Lactitol-Based Poly(ether polyol) Hydrogels for Controlled Release Chemical and Drug Delivery Systems

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The hydroxyl groups of lactitol were propoxylated to produce poly(ether polyol) (LPEP). The average pK_a value of hydroxyl groups of the polyol was 1.63. Cross-linked hydrogels were synthesized by esterification with chlorinated poly(ethylene glycol) bis(carboxymethyl) ether (PEGBCOCl). The swelling ratio decreased with increasing cross-linking ratio (PEGBCOCl:LPEP) from 2:1 to 4:1 in the hydrogels and was sensitive to temperature change between 25 and 55 °C and concentrations of salt and glucose. The swelling ratio did not change significantly with pH in the range of 4−9. The release profiles of a model active agent, acetylsalicylic acid, from the hydrogels showed that the diffusional release rate had a half-order dependence on time, and the diffusivity decreased with increasing cross-linking ratio. This work demonstrated that LPEP-based hydrogels can be used for controlled delivery of drugs and agrochemicals and the release rates can be controlled with the cross-linking ratio of the hydrogel.

Keywords: *Hydrogel; environmental sensitivity; diffusion; acetylsalicylic acid (aspirin); controlled release technology*

INTRODUCTION

Responsive delivery and site-specific delivery systems are of interest as future drug delivery systems to improve the efficacy of drug therapies (Kikuchi et al., 1997). The responsive delivery can also be useful for agrochemicals such as fertilizers, pesticides, herbicides, and insecticides. Polymeric materials are promising tools as drug delivery matrices because the relevant polymer properties can be modified as needed to achieve the potential of new delivery systems and their matrices provide characteristic release. The diffusional release rate usually decreases over time. Therefore, active agent release often does not show zero-order but rather first-order kinetics. There are methods to alter the first-order kinetics to achieve a constant release rate that include geometric changes, erosion/dissolution control, swelling control, nonuniform active agent loading, and matrix/membrane combination (Lee, 1992; Langer, 1995). If the matrices are erodable (degradable), erosion rates also influence the release rate. When the erosion rate is much larger than the Fourier number (D/l^2, D being the diffusion coefficient and l being the matrix thickness), the erosion rate has a predominant effect on the release rate constant; otherwise, the release rate is a combination of erosion and diffusional release. Because diffusional release and erosional release have different release kinetics, the combination can vary with time. However, when the active agent loading is much greater than its solubility in a nonerodable matrix, the release rate is expected to be dependent on the dissolution rate with square root release kinetics.

Polymers for biological applications must have appropriate physical strength and properties. Swelling is also important, because the density of the polymer structure decreases and the cavity or void volume in the structure increases. This swelling property may significantly affect the diffusional movement and release rate.

Hydrogels are hydrophilic three-dimensional network gels that can absorb much more water than their own weight (Dordick et al., 1994; Park and Park, 1996). The affinity of hydrogels to aqueous media makes them an ideal absorbing matrix for biocompatible applications such as implants. Their moisture capacities may also be of great benefit to tissue culture and agrochemical release. Environmentally sensitive hydrogels have added sensing and responsive release abilities useful in delivery systems. In the case of insulin-dependent diabetics, as an example, an ideal insulin delivery system can sense the blood glucose concentration and release insulin when needed (Langer, 1995).

A series of thermally sensitive hydrogels has been prepared from lactitol-based polyether polyols (LPEPs). The LPEPs were prepared by propoxylation of lactitol under basic conditions and characterized by their unsaturation content, alpha color, hydroxyl number, viscosity, hygroscopicity, and molecular weight distribution (Wilson et al., 1996; Hu et al., 1997). The disaccharide structure of lactitol remained intact after propoxylation under reaction conditions (Wilson et al., 1996). The average numbers of propylene oxide (PO) repeating units per OH group in the LPEP branches after propoxylation, measured with ^{1}H NMR, were 1.5, 2.5, 4.6, and 7.1 for 1337, 1672, 2726, and 4055 molecular weights of LPEPs (Hu et al., 1997; Lin et al., 1998).

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10.1021/jf991329a CCC: $19.00
Published on Web 09/29/2000

Lactitol-based hydrogels were synthesized by cross-linking LPEPs with chlorinated poly(ethylene glycol) bis(carboxymethyl) ether (PEGBCOCl) (Lin et al., 1998). The formation of ester linkages resulted in a three-dimensional cross-linked structure. These hydrogel networks consisted of lactitol moieties connected with PPO-*b*-PEO-*b*-PPO block copolymer cross-links. These hydrogels have reversible thermosensitive swelling behavior at the phase transition temperature. The hydrogels were characterized by determining swelling properties, thermosensitivity, and thermal properties using differential scanning calorimetry. The swelling ratios of these hydrogels showed close dependence on the molecular weight or the PO lengths of the LPEPs and the cross-linking ratios (Lin et al., 1998).

This paper further examines the swelling ratio changes of these LPEP hydrogels in response to environmental conditions and the release profile of acetylsalicylic acid (aspirin), a model hydrophobic drug. Aspirin is a well-suited model chemical for this study because of its relatively low molecular weight, marginal solubility in water, and both hydrophilic and hydrophobic molecular structure, which are common properties of drugs and agrochemicals. Aspirin is an effective antiplatelet agent widely in use to prevent arterial thrombosis by irreversible inactivation of platelet activation enzyme with low dose (100 mg/day) (McAdam et al., 1996; Budd et al., 1993; Otsuka et al., 1993). Understanding the controlled release behavior of LPEP hydrogels expands the utilization of value-added products from lactose, an underutilized byproduct in cheese and whey protein industries.

MATERIALS AND METHODS

Lactitol Polyether Polyol Preparation. The LPEP was synthesized using a previously published method (Wilson et al., 1996). PO (Fisher Scientific, Fair Lawn, NJ) and monohydrated lactitol (Purac) were mixed to achieve 2.5 molar equiv of PO/OH of lactitol. The reaction mixture was placed in a 1 L high-pressure vessel (Autoclave Engineers) with dry KOH as a catalyst. The system was sealed and purged with dry N_2. The reactions were run at 110 °C with 800 rpm of stirring and terminated when the pressure had dropped and stabilized. The LPEP was diluted with water, purified with Amberlite IR-120 (H^+) (Aldrich Chemical Co., Milwaukee, WI), and decolorized with active carbon. Water and unreacted PO were removed by benzene−azeotrope and evaporation under reduced pressure. The LPEP was dried at room temperature under high vacuum for 24 h. Wilson et al. (1996) found that the average molecular weight of the product was ~1672 when a 2.5 molar ratio of PO/OH of lactitol was achieved. The pK_a value of the hydroxyl group of polyol was measured by titrating with 0.05 N NaOH solution after the pH had been adjusted to 0.6−0.7 as a starting point using 1 N HCl. End point was determined by a sudden increase of pH using a pH meter. The pK_a value was determined as the pH at half the volume of titration.

Cross-Linker Preparation. Both carboxyl groups of poly(ethylene glycol) bis(carboxymethyl) ether (PEGBCOOH; Aldrich Chemical Co., MW 600) were chlorinated (to PEGBCOCl), stirring with an equal volume of distilled thionyl chloride (Aldrich Chemical Co.) at room temperature overnight. Unreacted thionyl chloride was removed under reduced pressure at 45 °C.

Hydrogel Synthesis. Several hydrogels were synthesized by varying the PEGBCOCl:LPEP ratio from 2:1 to 4:1. LPEP and PEGBCOCl were each dissolved in methylene chloride (Fisher Scientific, HPLC grade) and mixed. Desired amounts of LPEP and PEGBCOCl were transferred from stock solutions and weighed. The cross-linking reaction proceeded in a dry desiccator overnight at room temperature. After the solvent was evaporated, the cross-linked gel was washed with methanol for half an hour and then washed with excess water. Upon placement in water, the gel started to swell and form a hydrogel.

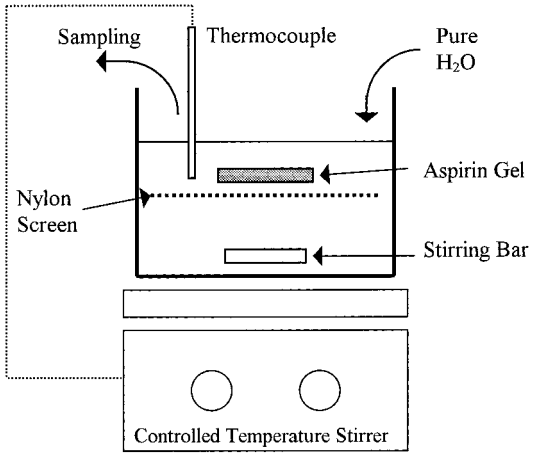

Figure 1. Experimental system for aspirin release test.

Swelling Ratio and Characterization. After swelling in pure water, buffer solution, or salt/glucose solution at room temperature, the hydrogels were gently wiped with tissue paper to remove excess water on the surface, placed in a 75% relative humidity humidity chamber for 30 min, and then weighed (W_{wet}). The hydrogels were dried in a vacuum desiccator for at least 48 h and weighed (W_{dry}). Swelling ratio (S) was calculated using eq 1.

$$S = (W_{wet} - W_{dry})/W_{dry} \quad (1)$$

To study the environmental effects on the swelling behavior of the hydrogels, the hydrogel synthesized at 3.5:1 (PEGBCOCl:LPEP) was used. Various levels of temperature, pH, NaCl, and glucose solution concentration were examined. Sodium phosphate buffer solutions (0.01 M) were used to vary the pH between 4.5 and 11.5. Mono- and dibasic sodium phosphate solution mixtures were used to adjust the pH below 8.5; and di- and tribasic sodium phosphate solutions were used for pH >8.5.

Swelling ratio data obtained by varying the cross-linking ratios and pH were used to characterize the swelling properties and to determine the swelling mechanism, and the results were compared to those reported by Lin et al. (1998). Factors assumed as potential variables for the swelling phenomena were initially (1) free end hydroxyl groups of LPEPs, (2) hydrophilicity of PPO−PEO−PPO chains, (3) hydrogel density (size of cavity space volume), (4) cross-linking ratio, and (5) the length of lactitol moieties (length of PPO−PEO−PPO chains).

Production of Aspirin-Loaded Gel. Hydrogels were dried in a vacuum desiccator and placed in an absolute ethanol solution containing 10% (w/v) aspirin, for overnight loading in darkness. Ethanol in the hydrogels was evaporated in a vacuum desiccator. The hydrogels loaded with aspirin turned white after the removal of ethanol. The dried hydrogels were stored in a desiccator.

Drug Delivery System. The aspirin-loaded hydrogels were placed in an aspirin-saturated water solution for 30 min to reswell to the original size, to avoid possible loss of aspirin in the hydrogel during reswelling. The hydrogels were quickly rinsed with water and then placed in 37 °C water (50−100 times the volume of the hydrogel). Figure 1 shows the experimental system. The soaking water was periodically sampled, and the same volume of water was added back to keep the water volume constant. The aspirin concentration of sample solution was measured spectrophotometrically (Spectronic 1001, Bausch & Lomb) at 275 nm. The concentration of aspirin in the soaking solution never increased to >1% of the

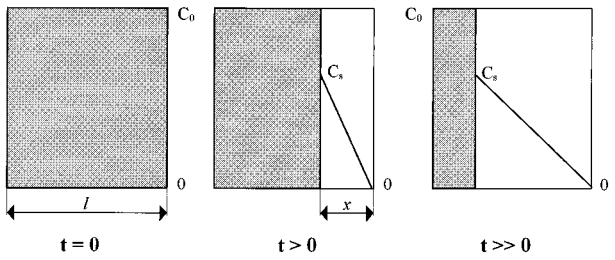

Figure 2. Monolithic system of dispersed solid drug in matrix. C_0, C_s, l, and x are initial concentration, solubility, half-thickness of the matrix gel, and distance from surface of matrix, respectively. Gray color of matrix indicates aspirin-loaded zone, and white part of matrix is depleted zone.

saturated concentration at 37 °C, thus allowing an assumption of near-zero concentration.

Drug Release Model and Diffusivity Determination. Aspirin-loaded hydrogel is an example of a homogeneous monolithic system that contains a dispersed solid drug in the gel matrix (Figure 2) (Roseman, 1980; Burnette, 1987; Flynn et al., 1974). The change of the amount of aspirin released from a unit area (dM_t), corresponding to a change in the thickness of the depleted zone (dx) over a steady-state time, t, is

$$dM_t = \frac{DC_s}{x}\,dt = \left(C_0 - \frac{C_s}{2}\right)dx \qquad (2)$$

where D, C_0, C_s, and x are diffusivity, initial aspirin concentration, aspirin solubility (saturated concentration), and distance from the surface of matrix with half thickness l, respectively (Roseman, 1980). After integration, the amount of drug released over steady-state time from a unit area is

$$M_t = [2(C_0 - C_s)C_sDt]^{1/2} \qquad (3)$$

If the loaded concentration (C_0) is much higher than the solubility ($C_0 \gg C_s$), then eq 3 becomes

$$M_t = (2C_0C_sDt)^{1/2} \qquad (4)$$

When M_t is plotted against $t^{1/2}$, the diffusivity can be calculated from the slope, $(2C_0C_sD)^{1/2}$ using

$$D = \text{slope}^2/2C_0C_s \qquad (5)$$

M_t data were plotted against $t^{1/2}$, and the linear relation range of the data that represent r^2 value over 0.99 was used to obtain the slope using linear regression.

RESULT AND DISCUSSION

Average pK_a Value of Hydroxyl Group of Polyol. End points were determined using NaOH titration of 0.33−0.36 molar ratio (hydroxyl groups of LPEP to NaOH). The average pK_a value was 1.63 (SD = 0.14, n = 5). With respect to the pK_a value of the hydroxyl groups in sugars, the pK_a value of the hydroxyl groups in polyol is acidic. The acidity of the unreacted residual hydroxyl groups of polyols after the cross-linking reaction may influence the pH sensitivity of hydrogels.

Hydrogel Integrity. All hydrated hydrogels had enough strength to maintain integrity during transfers and experiments. The less cross-linked hydrogels were weaker and smoother in appearance than highly cross-linked hydrogels. The hydrogels swelled and shrunk while maintaining their basic shape. After 1 month of storage in water at room temperature, the hydrogel started to lose strength, indicating hydrolysis and biodegradation. When stored at pH <7.0 at 4 °C, the gel maintained the original strength for >3 months.

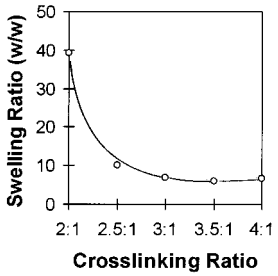

Figure 3. Effect of hydrogel cross-linking ratio (PEGBCOCl:LPEP) on swelling ratio at room temperature.

After aspirin loading, the transparent hydrogels obtained a white color.

Effect of Cross-Linking Ratio on Swelling Ratio. A 4.5:1 (PEGBCOCl:LPEP) molar ratio gives equal moles of acyl chlorides of PEGBCOCl and hydroxyl groups in LPEP because LPEP possesses nine hydroxyl groups and PEGBCOCl has two reactive acyl chlorides. A change of cross-linking ratio in these hydrogels resulted in changes of (1) the number of free end hydroxyl groups in LPEPs (below 4.5 of PEGBCOCl per LPEPs), (2) the number of PPO−PEO−PPO cross-linking chains in the hydrogels and their hydrophilicity, (3) the number of free COOH ends of cross-linking chains (in the case of ratio of PEGBCOCl per LPEP >4.5), and (4) the hydrogel density and average size of cavity space volume between the chains.

At a ratio >4.5 of PEGBCOCl per LPEP, all OH groups of the LPEP are expected to be consumed, leaving COOH groups from PEGBCOCl after hydrolysis. Although the effect of COOH groups on swelling ratio was found to be insignificant by Lin et al. (1998), these COOH groups were not considered a factor in this paper because the cross-linking ratio varied from 2:1 to 4:1.

The swelling ratios of the hydrogels at room temperature (25 °C) varied with the PEGBCOCl:LPEP cross-linking ratios. The values of swelling ratios of the hydrogels between 3:1 and 4:1 cross-linking ratios were similar. The hydrogel with a 2:1 cross-linking ratio swelled and absorbed water ∼40 times its weight (Figure 3). Below 4.5 of the PEGBCOCl per LPEP, acyl chloride groups of the PEGBCOCl should be completely reacted, leaving OH groups in LPEP as free end groups. Because the number of hydroxyl groups in LPEP is nine, the theoretical number of free hydroxyl groups in LPEP after reaction can be calculated using eq 6, provided that the PEGBCOCl:LPEP ratio is <4.5.

$$\text{no. of free OH} = 9 - (2 \times \text{PEGBCOCl:LPEP ratio}) \qquad (6)$$

Figure 3 shows that the hydration ability (swelling ratio) of hydrogels decreased when the number of free hydroxyl groups in the LPEP decreased, especially from five to three, corresponding to cross-linking ratios of 2:1 and 3:1, respectively. Because the swelling ratio of the hydrogels was affected by the cross-linking ratio below 3:1, it is suggested that more than three free hydroxyl groups in an LPEP may be required to hydrate and cause swelling of the hydrogel.

A higher degree of cross-linking by PEGBCOCl in the hydrogels increased the hydrophilicity of PPO−PEO−PPO chains because of the hydrophilic properties of PO and EO segments in the chain. Lin et al. (1998) found that there are two to five water molecules associated with each EO and/or PO unit after the hydrogel col-

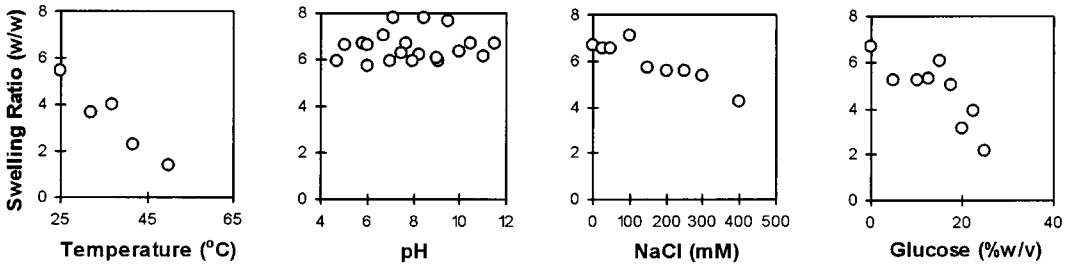

Figure 4. Effects of environmental conditions on the swelling ratio of hydrogels (3.5:1 cross-linking ratio).

lapses above the phase transition temperature. The water bound to the PPO−PPO chain was not able to liberate from the gel through thermal collapse around the phase transition temperature, producing a swelling ratio of 1−3.5 after gel collapse (Lin et al., 1998). Existence of bound water to the PEGBCOCl chain is very important, although most water molecules that participate in swelling and shrinking of the LPEP hydrogels exist as free water in the cavity between cross-linked chains. The extent of cross-linking, which affects the total hydrophilicity through EO segments, does not appear to influence the swelling behavior of those hydrogels with PEGBCOCl:LPEP ratios between 2.5 and 4. The superior swelling behavior of the hydrogel with a 2:1 cross-linking ratio suggested that the free cavity space volume is critical for the cross-linked LPEP hydrogels to absorb the water and swell. Figure 4 shows that there was no detectable swelling ratio change above 3:1 cross-linking ratio.

Effects of Aqueous Solution Conditions on the Swelling Ratio. Four different factors including temperature, pH, NaCl concentration, and glucose concentration were considered at various levels (Figure 4). Figure 4 shows the effects of aqueous solutions on swelling ratio of the 3.5:1 hydrogel. Swelling ratio decreased as temperature increased from 25 to 55 °C. Below 25 °C and above 55 °C, the swelling ratio remained constant. As temperature increased, water molecules that were associated with the hydrogel polymer components are liberated from the hydrogel, causing the gel to collapse.

The swelling ratio of the hydrogels with cross-linking ratio of 3.5:1 did not change significantly with pH. However, this result was not observed with the 3.5:1 hydrogel. This may be caused by an insufficient number of free hydroxyl groups (two in the 3.5:1 hydrogel) in the LPEP and/or by the salt cations in sodium phosphate buffer solution. An investigation to verify the pH effect on swelling and the effect of free hydroxyl groups with respect to the presence of salt is needed.

The swelling ratio of the 3.5:1 hydrogels decreased with increasing concentrations of NaCl and glucose. The hydrogel may be losing water molecules for hydration due to the presence of salt and glucose. Concentrations required to reduce the swelling ratio to half of the original value were ∼500 mM (= 0.5 M) of NaCl and 20% (= 1.1 M) of glucose. The effect of NaCl ion appeared to be stronger than that of glucose on the swelling ratio of the hydrogels.

The dramatic decrease of the swelling ratio above 15% glucose is shown in Figure 4. In the body, high glucose levels are controlled by insulin, which is normally triggered to be secreted at ∼0.1% (w/v) glucose in blood. Thus, the hydrogel may be useful as an on-line glucose sensor probe for high-concentration applications, such as syrup manufacturing, rather than a blood glucose sensor. However, if the glucose sensitivity of the hydrogels increased at ∼0.1% of glucose through increasing molecular weight of LPEPs and reducing cross-linking ratios, the hydrogel may have potential to be developed as a reversible insulin-releasing capsule for delivering insulin that depends on blood glucose level for insulin-dependent diabetics.

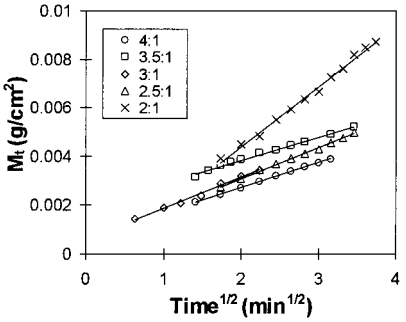

Figure 5. Aspirin release profile at various cross-linking ratios at 37 °C.

Table 1. Effect of Cross-Linking Ratio on Slope of M_t vs $t^{1/2}$ and on Diffusivity Determined from Slope (37 °C)

cross-linking ratio (PEGBCOCl:LPEP)	slope (g/cm^2 min$^{1/2}$)	r^2	diffusivity (cm^2/sec)
2:1	0.0025	0.9939	5.21×10^{-5}
2.5:1	0.0013	0.9975	1.41×10^{-5}
3:1	0.0013	0.9929	1.41×10^{-5}
3.5:1	0.0009	0.9903	6.75×10^{-6}
4:1	0.0010	0.9985	8.33×10^{-6}

Aspirin Release and Diffusivity from the Hydrogel. Figure 5 shows the amount of aspirin released from the unit surface area of the hydrogel to water. The data from the steady-state release show a very good fit to the linear model. The slopes of lines in Figure 5 were obtained by linear regression, and the slopes were found to decrease with increasing cross-linking ratio (Table 1).

Calculated diffusivities of aspirin, using eq 5, in the variously cross-linked hydrogels are shown in Figure 6. The diffusivity of aspirin from the hydrogels decreased as the cross-linking ratio increased. Therefore, the drug release rate from the hydrogel can be controlled by the cross-linking ratio of the hydrogel. This is also a very useful result for agrochemical delivery systems. The release rate of agrochemicals incorporated in hydrogels may be specifically controlled by modulating the cross-link ratio.

CONCLUSIONS

The swelling ratio of the hydrogels decreased as the cross-linking ratio increased. Free volume between cross-linked chains may act as an important factor during swelling to trap free water molecules. The

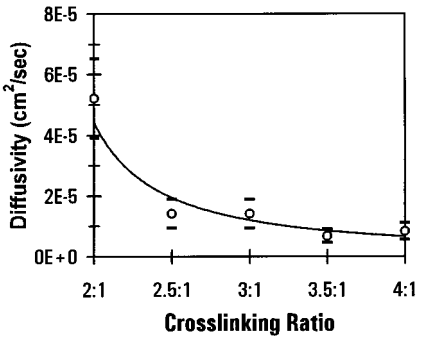

Figure 6. Effect of cross-linking ratio of hydrogels on the diffusivity of aspirin at 37 °C. Results given are averages of four replications.

swelling ratio also decreased with increasing temperature, NaCl concentration, and glucose concentration. The pH did not significantly affect the swelling ratio of the hydrogels. The hydrogels lose associated water molecules by temperature increase or when the water is competitively hydrated by salt and glucose. The swelling ratio of the hydrogels changed reversibly in response to the environmental solution conditions. This property may be used for developing environmentally responsive delivery systems or biosensor probes.

The aspirin release profiles from the hydrogels were sensitive to the cross-linking ratio. Highly cross-linked hydrogels showed slower release of aspirin than the lightly cross-linked hydrogels. The diffusivities of aspirin from cross-linked hydrogels were found to decrease as the cross-linking ratio increased. Therefore, the results suggest that the release rate of incorporated chemical may be controlled by changing the cross-linking ratio of the hydrogels.

ACKNOWLEDGMENT

We thank David Chacon (currently in the Department of Chemical Engineering, University of Colorado) for the synthesis of poly(ether polyol).

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Received for review December 7, 1999. Revised manuscript received August 1, 2000. Accepted August 3, 2000. We appreciate funding from the California Milk Advisory Board and Wisconsin Milk Marketing Board through the California Dairy Research Foundation and California Dairy Foods Research Center.

JF991329A