Photopatterning and Degradation Study of Dextran-Glycidyl Methacrylate Hydrogels*

Chi-Wei Lo,[1] **Hongrui Jiang**[1,2]
[1] *Materials Science Program, University of Wisconsin-Madison, Wisconsin 53706*

[2] *Department of Electrical and Computer Engineering, University of Wisconsin-Madison, Wisconsin 53706*

An approach to synthesizing photopatternable enzymatic degradable dextran hydrogel is presented. The glycidyl methacrylate derivatized dextran (Dex-GMA) was first prepared by reacting dextran with glycidyl methacrylate at 45°C with grafting efficiency of 10%. The degree of substitution (DS) was confirmed by ^{1}H-NMR. Next, Dex-GMA hydrogels were prepared by crosslinking in the presence of a crosslinker: *N*,*N*′-methylene-bisacrylamide (NMBA), and a photoinitiator: 2,2′-dimethoxy-2-phenyl acetophenone (DMPA) in dimethyl sulfoxide (DMSO) solution. Further, the Dex-GMA hydrogels were photopatterned using liquid-phase photopolymerization (LP^3) technique. The structure size ranged from 5 mm to 300 μm and three different shapes of structures—round, square, and star—were demonstrated. The patterned Dex-GMA hydrogel structures not only exhibited mechanical robustness but also biodegradability. The dextranase-catalyzed degradation of Dex-GMA hydrogels with different DS was investigated at 37°C. The morphology of the degraded Dex-GMA hydrogels determined by SEM revealed the degree of enzymatic degradation due to dextranase. The Dex-GMA hydrogel was fully degraded by dextranase with concentration of 2 U/ml in 5 days. The Dex-GMA hydrogel also showed the ability to be readily integrated with microfluidics. POLYM. ENG. SCI., 50:232–239, 2010. © 2009 Society of Plastics Engineers

INTRODUCTION

Biodegradable polymers have been widely investigated targeting controlled drug delivery systems [1]. However, the sensing of chemical and biological species using biodegradable polymers is also gaining interests for many potential applications in microelectromechanical systems (MEMS) [2, 3], healthcare [4], and homeland security [5, 6]. For example, it was recently shown that the degradation of a thin film in the presence of an enzyme can be utilized to produce a highly sensitive disposable biosensor [7–9]. Another promising approach was also recently demonstrated, utilizing microscale polymer membranes that were specifically dissolved by target analytes [10, 11]. In these works [7, 10, 12], dissolvable hydrogels with cleavable crosslinkers were designed and fabricated in microfluidic channels.

Hydrogels are superabsorbent natural or synthetic polymers which may contain over 99% water in their three-dimensional structure without dissolution [12]. Hydrogels, both synthetic and natural, are highly biocompatible and can be used for scaffolds in many biomedical applications [13], microoptics [14], and drug delivery [15]. Synthetic hydrogels are appealing for tissue engineering because their chemical and physical properties are tunable and reproducible through molecular design. For example, synthetic hydrogels can be produced with specific molecular weight, lowest critical solution temperature (LCST), or different mechanical robustness. These hydrogels are typically composed of hydrophilic monomers that can be crosslinked when suitable crosslinker is added. In rheological terms, once crosslinks between polymer chains are introduced, the so-called viscoelastic characters become phenomenal. Because of their water-absorbing capacity and biocompatibility, hydrogels are not only receiving great attentions from scientific researchers but have also found various applications in different technological areas [3, 16, 17].

Various types of synthetic and naturally derived hydrogels have been developed. Synthetic hydrogels include poly(ethylene oxide) (PEO), poly(vinyl alcohol) (PVA), poly(*N*-isopropy lacrylamide) (PNIPAAm), and poly(acrylic acid) (PAA). From the hydrogels found in nature, polysaccharides such as dextran have particular relevance in biomedical applications [18]. Dextran is a polysaccharide composed of straight chain consists of α-1,6 glycosidic linkages between glucose molecules, while branches begin from α-1,4 linkages and there are three

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Correspondence to: Hongrui Jiang; e-mail: hongrui@engr.wisc.edu
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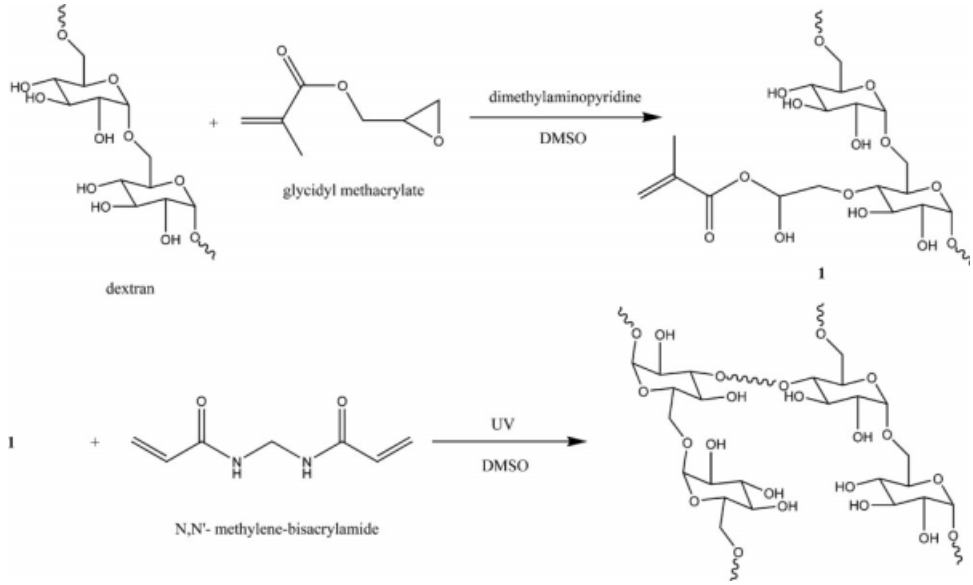


SCHEME 1. Synthesis route of Dex-GMA hydrogel. The dextran is first reacted with glycidyl methacrylate to form crosslinking side chain. The Dex-GMA is then photocrosslinked in DMSO solution under UV exposure.

hydroxyl groups per anhydroglucose unit, which makes it very soluble in water. Dextran is glucose polymers which have been used as a plasma expander for five decades to reduce blood viscosity [19, 20]. Recently, they have been found capable of serving as molecular carriers for delivery of drugs and proteins because of its good water-solubility and high biocompatibility [21]. Dextrans contain a large number of hydroxyl groups which can be easily modified and ready to form hydrogel by either direct attachment or through a crosslinker. Dextran hydrogels have been studied to be a promising candidate for drug delivery [22]. Although dextran hydrogels have been developed and studied for many years, particularly their interior structure in degraded states, it has not been reported so far to be photopatternable, thus limiting their further applications in microdevices, which usually rely on photolithography to accurately define the structures.

Here we introduce a gycidyl derivatized dextran hydrogel. Glycidyl methacrylate is less harmful to the human body than other reagents commonly used for the incorporation of vinyl groups, such as acryloyl chloride are more reactive than glycidyl methacrylate [18]. The epoxy group of glycidyl methacrylate is not stable enough and can be readily broken by a nucleophilic attack of the hydroxyl groups in dextran under the aid of catalysts. Therefore, dextran-glycidyl methacrylate (Dex-GMA) could easily be synthesized as a hydrogel precursor by taking advantage of the functionality of the hydroxyl groups in dextran as well as the instability of the epoxy group in glycidyl methacrylate. Upon exposure to a sample solution that contains dextranase, the polymer chain is cleaved and the synthesized hydrogels incorporating Dex-GMA can dissolve in the sample solution. In this paper, we report a technique for photopatterning Dex-GMA hydrogel that is capable of enzymatic degradation.

EXPERIMENTAL

Materials

The dextran (MW = 70,000) was obtained from Sigma-Aldrich Chemical (St. Louis, MO). Glycidyl methacrylate (GMA), dimethylsulfoxide (DMSO), 2,2′-dimethoxy-2-phenyl acetophenone (DMPA), 4-(*N*,*N*-dimethylamino)pyridine (DMAP), hydrochloric acid (HCl), isobornyl acrylate (IBA), tetraethylene glycol dimethacrylate (TGDA), and *N*,*N*′-methylene-bisacrylamide (NMBA) were purchased from Aldrich Chemical (Milwaukee, WI). A Phosphorus buffer saline (PBS) buffer solution (pH 7.4) was purchased from Fisher Scientific (Fair Lawn, New Jersey). Dextranase (100 U/mg) was obtained from MP Biomedicals (Santa Ana, CA).

Synthesis of Dextran-Methacrylate

The synthesis of dextran-methacrylate leverages the methods published by Edman et al. [23]. The general synthesis route is shown in Scheme 1. In summary, dextran (2 g) and DMAP (0.2 g) was dissolved in 150 ml of DMSO at room temperature. After dissolution of DMAP, a certain amount of glycidyl methacrylate as listed in Table 1 was added. The mixture was stirred at 45°C for 24 h in ambient condition. To quench the reaction, an equimolar amount of HCl was added to the solution to neutralize DMAP. The neutralized dextran polymer was then precipitated with isopropanol (IPA) and the white fluffy dextran-methacrylate (Dex-GMA) polymers were obtained. The polymers were further dissolved in deionized water and reprecipitated out with IPA three times. To increase the yield, the precipitates were obtained in a centrifuge at 3000 rpm for 2 min. Centrifugation was per-

TABLE 1. Amount of glycidyl methacrylate and hydroxyl group of dextran and the measured DS for the synthesis of glycidyl methacrylate-substituted dextran.

[Hydroxyl Group] (mole)	[Glycidyl Methacrylate] (mole)	DS*
0.0124	0.005	3
0.0124	0.010	7
0.0124	0.016	9

* The DS is defined as the number of substituent per 100 glucose residues.

formed with a Thermo Electron Centra Biofuge Primo equipped with a rotor (Model 854). The product was dried in vacuum at room temperature for 24 h. The purified Dex-GMA was characterized by NMR spectroscopy.

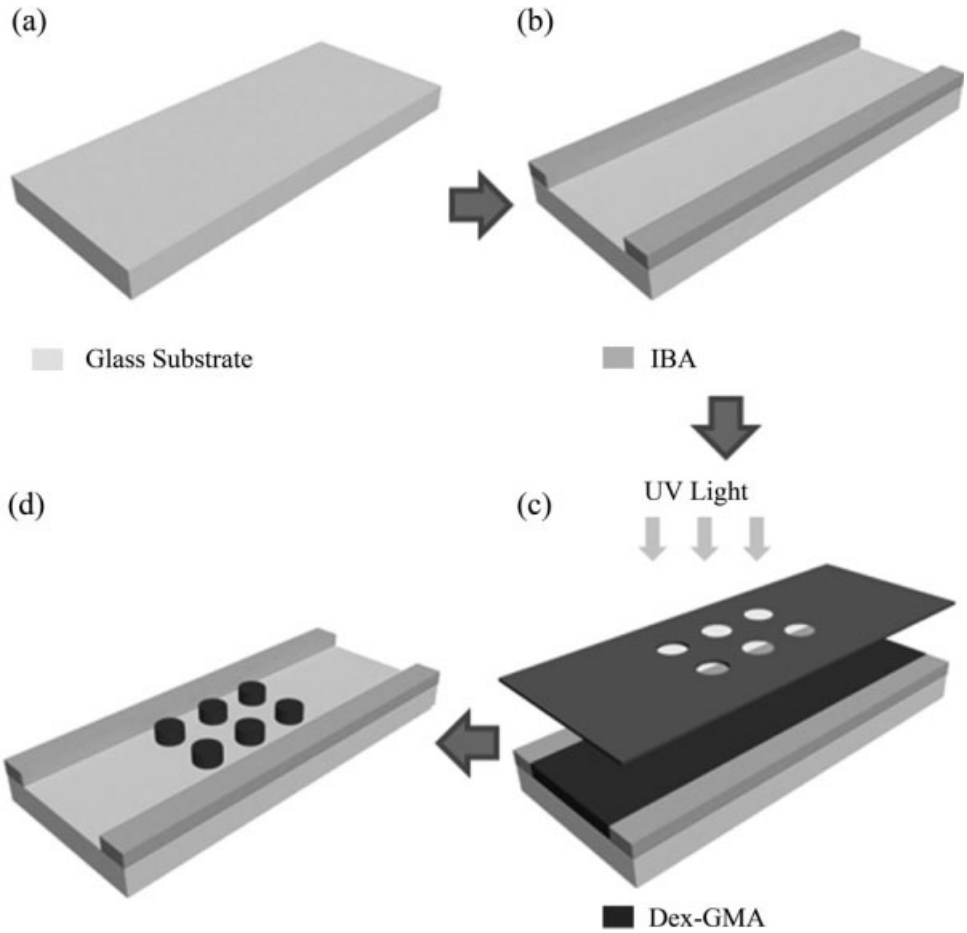
Preparation of Dex-GMA Hydrogel

To synthesize Dex-GMA hydrogels, Dex-GMA (0.5 g), and NMBA (0.06 g, 0.39 mmol) were dissolved in DMSO (2.0 ml), and the solution was stirred for 10 min. The photoinitiator, DMPA (0.04 g, 0.33 mmol), was added to the stirred solution to reach complete dissolution.

Photopatterning of Dex-GMA Hydrogel

To pattern the Dex-GMA structures, we employed liquid-phase photopolymerization (LP^3), which has been found very helpful in microfluidic fabrication. This process is described in detail elsewhere [24–26]. The step-and-repeat LP^3 process is illustrated in Scheme 2.

A micro chamber was first created by placing a cartridge with a thickness of 250 μm on a glass slide. The chamber was then filled with IBA prepolymer solution. This solution consists of a monomer: IBA, crosslinker: TGDA, photoinitiator: DMPA in the ratio (by weight) 1.9:0.1:0.06. The device was exposed to a 365 nm UV lamp (Acticure 4000, Exfo Life Sciences and Industrial Division, Mississauga, Ontario, Canada) through a film photomask (3000 dpi, Imagesetter, Madison, WI) having the pattern of the microfluidic channels. The photopolymerization conditions were intensity = 7.8 mW/cm^2 and



SCHEME 2. The fabrication process. The drawing is not to scale. (a) A microscope glass slide is cleaned with isopropanol alcohol. (b) Formation of the fluidic channels: liquid-phase photopolymerization is employed to form the fluidic channels. (c) Forming the hydrogel structures: the Dex-GMA prehydrogel liquid mixture is introduced into the fluidic channels through filling ports (not shown). A masked liquid-phase photopolymerization step is used to define the Dex-GMA. (d) The unexposed Dex-GMA is washed away with water and the patterned Dex-GMA structures are formed.

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exposure time = 22.5 s. The liquid pre-polymer polymerized in regions exposed to UV, forming the channel walls, and the unpolymerized prepolymer was flushed in a bath of ethanol (100%) for 3 min.

Next, Dex-GMA hydrogel structures were defined in the microfluidic channels using the LP^3 method. Upon UV exposure, DMAP produced free radicals which initiated the crosslinking reaction of Dex-GMA and NMBA. The dimension of the patterned structure ranged from 5 mm to 300 μm in width, and the shapes included round, square, and star. The prehydrogel solution was introduced into the microfluidic channels, followed by photopatterning with intensity = 30 mW/cm^2 and exposure time = 30 s to form the Dex-GMA hydrogel structures. The device was flushed with water and ethanol to remove the residual unpolymerized chemicals in the hydrogel. The whole device was taken to stereoscope for further inspection for structural defects and degradation tests.

Characterization

^{1}H-NMR spectra were recorded with a Bruker AC at 300 MHz with tetramethylsilane (TMS) as the internal reference and DMSO-d_6 as solvent. The degree of substitution was calculated by dividing the peak area of double bond regions (6 $\sim$ 7 ppm) by the peak area of hydroxyl hydrogen in dextran (4.5 $\sim$ 5.5 ppm) in ^{1}H-NMR spectra.

Degradation Tests

For the degradation test, a Dex-GMA hydrogel thin film was used. The prehydrogel solution was first cast onto a glass slide to form a thin film. The prepolymer solution was then exposed by the UV light source for 30 s with the intensity of 30 mW/cm^2. After UV exposure was completed, the hydrogel was rinsed with DI water and DMSO to wash away unwanted initiators and crosslinkers.

The degradability of Dex-GMA hydrogels was determined by flowing pH 7.3 PBS solution containing dextranase enzyme. Enzyme solutions were prepared on the day of experiment using the same phosphate buffer. Dextranase (2 U/ml, or 0.02 mg/ml) was added to 200 ml of buffer solution. The whole assembly carrying the Dex-GMA hydrogel film was dipped into the dextranase buffer solution at room temperature for 72 h. The weight loss was recorded every 6 hours to monitor the rate of degradation. The enzyme degraded film was then carefully removed from the buffer solution and rinsed with deionized water followed by drying in vacuum. The degradation of the hydrogels was estimated by measuring the weight of the hydrogels. The dried hydrogels were then taken for topographical analysis under SEM.

Scanning Electron Microscopy (SEM) Characterization

For the preparation of the degraded Dex-GMA hydrogel specimen for SEM observation, a Dex-GMA film was placed in the dextranase buffer solution with pH 7.3 for 24 h. For comparison, the control Dex-DMA film was equilibrated in PBS solution without dextranase for 24 h at room temperature. The Dex-GMA films were then air-dried. Glass slides with the specimens were next mounted onto an aluminum stud and sputter-coated with gold/palladium for 120 s. The thickness of gold/palladium thin film was about 25 nm. Both the degraded and the undegraded Dex-GMA hydrogel specimens were investigated by a field emission scanning electron microscope (Leo Model 4500) at 5.0 kV.

RESULTS AND DISCUSSION

Synthesis

The synthesis of Dex-GMA is illustrated in Scheme 1. The hydroxyl groups of dextran were polarized by the base catalyst and reacted subsequently with the less hindered epoxy carbon of glycidyl methacrylate with the aid of catalyst DMAP at 45°C for 24 h. DMAP was added as Lewis base to enhance the nucleophilicity of the hydroxyl groups of the dextran polymers to form 3-methacryloyl-1-glyceryl ether of dextran [27]. The reaction was quenched by adding equimolar amount of HCl as DMAP, which was then washed away by repeated precipitation in IPA. The yield of the Dex-GMA was 45 $\sim$ 60%, depending on the degree of substitution. The yield decreased as the degree of substitution increased due to the increasing solubility which made precipitation difficult during purification. The efficiency of the grafting reaction was calculated, based on data shown in Table 1, to be about 10%. It was also observed that the solubility of Dex-GMA polymers in common organic solvents and water was enhanced significantly compared to that of the original dextran polymers. The enhanced solubility of Dex-GMA polymer in DMSO also increased the loss of product during water/IPA precipitation purification process. It was also observed that the solubility of Dex-GMA decreased as the pH value decreased. These observations were consistent with a previous report [18]. A small amount of acid and the use of centrifuge helped Dex-GMA to precipitate more efficiently in order to increase yield during purification process.

The methacrylate groups in Dex-GMA hydrogel can polymerize to form a crosslinked structure. The crosslinking reaction can be carried out in mixture of water and kDMSO and thus a hydrogel is formed. Previously Kim and Chu [18] reported a method of direct photocrosslinking that took 2 h to form dextran hydrogels without the addition of external crosslinkers. The long crosslinking process might be due to a methacrylate side group that is attached to the dextran polymer chain, which reduces the

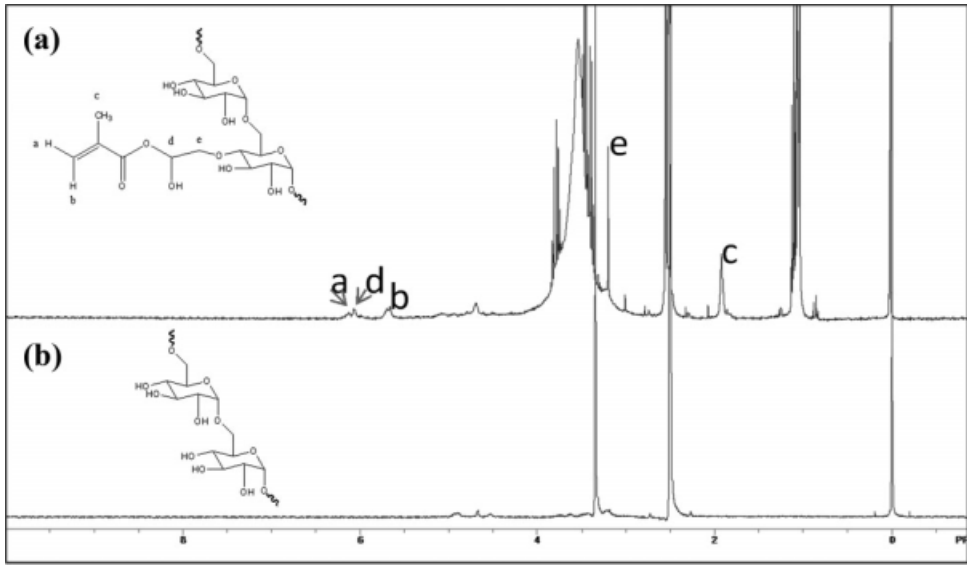

FIG. 1. ^{1}H-NMR spectra of (a) dextran and (b) Dex-GMA. There are two distinctive peaks in the double bond region (5.690 and 6.115 ppm) that correspond to the two hydrogens adjacent to the double bond ($C = CH_2$).

degree of freedom in the absence of additional crosslinkers. Thus, the less degree of freedom, the slower the reaction rate was. Based on this assumption, we introduced NMBA as the external crosslinker into the Dex-GMA hydrogel. A noncrosslinking monomer might be better for uniform degradation, but we need to balance between degradability and photopatternability of Dex-GMA hydrogel. In our case, NMBA was dissolved in solution and had more degree of freedom, which is conducive to the photocrosslinking process. The crosslinking reaction was initiated by adding photoinitiator DMPA in the dextran prehydrogel solution which contained Dex-GMA and NMBA, followed by UV exposure. The results were significant in that the reaction time was reduced to as short as 30 s. The pre-hydrogel thin film switched from transparent to opaque, indicating that crosslinking reaction had occurred. The mechanical robustness of the as-produced film was strong enough to sustain the following patterning steps in the micrifluidic channels. The reaction time was short so that it is suitable for microfabrication applications, and could be readily integrated with microfluidics.

The presence of pendant glycidyl methacrylate groups in Dex-GMA, was confirmed further by the ^{1}HNMR spectrum shown in Fig. 1. There were two distinctive peaks in the double bond region (5.690 and 6.115 ppm) that correspond to the two hydrogens adjacent to double bond ($C = CH_2$). These two peaks were not present in the spectrum of the original dextran shown in Fig. 1(b). An integration and normalization of these double bond peaks in the methacrylate segment and the hydroxyl hydrogen peaks of the dextran backbone (4.3∼5.5 ppm) could provide us with a consistent means for calculating the degree of substitution of hydroxyl groups in dextran by the methacrylate group, and such data are shown in Table 1. In this table, methacrylate content was assigned 100% when all of the three hydroxyl groups per anhydroglucose residue unit in dextran were substituted. The hydrogens of the methyl substitute (CH_3) in the glycidyl methacrylate group were also observed as a single peak, at 1.903 ppm. This strong peak might also be contributed by IPA residue due to its strong peak intensity.

In this study, we also found that gelation time was shortened by increasing the crosslinker concentration. Yamaguchi et al. [28] previously reported that gelation time could be shortened by increasing the initiator concentration. They suggested that the observed faster rates at a higher photoinitiator concentration reflect a greater fraction of light absorbed by the sample and the corresponding increase in the concentration of the photogenerated species that were responsible for initiating polymerization. We found that a higher concentration of crosslinker could also decrease the gelation time due to the greater chance of reacting with glycidyl methacrylate side group in Dex-GMA hydrogel. It seems that the crosslinker concentration is more effective in improving the reaction time, because much shorter reaction time (∼30 s) was observed than previous report [28].

Photopatterning of Dex-GMA Hydrogel in Microfluidics

The Dex-GMA hydrogel precursor synthesized by our method had very good water/solvent solubility. A good water/solvent solubility of hydrogel precursors is a useful property, especially when these hydrogels are integrated into microfluidics. Here, we demonstrate the photopatterning of Dex-GMA hydrogel structures within microfludic

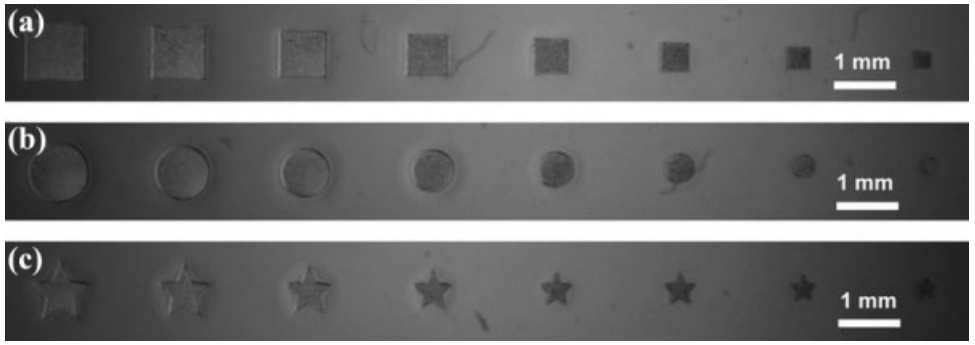

FIG. 2. Optical images of patterned Dex-GMA hydrogels of different feature sizes taken with a microscope: 1000 μm, 900 μm, 800 μm, 700 μm, 600 μm, 500 μm, 400 μm, and 300 μm from left to right. The shapes included (a) square, (b) round, and (c) star. The double images were due to the reflection from the glass substrate.

channels using LP^3. The structure size ranged from 5 mm to 300 μm and the structures included three shapes—round, square, and star. The thickness of the microfluidic channels was 250 μm. We chose the Dex-GMA hydrogel with the highest DS (DS = 9) among those three shown in Table 1. The results show that the Dex-GMA can be photocrosslinked within 30 s in microfluidic channels; good fidelity was achieved for structures as small as 300 μm. The Dex-GMA hydrogels in the microfluidic channel maintained acceptable integrity and shape compared to the designed patterns as the hydrogels were formed. The minimum dimension reached for the patterned Dex-GMA structures here is consistent with those obtained for other photopatternable polymers that we previously reported using LP^3 [10]. The minimum feature size was limited by our instrument, because the UV light from the source was not collimated. With better lithography tools, the feature size could be even smaller. The patterned structures of the selected Dex-GMA hydrogel are shown in Fig. 2.

There is a tradeoff between increasing the crosslinking density and the degradation response. It is desirable to have a fast response hydrogel while maintaining mechanical robustness. We might improve the degradation response by shrinking the structure size, or increasing the surface area in order to increase the accessibility of dextranse, while maintaining the mechanical strength. In addition, the hydrogel structures need to be homogeneous. Since the prehydrogel liquid is homogeneous, the other factor that can cause inhomogeneity is the spatial distribution of light intensity during photopolymerization. To compensate for this, the sample was kept on a rotating circular disc during photopolymerization, which spatially averaged the dose applied to the sample.

Here we chose NMBA as crosslinker because we intend to use the resulting dextran hydrogel in microfluidics, which might be subject to physical stimuli such as temperature and pH. NMBA is relatively insensitive to both. According to Kumashiro et al. [29], the introduction of acrylamide based crosslinker will change the degradation behavior. It was found that the enzymatic degradation of all the hydrogels was significantly inhibited below the lower LCST and above the higher LCST because of the steric hindrance of the graft chain (below the lower LCST) and shrinking of the poly(NIPAAm) copolymer crosslinker (above the higher LCST). Based on these findings, we assume that using methyl acrylamide or HEMA as crosslinkers might affect the degradation behavior of the dextran gel. We should note, though, that these non-crosslinking monomers would reduce the porosity of the Dex-GMA gel for more uniform degradation.

Degradation

The dextranase-catalyzed degradation of bulk Dex-GMA hydrogels with different DS was assessed by measuring the residual weights at room temperature (see Fig. 3). Without dextranase, there was no significant weight change in any of the hydrogels as a function of time. The weight loss of the hydrogels was observed only in the presence of dextranase. These results indicate that the dextran chain in these Dex-GMA hydrogel can be

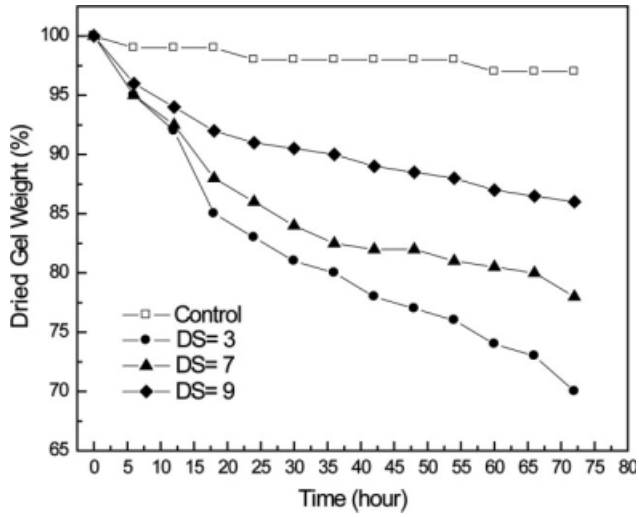

FIG. 3. Enzymatic degradation of dextran hydrogels. The data was taken every 6 h for 72 h. The results show that the percent of weight loss decreases with increased DS.

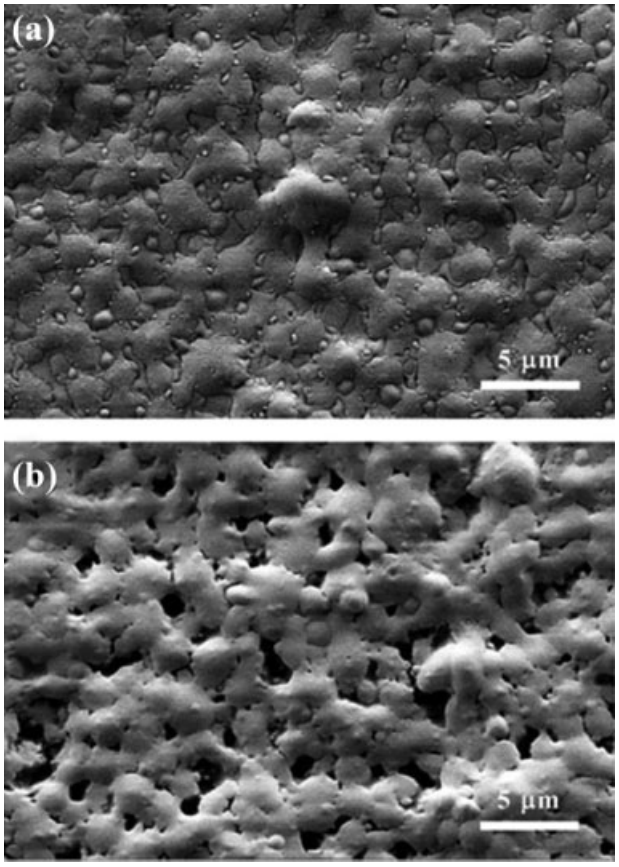

FIG. 4. Surface morphologies of Dex-GMA hydrogel with and without degradation by dextranase are studied by SEM: (a) nondegraded Dex-GMA hydrogel; (b) Dex-GMA hydrogel degraded by dextranase containing buffer solution for 24 h.

accessible to dextranase diffused into the hydrogel. The results are shown in Fig. 3. The degree of degradation decreases as DS increases which is consistent with the results reported by Hennink and coworkers [30]. A possible explanation is that the dextran chains are not only severely strained in hydrogels but their accessibility for dextranase is reduced as well, because of the formation of interpenetrating crosslinking networks. As the DS increases, the degree of crosslinking increases, so the accessibility of dextranase would be decreased and thus showing slower rate of degradation.

Surface structures of degraded Dex-GMA hydrogel (DS = 3) for 24 h were studied by SEM and are shown in Fig. 4. The undegraded Dex-GMA hydrogel shows a relatively smooth surface with many random small cracks without any pores, while the degraded hydrogel exhibits rugged and porous morphologies [Fig. 4(b)], due to the degradation of dextranse in the buffer solution. The pores assumed an irregular shape and the diameter of these pores was around 1 μm. The degraded Dex-GMA films were relatively weak in terms of mechanical robustness compared to undegraded Dex-GMA hydrogel films. We should note that this SEM image is of a dried film which does not necessarily represent the film as the microfluidic channel. Further study of the porosity of the film within microfluidics, e.g., as a filtering device, will be performed.

We also performed degradation of Dex-GAM hydrogel in microfluidic channels. The results are shown in Fig. 5. The Dex-GMA hydrogel membrane bore a rectangular shape after fabrication with the dimension of 3 mm $\times$200 μm $\times$ 250 μm (length $\times$ width $\times$ height). As degradation proceeded, the Dex-GMA membrane became blurry and transparent. The Dex-GMA membrane completely disappeared after 5 days. The degradation rate was faster than that of the bulk Dex-GMA hydrogels tested for Fig. 3 because the membrane in the microfluidic device is much smaller and thinner than the casted films. Therefore,

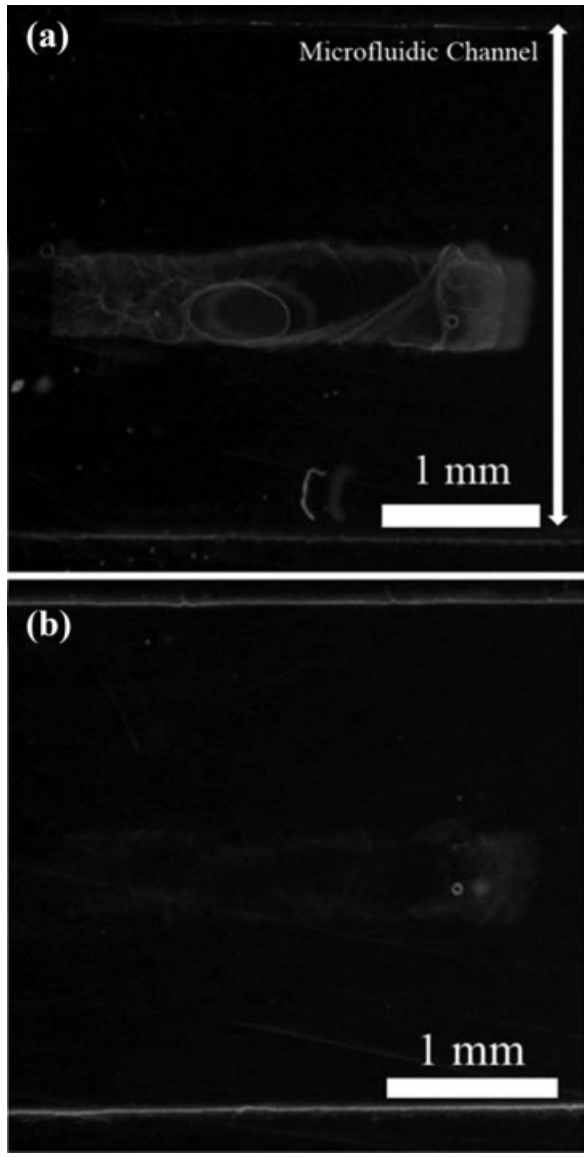

FIG. 5. Degradation of a Dex-GMA hydrogel membrane patterned in a microfluidic channel. The images were taken under a microscope: (a) The patterned Dex-GMA hydrogel fabricated in the microfluidic channel; (b) the Dex-GMA hydrogel was completely degraded in dextranase solution after 5 days.

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dextranase in microfluidic device had larger degree of accessibility. With this degradation behavior, the Dex-GMA hydrogel could potentially be used as a sacrificial material for microfluidic fabrication [31]. Further investigation on the material properties of the Dex-GMA hydrogel includes approaches to shorten the degradation time. It is also interesting to extend the synthesis approach to other biological and chemical analytes for immunosensors based on the detection of enzymes.

CONCLUSION

The synthesis and photopatterning in microfluidic channels of Dex-GMA hydrogel was studied. Dextran derivatives with different DS were synthesized and confirmed by ^{1}H-NMR. The photopatterning of Dex-GMA hydrogel in microfluidic channels was realized utilizing LP^3 photopatterning process. A feature size of 300 μm was easily achieved in different shapes (round, square, and star), while acceptable integrity was maintained. The addition of NMBA shortened the duration of photocrosslinking process and enabled the integration with microfabrication processes. Degradation of Dex-GAM hydrogel in microfluidic channels was also investigated. Results show that Dex-GMA hydrogels can be degraded in the presence of dextranase in microfluidic channels. The morphology of the degraded Dex-GMA hydrogel was studied under SEM and results show that porosity increased after Dex-GMA hydrogel was degraded. Dex-GMA hydrogel was fully degraded in microfluific channels in 5 days.

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