# Synthesis of Nonionic and Anionic Hydrogels Bearing a Monosaccharide Residue and Their Properties

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SYNOPSIS

Nonionic hydrogels bearing glucoside residues were synthesized by free-radical copolymerization of glucosylethyl methacrylate (GEMA) and *N,N'*-methylenebisacrylamide (BisA) at 0°C for 2 h using ammonium peroxodisulfate and *N,N,N',N'*-tetramethylethylenediamine as the initiator. The cross-linked polymer gel was obtained quantitatively. The nonionic gels absorbed 30 times as much water as their own weight. Copolymerization of GEMA, sodium acrylate, and BisA gave anionic hydrogels, which absorbed ca. 100 times as much water as their own weight at pH 6.5. The swelling behavior of the nonionic and the anionic hydrogels bearing glucose residues was studied in detail. © 1994 John Wiley & Sons, Inc.

## INTRODUCTION

Water-soluble vinyl monomers can produce hydrogels by free-radical copolymerization with suitable divinyl compounds as a cross-linking agent. In a previous article,[1] we reported that the copolymers of *N*-vinylacetamide (NVA) and bis-NVAs are novel nonionic hydrogels that absorb more than 35 times as much water as their own weight. The nonionic hydrogels were easily converted to cationic hydrogels by the partial acid hydrolysis of acyl groups in the side chains, which exhibited a high swelling behavior like that of superabsorbent hydrogels. Since hydrogels are particularly important as a biomaterial, especially when they show a high degree of biocompatibility, development of new hydrogels is of interest for, e.g., drug delivery system (DDS) devices and soft contact lenses.

Recently, vinyl monomers bearing monosaccharide residues such as glucoside, e.g., glucosylethyl methacrylate (GEMA) and galactoside, were synthesized by Kitazawa et al.,[2] and the application for their use as a DDS device has been investigated.[3] It is known that the saccharide chain is one of the important constitutions of living tissue and plays an important role in the cell-recognition process. Therefore, many biomaterials bearing the saccharide chain have been prepared with a molecular design[4-6] and their biocompatibilities have been investigated. Vinyl monomers bearing a monosaccharide residue may be one of the important starting materials for biomaterials, because they have high radical homo- and copolymerizability.[7] Moreover, as they possess high water solubility, they are expected to afford biocompatible hydrogels.

In this article, we report the synthesis of nonionic and anionic hydrogels bearing a glucosyl residue by homo- and copolymerization of GEMA using *N,N'*-methylenebisacrylamide (BisA) as a cross-linking agent, and their swelling properties were also investigated.

## EXPERIMENTAL

### Materials

GEMA was provided by Nippon Fine Chemical Co. Electrophoresis-grade BisA and reagent-grade ammonium peroxodisulfate (APS), *N,N,N',N'*,-tetramethylethylenediamine (TEMED) (Nacalai Tesque

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Co.), sodium acrylate (SA) (Wako Pure Chemical Industries), and arlacel A (mannide monooleate, Sigma) were used without further purification. Water was distilled prior to use.

### Preparation of Hydrogels

A typical procedure was as follows: A mixture of 1.168 g of GEMA (2.159 g of a 54.1% aqueous solution), 0.77 mg of BisA (0.077 mL of a 10 mg/mL solution), 9.13 mg of APS (0.913 mL of a 10 mg/mL solution), and 2.11 mL of distilled water were placed in a test tube at 0°C. After 4.65 mg of TEMED (0.046 mL of 100 mg/mL of aqueous solution) was added, the reaction mixture was allowed to stand at 0°C for 2 h. The resulting hydrogel, poly(GEMA-*co*-BisA) hydrogel, was immersed for 2 days in a large amount of distilled water in order to remove initiator residues and the unreacted monomer in polymer networks and then lyophilized to store.

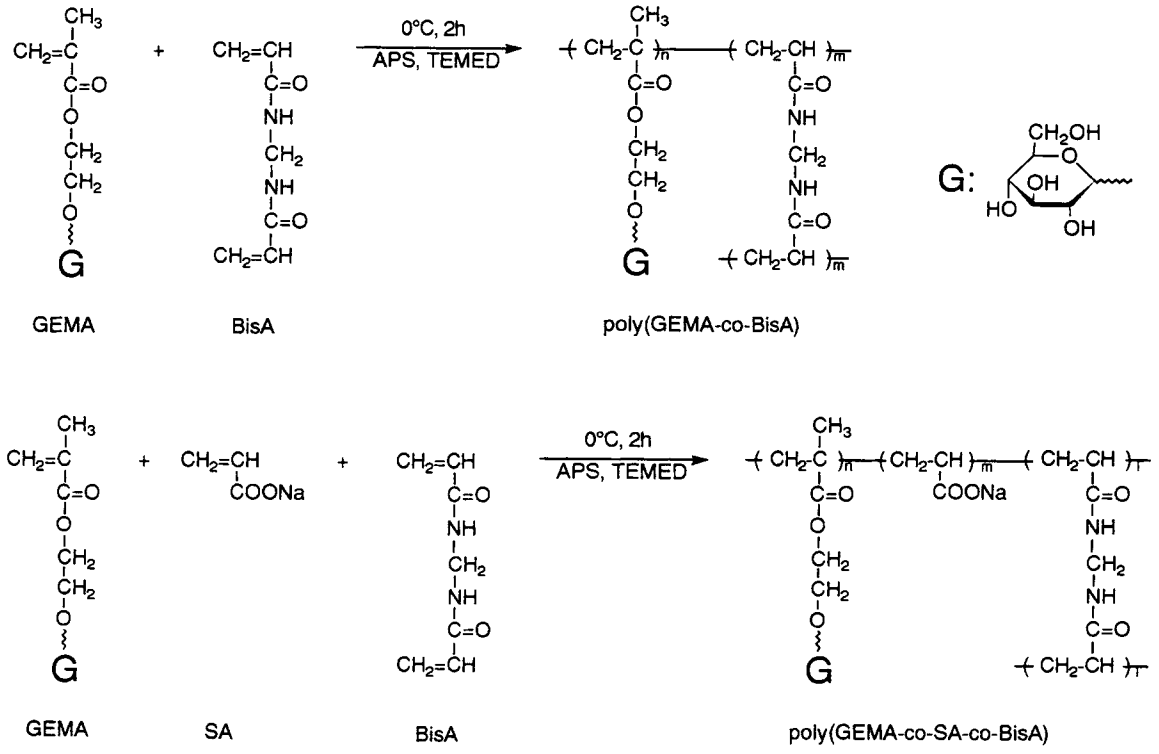
### Measurements

A Hitachi H-7010 A scanning electron microscope was used to observe the morphology of the gels. Gel permeation chromatographic (GPC) analysis was performed on a Shimadzu LC-6A equipped with RI detector (Shodex SE-51) with a Shodex column (AC-8034, 8 × 500 mm). Poly(ethylene glycol) was used as the standard for $M_n$ calibration.

## RESULTS AND DISCUSSION

### Synthesis of the Hydrogels

Scheme I represents the synthesis of the hydrogels bearing glucose residue by free-radical copolymerization using a redox initiator. GEMA is soluble in water, similar to glucose, and the methacryloylhydroxyethyl group of GEMA is expected to possess high radical polymerizability in analogy with other methacryloylhydroxyethyl-type monomers.[8] As mentioned in the previous paper,[1] the copolymerizability of the cross-linking agent is important for the structure of the resulting GEMA gel. For example, the Alfrey–Price's $e$ and $Q$ values for the methacryloyloxyethyl derivative of theophylline were obtained as 1.35 and 2.40, respectively,[8] which suggests that methacryloyl monomers are conjugated monomers, as expected. Consequently, gelation of GEMA using the conjugated cross-linking agent, i.e., BisA, in the presence of redox initiators




**Scheme 1**

can be performed similarly to that of acrylamide with BisA. Moreover, when anionic hydrogels are synthesized, SA can be chosen as a suitable comonomer because of its copolymerizability.

Table I shows the results of copolymerization of GEMA and BisA or of GEMA, SA, and BisA. Copolymerization was carried out in the presence of APS with TEMED as the redox initiator in an aqueous solution at 0°C for 2 h. When TEMED was added to the reaction mixture, gelation occurred very rapidly, similarly to that of acrylamide with BisA. After standing for 2 h, the cross-linked polymers, poly(GEMA-*co*-BisA) and poly(GEMA-*co*-SA-*co*-BisA), were washed with water and then were freeze-dried. All hydrogels were transparent specimens. Even when a small amount of BisA was used, hydrogels were obtained. When BisA was not used (Run 1), the resulting polyGEMA was not completely soluble in water after being freeze-dried, probably because of the extremely high $M_n$ of the polyGEMA. If water-soluble polyGEMA is desired, the following procedure is recommended: A mixture of GEMA (3.702 mmol) and APS (0.037 mmol) in water (9.74 mL) was poured into a three-necked flask and stirred under a $N_2$ atmosphere at 55°C for 5 h. The reaction mixture was precipitated with acetone and dried *in vacuo*. The resulting polymer was soluble in water, water-soluble polymer, *N,N'*-dimethylformamide, and dimethyl sulfoxide with ease and showed $1.8 \times 10^5$ in the number-average molecular weight by GPC analysis using polyethylene glycol as a standard.

Generally, suspension polymerization, involving the use of monomer droplets in water, is easily carried out with a initiator soluble in the monomer in order to prepare polymer beads, when vinyl monomers are not soluble in aqueous media. In the present study, since GEMA is well soluble in water and entirely insoluble in some organic solvents such as benzene, the inverse suspension polymerization system was applied for preparing hydrogel beads similarly as for the polymerization of *N*-vinylacetamide.[1] To the hydrophobic phase containing 200 mL of benzene and 2 mL of arlacel A (mannide monooleate) in a 300 mL three-necked flask that was replaced with $N_2$ for 30 min, a mixture of GEMA, BisA, APS, and TEMED in water, which amounts were the same as for Run 7, was added. After sonication for 1 min, the reaction mixture was stirred at 0°C for 1 h under $N_2$ atmosphere. As shown in Figure 1, the resulting hydrogels were spherical beads with 15–25 $\mu$m in diameter. This may suggest that the poly(GEMA-*co*-BisA) hydrogel beads are an applicable support for immobilization of biopolymers such as enzyme, DNAs, and antibody.

## Swelling Properties

The swelling properties of nonionic and anionic hydrogels bearing glucose residue were studied. Cubical freeze-dried gels ($1 \times 1 \times 1$ cm; ca. 0.6 g) were used in the course of this study. The degree of swelling of the gel was calculated by use of the equation $(W - W_0)/W_0$, where $W$ is the weight of swollen hy-

**Table I Preparation of Hydrogels by Copolymerization of GEMA and SA with BisA as the Cross-linking Agent at 0°C for 2 h[a]**

| | Monomer (mmol) | | | | | |
|---|---|---|---|---|---|---|
| Run | GEMA | SA | BisA ($\times 10^2$) | Percent of Cross-linker | Solvent ($H_2O$) (mL) | Yield[b] (%) |
| 1 | 4.00 | | 0 | 0 | 3.14 | 92 |
| 2 | 4.00 | | 0.3 | 0.08 | 3.64 | 96 |
| 3 | 4.00 | | 0.5 | 0.13 | 3.64 | 97 |
| 4 | 3.98 | | 2.0 | 0.50 | 3.64 | 95 |
| 5 | 3.96 | | 4.0 | 1.00 | 3.64 | 97 |
| 6 | 3.92 | | 8.0 | 2.00 | 3.64 | 99 |
| 7 | 4.00 | | 0.3 | 0.08 | 4.14 | 94 |
| 8 | 3.92 | 0.080 | 0.3 | 0.08 | 4.14 | 96 |
| 9 | 3.84 | 0.160 | 0.3 | 0.08 | 4.14 | 98 |
| 10 | 3.60 | 0.400 | 0.3 | 0.08 | 4.14 | 95 |
| 11 | 3.20 | 0.800 | 0.3 | 0.08 | 4.14 | 96 |

[a] [Total monomer]/[initiator] = 100; initiators: APS and TEMED.
[b] Calculated by the weight of the dried gel.

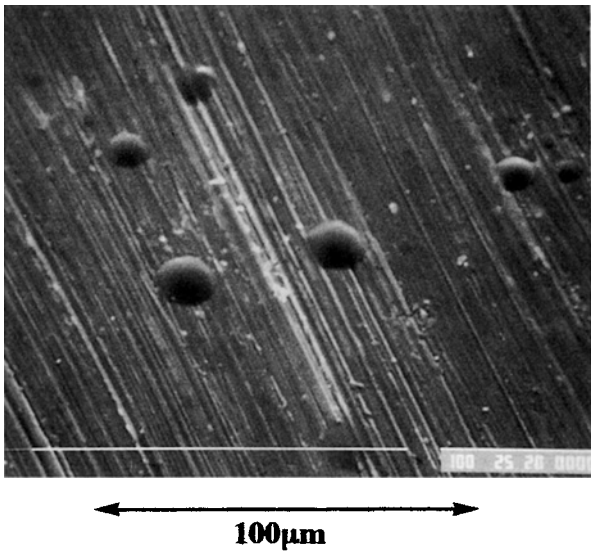



**Figure 1** Scanning electron micrograph of poly(GEMA-*co*-BisA) particles prepared by the inverse suspension polymerization system.

drogel and $W_0$ is that of the dried gel. The swollen hydrogel was weighed after wiping with filter paper.

Figures 2 and 3 show the degree of swelling ratios of poly(GEMA-*co*-BisA) hydrogels and poly (GEMA-*co*-SA-*co*-BisA) with various degrees of cross-linking as a function of time. As shown in Figures 2 and 3, those are strongly dependent on the structure of hydrogels. After 4 days, the degree of swelling ratios of by poly(GEMA-*co*-BisA) hydrogels reached equilibrium in most cases, and the hydrogel (Run 7 in Table I) obtained using a considerably large amount of water and a small amount of

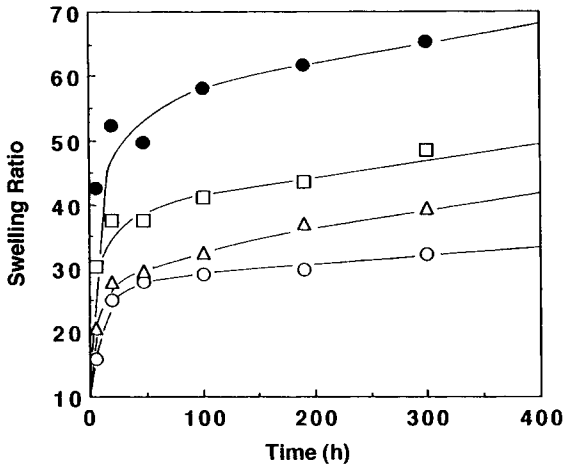



**Figure 3** Swelling behavior of poly(GEMA-*co*-SA-*co*-BisA) in distilled water at 25°C: (○) Run 8, (△) Run 9, (□) Run 10, and (●) Run 11 in Table I.

cross-linking agent was swollen in water 30 times its own weight. It is, therefore, thought that when the amount of the cross-linking agent increased or that of the solvent decreased, the gel swelling ratio decreased. In the case of poly(GEMA-*co*-SA-*co*-BisA), when the same amount of cross-linking agent was used and the amount of SA increased, the gel swelling ratio of the gels in distilled water increased (Fig. 3). This tendency is almost the same as that of other superabsorbent hydrogels prepared by the copolymerization of water-soluble monomers with SA.[9,10]

Figure 4 shows the relationship between pH and the swelling ratio of hydrogels prepared. The pH was adjusted with 0.1*N* HCl and 0.1*N* NaOH.

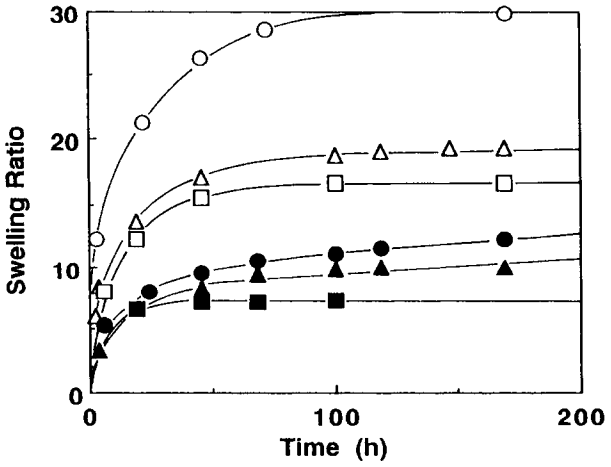



**Figure 2** Swelling behavior of poly(GEMA-*co*-BisA) in distilled water at 25°C: (○) Run 7, (△) Run 2, (□) Run 3, (●) Run 4, (▲) Run 5, and (■) Run 6 in Table I.

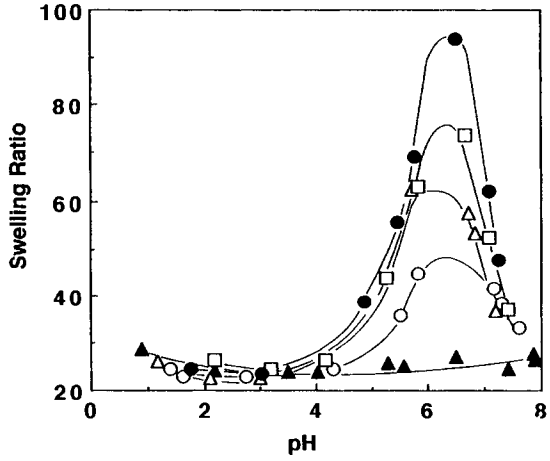



**Figure 4** pH dependence of gel swelling ratio at 25°C: (○) Run 8, (△) Run 9, (□) Run 10, (●) Run 11, and (▲) Run 7 in Table I.

**Table II Relative Swelling Ratio of Hydrogels in Hydrochloric Acid, NaOH, and NaCl Aqueous Solution at 25°C**

| Solution (pH) | Poly(GEMA-*co*-BisA)[a] | Poly(GEMA-*co*-SA-*co*-BisA)[b] |
|---|---|---|
| $H_2O$[c] (5.8) | 1.00 | 1.00 |
| 0.01*M* HCl (2.2) | 1.08 | 0.40 |
| 0.10*M* HCl (1.2) | 1.15 | 0.49 |
| 1.0*M* HCl (0.1) | 1.45 | 0.66 |
| 0.01*M* NaOH (11.8) | 1.11 | 0.59 |
| 0.10*M* NaOH (12.9) | 1.19 | 0.51 |
| 1.0*M* NaOH (13.5) | 1.63 | 0.74 |
| 0.01*M* NaCl (6.6) | 1.01 | 0.42 |
| 0.10*M* NaCl (6.4) | 1.04 | 0.42 |
| 1.0*M* NaCl (6.4) | 1.04 | 0.43 |

[a] Run 7 in Table I.
[b] Run 8 in Table I.
[c] Distilled water was used.

The swelling ratios of the nonionic hydrogel Poly(GEMA-*co*-BisA) were hardly influenced by pH. On the other hand, in the case of anionic hydrogel, the swelling ratio was considerably affected by pH and it has a maximum value at pH 6.5. Because the p$K_a$ value of poly(acrylic acid) is about 4.7, the carboxyl group of the hydrogels is not ionized at lower pH than 4.7. The maxima in the swelling curves along pH are similar to those of anionic polyacrylamide–acrylic acid copolymer[10] or poly(vinyl acetamide)–vinylamine copolymer[11] hydrogels.

Table II shows relative swelling ratio of hydrogels in hydrochloric acid, NaOH, and NaCl aqueous solution at 25°C. Anionic hydrogel poly(GEMA-*co*-SA-*co*-BisA) showed lower swelling properties in hydrochloric acid, NaOH, and NaCl aqueous solution than in distilled water. On the other hand, the nonionic poly(GEMA-*co*-BisA) hydrogel can swell in these solutions, especially even in high concentrated hydrochloric acid or NaOH solution, as well as in water, as expected. It is well known that the reduction in swelling at lower pHs or in the presence of high concentrated ions is due to the decrease in ionization of the network.[12,13] Moreover, it may be assumed that some of the amide group of the crosslinking agent are hydrolyzed to loosen the gel network, and then the gel expands to swell in the solution.

In conclusion, GEMA is a suitable starting material for preparing hydrogels bearing a monosaccharide residue. As copolymerizability of GEMA is similar to other methacryloyl monomers,[7] it is possible to design and prepare cross-linked copolymers with various vinyl monomers to give various novel gels bearing glucose residue. Functionalities and applications of polyGEMA hydrogels will be reported in a further study.

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