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Synthesis of Poly(Sorbitan Methacrylate) Hydrogel by Free-Radical Polymerization

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Abstract

Hydrogels are materials with the ability to swell in water through the retention of significant fractions of water within their structures. Owing to their relatively high degree of biocompatibility, hydrogels have been utilized in a host of biomedical applications. In an attempt to determine the optimum conditions for hydrogel synthesis by the free-radical polymerization of sorbitan methacrylate (SMA), the hydrogel used in this study was well polymerized under the following conditions: 50% (w/v) SMA as monomer, 1% (w/w) α, α′-azo-*bis*(isobutyro-nitrile) as thermal initiator, and 1% (w/w) ethylene glycol dimethacrylate as cross-liking agent. Under these conditions, the moisture content of the polymerized SMA hydrogel was higher than in the other conditions. Moreover, the moisture content of the poly(SMA) hydrogel was also found to be higher than that of the poly(methyl methacrylate [MMA]) hydrogel. When the Fourier transform–infrared spectrum of poly(SMA) hydrogel was compared with that of poly(MMA) hydrogel, we noted a band at 1735–1730/cm, which did not appear in the Fourier transform–infrared spectrum of poly(MMA). The surface of the poly(SMA) hydrogel was visualized through scanning electron microscopy, and was uniform and clear in appearance.

Index Entries: Free radical hydrogel; moisture content; polymerization; sorbitan methacrylate.

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Introduction

Biomaterials can be made up of metals, ceramics, biocompatible polymers, and their composites. Biocompatible polymers diverge regarding modulus from flexible elastomers to strong fibers, and can be readily processed into a variety of shapes. Hydrogels constitute one of the more promising classes of biomaterials. Hydrogels are hydrophilic polymeric networks, which have been shown to absorb significant quantities of water, in a range of 10% up to thousands of times their dry weight *(1–4)*. Recently, a host of studies have reported on the myriad possible applications of sugar-containing polymeric materials, which can be synthesized from sugar esters. Sugars are a relatively attractive group of multifunctional compounds, owing to the fact that they are both biologically relevant, and contain multiple hydroxyl groups. Sugar esters, which contain sugar molecules, have become the focus of increased interest of late, and have already been utilized in a variety of applications in the medical and industrial fields *(3–6)*. Sugars can also harbor functional glycosylation groups, which serve multifarious functions, evidencing different biological activity, surface activity, optical activity, optical separation activity, stereostructure, biodegradability, biocompatibility, and biostability, depending on the type of functional group harbored and the stereo-structural bonding methods utilized *(1,7)*.

The term "hydrogel" refers to a class of materials with the ability to swell in water, and to retain a significant fraction of that water within their structures. The classic hydrogel is a colloid gel consisting of water molecules held together by crosslinked molecular chains. The characteristic water absorption capabilities of hydrogels are dependent on the presence of hydrophilic groups within the substrate. Hydrogels have been used extensively in a host of biomedical applications, including wound dressings, artificial organs, and delivery carriers for bioactive agents, largely because of their considerable biocompatibility *(1,3,8,9)*. High moisture content and low interfacial tension with the surrounding biological environment are the two most salient factors regarding hydrogel biocompatibility *(10,11)*.

The moisture content of hydrophilic materials has important properties, and bears a great deal of importance in regard to other characteristics of the materials. In order to overcome the problems inherent to inadequate moisture content, acryl groups can be glycosylated using glycosyl materials, the molecules of which harbor a wealth of hydroxyl groups. Then, according to the regioselective synthesis method used and the degree of substitution, the glycosylated materials can be constructed for enhanced moisture contents *(12,13)*.

The development of acryl monomers such as poly(MMA), which have fairly simple structures with a small number of carbons, and exhibit polymerizational vinyl radical sharing among the hydroxyl and carboxyl groups, was followed rapidly by the development of a wide

variety of novel hydrogel polymers. This pursuit for new compounds was driven by competition for a favorable position within this new emerging market *(1,3)*.

The hydrogel synthesis of several glycosylated esters had reported *(2,14–16)*. The poly(MGAA) and poly(MGMAA) that seeded to applicable for wound dressing agent was well conformed by free-radical polymerization with α, α′-azo-*bis*(isobutyro-nitrile) (AIBN) *(2)*. Magnani et al. *(14)* reported polysaccharide hydrogels, which were made with polysaccharide components of hyaluronane, alginate, and carboxymethyl-cellulose. Sucrose-based hydrogels were found to be nontoxic, highly water absorbable, and eventually had applications for medical applications *(15)*. Draye et al. *(16)* reported the dextran dialdehyde crosslinked hydrogels for wound dressing agents. However, the hydrogel synthesis of poly(sorbitan methacrylate [SMA]) and its property have not previously reported.

Polymerization is the process by which monomer molecules are induced to react chemically, resulting in the formation of either linear chains or a three-dimensional network of polymer chains. There are many forms of polymerization, and different systems have been formulated for their categorization. The primary categories of polymerization are chain-growth reaction and step-growth reaction *(15)*.

The principal objective of this study was to determine the optimum conditions for the polymerization of SMA, which is glycosylated with sorbitan and vinyl methacrylate, and to compare the moisture content with poly(SMA) and poly(MMA). We conducted experiments in which the monomer, thermal initiator, and crosslinking agent were tested at a variety of concentrations for optimization of polymerization. The polymerized hydrogels were then assessed specifically regarding moisture content, which is one of the primary criteria relevant to the flexibility and biocompatibility of a constructed hydrogel.

Materials and Methods

Chemicals

Novozym 435 (Lipase B from *Candida antarctica,* EC 3.1.1.3, a nonspecific lipase immobilized on a macroporous acrylic resin, 1–2% moisture content, 10,000 Propyl Laurate Units/g) was purchased from Novo Nordisk A/S (Bagsvaerd, Denmark). The D-sorbitol and *t*-butanol used in this study was obtained from the Sigma-Aldrich Chemical Co. (St. Louis, MO). The *p*-toluenesulfonic acid (*p*-TSA) and MMA were purchased from Yakuri Pure Chemicals (Osaka, Japan). The vinyl methacrylate was purchased from Tokyo Kasei Kogyo Co. (Tokyo, Japan). AIBN, used as a thermal initiator in this study, was provided by Junsei Chemicals (Japan), and the ethylene glycol dimethacrylate (EGDMA) used in this study was from the Sigma-Aldrich Chemical Co. All other chemicals used were of analytical

grade, and the solvent was dried using molecular sieves (Yakuri Pure Chemicals Co.) for 1 d before use.

1,4-Sorbitan Preparation and Enzymatic Esterification

All dehydration reactions (sorbitol cyclization) for the synthesis of 1,4-sorbitan using *p*-TSA in a solvent-free process were conducted as was previously described *(4)*. The dehydration reactions were carried out for 2 h at 130 ± 1°C, under reduced pressure (200 mmHg). The reactor volume was 50 mL. The reaction temperature was controlled with an oil bath, equipped with a proportional and integral differential (PID) temperature controller. Agitation was conducted with a magnetic bar, spinning at approx 200 rpm.

We conducted esterification through alcoholysis. Esterification for the synthesis of 1,4-sorbitan esters with immobilized lipase was conducted as described in a previous report *(4)*. The reactions were initiated through the addition of 7.5% (w/v) of Novozym 435 and 0.05% (w/v) of hydroquinone, with an initial 1,4-sorbitan concentration of 50.0 g/L. The reaction of 1,4-sorbitan to vinyl methacrylate (at a molar ratio of 1 : 4) resulted in 170 min of synthesis at 45 ± 1°C. The reaction temperature was controlled using a water bath equipped with a PID temperature controller. Mixing was conducted using a magnetic stirrer, spinning at approx 200 rpm. The condenser prevented the evaporation of the reactant (*t*-butanol).

Purification of SMA

After esterification, the mixture was filtered to remove enzymes, and dried under reduced pressure at 40°C. An equivalent volume of *n*-hexane was added to the reaction mixture. The mixture was then vigorously stirred for 2 h, and the upper phase was recovered and then vaporized at 40°C under reduced pressure. In order to separate the SMA and other compounds from the reaction mixtures, open column chromatography (PYREX®, 25×250 mm^2) was conducted, using silica gel (Merck 7734, 70–230 mesh, 300.0 g) and an autofraction collector, at 180-s time intervals. A chloroform : hexane (2.5 : 1 [v/v]) mixture was used as the mobile phase. The flow rate was 10 mL/min, and 20 mL volume of the sample was loaded into the chromatograph.

Synthesis of Hydrogel by Free-Radical Polymerization

The synthesized and purified monomers, SMA and MMA, were then utilized in the free-radical polymerization process. The monomers were dissolved in chloroform. The initial volume of monomer solution was 5 mL. The thermal initiator (AIBN) and crosslinking agents (EGDMA) were added on the basis of the total monomer concentration. Free-radical polymerizations were conducted with five concentrations of monomer (10, 25, 50, 75, and 90% [w/v], respectively), 0.5–5% (w/w) of thermal initiator and 0.5–5% (w/w) of crosslinking agent, as was described in Table 1. Polymerization was allowed to proceed for 2 h at 70°C, without agitation.

Table 1
Experimental Conditions of Free-Radical Polymerization

Experimental variables	Experimental conditions		
	Monomer (% [w/v])	Thermal initiator (% [w/v])	Crosslinking agent (% [w/v])
Monomer concentration	10, 25, 50, 75, 90	1	1
Thermal initiator concentration	50	0.5–5	1
Crosslinking agent concentration	50	1	0.5–5

Purification of Poly(SMA) and Poly(MMA)

In order to remove the initiator, unreacted monomer and impurities potentially present in the synthesized hydrogels, the poly(SMA) and poly(MMA) were purified as described below. At the end of the polymerization, the synthesized poly(SMA) and poly(MMA) hydrogels were immersed in 10 vol of ethanol (ethanol : reactant [v/v]) for 24 h, and subsequently treated with distilled water for an additional 24 h. Three treatments with ethanol and distilled water were applied. Then, the synthesized hydrogels were immersed in 10 vol of acetone for 24 h. Finally, after acetone removal, the hydrogels were washed with water, dried, and stored in a desiccator.

Structural Analysis of Poly (SMA) by FT–IR and SEM

The poly(SMA) was structurally analyzed through Fourier transform–infrared (FT–IR) (Nicolet 520P, Nicolet). The FT–IR sample of polymerized SMA was used in powder form. The surface of the poly(SMA) synthesized under optimal conditions was then visualized through scanning electron microscopy (SEM; JSM-5400, JEOL).

Moisture Content Measurement of Poly(SMA) and Poly(MMA) Hydrogels

Dried poly(SMA) and poly(MMA) hydrogels were cut to a diameter of 10 mm and a thickness of 5 mm, then immersed for 48 h in distilled water at room temperature. After removing the water from the surface of the hydrogels using filter paper, the hydrogels were then weighed. After weighing, the hydrated hydrogels were dried for 48 h at 40°C, and then measured. The moisture contents of the hydrogels were calculated through the following formula:

$$\text{Moisture content } (\%) = \frac{Ws - W_0}{Ws} \times 100$$

where W_s is the weight of the swollen hydrogel (g) and W_0 is the weight of the dried hydrogel (g).

Results and Discussion

In the free-radical polymerization process used in the synthesis of poly(SMA) from SMA, several factors have been shown to affect both the polymerization and moisture content, including the reaction solvent, reaction temperature, monomer, thermal initiator, crosslinking agent, and so on *(1,14)*. The initial step of this study involved the identification of factors likely to affect polymerization. In order to achieve this objective, we assessed the screening of several factors for the free-radical polymerization experiments, testing the monomer, thermal initiator, and crosslinking agent at different concentrations.

Effect of Different Monomer Concentrations

Free-radical polymerizations were conducted with three different monomer concentrations (10, 25, 50, 75, and 90% [w/v], respectively of reaction solution), in order to characterize the effects inherent to monomer concentration. Figures 1 and 2 show the results regarding polymerization degree and moisture content. In Fig. 1, sample A, which had a lower monomer concentration (10% [w/v]) than the other samples, exhibited a lower degree of polymerization when compared with the others. Sample E, which contained an abundant quantity of SMA as a monomer, evidenced a higher degree of polymerization than did the other samples. Sample C exhibited a suitable degree of polymerization, with no decrease in total volume. The experiments in which MMA was used as a monomer exhibited similar tendencies to those in which SMA was used as a monomer. Sample F, with a lower concentration of MMA than the other samples, exhibited a lower degree of polymerization when compared with the others; and sample J, with an abundant amount of monomer, scored higher than the other samples. The moisture contents of the polymerized hydrogels are compared in Fig. 2. The moisture content of the polymerized hydrogels was altered by the residual water contained in the hydrogels. The moisture content of the hydrogels polymerized with SMA was found to be higher than in those polymerized with MMA. Also, the moisture contents of hydrogels containing 75% or higher concentrations of monomer were lower than in the other samples. The samples polymerized with 25 and 50% of monomer evidenced similar moisture contents, of approx 37%.

Effect of Different Thermal Initiator Concentrations

In order to evaluate the effects of different concentrations of thermal initiator on polymerization, 0.5, 1, 2, 3, and 5% (w/w) of thermal initiator (AIBN), relative to total monomer concentration (50% [w/v]) was added to the monomer solution, and subsequently polymerized for 2 h at 70°C,

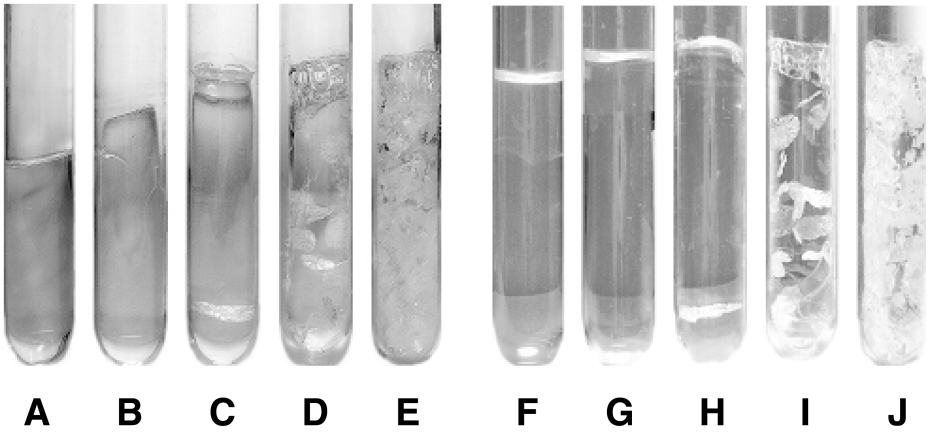

Fig. 1. Photographs of polymerization with different monomer concentrations. Monomers: SMA and MMA; **(A)** SMA 10% (w/v), **(B)** SMA 25% (w/v), **(C)** SMA 50% (w/v), **(D)** SMA 75% (w/v), **(E)** SM A 90% (w/v), **(F)** MMA 10% (w/v), **(G)** MMA 25% (w/v), **(H)** MMA 50% (w/v), **(I)** MMA 75% (w/v), and **(J)** MMA 90% (w/v).

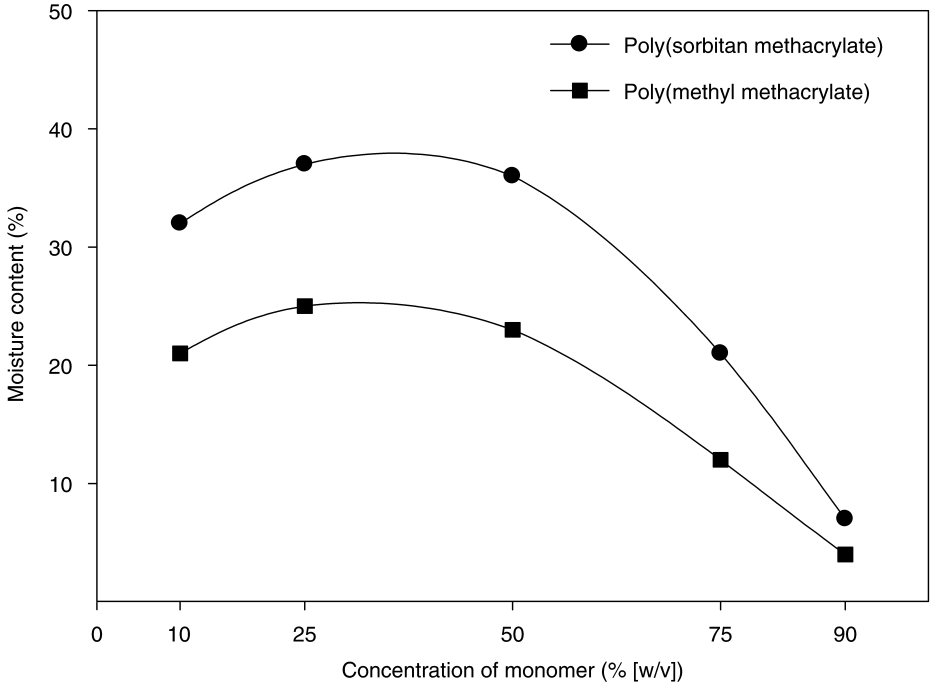

Fig. 2. Moisture contents of hydrogel polymerized with concentration changes of monomer.

without agitation. The results of polymerization are shown in Figs. 3 and 4. In Fig. 3, sample A, with lower thermal initiator concentration (0.5% [w/w]) than was seen in the other samples, exhibited a lower degree of polymerization when compared with the others. A greater degree of polymerization

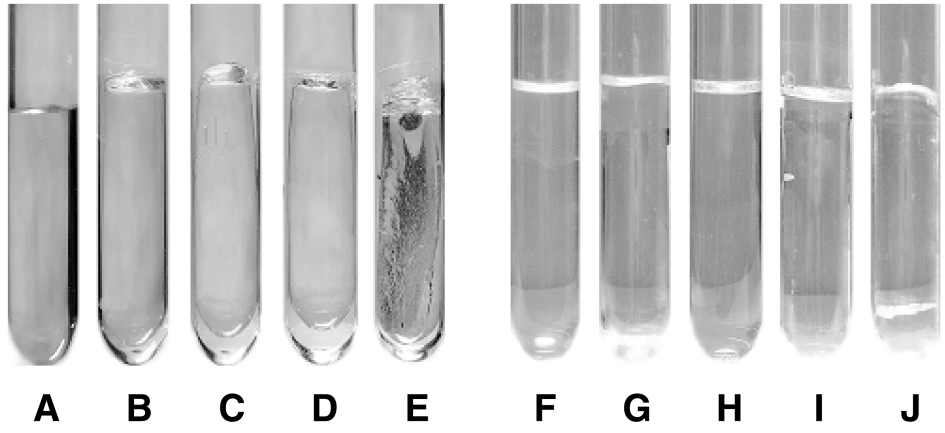

Fig. 3. Photographs of polymerization with different thermal initiator concentrations. Monomers: SMA **(A–E)** and MMA **(F–J)**; thermal initiator (AIBN) concentration, **(A)** 0.5% (w/w), **(B)** 1% (w/w), **(C)** 2% (w/w), **(D)** 3% (w/w), **(E)** 5% (w/w), **(F)** 0.5% (w/w), **(G)** 1% (w/w), **(H)** 2% (w/w), **(I)** 3% (w/w), and **(J)** 5% (w/w).

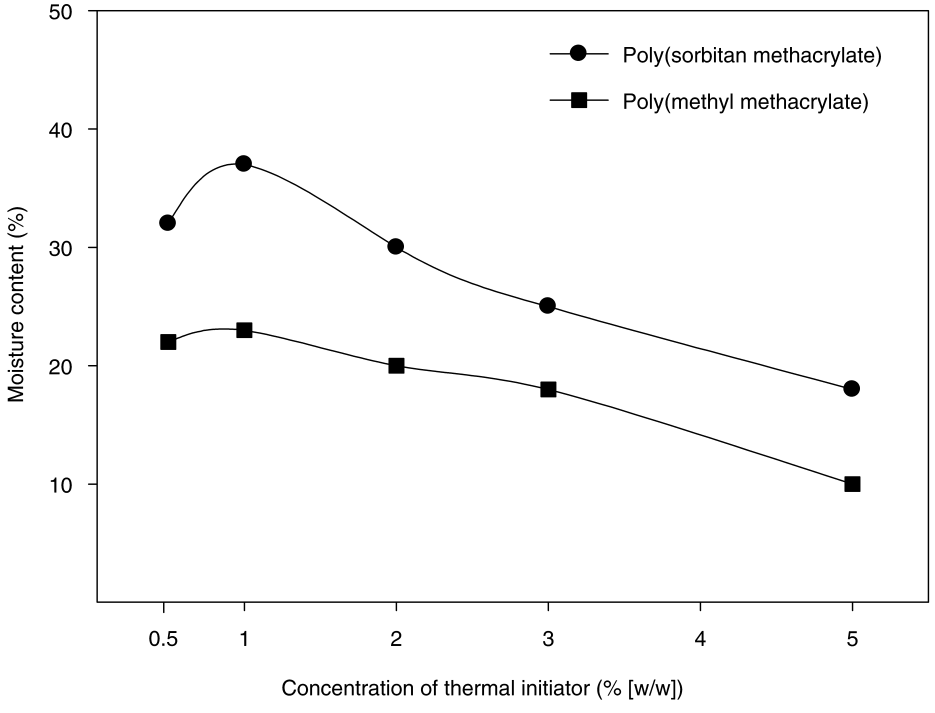

Fig. 4. Moisture contents of hydrogel polymerized with different thermal initiator concentrations.

was detected in sample E than in the other samples. Sample F, which contained less AIBN than the other samples, evidenced a degree of polymerization similar to the other samples. Polymerization degree, then, was not particularly influenced by the concentration of added AIBN, but when the

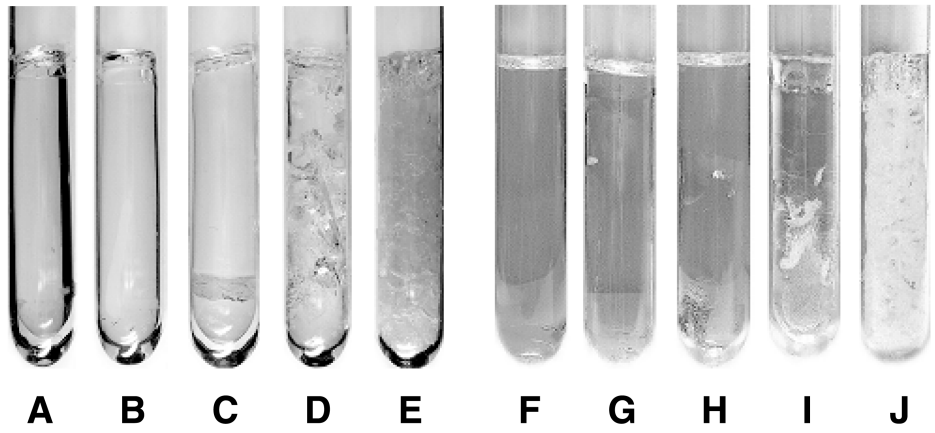

Fig. 5. Photographs of polymerization with different crosslinking agent concentrations. Monomers: SMA **(A–E)** and MMA **(F–J)**; crosslinking agent (EGDMA) concentration, **(A)** 0.5% (w/w), **(B)** 1% (w/w), **(C)** 2% (w/w), **(D)** 3% (w/w), **(E)** 5% (w/w), **(F)** 0.5% (w/w), **(G)** 1% (w/w), **(H)** 2% (w/w), **(I)** 3% (w/w), and **(J)** 5% (w/w).

AIBN concentration was in excess of 5% (w/w), node formation was detected. We noted no obvious differences in the types of monomers. Changes in moisture content according to the amount of added AIBN are presented in Fig. 4. The moisture contents of the hydrogels polymerized with SMA were generally higher than the hydrogels polymerized with MMA. The moisture contents of the hydrogel to which more than 3% (w/w) AIBN was added were lower than in the others. In the samples to which 1% (w/w) AIBN was added, the moisture content was higher than that of others.

Effect of Different Crosslinking Agent Concentrations

The effects exerted by different concentrations of crosslinking agent (EGDMA; 0.5, 1, 2, 3, and 5% [w/w], respectively) on the degree of polymerization degree and moisture contents in the hydrogels were determined through free-radical polymerization, as is shown in Figs. 5 and 6. In Fig. 5, sample A, to which less EGDMA (0.5% [w/w]) was added than to the other samples, exhibited a lower degree of polymerization than was seen in the other samples. A higher degree of polymerization was detected in sample E (5% [w/w]) than in the other samples. Sample A evidenced a degree of polymerization comparable with those of the others. Node formation was detected in the samples to which more than 1% (w/w) EGDMA was added, the polymerized hydrogel evidenced nodes. The effects of EGDMA on hydrogel moisture contents are shown in Fig. 6. The moisture contents of hydrogels polymerized with SMA were found to be higher than those polymerized with MMA. The moisture contents of hydrogels containing 1% or more EGDMA were lower than those of the other samples. 0.5 and 1% (w/w) of EGDMA did not appear to influence the moisture contents of hydrogels of polymerized SMA to a significant

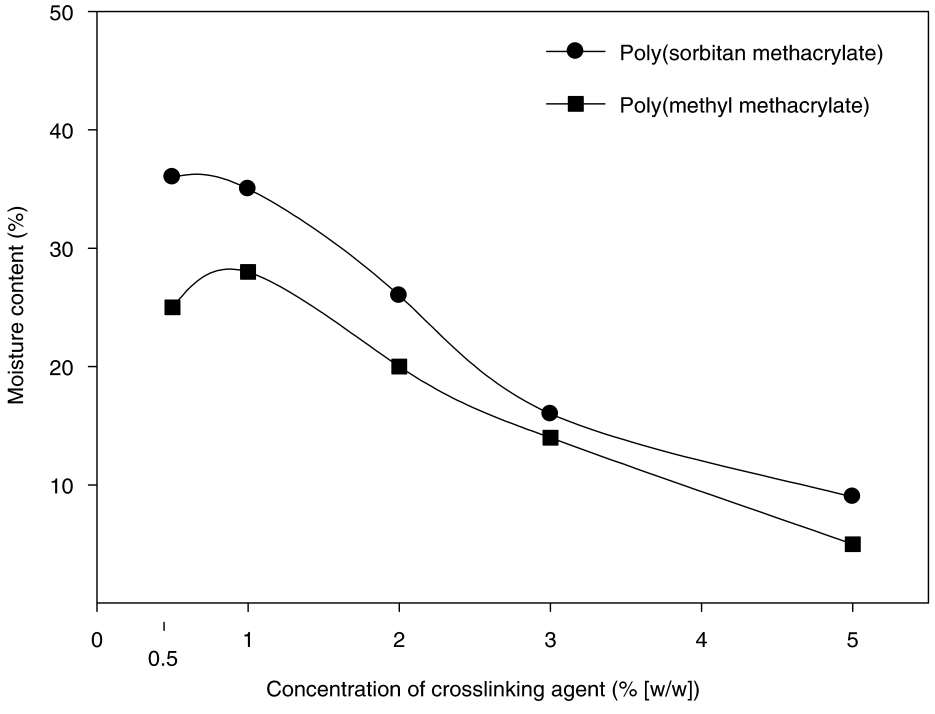

Fig. 6. Moisture contents of polymerized hydrogel with different crosslinking agent concentrations.

degree. Whereas, the moisture content of hydrogel of polymerized MMA is high at the concentration of 1% (w/w) of EGDMA.

Structure Analysis and Surface Observation of Poly(SMA)

To confirm the polymerization of SMA, the structural analysis results of poly(SMA) were compared with the results of poly(MMA), through FT–IR spectroscopy. The FT–IR results are shown in Fig. 7. The band of polymerized SMA was confirmed at 1735–1730/cm (C=C), but the band of poly(MMA) was not confirmed. The band for the C–O span of the secondary alcohols appeared at 1200–1300/cm, and the O–H span evidenced a strong band at 2900–3000/cm, as well as a broad band at 3400–3500/cm, thereby indicating the presence of SMA. The surface of the poly(SMA), synthesized under optimal conditions and treated, was then observed through SEM, as was shown in Fig. 8. The surface was observed to have a uniform, clear appearance.

In this study, in order to maintain proper moisture contents in such hydrogel materials, we utilized SMA as a new monomer, which was glycosylated with a methacryl group and included many hydroxyl molecules for hydrogel polymerization, in order to overcome the aforementioned problem. Then, according to the selective synthesis method

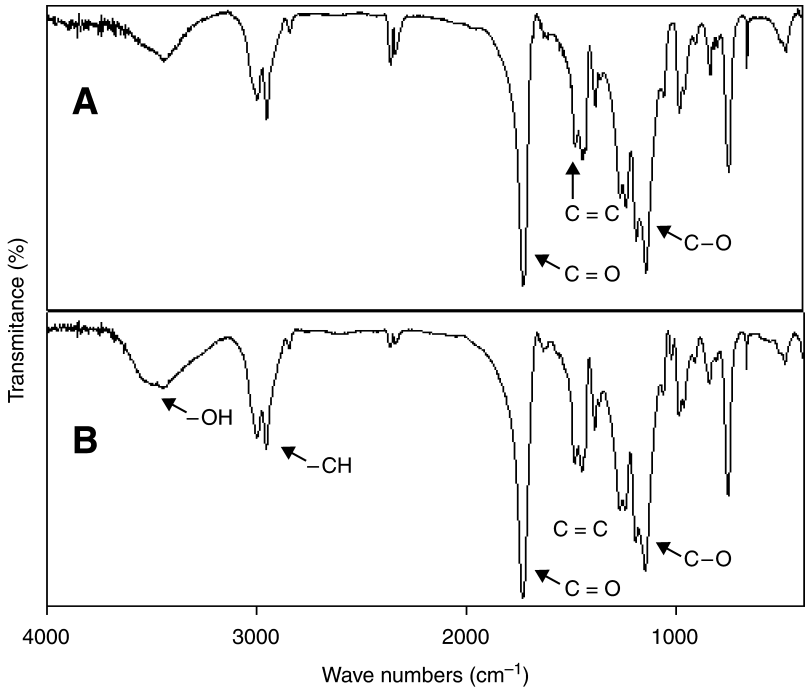

Fig. 7. Comparison of FT–IR spectra of poly(MMA) and poly(SMA). **(A)** Poly(MMA), **(B)** Poly(SMA).

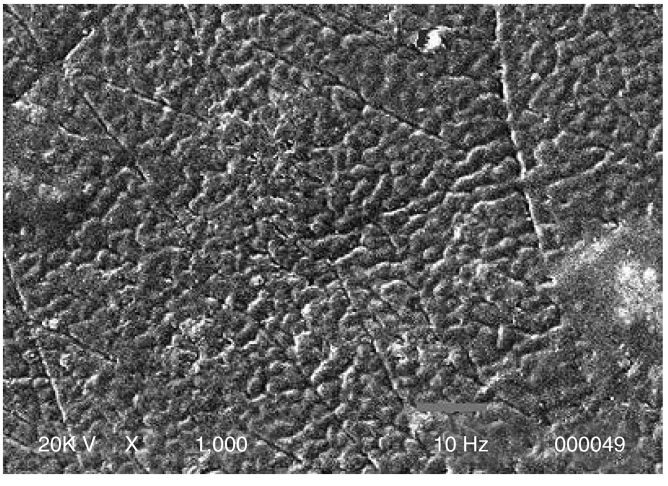

Fig. 8. SEM photograph of poly(SMA) under optimal conditions.

and degree of substitution, glycosylated materials such as SMA can enhance the moisture contents of polymerized hydrogels. Therefore, SMA is expected to prove an efficient monomer for sugar polymers with high hydrophilicity and biocompatibility, which might be used in the construction of medical materials.

Acknowledgments

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