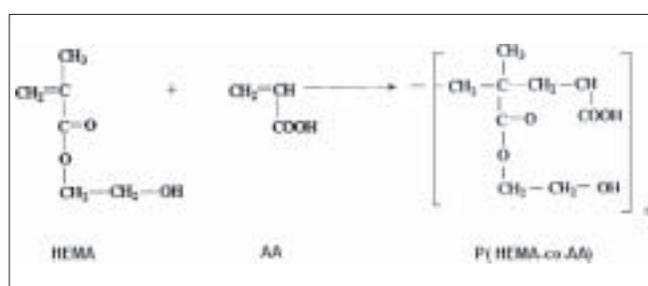
A marked release of CO<sub>2</sub> from the sample was seen in Figures 1 and 2. The trend of release of CO<sub>2</sub> in the first 7 days is more and then after, the rate of release of CO<sub>2</sub> is less. From the two microorganisms, it has been seen that *S. viridae* is more efficient in degrading the polymer than *E. coli*, as the amount of CO<sub>2</sub> release is higher. From Figures 1 and 2, it has been seen that P(HEMA-co-AA) cross-linked polymer is more degraded in both the microorganisms than PAA and P(HEMA).



**Figure 1:** Biodegradation by *E. coli*. (a) P(HEMA), (b) PAA, (c) P(HEMA-co-AA) cross-linked polymer



**Figure 2:** Biodegradation by *S. viridae*. (a) P(HEMA), (b) PAA, (c) P(HEMA-co-AA) cross-linked polymer



**Scheme 1:** Formation of P(HEMA-co-AA) cross-linked polymer

### Quantitative estimation of free CO<sub>2</sub>

The cultured sample ( $X$  ml) and blank solution were titrated against  $\text{Na}_2\text{CO}_3$  ( $N/50$ ) ( $Y$  ml) using phenolphthalein indicator until the pink color persists for at least 30 s. The amount of  $\text{CO}_2$  released was determined using the following calculation.

$$N_1 V_1 (\text{CO}_2) = N_2 V_2 (\text{Na}_2\text{CO}_3)$$

$$N_1 \times X = (1/50) \times Y$$

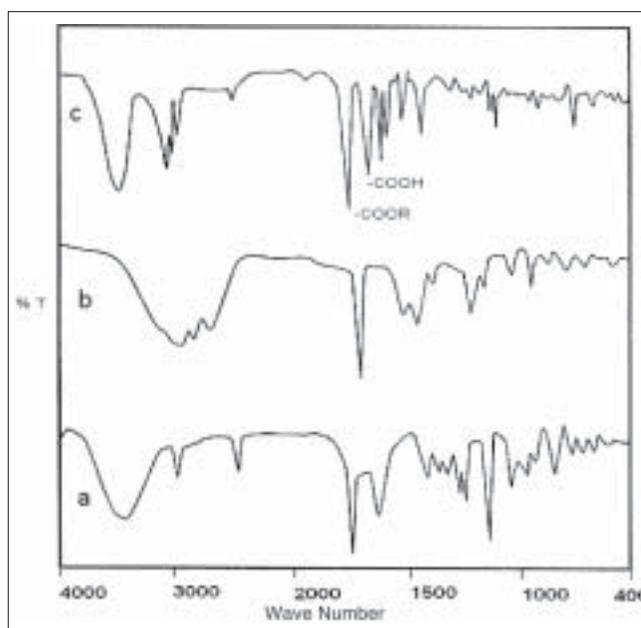
$$\text{Strength} = (Y \times 22)/(50 \times X)$$

$$\text{Free CO}_2 = [(Y \times 22 \times 1000)/(50 \times X)] \text{ mg/l}$$

$$\text{Free CO}_2 = [(440 \times Y)/X] \text{ ppm.}$$

### Swelling behavior

In the presence of an aqueous solution, the polymer chains absorb water and the association, dissociation and binding of various ions to polymer chains cause the hydrogel to swell. Ionic polymer gels are composed of a solid phase and a liquid phase. In the present polymer gel, the solid portion of the gel consists of a cross-linked polymer network with acidic or basic groups bound to the polymer chains. Cross-linking prevents complete mixing of the polymer chains and the solvent provides an elastic restoring force that counters the expansion of the network. Hydrogel is the combination of the chains as shown in Scheme 1. As the prepared polymer is made up of P(HEMA-co-AA), the acidic group bound to their polymer chains from where the  $\text{H}^+$  comes off and combines with  $\text{OH}^-$  to form  $\text{H}_2\text{O}$ . The charge is compensated by cations



**Figure 3:** FTIR spectra of (a) P(HEMA), (b) PAA, (c) P(HEMA-co-AA) cross-linked polymer

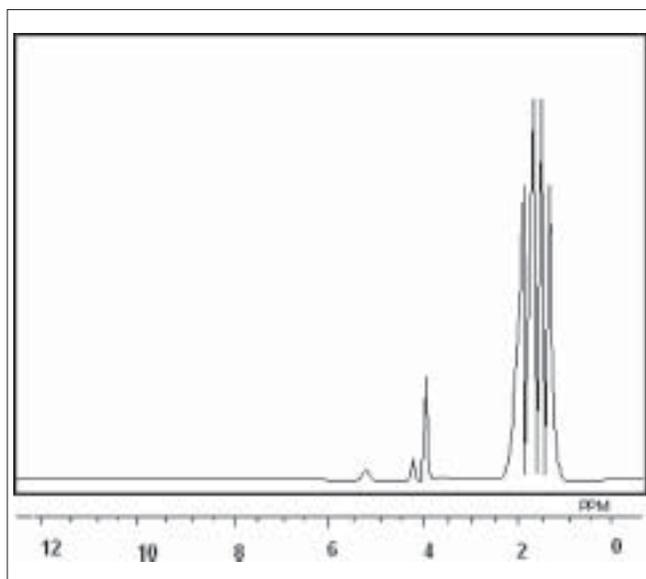
that enter the gel together with another OH, thus charge neutrality is maintained. The increased cation concentration gives rise to an osmotic pressure that causes the gel to swell/deswell. An equilibrium ionic gel occurs when the elastic restoring force of the network balances the osmotic forces. It has been marked that gels swell faster in the presence of buffered solutions. The hydrogels formed by the homogenous copolymer of AA and HEMA with MBA as cross-linker where the acidic group bound to the polymer chains are carboxyl groups, which made the gels pH sensitive. The water intake or the swelling responses of the P(HEMA-co-AA) at intervals are shown in Table 1, in distilled water, saline water ( $\text{NaCl} = 1\%$ , ionic conductivity = 11.2 HmS,  $\text{pH} = 6.01$ ), and buffer solutions of  $\text{pH} 4$  and  $9.2$ . It has been marked that the hydrogel swells more in buffer  $\text{pH} 9.2$ .

### FT-IR spectra studies

The FT-IR spectra of the copolymer along with the homopolymers are shown in Figure 3. The sharp peaks at  $1690/\text{cm}$  in figures correspond to the ester group present in both P(HEMA) and the copolymer P(HEMA-co-AA). The copolymer and the homopolymer P(HEMA) show characteristic broadbands at  $3500/\text{cm}$  for hydroxyl group -OH. Peaks at  $3000/\text{cm}$  are for C-H str. Another sharp peak at  $1720/\text{cm}$  is characteristic for -COOH vibrations, for PAA and the copolymer. Other peaks at  $1500/\text{cm}$  and  $1230/\text{cm}$  are due to C-O-H bonding and C-O asymmetric coupled vibrations, respectively. N-H stretching in between  $3330$  and  $3060/\text{cm}$  and C-N stretching at  $1650/\text{cm}$  indicate the presence of the cross-linker MBA.

### <sup>1</sup>H-NMR studies

The high-resolution <sup>1</sup>H-NMR spectrums of the copolymer are



**Figure 4:**  $^1\text{H-NMR}$  studies of P(HEMA-co-AA) cross-linked polymer

shown in Figure 4. The signals around 1.5-2.25 ppm are due to the  $-\text{CH}_2$  and  $-\text{CH}_3$  protons. There occur signals around 3.5 and 3.9, indicating the  $-\text{OH}$  protons and the protons conjugate to the  $-\text{OH}$  group. The signal near 4.2 is due to the terminal  $-\text{COOH}$  proton from the acrylic acid moiety. A broad peak signal close to 5.0 is due to N-H bond of MBA.

#### Scanning electron microscopy studies

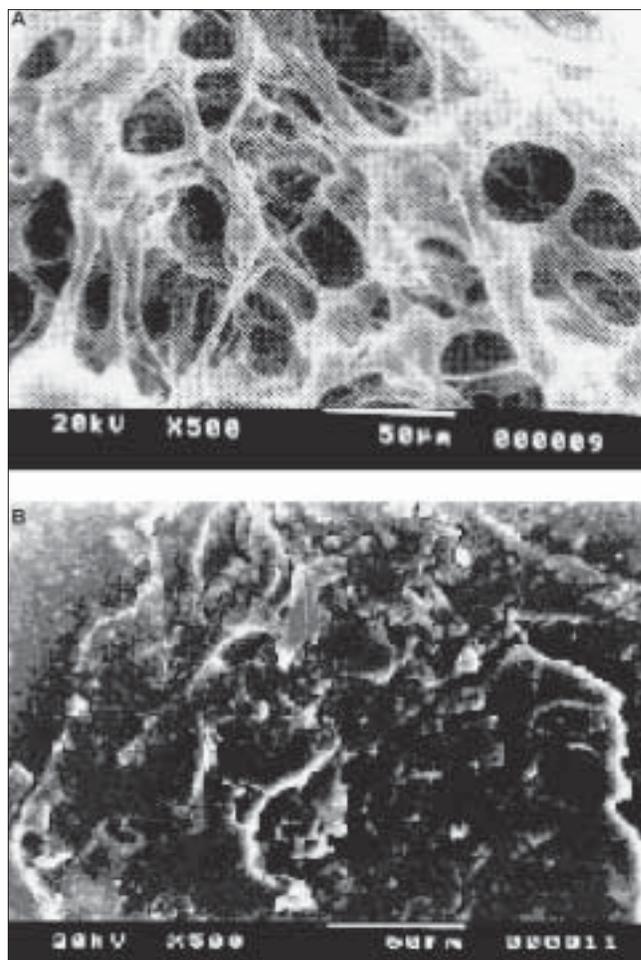
The SEMs of the copolymer samples before and after biodegradation are shown in Figure 5A,B. The surface of the copolymer was found to be smooth with occasional white spots due to probable impurities. The surface of the samples after biodegradation was somewhat uninformed and rugged, suggesting the action of degrading the samples, which were further confirmed by calculating the  $\text{CO}_2$  release from the medium.

#### Thermogravimetric analysis

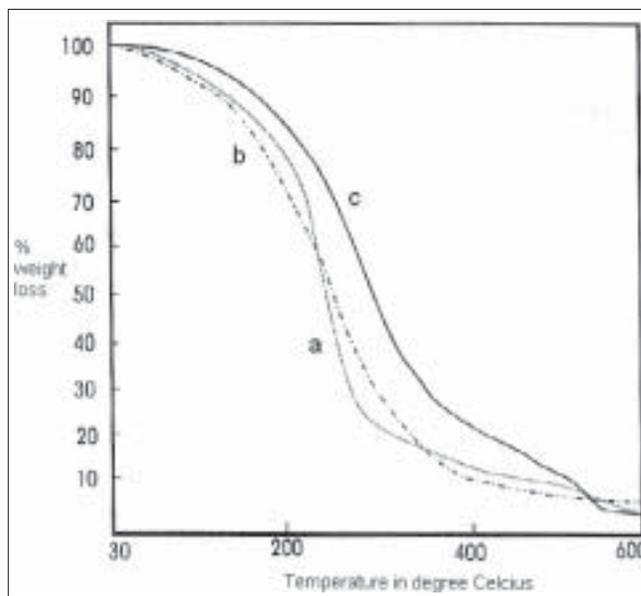
The thermal behavior of P(HEMA), PAA, and P(HEMA-co-AA) were studied at room temperature at  $28 \pm 2^\circ\text{C}$  by comparing their thermogram curves as shown in Figure 6. From the curves, the temperatures of decomposition were found to be  $215^\circ\text{C}$  for P (HEMA),  $170^\circ\text{C}$  for PAA, and  $245^\circ\text{C}$  for P(HEMA-co-AA). The results obtained from TGA graph indicate an increase in thermal stability by copolymerization and cross-linking.

#### CONCLUSION

The prepared cross-linked acrylic-based polymer was found to have high swelling property, biodegradability, and also having comparatively higher thermal stability. Therefore, from these studies, it can be concluded that the prepared polymer system can be used in drug delivery studies in future.



**Figure 5:** (A) Scanning electron microscopy (SEM) of P(HEMA-co-AA) hydrogel before biodegradation. (B) Scanning electron microscopy (SEM) of P(HEMA-co-AA) hydrogel after biodegradation



**Figure 6:** Thermogravimetric analysis (TGA) of (a) P(HEMA), (b) PAA, (c) P(HEMA-co-AA) cross-linked polymer

## ACKNOWLEDGEMENT

Authors acknowledge Mr. Ranjit K. Mohapatra, UDPS, Utkal University for his support throughout the study.

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**Source of Support:** Nil, **Conflict of Interest:** None declared.