Verification of Scaling Laws for Degrading PLA-*b*-PEG-*b*-PLA Hydrogels

Andrew T. Metters and Christopher N. Bowman
Dept. of Chemical Engineering

Kristi S. Anseth
Dept. of Chemical Engineering and Howard Hughes Medical Inst.

University of Colorado at Boulder, Boulder, CO 80309

Several macroscopic properties of degrading poly(lactic acid)-b-poly(ethylene glycol)-b-poly(lactic acid) (PLA-b-PEG-b-PLA) hydrogels were compared to one another as functions of degradation time. The specific hydrogel properties measured were the compressive modulus (K), the volumetric swelling ratio (Q), and the normalized compressive modulus ($K_{NORM} = KQ^{1/3}$). Their comparisons were used to evaluate the applicability of fundamental thermodynamic theories developed for nondegradable hydrogels on a degradable system. The equations predict scaling factors of -2, $-5/3$, and 6/5 for the dependence of K on Q, K_{NORM} on Q, and K on K_{NORM}, respectively. These important experimental data for a degrading hydrogel system initially show good agreement with the scaling predictions. Further examination, however, reveals the scaling factors to change over the course of the degradation process. These changes are attributed, at least in part, to the changing chemical, mechanical, and ionic properties of the degrading copolymer networks.

Introduction

As a result of their unique combination of relatively high mechanical strength and high water content, hydrogels have found use in a wide range of important applications, including contact lenses, adhesives, and drug-delivery vehicles (Peppas, 1987). Furthermore, new synthesis procedures that allow the attachment of degradable functionalities and cross-linkable units to hydrophilic segments have led to the recent development of many hydrolytically degradable hydrogels. Degradable networks offer the same advantages as traditional hydrogels, but also contain bonds that can be cleaved hydrolytically or enzymatically. Applications for these degradable, cross-linked networks include improved drug-delivery devices, tissue adhesives, orthopedic implants, and adhesion barriers (West and Hubbell, 1995; Hill-West et al., 1994a,b; Elisseeff et al., 1999; Lu and Anseth, 2000). For many specialized uses, including tissue-engineering applications, the ability to use a degradable hydrogel, as opposed to a material that remains in the body indefinitely, is very attractive.

Previous investigations have shown that the physical and mechanical behavior of a nondegradable hydrogel is highly dependent on the cross-linking density of the gel, which controls the mesh size of the network (Flory, 1953; Peppas, 1986; Anseth et al., 1996). Recently, additional work has shown that these relationships also hold true for degradable PLA-*b*-PEG-*b*-PLA hydrogels (Metters et al., 2000a). These hydrogels were first described by Sawhney et al. (1993), and consist of triblock PEG-*b*-PLA copolymer cross-links connected by backbone polyacrylate chains. The degradation behavior of these PEG-*b*-PLA hydrogels was characterized by taking a number of macroscopic measurements of numerous gel properties during hydrolytic degradation (Metters et al., 2000a). The parameters measured included volumetric swelling ratio, compressive modulus, normalized compressive modulus, and percent mass loss. The swelling ratio, compressive modulus, and normalized compressive modulus were theorized to be qualitatively related to the changing cross-linking density of the degrading gel through the application of various thermodynamic relationships. Since the degradable units for the hydrogel are located in the network cross-links, the cross-linking density of the gels, as a function of time, is directly related to the hydrolysis kinetics for the PLA blocks. Experimentally observed exponential changes in all three macroscopic properties with degradation time were thus explained by the justifiable assumption of a pseudo-first-order kinetic

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Correspondence concerning this article should be addressed to K. S. Anseth.

equation for the hydrolysis of network cross-links, which dictates an exponential decay in the cross-linking density of the hydrogels (Metters et al., 2000a; Siparsky, 1995). To explain the more complex erosion behavior (that is, mass loss) of these gels, a statistical model incorporating structural characteristics of the networks together with kinetic equations for the hydrolysis of the individual lactide bonds was developed and presented in a separate paper (Metters et al., 2000b).

This contribution focuses on identifying and understanding the direct relationships between several macroscopic properties of degrading PEG-*b*-PLA hydrogels. Since hydrogel characteristics such as swelling and mechanical stiffness can be related to the cross-linking density of the gel through relationships such as the Flory-Rehner equation (Flory, 1953) and classic rubber elasticity theory (Anseth et al., 1996), these macroscopic properties can be related directly to one another. Although this analysis has been used previously with many *nondegradable* hydrogel systems, this is the first known report of applying such a methodology to *degradable* networks. Establishing these fundamental relationships is necessary to understand the complex degradation behavior of these bulk-eroding hydrogels. The determination of the correct scaling factors for a degrading system will allow a multitude of useful macroscopic properties to be predicted from a minimum amount of data. Properties that are difficult or even impossible to measure experimentally will be predicted from ones that are readily measured, saving enormous amounts of time and effort in the development and optimization of these materials for the aforementioned applications.

Materials and Methods

The multifunctional, degradable macromer used in this study was synthesized according to the techniques and procedure first described by Sawhney et al. (1993). The notation given for the PLA-*b*-PEG-*b*-PLA macromer refers to the molecular weight of the PEG chain, followed by the symmetrical number of lactide repeat units on each end. For example, 4600-5, the macromer used for all experiments, refers to a macromer containing a 4600-dalton PEG chain with an average of five lactide repeat units on either side. Both ends of this copolymer chain are then end-capped with acrylate functionalities to allow photoinitiated polymerization and cross-linking of the macromer chains.

Photopolymerization of the macromers was carried out with a visible light source (Electro-Light Corporation) with a peak intensity of 15 mW/cm^2 at a wavelength of 420 nm. The solid 4600-5 macromer was dissolved in deionized water to a specified concentration. A 10 wt. % solution of Quantacure ITX photosensitizer (Biddle Sawyer Corporation) and Irgacure 907 (I-907) initiator (Ciba Geigy) dissolved in ethanol was then added to the final macromer solution until the total I-907 concentration was 0.10 wt. %. For 1-mm-thick samples, these conditions produce a uniform light intensity throughout the polymerizing gel.

Degradation of the polymerized hydrogel was carried out in a 0.05-M phosphate-buffered saline solution (Fisher) at 37°C. Each gel was placed in an excess of PBS buffer to maintain sink conditions with a constant pH of 7.4 and an ionic strength of 0.13 M throughout the degradation. At specified time points, one to three samples were removed from the degradation medium; their swollen mass was measured in both air and heptane to obtain the swollen polymer volume; their static compressive modulus was then obtained using a dynamic mechanical analyzer (Perkin-Elmer DMA-7) with a parallel-plate configuration and a ramping stress of 400 mN/min; and their final mass was obtained after complete drying in a vacuum oven.

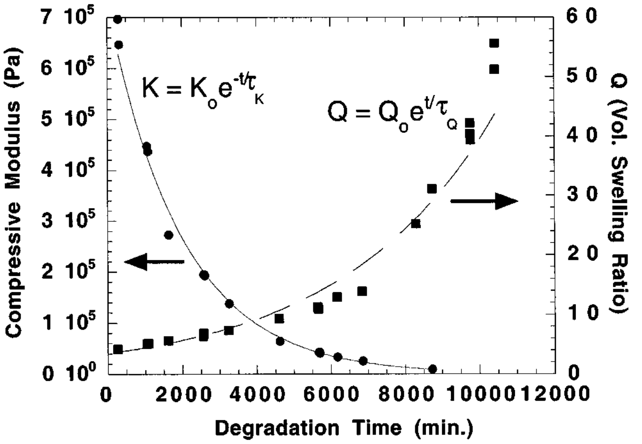

Figure 1. Typical *in vitro* degradation behavior of a PEG-*b*-PLA hydrogel: compressive modulus (●) and volumetric swelling ratio (■).

The solid and dashed lines are exponential curves fit to each property, with time constants of $\tau_Q = 4{,}200$ min and $\tau_K = 2{,}000$ min.

Further details of the chemical synthesis and polymerization of the PEG-*b*-PLA macromers used in this study, as well as the degradation and measurement procedures for characterizing the polymerized hydrogels, are described elsewhere (Metters et al., 2000a).

Results and Discussion

The degradation behavior of several chemically cross-linked hydrogels was monitored through mass, swelling, and mechanical strength measurements. Figure 1 illustrates the typical *in vitro* degradation behavior of a hydrogel constructed from the triblock PEG-*b*-PLA monomer. The compressive modulus and swelling ratio of the degrading gel are plotted vs. the time spent in the aqueous buffered solution. Immediately following polymerization, the hydrogel displays a high modulus and a low degree of swelling, indicative of a network with a relatively high degree of cross-linking. As degradation proceeds, the degradable PLA segments within the gel are hydrolyzed homogeneously, cleaving the network cross-links. This process leads to a gel with a progressively lower cross-linking density, a high degree of swelling, and an almost immeasurable compressive modulus.

As indicated by the best-fit exponential curves in Figure 1, the swelling of the hydrogel increases exponentially with a time constant τ_Q while the compressive modulus decays exponentially with a time constant τ_K. Although not shown here, the normalized modulus decays in an exponential fashion as well. These exponential changes occur as a result of the exponential decay in the cross-linking density of the gel with

Table 1. Time Constants from Exponential Best-Fit Curves During the Degradation of a PEG-*b*-PLA Hydrogel Photopolymerized in Solution from a Monomer with a 10:1 Ratio of PEG to PLA Repeat Units and a Total Molecular Weight of ~5,450 g/mol

wt. % Monomer Polymerized in Solution	Time Constants (min)			Ratios		
	K	K_{NORM}	Q	Q/K	Q/K_{NORM}	K_{NORM}/K
25	1,500	1,800	2,200	1.5	1.2	1.2
50	2,000	2,300	4,100	2.0	1.8	1.2
70	2,300	2,800	4,800	2.1	1.7	1.2

degradation time (Metters et al., 2000a,b). Further comparison of the time constants for the modulus and swelling degradation curves in Figure 1 indicates that the rate at which the modulus *decreases* is approximately twice as fast as the rate at which swelling *increases* ($\tau_Q = 2\tau_K$). As shown in Table 1, a similar relationship between the various macroscopic time constants exists for a series of gels prepared from increasing concentrations of monomer polymerized in solution. Changing the processing conditions of the hydrogels affects the magnitude of the individual time constants, but does not alter the exponential nature of the macroscopic property changes during degradation nor significantly alter the ratio of the time constants (Metters et al., 2000a). These observations suggest a distinct relationship between the macroscopic properties themselves and the ongoing hydrolysis.

One can support the experimental results presented in Table 1 by investigating the fundamental equations governing the macroscopic properties of swollen hydrogels. The most commonly used thermodynamic relationships for hydrogels were developed by Flory over 50 years ago for nondegradable networks (Flory, 1953). Utilizing the same methodology, these equations can be applied to the current systems as long as the degradation time scales of the current gels are much longer than the time scales needed to reach macroscopic equilibrium. As mentioned earlier, almost every macroscopic property of a hydrogel depends, to some extent, on its cross-linking density. The Flory-Rehner equation is used to relate the volumetric swelling ratio of the gel (Q), which is the inverse of the polymer volume fraction, to its cross-linking density (ν_C). Assuming high degrees of swelling ($Q > 10$), the Flory-Rehner equation can be simplified to (Flory, 1953):

$$Q = \left[\frac{1}{V_1} \left(\frac{1}{1 - \left(\dfrac{2\overline{M}_C}{\overline{M}_N} \right)} \right) (1/2 - 2\chi_{12}) \right]^{3/5} \left(\nu_C^{-3/5} \right) = \beta \left(\nu_C^{-3/5} \right). \tag{1}$$

Here, V_1 is the molar volume of the solvent, $\overline{M}_N$ is the number-average molecular weight of the polymer chains if they were not cross-linked, and $\overline{M}_C$ is the number-average molecular weight between cross-links of the network. If it is further assumed that all parameters besides Q and ν_C are held constant and $(\overline{M}_C/\overline{M}_N) \ll 1$ during the course of degradation, then

$$Q \sim \nu_C^{-3/5}. \tag{2}$$

Similarly, Eq. 3 shows the direct correlation between cross-linking density and normalized compressive modulus (K_{NORM}) derived from classic rubber elasticity theory for a swollen system (Anseth et al., 1996):

$$K_{\mathrm{NORM}} = KQ^{1/3} = \frac{2(1+\sigma)}{3(1-2\sigma)} RT(\nu_C) = \gamma(\nu_C). \tag{3}$$

Here, σ is Poisson's ratio, R is the ideal gas constant, and T is absolute temperature. Assuming all parameters in this equation to be constant during degradation, K_{NORM} then directly scales with cross-linking density.

Without any further assumptions, solving for ν_C in Eqs. 2 and 3 gives the following three simplified scaling relationships between the mechanical and swelling properties of polymeric hydrogels:

$$K \sim Q^{-2} \tag{4}$$

$$K_{NORM} \sim Q^{-5/3} \tag{5}$$

$$K \sim K_{NORM}^{6/5}. \tag{6}$$

If the swelling and mechanical properties of the PLA-*b*-PEG-*b*-PLA gels are assumed to change exponentially with degradation time, as has been observed experimentally and predicted theoretically (Metters et al., 2000a,b), then Eqs. 4–6 can be used to predict the ratio of their respective time constants. With the previous assumptions, Table 2 shows the ratios of the theoretical time constants for each of the three macroscopic properties, which compare reasonably well to the measured ratios in Table 1.

While comparison of the exponential time constants gives good agreement between the macroscopic degradation studies and the fundamental thermodynamic equations derived by Flory, it does not present a clear picture of the relationships between the macroscopic properties of these degrading networks. As seen in Table 1, some of the experimentally derived time-constant ratios deviate more significantly than others when compared to the theoretical predictions. Whether this discrepancy is due to an incorrect fit of the data or a breakdown of the theory is hard to determine from this type of analysis. What is clear, however, is that the scaling laws presented in Eqs. 4–6 and Table 2 are built upon many assumptions such as a relatively high degree of swelling and constant physical parameters. A quick analysis of the complex degradation of the PLA-*b*-PEG-*b*-PLA gels indicates that none of these assumptions is valid over the entire course of the degradation. Initially, the hydrogels exhibit swelling ra-

Table 2. Theoretical Ratios of Time Constants from the Flory-Rehner Equation and Rubber-Elasticity Theory

Q/K	Q/K_{NORM}	K_{NORM}/K
2.0	1.7 (5/3)	1.2 (6/5)

tios much less than 10. During the degradation process, the hydrogels also change from a rubbery, but strong network, to a fragile, loosely cross-linked system that cannot maintain its shape. This behavior implies that some change in σ very likely occurs. A change in χ_{12} will also occur with degradation of the PLA-*b*-PEG-*b*-PLA hydrogels. It has already been shown by numerous researchers that χ_{12} is a function of solvent concentration and will therefore vary with swelling ratio (Brandrup, 1999). In addition, degradation of these gels primarily involves removal of their PLA-*b*-PEG-*b*-PLA cross-links. Initially, these gels are composed of approximately 95 wt. % PLA-*b*-PEG-*b*-PLA segments with only 5 wt. % along their polyacrylate backbone. As degradation occurs, the PLA-*b*-PEG-*b*-PLA segments are eroded first, producing a partially degraded gel with a significantly higher fraction of polyacrylate chains and poly(acrylic acid) segments (Metters et al., 2000b). Because the network chemistry is changing, χ_{12} must therefore change.

In most swelling studies of highly cross-linked gels, the correction factor due to the presence of chain ends $(1-(2\overline{M}_C/\overline{M}_N))$ is found to be insignificant. Due to the high degree of swelling and therefore low cross-linking density of the current gels, however, this chain-end correction factor cannot be neglected. In addition, the value of the correction factor will change significantly during the degradation due to the hydrolytic cleavage of network cross-links and the resulting increase in $\overline{M}_C$ relative to $\overline{M}_N$. These changes do not occur during osmotic deswelling measurements, the technique most often used to test theoretical scaling laws on polymeric systems.

An alternative and more detailed procedure for analyzing the experimental degradation data and comparing it to existing scaling theories is to use log-log plots. Since the cross-linking densities of swollen hydrogels can only be inferred indirectly through macroscopic measurements, log-log plots of macroscopic gel properties have been used by many researchers to analyze their data (Dubrovskii and Radkova, 1997; Rubinstein et al., 1996). Flory himself used such an analysis to verify the accuracy of his original theories on nondegradable, swollen systems (Flory, 1953). Taking the logs of the scaling laws presented in Eqs. 4–6 yields linear relationships between each of the reduced macroscopic properties:

$$\log(K) = \alpha - 2\log(Q) \tag{7}$$

$$\log(K_{\mathrm{NORM}}) = \omega - 5/3\log(Q) \tag{8}$$

$$\log(K) = \lambda + 6/5\log(K_{\mathrm{NORM}}), \tag{9}$$

where α, ω, and λ are simply constants. The slopes of these linearized equations are equivalent to the values determined for the theoretical time constant ratios given in Table 2.

Figure 2 shows direct comparison on a log scale of the swelling and compressive modulus for three degrading hydrogels polymerized with various concentrations of monomer. These three data sets represent the same hydrogels shown in Table 1 and Figure 1. Equations 7–9 predict that all three plots should be linear with a constant slope over the entire range of data. Comparison of K and K_{NORM} in Figure 2c produces a very linear relationship over the course of the degradation, as predicted by Eq. 9. In Figures 2a and 2b, however, nonlinear behavior is observed in the K and K_{NORM} curves as functions of Q with a decreasing slope at higher Q values ($Q > 10$).

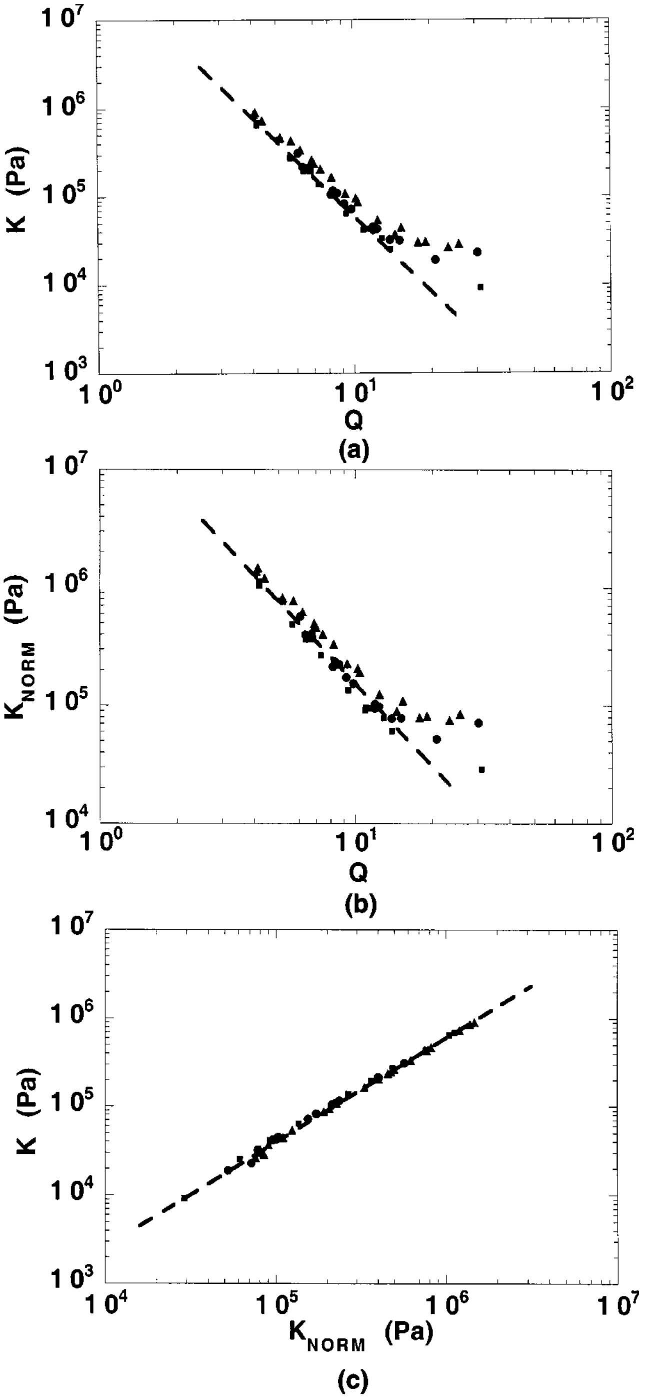

Figure 2. Log-log comparisons of three macroscopic properties of a degrading PEG-*b*-PLA hydrogel polymerized at varying concentrations of monomer: 25 wt. % (●), 50 wt. % (■), and 70 wt. % (▲).

Plot (a) compressive modulus vs. swelling ratio; plot (b) normalized compressive modulus vs. swelling ratio, and plot (c) compressive modulus vs. normalized compressive modulus. The dashed lines represent linear best fits to all or a section of the data, with slopes of (a) −2.8; (b) −2.3; and (c) 1.2.

Equations 7–9 predict slopes of -2, $-5/3$, and $6/5$, respectively, for the data in Figures 2a–2c. The best-fit slopes for the data at low swelling ratios ($Q < 10$) are plotted in each figure for comparison. In Figures 2a and 2b, the slope of the data changes with Q. At low Q values (early degradation times) the slope of the data in Figure 2a has a value of approximately -2.8, somewhat higher than the theoretical slope of -2 derived from Eq. 7. As the magnitude of Q increases past a value of 10, the slope decreases, indicating a weaker dependence of K on Q. Although lower, the slope of the K_{NORM} data in Figure 2b exhibits the same trend, undergoing a drastic reduction at a Q value of approximately 10. The data in Figure 2c, on the other hand, agrees quite well with the theoretical prediction of Eq. 8 over the entire data range, producing a linear relationship with an average slope of approximately 1.2 (6/5).

The log-log plots shown in Figure 2 reveal the complex nature of the degrading gels and the true relationships between their macroscopic properties. Although the three gels in Figure 2 exhibit differences in their degradation time scales and time-constant ratios (Table 1), it is interesting to note that all data sets fall consistently on top of one another throughout Figure 2, indicating similar chemistries and physical parameters for the three systems. Figures 2a and 2b, however, suggest that no single scaling law can predict the macroscopic property relationships in the PLA-*b*-PEG-*b*-PLA hydrogels over the entire course of their degradation without incorporating the chemical and physical changes that occur within the degrading networks. At early times where the degree of swelling is less than 10 and the compressive modulus is changing rapidly, scaling laws established by de Gennes may be more applicable than Eqs. 7–9 (de Gennes, 1979). This more generalized theory predicts that K will scale as Q^{-m}, where $m = 2.25$, 3.0, and ∞ for good, theta, and poor solvents, respectively. Values for m ranging from 2.32 to 3.2 have been recorded for nondegradable PEG networks of varying cross-linking densities swollen in water (Hild et al., 1986; Kazanskii et al., 1997; Iza et al., 1998). These values agree well with the slope of 2.8 obtained in Figure 2a. It is reasonable that the exponent for the degradable network lies on the high side of the range due to the presence of the hydrophobic PLA linkages, which should reduce attractive polymer-solvent interactions in the aqueous buffer solution.

At the other end of the degradation spectrum (long degradation times and high degrees of swelling, $Q > 10$), the decreasing dependence of the compressive modulus on the swelling can be accounted for in several ways. One explanation is the increasing ionic nature exhibited by these degrading gels. With every PLA-*b*-PEG-*b*-PLA segment that is broken or eroded from the gel, a network more closely resembling cross-linked poly(acrylic acid) is produced. Acrylic acid is acidic in nature with a $\mathrm{p}K_a$ of 4.25. In the phosphate-buffered solution at a controlled pH of 7.4, a majority of the acrylic acid segments that make up the backbone chains of the network are therefore deprotonated, leaving fixed, negatively charged carboxyl groups attached to the network. Previous studies from the literature have shown that for a variety of nondegradable, polyelectrolyte gels, including poly(acrylic acid), regions of constant elastic modulus or increasing modulus can occur during increases in volumetric swelling (Nisato et al., 1996; Dubrovskii and Rakova, 1997). These observations are further supported by scaling theories for ionic gels that predict similar behavior (Ilavsky, 1982; Rubinstein et al., 1996; Dubrovskii and Rakova, 1997). These effects occur due to the electrostatic repulsions between similar fixed charges that tend to expand and stiffen the networks. For the degrading polymer networks in the current study, this ionic effect will mainly influence the gel during late stages of degradation (high Q values) when the greatest number of fixed charges are present. The strength of the ionic effect, however, will be minimized due to the low concentration of carboxyl groups possible in these highly swollen gels and the relatively high ionic strength of the PBS buffer solution (0.13 M) used to swell the gels.

Even with the charge shielding provided by the large, constant concentration of buffer ions, the observed deviations from the generalized scaling laws could still occur during degradation as a result of changes in other chemical and physical properties of the gels. As mentioned, changes in χ_{12} and $(\overline{M}_C/\overline{M}_N)$ occur during the degradation of the PLA-*b*-PEG-*b*-PLA gels and will affect the scaling behavior predicted from Eqs. 1 and 3. A statistical-kinetic model developed to predict mass loss from these systems (Metters et al., 2000b) indicates that the χ_{12} value for the network would have to drop significantly during degradation to explain the nonlinear behavior observed in Figures 2a and 2b. This is highly unlikely given the similar χ_{12} values reported in the literature for PEG and poly(acrylic acid) (Bell and Peppas, 1996; Merrill et al., 1993). Additionally, the increasing chain-end effect that would occur with network degradation would cause the opposite behavior of that observed in Figure 2, increasing rather than decreasing the slopes of the log-log plots.

A final explanation for the data in Figures 2a and 2b is that the nonlinear behavior is simply an artifact of the modulus measurement technique. During the final stages of degradation, a limiting compressive modulus on the order of 10^3 Pa is observed. This value is approximately equal to the lower modulus limit recommended by Perkin-Elmer for the DMA-7, with a parallel-plate configuration such as the one used in the current experiments. The constant compressive modulus values observed during the end of the degradation process could therefore be due to limited sensitivity of the analytical technique at these relatively low modulus values.

Although each of the factors listed previously needs to be investigated further, the unique scaling behavior observed during the final stages of degradation is most likely due to a combination of all three effects.

Conclusions

Fundamental thermodynamic equations that relate the mechanical and physical properties of a swollen hydrogel to its microscopic cross-linking density were used to characterize degradable PLA-*b*-PEG-*b*-PLA hydrogels. Although initial results agreed quite well with theoretical predictions, the accuracy of these simplified scaling laws in predicting macroscopic property relationships during the late stages of degradation was limited. The compressive modulus (K) was observed to scale with $Q^{-2.8}$ at low degrees of swelling (early degradation times). Late in the degradation process and at high degrees of swelling ($Q > 10$), the scaling exponent changes with Q and approaches zero, mimicking the behavior seen in cross-linked poly(acrylic acid) and other ionic gels. This behavior is due either to the chemical and structural changes that take place within the network as a result of the degradation or to limitations in the current compressive modulus measurement technique.

A log-log comparison of the macroscopic properties of the degrading hydrogels revealed their complex nature. This analysis illustrated obvious deviations from thermodynamic scaling laws not readily observed from simple exponential fits to macroscopic property data. While no simplified scaling law can universally describe the physical properties of these gels over the entire course of their degradation, common relationships developed by Flory and de Gennes can be applied over significant portions of the data. Even with their observed limitations, the application of these scaling laws to degradable PLA-*b*-PEG-*b*-PLA hydrogel networks allows prediction, at least to a first-order approximation, of a wide array of changing macroscopic properties based only on one experimentally measured data set. In addition, once the initial material parameters are known, this approach allows quantitative prediction of these properties without needing to know the multitude of physical constants involved with the fundamental equations. For example, the swelling data could be used to predict quantitatively mechanical properties of the gels during degradation. The results in this article represent the first such characterization reported for a degrading hydrogel system.

Acknowledgments

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