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Synthesis of fast-swelling, superporous sucrose hydrogels

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Abstract

Sucrose was reacted with glycidyl acrylate to introduce double bonds. The extent of modification was quantitated using ^{13}C NMR. The reaction time and the molar ratio were varied to adjust the degree of substitution. The average number of double bonds introduced in sucrose varied from 0.2 to 6.7. Since the reaction mixture contained sucrose modified with more than one double bond, its polymerization resulted in a crosslinked network of sucrose hydrogels (sucrogels). Superporous sucrogels were also prepared by adding a gas forming agent during polymerization. They swelled faster with higher swelling ratio and degraded faster in both acidic and basic conditions than sucrogels. The fast swelling superporous sucrogels can be used in various applications, including controlled drug delivery.

Keywords: Sucrose; Hydrogels; Sucrogels; Superporous sucrogels; Swelling; Degradation

1. Introduction

Sucrose is ubiquitously present in plants. It has a world production amounting to well over 10 million tons annually and is almost entirely consumed as a sweetener of foods. Since it is an inexpensive organic chemical with extremely high purity, the potential of sucrose as a chemical raw material for synthesis of various applications has been explored extensively. Various sucrose derivatives have been prepared, such as Sucralose, Isomalt, Sucralfate, and Olestra (Gardner & Sanders, 1990; Hough, 1991; Schiweck, Munir, Rapp, Schneider & Vogel, 1991). Synthesis of polymeric materials based on sucrose has been extensively studied since the 1950s (Marcy, 1977).

Since sucrose has eight chemically active hydroxyl groups, regio-selective derivatization is important in the synthesis of sucrose-containing linear polymers. It is also important to introduce only one or two functional groups to each sucrose molecule. Although regio-selective modification can be achieved by using specific blocking reagents, the chemical reaction still results in a mixture of mono- and multi-substituted sucrose molecules. For this reason, polymerization of chemically modified sucrose tends to result in some degree of crosslinking, i.e. formation of insoluble sucrose gels. Crosslinking was observed even when sucrose was attached to the backbone of poly(butadiene-*co*-acrylic acid) linear polymers (Alvarez, Strumia & Bertorello, 1988). A higher degree of regioselectivity on sucrose can be achieved by the enzymatic approach. The chemoenzymatic method was used to prepare poly(sucrose acrylate) linear polymer (Patil, Dordick & Rethwisch, 1991; Patil, Rethwisch & Dordick, 1991).

Crosslinked sucrose networks (sucrose hydrogels) have also been prepared extensively (Garcia-Gonzalez et al., 1993; Gruber & Greber, 1991). Sucrogels are generally prepared by introduction of vinyl groups to sucrose and subsequent polymerization. Sucrose methacrylic ester (Castellano & Martinez de Bertorello, 1989) is commonly used. The number of vinyl groups introduced varies depending on the experimental conditions. Vinyl-group-containing sucrose molecules (6,1′,6′-tri-*O*-(*p*-vinylbenzoyl)sucrose) were prepared and copolymerized with styrene or methyl methacrylate in the presence of crosslinking agent to impart a certain degree of hydrophilicity as well as biodegradability (Khan, 1976). Sucrose resins were prepared by crosslinking sucrose diacids with diepoxide crosslinking agents (Faulkner, 1977). Sucrose gel was also prepared by transesterification (Pastoriza & Bertorello, 1986). In addition, the condensation between organnostannane dihalides and sucrose was used to form a crosslinked network (Carraher et al., 1981). Sometimes sucrogel was prepared for a specific application, such as separation of heavy metal ions (Alvarez, Bertorello & Strumia, 1991). Recently, Gruber

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and Greber (1991) synthesized sucrose hydrogels with functional groups exhibiting reactivities different from the hydroxyl groups. Such hydrogels were used for immobilization of reagents or catalytic active groups, photoactive groups, or biologically active groups. Sucrogels were never prepared for a specific application of drug delivery, except by Gruber and Greber (1991) who have attached several drug molecules.

We were interested in the synthesis of sucrose hydrogels (sucrogels) for potential application as a platform for oral drug delivery. One of the properties necessary for gastric retention for long-term oral drug delivery is rapid swelling of the dried gels. A recent study in our laboratory showed that superporous hydrogels swelled rapidly, in a matter of a minute. For this reason, we were interested in preparing superporous hydrogels based on sucrose monomers, i.e. superporous sucrogels.

2. Experimental

2.1. Synthesis of sucrose monomers

Initially, sucrose in aqueous solution was modified with three different alkylating agents: glycidyl acrylate (Lancaster Synthesis, Inc.); glycidyl methacrylate (Aldrich Chemical Company); and 1,2-epoxy-5-hexene (Aldrich Chemical Company). Since glycidyl methacrylate (GM) and 1,2-epoxy-5-hexene (EH) are hydrophobic, their heterogeneous reaction proceeds very slowly in aqueous solution. Glycidyl acrylate (GA), on the contrary, did not have such a problem. For this reason, GA was used for all subsequent experiments.

Four batches of sucrose acrylate monomers were prepared. For each batch, 10 g of sucrose (J.T. Baker), 1.9 g of tetrabutyl ammonium bromide (Aldrich, 99%), and a small amount of *p*-methoxyphenol (Aldrich, 98.5%) were dissolved in 20 ml phosphate buffered solution (pH 7.2, 0.05 M) in a 200 ml Erlenmeyer flask equipped with magnetic stirrer. Tetrabutyl ammonium bromide (TAB) was used as a phase transfer catalyst to accelerate the heterogeneous reaction (Starks, 1971), and *p*-methoxyphenol was used as a polymerization inhibitor. GA was added to each batch to make sucrose:GA ratios of 1:4, 1:1.5, 1:1.5, and 1:8. The reaction was continued at room temperature with continuous stirring. The flasks were covered with aluminum foil to avoid light. The four batches were allowed to react for 3 h, 1.5 days, 2.5 days, and 10 days, respectively. The synthesized monomers were labeled as S-3h, S-1.5d, S-2.5d, and S-10d, respectively, in the subsequent studies. The reaction was stopped by adding 70 ml methylene chloride to the reaction solution to extract the unreacted GA. The water phase was further extracted with methylene chloride four times to remove unreacted GA. The reaction mixtures in the water phase were tested by thin layer chromatography (TLC) on silica gel (Analtech) to ensure that no unreacted GA remained in the water phase.

2.2. Quantitative ^{13}C NMR

The extent of reaction was examined by the quantitative ^{13}C NMR technique. One milliliter of sucrose monomer was dried in vacuum. To this were added D_2O, 15 mg of chromium(III) disodium pentetate (CDP) (Aldrich) (final concentration 0.025 M), and 10 mg of 3-(trimethyl silyl)-1-propanesulfonic acid (sodium salt) (TMSPSA) (Aldrich). CDP was used as a spin–lattice relaxation reagent, and TMSPSA was used as a water-soluble internal standard. Gate-decoupled pulse sequence was used to eliminate the NOE effect. The average area of double bond peaks at 128 and 134 ppm was compared with the area of the anomeric sucrose carbon peak at 106 ppm. The ratio reflected the reaction extent. Since S-10d was only slightly soluble in D_2O, deuterated methanol was used as a solvent for this monomer. The other three monomers were dissolved in D_2O.

2.3. Synthesis of sucrogels and superporous sucrogels

Sucrogels were prepared either by γ-irradiation or by chemical initiation of sucrose monomers, i.e. sucrose modified with GA (S-GA). For polymerization by γ-irradiation, S-GA in a clean glass test tube was exposed to the total γ-dose ranging from 0.008 to 0.24 Mrad. When chemical initiation was used, 30 μl of 10% ammonium persulfate (APS, Aldrich Chemical Co.) and 30 μl of 10% *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TEMED) (Bio-Rad Laboratories) were added to 1 ml of S-GA monomers. Sucrogels formed within 20 s to 2 min. No crosslinker was added because the monomer solution contained di- and multi-substituted sucrose, which acted as the crosslinker. All sucrogels in this study were prepared by chemical initiation. The gels were washed with a copious amount of deionized, distilled water (DDW) for 10 days to remove the nonpolymerizable impurities and unreacted sucrose and then dried in a 60°C oven or food dehydrator (Mr. Coffee, Inc., Bedford Heights, OH) to a constant weight. S-GA monomer concentration (excluding all the nonpolymerizable impurities) was determined by dividing the dried gel weight by the weight of monomer solution used. The concentration of S-2.5d monomer solution was determined to be 18%.

Superporous sucrogels were prepared using S-GA with four different degrees of modification: S-3h, S-1.5d, S-2.5d, and S-10d. The following ingredients were added sequentially to a plastic test tube (17 × 100 mm, Falcon): 1 ml of S-GA; 100 μl of 5% Pluronic® F127; 100 μl of 10% APS in DDW; 30 μl of acrylic acid; and 100 μl of 10% TEMED. The test tube was shaken to mix the solution after each ingredient was added. Finally, 85 mg of $NaHCO_3$ powder was added to the mixture, and the mixture was immediately stirred vigorously using a spatula for 5–10 s. The solution

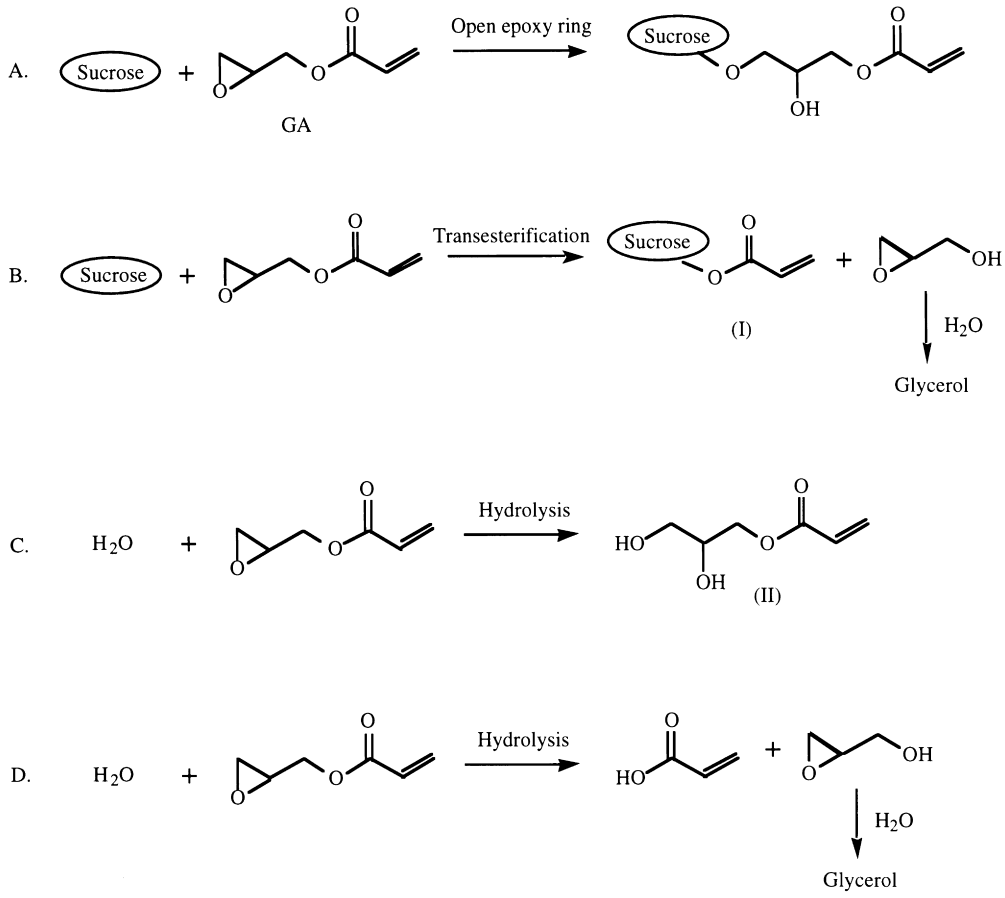

Fig. 1. Reactions thought to be involved in the synthesis of glycidyl acrylate-sucrose monomer.

started foaming immediately after the addition of $NaHCO_3$. After 15–60 s, bubbling stopped and the foam settled. During this time period, polymerization became complete. The synthesized superporous hydrogel was cured at room temperature for at least 10 min. Since the S-GA solution contained mono-, di-, and multi-substituted sucrose, no external crosslinker was necessary to form a hydrogel. After the synthesis, a superporous hydrogel was retrieved and washed with a copious amount of DDW. A washed, swollen superporous hydrogel was soaked in absolute ethanol containing 1% $Voranol_{240–800}$. $Voranol_{240–800}$ is a polyol from Dow Chemical Company, and the subscript numbers are related to its hydroxy number and molecular weight. It was used as a wetting agent in our study. Repeated dehydration with fresh ethanol solution replaced all the water from the hydrogel. The superporous hydrogel was then dried in a 60°C oven or in a food dehydrator to a constant weight.

2.4. Swelling properties of the sucrogels

To characterize the swelling behavior, 200 mg of dried sucrogels were allowed to swell in DDW, 0.9% NaCl solution, or 0.03 M HCl solution. At timed intervals, the swelling ratio, Q, was measured. $Q = W_s/W_d$ where W_s is the weight of a swollen sucrogel and W_d is the weight of a dried sucrogel.

2.5. Comparison of surfactants for the synthesis of superporous sucrogels

Pluronic® F127 (obtained from BASF), bovine serum albumin (BSA), and sodium dodecyl sulfate (SDS, BioRad) were compared for their effectiveness in foam formation. Pluronic® F127, with a hydrophilic–lipophilic balance (HLB) value of 18–23, was chosen from about 20 Pluronic® surfactants since it showed the best properties. BSA was used as a biodegradable protein surfactant. SDS has long been used as a surfactant in aqueous systems.

In a scaled plastic test tube (17×100 mm^2) containing 0.5 ml of S-2.5d monomer solution was added 15 μl of acrylic acid, surfactant solution, and DDW to make the final volume of 0.53 ml. $NaHCO_3$ powder (42 mg) was added to the test tube, and the contents were stirred vigorously for 2–5 s. Foam rose immediately to reach its maximum height within several seconds, then started to subside.

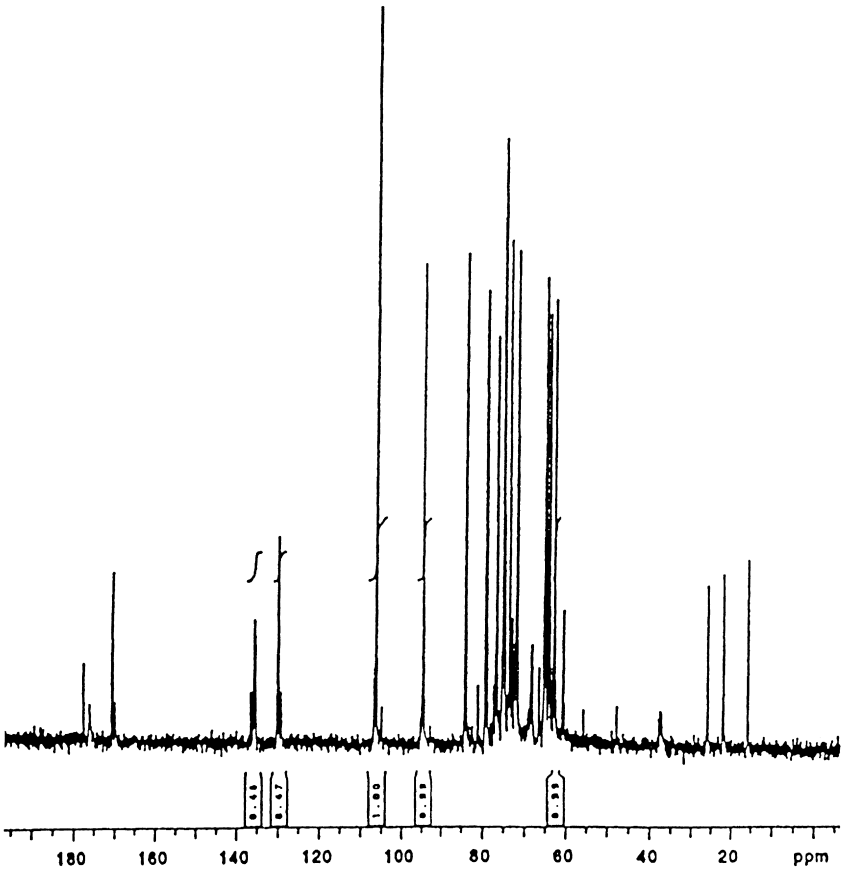

Fig. 2. ^{13}C NMR spectrum of sucrose monomer in D_2O. The degree of substitution of sucrose monomer was 0.47.

2.6. SEM

Effect of dehydration on the morphology of superporous sucrogels was examined using a scanning electron microscope (SEM). Samples were coated with a thin layer of palladium gold alloy in a Hummer I Sputter Coater, and imaged in a SEM (JSM-840, JEOL).

2.7. Effect of amount of acid on the properties of superporous sucrogels

Six batches of S-2.5d superporous hydrogels were prepared according to the method described above, except that the amounts of all the ingredients were reduced to half and the amount of acrylic acid was varied. The superporous sucrogels were washed in DDW, dehydrated in absolute ethanol, and then dried in 60°C oven. The density of the dried superporous sucrogel was calculated by:

$$d = W_d/V_d$$

where W_d and V_d are the weight and the volume of the dried superporous sucrogel, respectively. V_d was determined using a solvent displacing method. The swelling ratios of these gels were determined in 0.9% NaCl solution by a titration method. A superporous sucrogel was placed in a plastic weighing boat, and 0.9% NaCl solution was added dropwise from a burette. The added solution was quickly absorbed by the sucrogel. Titration was stopped when no more liquid was absorbed, i.e. when freely flowing liquid appeared. The amount of liquid absorbed was easily read from the burette. This method was used because the swollen samples were sometimes too fragile to be handled and weighed on a balance.

2.8. Degradation study

Sucrogels and superporous sucrogels prepared with S-2.5d were incubated in 0.1 M HCl or 0.3 M NaOH at 37 or 90°C. For complete degradation, they were incubated in 6 M HCl and 1 M NaOH solution at 85°C for 20 h. The solutions were then filtered and neutralized. TLC spectra on silica gel (Analtech) was developed with a mixture of chloroform and methanol (chloroform : methanol = 1 : 1). Sulfuric acid spray agent (Sigma) was used to detect sucrose and its derivatives.

Table 1
Comparison of the swelling ratio (Q) of sucrogels and superporous sucrogels with different degrees of modification (the swelling ratio was measured in distilled deionized water)

	S-10d	S-2.5d	S-1.5d	S-3 h
Sucrogels	1.02	5.2	12	27
Superporous sucrogel	9	52	98	200

3. Results

3.1. Reaction between sucrose and glycidyl acrylate

The reaction between sucrose and glycidyl acrylate (GA) in aqueous solution appears to be complex as described in Fig. 1. GA is thought to react with sucrose as shown in Fig. 1a (Artursson, Edman, Laakso & Sjoholm, 1984). A plasma desorption mass spectrum of sucrose monomers modified with GA (S-GA), however, showed a large peak of Compound I, which was derived most likely from Reaction B in Fig. 1 by transesterification. From the thin layer chromatography analysis of the S-GA monomers (silica gel, methanol : chloroform = 1 : 4), we found the presence of two spots with r_f values of 0.75 and 0.61 as detected using a UV lamp. These two spots did not show up when detected by a sulfuric acid spray agent (Sigma), suggesting that no sucrose moiety was present in these two compounds. After analyzing the incubation solution of GA in 0.2 M NaOH for 8 days, we found the same spots at r_f 0.75 and 0.61 (as detected by a UV lamp), while the spot of GA (at r_f = 0.84) disappeared. The spot at r_f 0.75 was thought to be acrylic acid derived from Reaction C in Fig. 1, since pure acrylic acid had an r_f value of 0.75. The spot at r_f 0.61 was expected to be the other hydrolysis product (Compound II in Fig. 1). Thus, it appears that at least four reactions occurred.

Since this reaction was not stereo specific, the reaction mixture contained unreacted sucrose, mono-, di-, and multi-substituted sucrose. In addition, there were impurities such as acrylic acid (AA) resulting from side reactions. Since preparative separation was difficult, the mixtures were used to make sucrogels and superporous sucrogels without further purification. The presence of acrylic acid in the monomer mixture makes the swelling of sucrogels pH-dependent.

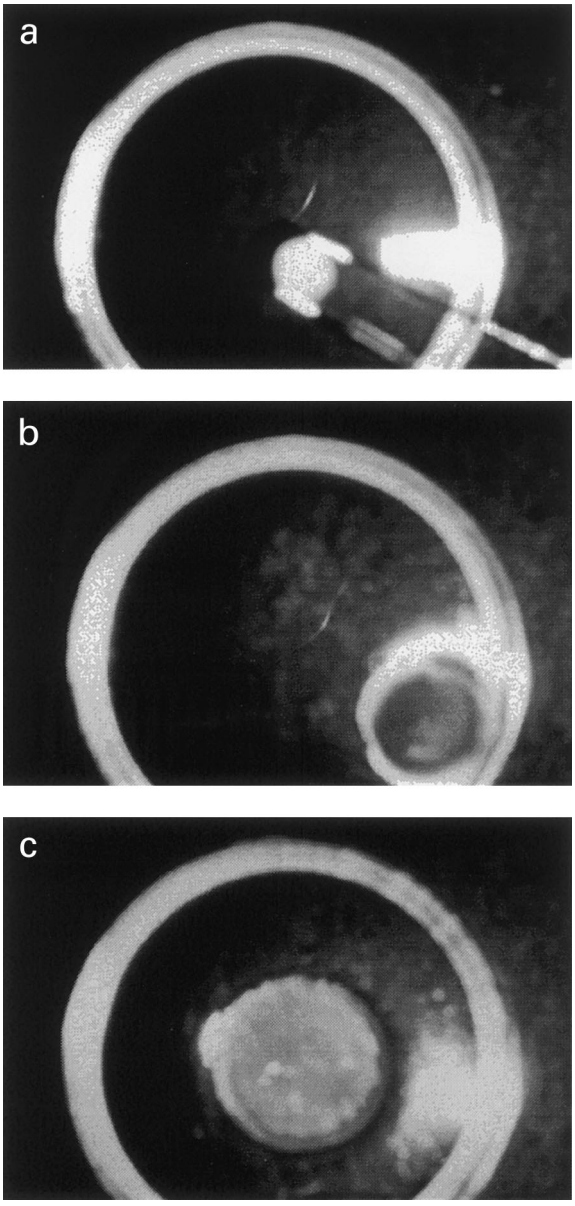

Fig. 3. Photographs of superporous sucrogels swelling in water. Pictures were taken at: (a) 0 s; (b) 2 s; (c) 5 s after a dried superporous sucrogel was immersed in water.

3.2. NMR study

Fig. 2 is the quantitative ^{13}C NMR spectrum of S-2.5d monomer from which the extent of the reaction was measured. Signals at 16, 22, 26, and 61 ppm are peaks from TAB. Sucrose signals are between 63 and 106 ppm. Acrylate vinyl peaks are at 129 and 137 ppm, and carbonyl peaks are at 170 and 176 ppm. Because of the presence of side reactions, we could not get the exact degree of substitution from the spectrum. However, the ratio of the average peak area of two vinyl carbons (129 and 137 ppm) to the peak area of the anomeric sucrose carbon at 106 ppm allowed us to estimate the extent of the reaction. The extents of the reactions of S-3h, S-1.5d, S-2.5d, and S-10d were 0.2, 0.35, 0.47, and 6.7, respectively.

3.3. Swelling properties

The swelling kinetic study of S-2.5d gels in DDW, 0.9% NaCl, and 0.03 M HCl solution showed that it took about 1.2 h for the sucrogels to reach 50% of the equilibrium swelling. It took 12 h to reach the equilibrium swelling state. In the saline and HCl solution, the swelling ratio of the gel was lower than that in water ($Q = 3$ vs. $Q = 5$). This was because of the presence of the acrylic acid moiety, a product of a side reaction, in the sucrogels. Its negative

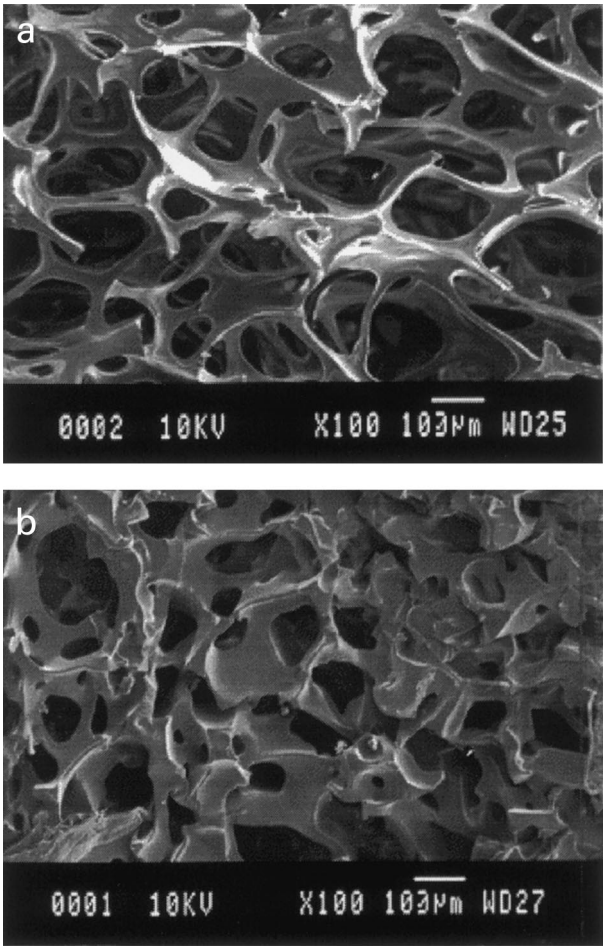

Fig. 4. SEM pictures of cross-sections of superporous sucrogels. Sucrogels were dehydrated with ethanol before being (a) oven dried or (b) oven dried without ethanol dehydration.

charge at neutral pH caused the gel to swell to a greater extent. The swelling properties of sucrogels and superporous sucrogels are compared in Table 1. The swelling ratios were different by an order of magnitude. Under the same swelling condition, superporous sucrogels swelled about $7 \sim 10$ times larger than sucrogels. This remarkable difference is due to the unique structural characteristics of the superporous hydrogels. The superporous hydrogels contain numerous empty cells, which are dispersed throughout the polymer matrix. When superporous hydrogels swell in aqueous solution, not only do the polymer chains expand with the uptake of water, as in conventional hydrogels, but also numerous empty cells expand to larger sizes. This accounts for the much higher Q values of superporous sucrogels. The order of the swelling ratios is S-3h > S-1.5d > S-2.5d > S-10d. This is as expected, since a superporous sucrogel with higher crosslinking density swells less. Unlike sucrogels which took hours, swelling of superporous sucrogels, especially those dried with ethanol dehydration, was complete in less than 10 s as shown in Fig. 3. To understand such a fast swelling, the surface morphology was examined by SEM. As shown in Fig. 4a, the porous structure of the ethanol-dehydrated superporous sucrogels remained intact after oven drying. On the contrary, it collapsed if dried without ethanol dehydration (Fig. 4b). The low surface tension of ethanol is thought to maintain the intact polymer structure during drying.

Table 2
Comparison of foaming properties of Pluronic® F-127, BSA, and SDS in sucrose monomer solution (The solution volume before foaming was 0.53 ml. Foaming agent was added to each test tube (17×100 mm^2, plastic and scaled) containing a different amount of surfactant. The foam started to rise and the foam volume in the test tube was recorded)

Final surfactant concentration(%)	Foam volume (ml)		
	Peak	At 1 min	At 5 min
Control	1.4	0.53	0.53
Pluronic® F-127			
0.05	4.6	3.8	0.62
0.10	4.8	4.6	0.71
0.20	4.8	4.6	0.80
0.35	4.5	4.3	0.98
0.50	4.5	4.3	1.04
0.75	4.5	4.3	1.03
BSA			
0.01	4.3	1.0	0.53
0.02	4.4	2.1	0.53
0.05	4.6	3.7	0.62
0.10	4.6	3.8	0.63
0.25	4.6	3.8	0.62
SDS			
0.05	1.2	0.53	0.53
0.10	1.1	0.53	0.53
0.20	1.1	0.53	0.53
0.50	2.1	0.53	0.53
1.00	2.2	0.80	0.53

3.4. Comparison of surfactants for the synthesis of superporous hydrogel

The foam formed during the synthesis of superporous sucrogels reached the maximum height within several seconds and then started to subside. The volumes at the time of the maximum foam height, and at 1 and 5 min are given in Table 2. In terms of foaming ability, the larger the peak foam volume, the better is the foaming agent. Foam volumes at 1 and 5 min reflect foam stability. The longer the foam is sustained, the better is the surfactant. Both Pluronic® F127 and BSA were good foaming agents based on peak foam volumes, which are an order of magnitude larger than that of the starting monomer solution. Pluronic® F127, however, was a better foam stabilizer. When the concentration of Pluronic® F127 was 0.5%, foam did not subside much after 1 min. Even after 5 min, the volume of the foam was twice that of the starting solution. BSA could only sustain the foam for 1 min. After that the foam subsided rapidly. SDS was a poor foaming agent and foam stabilizer for the S-2.5d monomer solution. The foaming and foam stabilizing effects improved as the surfactant concentration increased up to a certain level.

Table 3
Effect of acrylic acid on the properties of superporous sucrogels (Swelling ratio was measured in 0.9% NaCl solution. The gels were prepared using monomer S-2.5d. The peak foam size is the volume when the foam rises to the maximum size after $NaHCO_3$ was added and mixed)

Acrylic acid (μl)	Peak foam size (ml)	Density of the dried superporous sucrogels (g/cm^3)	Swelling ratio (Q)
5	1.0	0.60	10.4
10	1.6	0.30	16.9
15	2.5	0.12	33.7
30	4.2	0.09	50.6
50	6.5	0.07	58.0
80	8.1	0.53	16.0

3.5. Effect of acid on the properties of superporous sucrogels

Table 3 shows the effect of acrylic acid on the properties of superporous sucrogels when the amount of $NaHCO_3$ was maintained constant at 42 mg. When the amount of acrylic acid was increased from 5 to 50 μl, the peak foam size increased from 1.0 to 6.5 ml. In addition, the density of the dried superporous sucrogels decreased from 0.60 to 0.07 g/cm^3. Gels with lower density had higher porosity, and thus higher swelling ratio. However, gels prepared with 80 μl of acrylic acid did not follow the same trend. Although the peak foam size was the largest at 8.1 ml, the excess acrylic acid remaining after reaction with $NaHCO_3$ resulted in the acidic pH of the final solution. This greatly decreased the polymerization rate. Since the foam subsided and eventually collapsed before polymerization was complete, the density of the resulting gels was higher and the swelling ratio was lower than those prepared with 50 μl of acrylic acid.

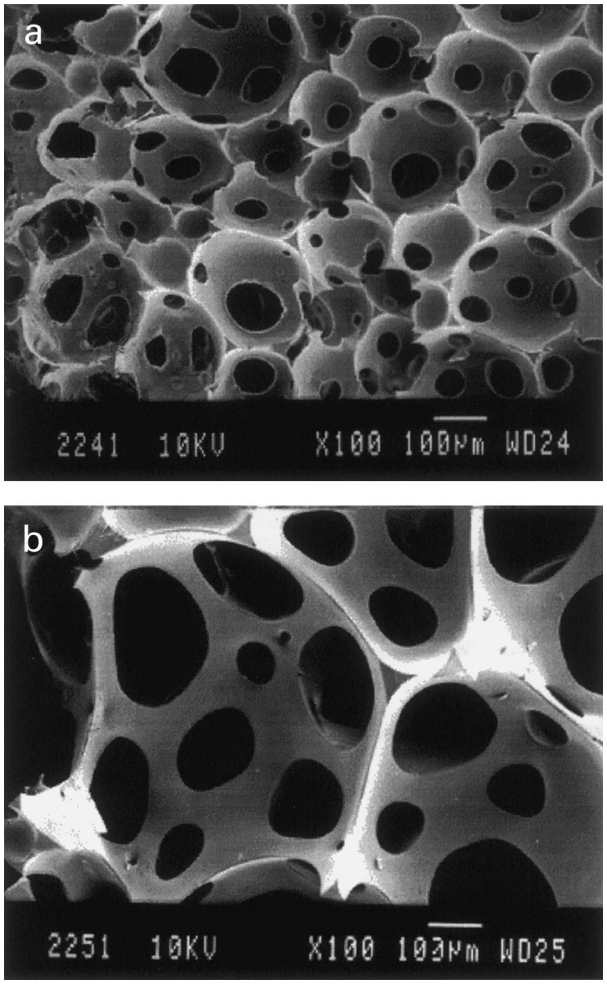

Fig. 5. SEM pictures of cross-sections showing pore structures of superporous sucrogels synthesized with: (a) 30 μl of acrylic acid; (b) or 50 μl of acrylic acid. The average pore diameters in (a) and (b) were 180 and 530 μm, respectively.

Gel structures were examined by SEM after dehydrating the gels using absolute ethanol to preserve the structure. Dried gels were cut to expose their inner structures. The pore size was estimated from SEM images by averaging the diameter of ten cells. As shown in Fig. 5a, the average pore diameter, in the case where 30 μl of acrylic acid was added, was 180 μm. On the contrary, the average pore size was 530 μm when 50 μl of acrylic acid was used (Fig. 5b).

3.6. Degradation time

Degradation of sucrogels and superporous sucrogels was examined by exposing them to acidic (pH 1) or basic (pH 12.5) solutions at 37 or 90°C. The pH was maintained by periodically monitoring it and adding the necessary amount of either HCl or NaOH. Complete degradation was indicated by disappearance of bulk sucrogels or superporous sucrogels.

In acidic condition, degradation was slow, and none was observed in 0.1 M HCl at 37°C, even after 2 weeks. A stronger condition, 0.1 M HCl at 90°C, was employed for accelerating the hydrolysis to provide an understanding of its degradability. Here, the S-3h sucrogels degraded completely within 3 days, whereas the S-2.5d sucrogels required 9 days for degradation. Even the superporous sucrogels prepared from S-2.5d degraded very slowly. In basic solution, however, the degradation process was much faster. In 0.03 M NaOH solution, S-3h sucrogels degraded completely within 4 h at 37°C. However, S-2.5d sucrogels, which had a higher crosslinking density, still required 10 days

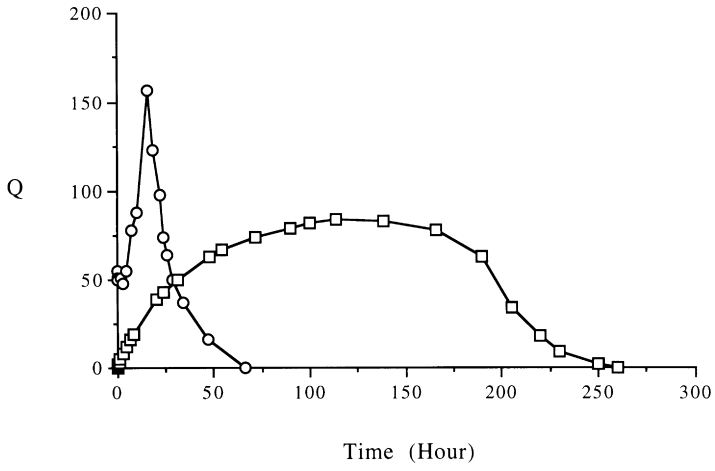

Fig. 6. Examples of degradation kinetics of a sucrogel (□) and a superporous sucrogel (○) in pH 12.5 NaOH solution at 37°C. It took 260 h to degrade the nonporous surcogel, but only 66 h for the superporous sucrogel.

before complete degradation. In contrast, S-2.5d superporous sucrogels degraded in only 3 days in the same solution.

Fig. 6 shows the degradation kinetics in pH 12.5 NaOH solution at 37°C. The complete degradation times of sucrogels and superporous sucrogels were 260 and 66 h, respectively. When placed in the degradation medium, they first swelled by absorbing the solution. Then, as degradation progressed, some of the crosslinks were cleaved. This resulted in a decreased crosslinking density and an increased swelling ratio. Therefore, equilibrium swelling was never reached. They kept swelling until they were totally dissolved. In this experiment, the sucrogels or superporous sucrogels became so flexible that they behaved like viscous liquid at a certain point.

4. Discussion

The choice of sucrose over other carbohydrates in this study was based on several considerations. First, sucrose had already been used widely in preparation of various pharmaceutical dosage forms. Second, sucrose has high functionality, which is useful in the synthesis of sucrogels with distinct properties. Third, sucrose is a nonreducing carbohydrate, which avoids undesirable side reactions. Fourth, sucrose is highly water-soluble, and this makes it easier to synthesize high-density sucrose hydrogels in water. The high solubility is even more important in the synthesis of superporous sucrogels. Finally, highly purified sucrose can be obtained at low cost. Another critical factor is the chemical advantage of sucrose over other polyols, i.e. very acid-labile glycosidic linkage. Sucrose is a good building block for crosslinked polymers, or hydrogels, with dilute acid lability (BeMiller, 1991). We expected that the sucrogels would be labile in acids as long as the modification of sucrose was not extensive. Such acid-labile sucrogels could be effectively used as a platform for oral controlled drug delivery systems. Unfortunately, however, the sucrogels and superporous sucrogels prepared in this study were not degradable easily in 0.1 M HCl at 37°C. This is rather unexpected, since the extent of modification was only 0.47 for the sucrogels used in the degradation experiment.

Modified sucrose will not be degraded by invertase as the natural sucrose is, if the fructose ring is modified (Straathof, Vrijenhoef, Sprangers, Bekkum & Kieboom, 1988). In our test, the sucrogels and superporous sucrogels were not degraded by invertase (Grade V from bakers yeast, Sigma Chemical Company), lipase (Type II crude from porcine pancreas, Sigma Chemical Company), acylase (Grade I from porcine kidney, Sigma Chemical Company), or protease (Type XXIII from *Aspergillus oryzae*, Sigma Chemical Company). To understand the degradation mechanisms of sucrogels, we incubated S-2.5d sucrogels in 6 M HCl and 1 M NaOH solution at 85°C for 20 h. The main degradation mechanism of the sucrogels and superporous sucrogels in base or acid is believed to be hydrolysis. Water reacts with the ester bonds in the polymer chains, and this leads to the degradation of the polymer. Both base and acid function as a catalyst in the hydrolysis, but under different mechanisms. In basic solution, degradation occurs at the ester bond and the kinetics are very fast. Acid, on the contrary, cleaves the ether linkage between the glucose and fructose ring in addition to the hydrolysis of the ester bonds. The degradation kinetics in acidic solution, however, was very slow. The degradation rate was dependent on the degradation media, crosslinking density, incubation temperature, and the polymer structure (nonporous sucrogel or superporous sucrogel).

Glycidyl acrylate and glycidyl methacrylate have been used to modify polysaccharides and proteins, such as starch (Artursson et al., 1984; Laakso, Stjarnkvist & Sjoholm, 1987; Lepisto, Artursson, Edman, Laakso & Sjoholm, 1983), dextran (Edman, Ekman & Sjoholm, 1980; Smedt, Lauwers, Demeester, Steenbergen, Hennink & Foefs, 1995), and albumin (Park, 1988; Shalaby & Park, 1990). In the absence of any added catalyst, the heterogeneous phase

reaction in aqueous solution proceeds very slowly. Tetrabutyl ammonium bromide, a phase transfer catalyst, was effective in accelerating the heterogeneous reaction (Starks, 1971). The degree of substitution of GA modified carbohydrates has been measured by bromine addition (Edman et al., 1980; Hoppe, Koppe & Winkler, 1977) or proton NMR (Lepisto et al., 1983) methods. The bromine addition method involves the use of toxic bromine. The proton-NMR method was not very accurate because of many peaks crowded in a small spectral window. Quantitative ^{13}C NMR spectroscopy has been suggested as a potential tool for determining the degree of substitution (Akoh & Swanson, 1987; Akoh & Swanson, 1989). In conventional ^{13}C NMR spectroscopy, most carbons have a different spin–lattice relaxation time, T_1. T_1 of some carbon atoms can be as long as a hundred seconds whereas T_1 of other carbon atoms can be as short as several seconds. This and the nuclear Overhauser effect (NOE) make quantitative analysis impossible. In quantitative ^{13}C NMR, a paramagnetic additive introduces a powerful relaxation that shortens the T_1 of all carbon atoms so that relaxation time differences become insignificant. Longer pulse delay time can ensure all carbons get full relaxation. Gate-decoupled pulse sequence can efficiently suppress the NOE effect (Wehrli & Wirthlin, 1976). In this study, quantitative ^{13}C NMR provided important information on the extent of modification of sucrose by GA.

Superporous sucrogels can also be made to respond to changes in environmental conditions. Our current method resulted in inclusion of acrylic acid moieties due to a side reaction during sucrose monomer preparation and an acidic component added for foam generation. Sucrose can be modified to attach many carboxyl groups, and such monomers will result in pH-sensitive sucrogels. Recently, we prepared new monomers containing hydrophobic groups, such as 6-(*N*-methacryloyl-6-aminocaproyl)sucrose, 6,6′-di(*N*-methacryloyl-6-aminocaproyl)sucrose, 6-(*N*-methacryloyl leucyl)sucrose, and 6-(*N*-methacryloyl-11-amino undecanoyl)sucrose (Jo & Park, 1999). When sucrogels were made from those monomers, they showed inverse temperature sensitivity, by swelling at low temperature, but shrinking at high temperature. Superporous sucrogels simply respond (i.e. either swell or shrink) to changes in environmental factors, orders of magnitude faster. Because of its many hydroxyl groups that can be modified with numerous agents, sucrose can be a valuable raw material for making new monomers with different properties. Since sucrogels and superporous sucrogels can be made in any size and shape and with attractive properties, they should find many industrial applications.

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