New Hydrolysis-Dependent Thermosensitive Polymer for an Injectable Degradable System

Zhanwu Cui, Bae Hoon Lee, and Brent L. Vernon*

The Harrington Department of Bioengineering, Center for Interventional Biomaterials, Arizona State University, Tempe, Arizona 85287-9709

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Novel, bioerodible, thermosensitive poly(NIPAAm-*co*-dimethyl-γ-butyrolactone acrylate), with a hydrolysis-dependent thermosensitivity, was synthesized by radical polymerization with a varying dimethyl-γ-butyrolactone acrylate (DBA) content, and the properties of the copolymers were characterized using differential scanning calorimetry, gel permeation chromatography in conjunction with static light scattering, Fourier transform infrared spectroscopy (FTIR), nuclear magnetic resonance (NMR), and acid titration. The lower critical solution temperature of the copolymers decreases with increasing DBA content, but then increases after ring-opening hydrolysis of the DBA side group. FTIR and NMR spectra showed the copolymerization of these two monomers and the hydrolysis-dependent ring-opening of the DBA side group. It was also found that there are no low-molecular-weight byproducts but rather dissolution of the polymer chains at 37 °C during the time frame of application. Models of the kinetics suggest that the hydrolysis reaction is self-catalytic due to an increase in hydrophilicity and charge, and thus accessible water concentration, caused by ring-opening of the DBA.

Introduction

A temperature-sensitive polymer, poly(*N*-isopropylacrylamide) (poly-(NIPAAm)), and its copolymers have been of interest for biomedical applications, such as drug delivery, cell immobilization, in situ gelling implantation, and tissue engineering.[1−3] Many thermosensitive polymer solutions have a lower critical solution temperature (LCST), a temperature at which these polymers in aqueous solution experience a phase change from a soluble state to an insoluble state. Poly(NIPAAm) exhibits a LCST at 32 °C.[4,5] It has been suggested that this temperature-induced phase transition of poly(NIPAAm) in aqueous solution is mainly driven by the thermal destruction of hydrogen bonds between water molecules and hydrophilic groups, such as −CO− and −NH− in the NIPAAm monomer and the increased interaction between the hydrophobic segments on the polymer with increased temperature.[6−10] The LCST of poly(NIPAAm) copolymers can be controlled by varying the monomer composition. Generally, the incorporation of hydrophobic comonomers leads to a lower LCST, and that of hydrophilic comonomers leads to a higher LCST. Acrylic acid increases the LCST of poly(NIPAAm) at neutral pH;[11−13] 2-hydroxyethyl methacrylate-monolactate (HEMA-monolactate) lowers the LCST of poly(NIPAAm).[14−17]

One challenge with using poly(NIPAAm) in biomedical applications such as controlled drug delivery is that poly-(NIPAAm) is not degradable, limiting its application in temporary implantation applications. The existence of a non-degradable polymer in the human body may cause chronic inflammatory response, and so biodegradable polymers for a controlled drug release system are preferred. In response, several groups have been working to make biodegradable NIPAAm copolymers. Neradovic et al. reported the synthesis of a new type of thermosensitive NIPAAm copolymers with hydrolyzable lactate ester side groups in which the LCST increases after the hydrolysis of the ester groups.[11,14−17] In this system, a low molecular weight byproduct of the degradation is lactic acid. Synthesis of NIPAAm with a cyclic monomer, 2-methylene-1,3-dioxepane (MDO), and its biodegradable properties have been described by Sun et al.[18] Yoshida et al. reported the synthesis of the NIPAAm copolymers cross-linked with biodegradable poly(amino acid).[19] Neradovic et al. and Lee et al. reported thermosensitive and bioerodible hydrogels with time-dependent LCST properties.[16,20] In these studies, there are various small molecules produced after the degradation of the polymers. Although small molecules can be cleared by the kidneys, they can also be toxic. As an example, decreases in pH in the local environment can be cytotoxic in the case of lactic acid.[21−23]

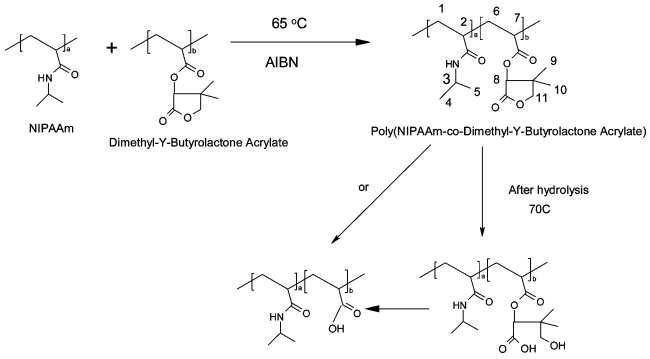

Figure 1. Synthesis scheme and hydrolysis of copolymer poly-(NIPAAM-*co*-DBA).

In this work, we propose the synthesis of a new type of NIPAAm copolymer that contains both thermosensitive and bioerodible properties without low molecular weight byproducts. This hypothesized copolymer would be useful in injectable, in situ gelling controlled drug delivery systems. The LCST property of poly(NIPAAm) copolymers makes them attractive candidate materials for injectable drug release systems. Such systems could avoid surgical implantations accompanied by drug administration. Drugs or cells can be suspended in the polymer solution,

* To whom correspondence should be addressed. E-mail: brent.vernon@asu.edu. Tel.: (480) 965-0929. Fax: (480) 727-7624.

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Table 1. Characterization Results: Feed Ratio, Chemical Composition, Molecular Weight, and LCST Before and After Complete Hydrolysis

	DBA content (mol %)				LCST (°C)	
polymer	Feed ratio	composition	M_w (g/mol)	Pd (M_w/M_n)	before	after
1	3	2.9 ± 0.2	1.6×10^5	1.94	25.8 ± 0.1	36.8 ± 0.1
2	5	5.5 ± 0.5	1.5×10^5	1.94	23.3 ± 0.1	41.8 ± 0.2
3	7	6.0 ± 0.2	1.3×10^5	2.00	20.8 ± 0.2	43.1 ± 0.4
4	10	7.2 ± 0.2	8.6×10^4	1.99	16.3 ± 0.1	50.0 ± 0.2

and then upon injection, the polymer solution will gel due to an increase in temperature from room temperature to body temperature. The suspended drugs will diffuse out of the gel. In a physiological environment, the polymer will undergo hydrolysis, and this is expected to lead to an increase in the LCST with time. When the LCST increases above body temperature, the polymer becomes soluble again and diffuses away.[24]

In this work, (*R*)-(+)-α-acryloyloxy-*β*,*β*-dimethyl-*γ*-butyrolactone (DBA) was selected as the second monomer. There are two ester groups in the DBA structure. One is connected to the polymer backbone, and the other is in the ring-structure. Because of these two ester groups, there are two possible reaction paths for the degradation of DBA. If the ester group in the ring-structure is broken sufficiently faster than the ester near the backbone, a thermosensitive and bioerodible copolymer will be obtained without low molecular weight byproducts, which is expected. If the reaction rates of hydrolysis of the esters are similar or the ester near the backbone degrades faster than the ring-ester, there will be an undesired low molecular weight byproduct after hydrolysis before the polymer would be cleared from the body. In this second mechanism, the ester group connected to the backbone is broken directly with or without ring-opening and the ring-structure separates from the backbone. In either route of hydrolysis, it is expected that this copolymer will have time-dependent thermosensitive properties. Therefore, the purpose of this work was to synthesize poly(NIPAAm-*co*-DBA) and evaluate its hydrolysis route and kinetics to determine the feasibility of designing injectable drug delivery systems with this material.

Materials and Methods

Materials. All materials were reagent grade and obtained from Aldrich unless otherwise noted. NIPAAm was dissolved in hexanes (10 g in 100 mL at 40 °C) and then recrystallized at room temperature. DBA was used as received. 2,2′-Azobisisobutyronitrile (AIBN) was dissolved in methanol (1 g/20 mL) at room temperature and recrystallized at −20 °C. Anhydrous 1,4-dioxane was used as the polymerization solvent and was treated by molecular sieve to remove the dissolved water before use. HPLC grade tetrahydrofuran (THF) was used as the mobile phase for static light scattering (MiniDawn, Wyatt Technology Corporation)/gel permeation chromatography (GPC) (Shimadzu Corporation). Phosphate buffered solution (PBS) at pH 7.4 was used as the solvent for multi-cell differential scanning calorimetry (DSC) (Calorimetry Science Corporation).

Synthesis of Poly(NIPAAm-*co*-DBA). Figure 1 shows the copolymerization scheme and the proposed degradation of the copolymer. Poly(NIPAAm-*co*-DBA) was synthesized in 1,4-dioxane at 65 °C for 16 h by radical polymerization. The feed ratio of DBA was varied from 3 to 10 mol % (Table 1). AIBN (7×10^{-3} mol of AIBN/mol of monomer) was used as the initiator for all reactions. The reaction was bubbled with nitrogen (N_2) for 15 min before adding the initiator and then maintained under a nitrogen environment throughout the reaction to reduce oxygen. After polymerization, the solution was filtered, and the solvent was evaporated. Then, the copolymer was dissolved in acetone and collected by precipitation in 14−15-fold-excess of diethyl ether. Finally, the copolymer was vacuum-dried for 24 h.

DSC. The LCST of the synthesized copolymers was evaluated by DSC. Scans were taken on 5 wt % solutions in 0.1 M PBS (pH 7.4) at 1 °C/min from 0 to 80 °C. A minimum of triplicates was performed for each copolymer before, after, and at various time points during hydrolysis.

Molecular Weight and Polydispersity Determination. The molecular weight and polydispersity of the synthesized copolymers were determined by GPC (Shimadzu VP) in conjunction with static light scattering using tetrahydrofuran THF as the mobile phase. The molecular weight for each copolymer was approximated from the light scattering data (Wyatt MiniDawn). The sample was prepared by dissolving the copolymer in THF with a concentration of 5 mg/mL.

Fourier Transformed Infrared Spectroscopy (FTIR). FTIR (Thermoelectron Nexus 470) was used to determine the chemical composition of the synthesized copolymer. ATR-FTIR was conducted on the copolymers as thin films cast from THF on a diamond ATR crystal before, after, and during hydrolysis. A minimum of 64 scans was used for each sample.

^{1}H Nuclear Magnetic Resonance (^{1}H NMR). ^{1}H NMR was used to determine the chemical composition of the synthesized copolymer. ^{1}H NMR was conducted on copolymers before, after, and during hydrolysis.

Copolymers of NIPAAm and DBA were synthesized as mentioned previously. ^{1}H NMR ($CDCl_3$): $\delta = 5.3-5.5$ (H_8), 3.8−4.2 (H_3, H_{11}), 1.2−2.4 (H_1, H_2, H_6, H_7), 1.1 (H_4, H_5, H_9, H_{10}). ^{1}H NMR (D_2O): $\delta = 5.2-5.4$ (H_8), 3.5 (H_3), 3.8(H_{11}), 1.0−2.2 (H_1, H_2, H_6, H_7), 0.8 (H_4, H_5, H_9, H_{10}).

Hydrolysis. Both time-dependent hydrolysis and complete hydrolysis were evaluated at 70 °C. Complete degradation of these materials is estimated to require nearly 1 year at normal physiological conditions; therefore, accelerated degradation conditions of 70 °C were used according to ISO 10993.[25] For time-dependent hydrolysis, solutions of each copolymer were prepared in 0.1 M PBS at 5 wt %, and the pH of the polymer solution was adjusted to 7.4 daily. For complete hydrolysis, in a separate experiment, the pH was adjusted to 10.5 daily to further accelerate the hydrolysis process. The pH of the polymer solutions was adjusted everyday to maintain a nearly constant pH. Daily changes in pH were less than 0.5 pH units. All solutions were maintained at 70 °C. In the complete hydrolysis experiments, complete hydrolysis was assumed to be complete when the pH value of the polymer solutions remained the same for two consecutive days. FTIR, ^{1}H NMR, and DSC were conducted after hydrolysis for each polymer. The polymers were dialyzed against water and lyophilized before FTIR, ^{1}H NMR, and DSC tests.

Titration. The DBA content was determined by acid titration after complete hydrolysis. Titration was conducted manually for each copolymer using a standard sodium hydroxide volumetric solution with a concentration of 0.01 N. The polymer was dissolved in distilled water with a concentration of 0.15 g/10 mL. A minimum of triplicates was used.

Degradation Model. The change in LCST with time was modeled to further elucidate the hydrolytic reaction in the poly(NDB) gels. The reaction was assumed to be self-catalytic due to an increase in water associated with the polymer as the DBA hydrolyzed and became more hydrophilic. The degradation of the DBA with time due to hydrolysis was modeled as follows:

$$-\frac{d[A]}{dt} = k_1[A][H_2O] \quad (1)$$

where [A] is the molar content of DBA in the polymer in units of mol %, t is time of hydrolysis, k_1 is the reaction rate constant, and $[H_2O]$ is the concentration of accessible water (water accessible to the DBA esters) in the gel. The concentration of accessible water was assumed to be related to the fraction of DBA hydrolyzed as follows:

$$[H_2O] = k_2([A]_o - [A] + b) \quad (2)$$

where k_2 is a constant that defines the proportionality between the polymer content and the water content accessible to DBA (assuming a linear relationship between monomer content and water content),[13] $[A]_o$ is the initial DBA content of the polymer, [A] is the current DBA content of the polymer, and b is included to incorporate the initial accessible water before hydrolysis of any DBA content. Without this term, or the associated initial water content, there is no reaction. The solution to eq 1 with eq 2 substituted for the water content and $k = k_1k_2$ is shown here

$$[A]_t = \frac{[A]_o + b}{1 + e^{[k([A]_o+b)(t-c)]}} \quad (3)$$

where $[A]_o$ was determined from the titration experiments and c is a constant of integration, which physically corresponds to the time until 50% hydrolysis. The LCST resulting from the monomer content of the polymer with time was modeled as follows:

$$T_{LCST} = p1[A] + p2([A]_o - [A]) + T_{avg} \quad (4)$$

where $p1$ is the slope determined from a linear fit to the LCST content before hydrolysis versus the DBA content found in DSC experiments seen in Figure 5, $p2$ is the slope from a linear fit to the LCST after complete hydrolysis versus the DBA content seen in Figure 5, and T_{avg} is approximately the LCST of NIPAAm determined as the average intercept for the same data in Figure 5. The parameters k, c, and b were all determined by fitting the data using least-squares method in MathCAD 11.

Statistics. LCST data for each polymer are reported as the average temperature for three DSC runs per sample, and the error is reported as a standard deviation. The DBA content is reported as the mean ± standard deviation for three samples. The adjusted R^2 is reported for the model fits.[26]

Results and Discussion

The synthesis scheme for polymerization is shown in Figure 1. Feed ratios of polymerization, chemical composition, molecular weight, and LCST before and after complete hydrolysis are presented in Table 1.

The molecular weights ranged from 86 to 160 kg/mol. Polydispersities were from 1.94 to 2.0. The DBA contents of the copolymer were from 2.9 to 7.2 mol %. FTIR (Figure 2), and ^{1}H NMR results show the copolymerization of the two monomers (Figures 3 and 4). In the FTIR spectra, there are two peaks appearing at 1785 and 1750 cm^{-1}, respectively. These two peaks are ascribed to the two carbonyl groups in DBA. The peak at 1785 cm^{-1} is ascribed to the carbonyl group in the DBA ring-structure, and the peak at 1750 cm^{-1} is the carbonyl group connected to the polymer backbone. Another two NIPAAm characteristic peaks around 1640 and 1550 cm^{-1}[27] were used as reference peaks for NIPAAm. By comparing the ^{1}H NMR (in $CDCl_3$, Figure 3) spectra of the DBA monomer, PNIPAAm homopolymer, and synthesized copolymer, it was

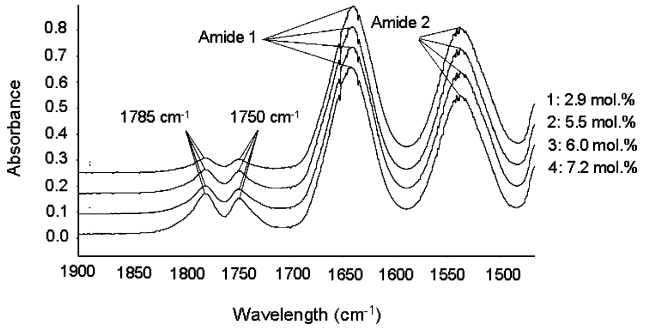

Figure 2. FTIR Spectra of poly(NIPAAm-*co*-DBA) with different DBA contents before hydrolysis: 1: 2.9 mol %; 2: 5.5 mol %; 3: 6.0 mol %; and 4: 7.2 mol %.

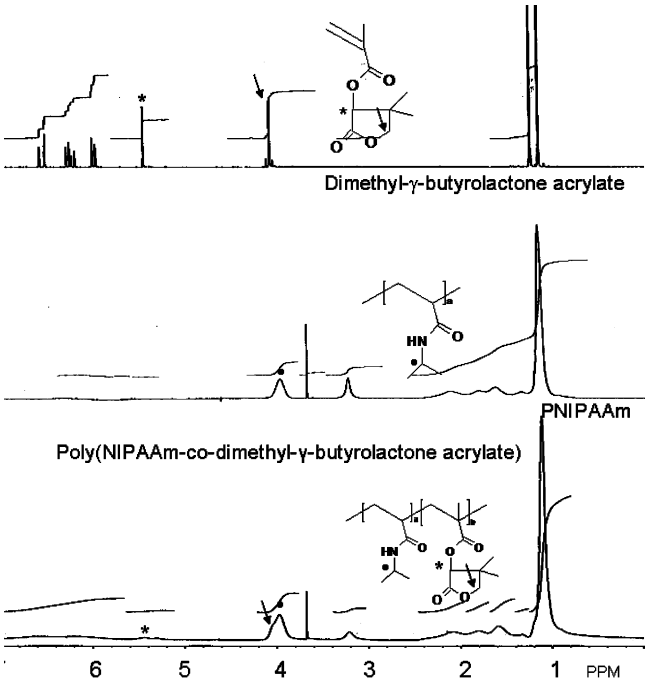

Figure 3. ^{1}H NMR spectra of DBA, PNIPAAm, and poly(NIPAAm-*co*-DBA) in $CDCl_3$.

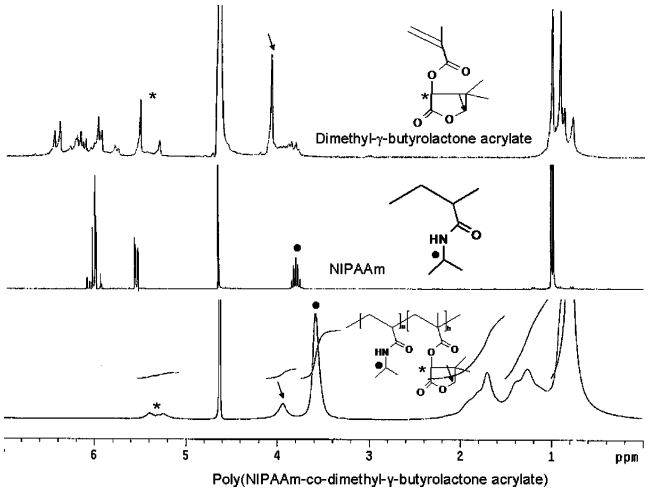

Figure 4. ^{1}H NMR spectra of DBA, NIPAAm, and poly(NIPAAm-*co*-DBA) in D_2O.

concluded that two peaks around 5.4 ppm are from DBA. The peak at 4.0 ppm is from NIPAAm, and the shoulder on the left of this peak is from DBA. The reason for the double peaks around 5.4 ppm (see the asterisk on the lower ^{1}H NMR of Figure

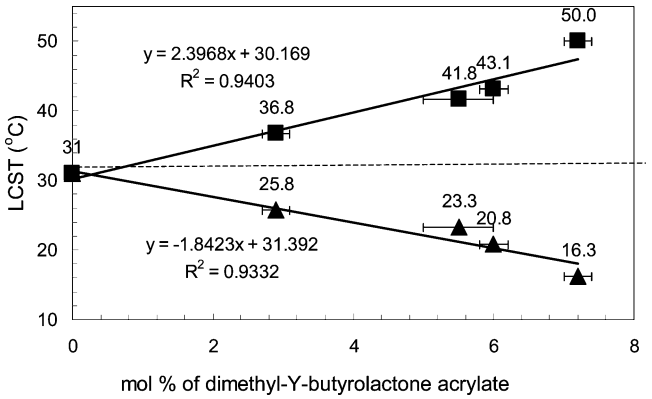

Figure 5. LCST with different DBA contents before and after complete hydrolysis: ▲: before hydrolysis and ■: after complete hydrolysis, $n = 3$ (*y*-error bars smaller than data points). Complete hydrolysis conditions: pH = 10.5 at 70 °C.

3) might be due to the heterogeneity in the DBA distribution in the polymer during polymerization. In ^{1}H NMR (in D_2O, Figure 4), the two peaks at 5.3 and 5.5 ppm from DBA appear at approximately the same position as seen in the NMR spectra of poly(NIPAAm-*co*-DBA). The peak from DBA at 4.1 ppm shifted to 3.9 ppm in the NMR spectra of poly(NIPAAm-*co*-DBA). The peak at 3.8 ppm from NIPAAm shifted to 3.5 ppm in the NMR spectra of poly(NIPAAm-*co*-DBA). Thus, both FTIR and ^{1}H NMR spectra show evidence of the copolymerization of these two monomers.

The relationship between DBA content and the LCST before and after complete hydrolysis is shown in Figure 5. This data indicate that for these four copolymers, an increase of DBA content from 2.9 to 7.2 mol % results in a decrease in the LCST from 25.8 to 16.3 °C. This trend could be explained by the hydrophobicity of DBA. With more DBA copolymerized with NIPAAm, the copolymer becomes more hydrophobic and the LCST decreases. With a lowest DBA content of 2.9 mol %, the LCST is around room temperature, 25.8 °C. As the content of DBA increases, the hydrophobicity of the polymer increases, and this increased hydrophobicity further lower the LCST of the polymer. During incubation of aqueous solutions of these polymers, the ester groups in DBA are hydrolyzed, and this process results in an increase in hydrophilicity and charge of the polymer. Because of increased hydrophilicity, the LCST of the polymer also increases. For the lowest DBA content of 2.9 mol %, the LCST increased to 36.8 °C after complete hydrolysis. With the DBA content increased to 7.2 mol %, accordingly, the copolymer becomes more hydrophilic, and the LCST increases to about 50 °C after complete hydrolysis. Figure 5 also indicates that except for the copolymer with 2.9 mol % DBA, all other copolymers had a LCST above body temperature after complete hydrolysis. The complete hydrolysis was investigated at pH 10.5 and 70 °C. Under this condition, hydrolysis was completed after 15, 18, 20, and 22 days for poly(NDB) with 2.9, 5.5, 6.0, and 7.2 mol % DBA contents, respectively.

Figure 6 shows the endotherms from DSC. These data indicate that with an increase in DBA content, the LCST decreases. This phase change occurred over a broad temperature range. Figure 7 shows the concentration dependence of the LCST for poly(NIPAAm-*co*-DBA). At concentrations below 5 wt %, the LCST was increased relative to the LCST at 5 wt %, but at a concentration above 5 wt %, the LCST remained constant relative to 5 wt %. A time-dependent hydrolysis

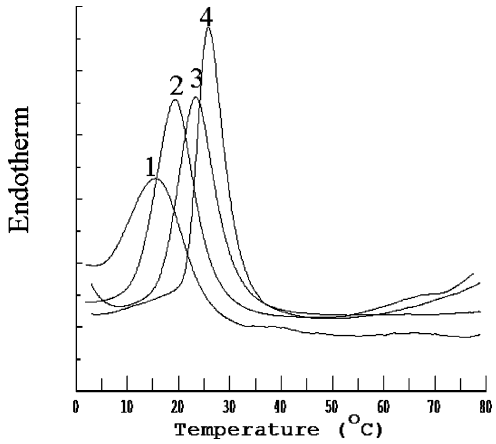

Figure 6. Endotherms of poly(NIPAAm-*co*-DBA) with different DBA contents: 1: 7.2%; 2: 6.0%; 3: 5.5%; and 4: 2.9%.

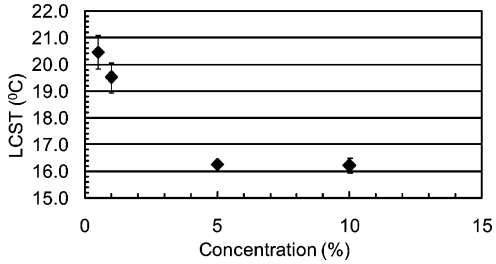

Figure 7. Concentration-dependent LCST of poly(NIPAAm-*co*-DBA) with 7.2% DBA content ($n = 2$).

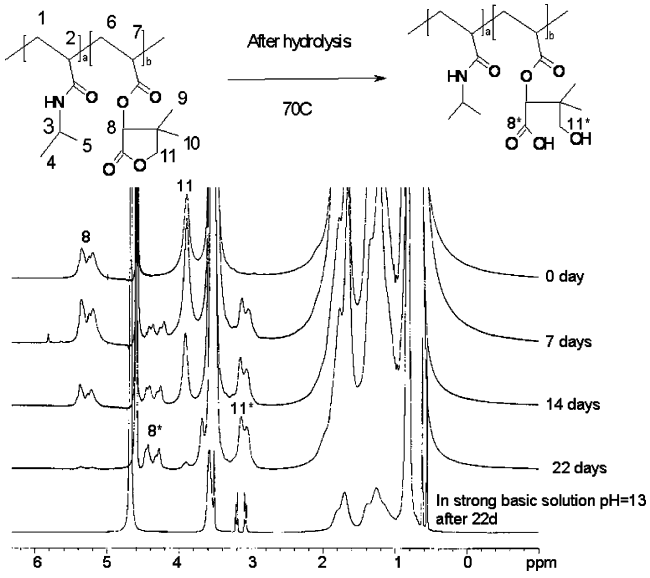

Figure 8. Time-dependent ^{1}H NMR spectra of poly(NIPAAm-*co*-DBA) with 7.2 mol % DBA content in D_2O.

study was also conducted at 70 °C. ^{1}H NMR, FTIR, and LCST tests were conducted after time-dependent hydrolysis. Figures 8 and 9 show ^{1}H NMR and FTIR spectra of the copolymer with 7.2 mol % DBA. D_2O was used as the solvent for ^{1}H NMR after degradation. In the ^{1}H NMR spectra, it is noticed that the two peaks around 5.2−5.4 ppm decrease at 7 days and 14 days, and at 22 days, these peaks are almost gone. Meanwhile, there are another two peaks that show up around 4.4 ppm and increase with time. It is also observed that the peak at 3.8 ppm decreased with time and that two more peaks appeared around 3.1 ppm and grew with time. All the materials after degradation were dialyzed against water and lyophilized before ^{1}H NMR and FTIR tests. Dialysis would have removed the DBA had the

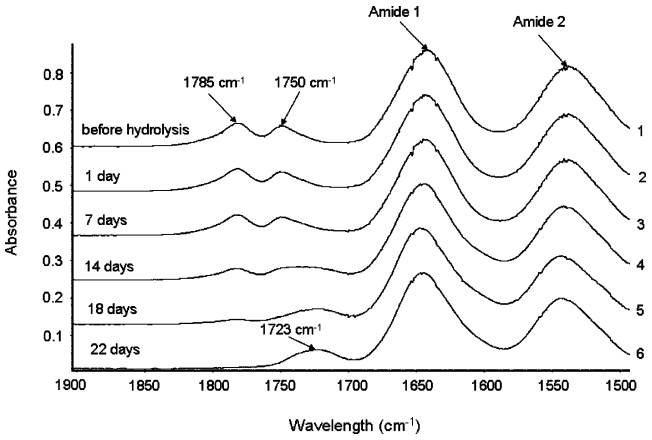

Figure 9. Time-dependent FTIR spectra of poly(NIPAAm-*co*-DBA) 7.2 mol % DBA content. 1: before hydrolysis; 2: 1 day of hydrolysis; 3: 7 days of hydrolysis; 4: 14 days of hydrolysis; 5: 18 days of hydrolysis; and 6: 22 days of hydrolysis.

backbone ester broken especially if the ring-ester had also broken, making the low molecular weight product very hydrophilic. Also, the peaks associated with the DBA remained broad in ^{1}H NMR, suggesting that the monomer was still attached to the polymer. Generally, lower molecular weight compounds exhibit much sharper NMR peaks as compared to polymers. So, combining all this evidence, it is believed that after hydrolysis, the ester bond in the ring-structure is broken, and thus, the ring in DBA opens but the monomer is still attached to the polymer backbone. To further confirm this degradation mechanism, NaOH was added into the polymer solution in D_2O after 22 days' degradation to make a strong basic solution (pH = 13), and this solution was put in a 37 °C water bath for one more day. Subsequently, ^{1}H NMR was conducted on this polymer in D_2O. It was found that the two peaks around 3.1 ppm became very sharp. There is also one sharp peak around 3.5 ppm and another two sharp peaks around 0.6 ppm. The appearance of these sharp peaks indicates that there are low molecular weight molecules in the polymer solution and suggests that hydrolysis of the backbone ester has led to the DBA ring separating from the polymer chain after opening. But, for the time frame of application for controlled drug delivery, there should be no low molecular weight byproducts after ring-opening hydrolysis before the material clears the kidney. In the FTIR spectra, the peak at 1785 cm^{-1} gradually decreased until it was near to background at 22 days. The peak at 1750 cm^{-1} shifted to the right and finally reached 1723 cm^{-1}. Both of these changes indicated a change in local environment due to ring-opening. The ^{1}H NMR and FTIR spectra of the copolymers with the other chemical compositions showed the same trend (data not shown). These results also show that there are no low molecular weight byproducts from this polymer during hydrolysis for the time frame of application.

The time-dependent LCST results at pH 7.4 and 70 °C are plotted in Figure 10. It is seen that the LCST increased over the hydrolysis time. It is also interesting to note that with an increase in DBA content, the LCST increased faster. After 22 days of hydrolysis for the copolymer with 2.9 mol % DBA, the LCST increased from 25.8 to 28.6 °C. For the copolymer with 7.2 mol % DBA, the LCST increased from 16.3 to 50.33 °C. The increased rate of LCST change is due to the carboxylic acid group remaining on the polymer chain after ring-opening hydrolysis of the DBA. The polymer thus becomes more

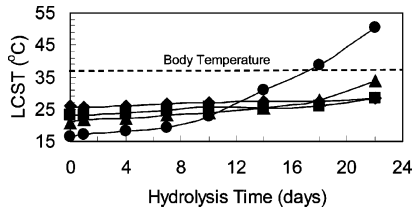

Figure 10. Time-dependent LCST of poly(NIPAAm-*co*-DBA) copolymer with different DBA contents: ♦: 2.9 mol %; ■: 5.5 mol %; ▲: 6.0 mol %; and ●: 7.2 mol %. Time-dependent hydrolysis conditions: pH = 7.4 at 70 °C; $n = 3$ with standard deviation; and error bars smaller than data markers.

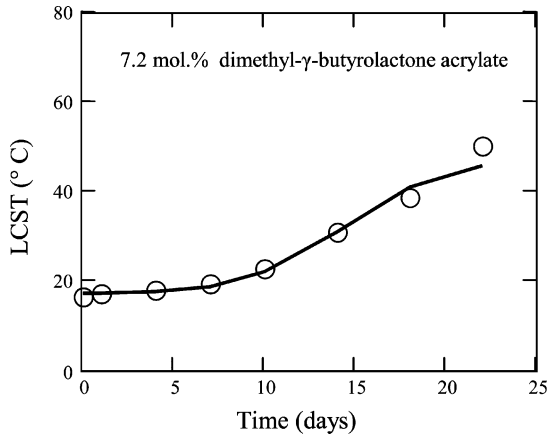

Figure 11. LCST vs time model fitting for poly(NIPAAm-co-DBA) with 7.2 mol % DBA ($n = 3$ for data points, error bars smaller than data markers): circle: data and solid line: model.

hydrophilic and becomes charged, increasing the accessibility of water to the ester structures on the polymer. When the copolymer has a higher DBA, this accelerates the hydrolysis as more of the DBA groups are opened. For the copolymer with 7.2 mol % DBA, the LCST increased above body temperature after 18 days of hydrolysis at the accelerated condition of 70 °C. Arrhenius kinetics suggests an approximately 10-fold acceleration under these conditions. For copolymers with a lower DBA content, the hydrolysis rate is slower. These time-dependent LCST results are further evidence that this new copolymer, poly(NIPAAm-*co*-DBA), should be bioerodible. Future work will also be focused on optimizing the original LCST; accelerating the hydrolysis process for drug delivery and tissue engineering applications; evaluating polymers with appropriate molecular weight, size, and shape for kidney clearance for in vivo application;[28,29] and investigating the in vitro and in vivo cytotoxicity/biocompatibility of these materials.

Figure 11 presents the LCST model fit for the polymer with 7.2 mol % DBA. In this fit, by the least-squares method, $k = 0.049/(\text{day} \times \text{mol \%})$, $b = 0.176$ mol %, and $c = 14.6$ days. This fit had an adjusted R^2 of 0.927.

The model supports the hypothesis that the hydrolysis is self-catalytic. The model suggests this could be due to an increase in accessible H_2O. The increased water content may result from an increase in polymer hydrophilicity and charge after hydrolysis. An alternate explanation for the self-catalytic nature of the hydrolysis might be pH effects as seen in lactic acid polymers.[30,31] However, in this case, the pH was adjusted frequently to keep the environmental pH nearly constant. Thus, the acceleration effect is probably due to other factors. Table 2 presents the model fits and correlation coefficients for all of the polymers. Particularly noteworthy in the data found in Table 2 and Figure 11 is the integration constant, *c*, being physically

Table 2. Degradation Model Parameters

	model parameters			
polymer	*k* (1/(mol % day))	*c* (days)	*b* (mol %)	R^2
1	0.034	34.16	0.001	0.862
2	0.011	35.21	0.001	0.904
3	0.025	21.84	0.0003	0.969
4	0.049	14.60	0.176	0.927

equivalent to the half-life of the DBA ring-opening. This further shows an increased rate of degradation with increased DBA content.

It is expected from the hydrophobicity of the monomer that an increased monomer content would reduce the water content of the gel, thus protecting the DBA monomer from hydrolysis. However, the data show that the charge resulting from the degradation of the butyrolactone ring increases the water accessible to the polymer chain enough to counter balance this effect and cause acceleration in degradation. In poly(NIPAAm-*co*-hydroxyethyl methacrylate [HEMA]-lactate), an increase in the HEMA-lactate monomer increases the time of degradation.[11] In that case, the degradation product, HEMA, left on the polymer chain does not produce a charge on the polymer and does not significantly affect the hydrophilicity. Charges resulting from the lactic acid diffuse from the polymer and so do not drive water to the polymer chains.

Conclusion

A novel thermosensitive, bioerodible copolymer, poly(NIPAAm-*co*-DBA), was synthesized and characterized. It shows a decrease of LCST from 25.8 to 16.3 °C, depending on the content of DBA, before hydrolysis and an increase in LCST from 36.8 to 50 °C after complete hydrolysis. FTIR and ^{1}H NMR spectra verified the copolymerization of these two monomers. FTIR and ^{1}H NMR spectra and LCST results after time-dependent hydrolysis indicate that incorporation of the DBA hydrolytic cyclic group provides the degradability of the copolymer, which makes this new copolymer a candidate material for controlled drug delivery and tissue engineering applications. The ring-structure in DBA was open due to hydrolysis without breaking the ester nearer the backbone, avoiding low molecular weight byproducts on applicable time scales desirable for drug delivery applications. An understanding of the kinetics of the degradation for these polymers will enable rational design of drug delivery materials with planned properties.

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