

## A Statistical Kinetic Model for the Bulk Degradation of PLA-*b*-PEG-*b*-PLA Hydrogel Networks

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A theoretical model has been developed to describe the bulk-degradation behavior of model PEG-*b*-PLA hydrogels. Utilizing a statistical approach to predict the cleavage of cross-links within these networks, the model accounts for both structural and kinetic issues during the degradation and, from direct comparison, can accurately predict the complex erosion profiles of the cross-linked hydrogels. The mass loss profiles of the cross-linked networks are shown to depend on parameters such as the order of the hydrolysis reaction, the value of the kinetic rate constant, the number of cross-links per backbone chain, and the mass fraction of network contained in the backbone as opposed to the rest of the network. Such an accurate degradation model based on fundamental parameters allows a greater understanding of the bulk-degradation process and its controlling factors.

### Introduction

Researchers have recently begun experimenting with a new class of degradable, polymeric hydrogels. Traditional synthetic hydrogels are generally insoluble, yet water-swelling, cross-linked polymer networks that have long histories of proven application as contact lenses, super-absorbent materials, drug delivery vehicles, and adhesives.<sup>1</sup> Their combined hydrophilic and cross-linked nature provides a unique combination of mechanical strength and high water content which can be matched by few materials. Degradable networks offer the same advantages as normal 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.<sup>2–5</sup> 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.

To function most effectively in any application, the degradation behavior of the hydrogels must be predictable and well understood under a wide variety of conditions. The relationships between this behavior and other macroscopic properties must also be known. Unfortunately, the correlations among a biodegradable hydrogel's design, composition, and ultimate function are not well understood. No theoretical models currently exist to describe the important features of their degradation behavior, and even experimental characterization of their degradation is limited. Thus, this work aims to provide a general framework for the bulk-degradation process of cross-linked gels. A more complete understanding of the controlling factors behind the degradation phenomenon and the relationships between the microscopic chemical structure of the hydrogels and their macroscopic performance during degradation will allow greater functional design of the network.

### Background

Although polymers degrade through several mechanisms, hydrogels that degrade chemically, via hydrolysis of the cross-

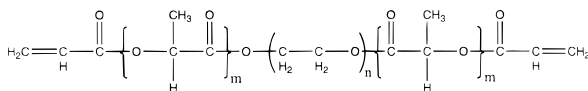
links, are the focus of this investigation. Hydrolytically labile polymers such as polyesters and polyanhydrides have found uses both inside and outside the human body.<sup>6</sup> Both classes of polymer undergo hydrolytic bond cleavage to form water-soluble degradation products, resulting in polymer erosion. In this context, the term “degradation” refers to the actual bond cleavage reaction, whereas “erosion” refers to the depletion of mass from the device or implant. While the degradation of many polymers follows first-order or pseudo first-order kinetics, their erosion, which is gauged by mass loss, is generally much more complicated.

Hydrolytic degradation occurs whenever degradable polymer segments (e.g., esters or anhydride linkages) come into contact with water. If water diffusion into a sample is slow compared to the hydrolysis reaction, then the water will be consumed on the surface by hydrolysis before it can penetrate into the bulk of the sample. Many polyanhydrides and poly(ortho esters) fall into this category and are designated as surface-eroding polymers. Bulk erosion, on the other hand, occurs when diffusion of water into the sample is much faster than the hydrolysis reaction. This type of mechanism occurs in linear polymers such as PLA and other, more hydrophilic polymer networks such as hydrogels.

This contribution examines the behavior of degradable, chemically cross-linked hydrogels, particularly those synthesized from macromers of poly(lactic acid)-poly(ethylene glycol)-poly(lactic acid) copolymer (PLA-*b*-PEG-*b*-PLA) as a model system. Sawhney et al.<sup>7</sup> originally described the synthesis of a triblock PLA-*b*-PEG-*b*-PLA copolymer with acrylate end groups (See Figure 1). Since that time, Hubbell and others have proven the usefulness of gels constructed from these macromers in a number of biomedical applications.<sup>2–5</sup> While the degradation behavior of these hydrogels has also been examined experimentally,<sup>8</sup> the fundamentals behind this behavior have not been thoroughly investigated nor are the complexities of the process well understood.

Currently, no theoretical models exist in the literature to explain the unique bulk-degradation and erosion behavior of cross-linked hydrogel systems. Predicting such behavior would allow the current materials to be strategically optimized.<sup>9</sup> In addition, an accurate degradation model based on fundamental

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**Figure 1.** Chemical structure of the biodegradable PLA-*b*-PEG-*b*-PLA macromer.

parameters would lend greater insight into the complex bulk-degradation process and its controlling factors. This advancement in understanding would allow researchers to tailor an optimum degradable hydrogel network for each current application, as well as extend the use of this class of materials into several new applications.

The goal of the current investigation, therefore, is to describe theoretically the behavior of model, bulk-degrading PLA-*b*-PEG-*b*-PLA hydrogels using a minimum number of quantifiable parameters taken directly from the physical system. Utilizing a statistical approach to predict the cleavage of cross-links within these networks, a model that accounts for both structural and kinetic issues during the degradation has been developed to predict the erosion profiles of these cross-linked materials. It should be noted that the theoretical framework developed in this study can be extended to describe the degradation behavior of any other bulk-degrading system where the network cross-links are hydrolyzed. Such systems will be the focus of future investigations.

## Experimental Section

The multifunctional, degradable macromer used in this study was synthesized according to the techniques and procedure first described by Sawhney et al.<sup>7</sup> 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 experimental comparisons to model predictions, 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 photopolymerization and cross-linking of the chains into a system similar to the ideal network illustrated in Figure 2.

Photopolymerization of the macromers was carried out with a visible light source (Electro-Light Corporation) with a peak intensity of 15mW/cm<sup>2</sup> 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 %. The solution was then placed between two glass slides approximately 1.0 mm apart and polymerized into solid disks 1.0 cm in diameter.

Degradation of the polymerized disks was carried out in a 7.4 pH phosphate-buffered saline solution (Fisher) at 37 °C. At specified time points (roughly three times per day), one to three disks were removed from the degradation medium. Their final mass ( $m_p$ ) was obtained after complete drying in a vacuum oven. The percent mass loss from a sample was determined using the following equation:

$$\% \text{ mass loss} = \frac{(m_{pi} - m_p)}{m_{pi}} \times 100\% \quad (1)$$

Here,  $m_{pi}$  is the initial dry polymer mass. The mass loss was

measured as a function of time spent in the buffer solution for each hydrogel system.

## Results and Discussion

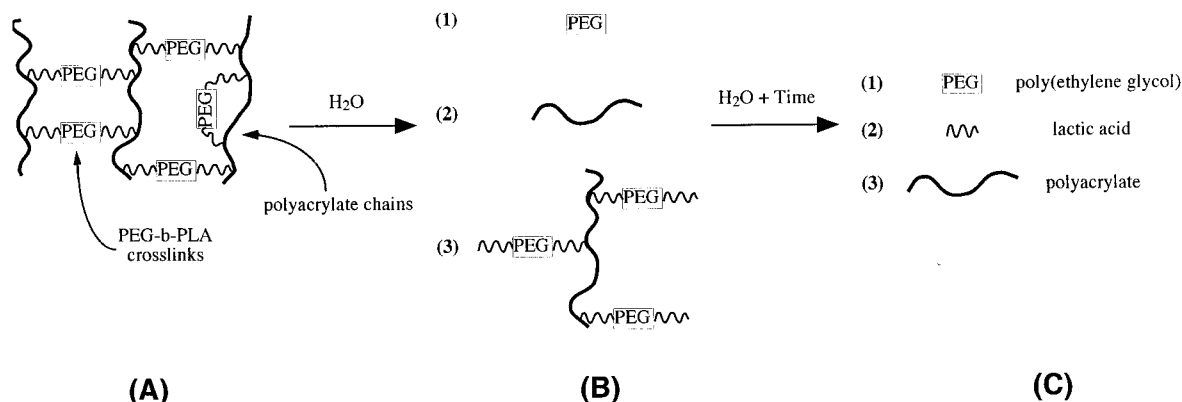
**Model Cross-linked Network.** The PLA-*b*-PEG-*b*-PLA macromers used to form the hydrogels under study in this paper are multifunctional with a double bond located on each end of the macromer chain. A three-dimensional network is formed through the chain polymerization of these acrylate functional endgroups. The result of such a reaction is a model degradable hydrogel consisting of two distinct building blocks: (1) polyacrylate chains formed through the polymerization reaction (referred to as *kinetic* chains) and (2) PLA-*b*-PEG-*b*-PLA copolymer segments from the macromer backbone. Since the polymerized backbone of the network consists only of the acrylate groups from the initial macromer, the vast majority of the network mass resides in the second type of building block, the PLA-*b*-PEG-*b*-PLA segment. In the 4600-5 macromer, for example, the PLA-*b*-PEG-*b*-PLA segments account for approximately 95% of the total macromer mass. The ideal way in which both block types assemble to form a continuous network complete with copolymer cross-links and cycles is illustrated in Figure 2.

As with all hydrogels, the physical and mechanical behavior of the gels is highly dependent on the backbone chemistry of the polymer, as well as the cross-linking density of the network.<sup>10,11</sup> This feature allows the degradation and microscopic changes occurring within the PLA-*b*-PEG-*b*-PLA hydrogels to be measured through observation of their macroscopic properties. As degradation occurs, lactide ester linkages are cleaved homogeneously throughout the entire hydrogel at a rate controlled by the reaction kinetics for their hydrolysis. As soon as one of these linkages is hydrolyzed, the PLA-*b*-PEG-*b*-PLA cross-link that contains that group is also broken. This ongoing cleavage of cross-links within the hydrogel systematically decreases the cross-linking density of the overall network. Thermodynamic relationships for cross-linked systems first described by Flory can be used to relate structural characteristics of hydrogels, such as cross-linking density, to their exhibited macroscopic properties, namely compressive modulus and degree of swelling.<sup>12</sup> The behavior of these macroscopic properties during the degradation of model PLA-*b*-PEG-*b*-PLA hydrogels was examined experimentally in an earlier paper.<sup>8</sup>

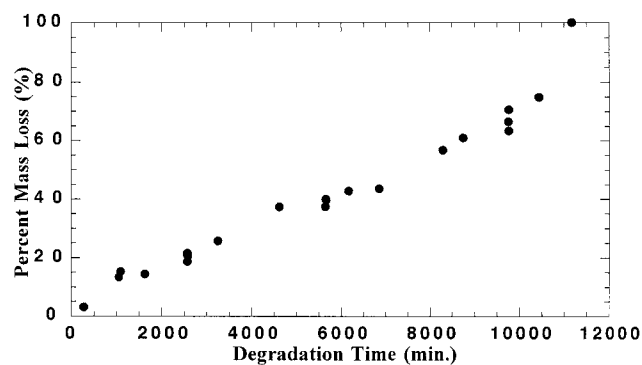
The microscopic cleavage of the network cross-links also leads to bulk-erosion of the samples over time and the eventual macroscopic breakdown of the hydrogel structure. Upon complete hydrolysis, only three species remain from the previously cross-linked PLA-*b*-PEG-*b*-PLA hydrogel. These are poly(ethylene glycol) (PEG), monomeric or oligomeric lactic acid, and poly(acrylic acid). Since all of these products are water soluble, the placement of degradable ester groups along the hydrogel cross-links will lead to complete erosion of the initially insoluble gel.

**General Mass-Loss Behavior.** Figure 3 shows a typical mass loss curve for a degrading PLA-*b*-PEG-*b*-PLA copolymer hydrogel. Mass loss begins immediately after the sample is placed in the aqueous buffer solution. The curve appears linear throughout most of the degradation, corresponding to an approximately constant mass-loss rate. During the last 20% of mass loss, the slope of the curve increases sharply and an essentially instantaneous dissolution of the remaining cross-linked network is observed.

Figure 3 demonstrates that the mass loss from a bulk-degrading, hydrogel system is a complex process composed of



**Figure 2.** Illustration of the three different stages during the bulk degradation of a PLA-*b*-PEG-*b*-PLA hydrogel network: (A) initial and ideal, nondegraded PLA-*b*-PEG-*b*-PLA network, (B) primary erosion products that are released during degradation, and (C) final degradation products after complete hydrolysis.



**Figure 3.** Experimentally measured mass loss as a function of degradation time for a hydrogel polymerized from a 50 wt % solution of 4600-5 PLA-*b*-PEG-*b*-PLA macromer in deionized water.

at least two distinct stages, and, unlike other macroscopic hydrogel properties, cannot be summarized simply with thermodynamic principles that relate equilibrium states.<sup>8,12</sup> In addition, the erosion profile for the PLA-*b*-PEG-*b*-PLA hydrogels observed in Figure 3 is much different from the degradation behavior of linear PLA systems.<sup>13,14</sup> The uniqueness of the curve in Figure 3 is related not only to the novel chemistry of the starting macromers and their hydrolysis kinetics, but also to the structure of the resulting cross-linked network. Therefore, a model which incorporates both structural and kinetic parameters of the degrading network was developed to predict this mass-loss behavior.

**Development of Bulk-Degradation Model.** The chosen modeling scheme uses a statistical, mean-field approach and assumes that the PLA-*b*-PEG-*b*-PLA macromer is fully reacted during network formation. This implies that in the assumed, ideal network structure shown in Figure 2, all PLA-*b*-PEG-*b*-PLA segments exist either as cross-links or as cycles between the backbone, polyacrylate chains. The lengths of the PEG-*b*-PLA segments and polyacrylate chains are assumed constant throughout the network and are incorporated into model parameters. Only homopolymerizations of the PLA-*b*-PEG-*b*-PLA macromers are modeled in this investigation, so each repeat unit along a kinetic chain has one PLA-*b*-PEG-*b*-PLA segment attached. However, the model could be readily modified to examine copolymer networks created from a variety of mono and divinyl monomers. Cyclization within the network is accounted for through a parameter that specifies the fraction of PLA-*b*-PEG-*b*-PLA segments which form cycles rather than cross-links. Chain transfer reactions are neglected, and the polyacrylate chains are assumed to be linear.

In this model, the lactic acid oligomers within each copolymer segment are considered as a single, degradable PLA unit. Therefore, one degradable unit is present on either side of the PEG chain. Incorporating this configuration into the model is necessary to capture the true degradation behavior of these systems. Breaking one PLA unit will result in cleavage of the cross-link or cycle that it resides upon, possibly affecting the cross-linking density of the network. More PLA units, however, must be broken for the copolymer segment to be eroded from the network. The hydrolysis of these PLA units is assumed to occur homogeneously throughout the hydrophilic network because of the high degree of swelling these gels exhibit when placed in an aqueous environment. For this same reason, crystalline regions within the gel and changes in water concentration with degradation are not accounted for in the model. Pseudo first-order reaction kinetics are also assumed because of the high water content and low acid-species concentrations that are generally present in hydrogels of this type,<sup>8</sup> although higher and more complex kinetic mechanisms could be readily incorporated to describe more complex cross-link degradation.

The current model accounts for mass loss by calculating the probability that a certain species is “released” from the cross-linked gel. Neglecting lactic acid residues, there are three primary erosion products: (1) pure, PEG chains, (2) pure polyacrylate chains, and (3) polyacrylate chains with any number of partial PLA-*b*-PEG-*b*-PLA segments still attached (Illustrated in Figure 2). These three species are considered eroded or “released” when all bonds connecting them to the remaining three-dimensional gel have been broken. The degradation occurs through first-order hydrolysis of the PLA linkages present between the PEG and poly(acrylate) chains. These bond cleavages and release events are calculated through statistical arguments that form the basis for this model. The time at which release of these products occurs depends primarily upon the number of degradable linkages connecting each species to the gel (structural parameters) and the kinetics for breaking each individual linkage (kinetic parameters). The diffusion of degradation products out of the highly swollen network is assumed to occur much faster than the degradation. Therefore, once the connecting linkages are broken, the mass of each erosion product immediately appears as a loss in the mass of the overall network.

To model the kinetics of the hydrolysis, the individual PLA units within the cross-linked gel are assumed to hydrolyze according to a pseudo first-order kinetic equation:

$$\frac{d[\text{PLA}]}{dt} = -k'[\text{PLA}] \quad (2)$$

Here,  $[PLA]$  is the concentration of degradable PLA units along the PLA-*b*-PEG-*b*-PLA segments within the network, and  $k'$  is the pseudo first-order reaction rate constant. The first-order simplification of the ester hydrolysis reactions was justified based upon (1) the constant pH during degradation experiments and low lactic acid concentrations in the copolymer gels that minimizes any acid-catalyzed effects, and (2) the highly swollen nature of these gels which means that the solvent concentration,  $[H_2O]$ , remains relatively constant during degradation and can be incorporated into the pseudo first-order kinetic constant,  $k'$ . The concentration of PLA units is currently monitored instead of the individual, water-labile ester concentration to simplify model calculations. Integrating and solving for  $[PLA]$  in eq 2 leads to an exponentially decaying PLA unit concentration versus time:

$$[PLA] = [PLA]_o e^{-k't} \quad (3)$$

Here,  $[PLA]_o$  is the original concentration of degradable PLA units within the undegraded hydrogel, and  $t$  is the degradation time. In statistical terms, the probability that any random PLA unit has been hydrolyzed ( $P$ ) equals the fraction of total PLA units hydrolyzed:

$$P = 1 - \frac{[PLA]}{[PLA]_o} = 1 - e^{-k't} \quad (4)$$

In combination with eq 4, structural information about the hydrogel must be incorporated into the model to relate bond degradation to sample erosion. Because each PEG chain, whether it is part of a cycle or a cross-link within the network, is attached to the rest of the gel by two PLA units, each PLA-*b*-PEG-*b*-PLA segment within the degrading network is in one of three different states at any given time. Those three states are (1) completely attached (segment still functioning as a cross-link or cycle with both PLA units intact), (2) one unit intact and one hydrolyzed (a dangling segment still attached to the network), and (3) both units hydrolyzed (segment "released" from the network). The fraction of PLA-*b*-PEG-*b*-PLA segments in each of these three states at any given time during the degradation process is calculated using combinatorial statistical arguments related to the random PLA unit degradation ( $P$ ):

(1) Fraction with neither PLA unit hydrolyzed:

$$y_1 = (1 - P)^2 \quad (5)$$

(2) Fraction with only one PLA unit hydrolyzed:

$$y_2 = 2P(1 - P) \quad (6)$$

(3) Fraction with both PLA units hydrolyzed:

$$y_3 = P^2 \quad (7)$$

The release of a single polyacrylate chain is an involved process. Since each polyacrylate chain is linked to the network through several PLA-*b*-PEG-*b*-PLA cross-links, at least one PLA unit along each of these cross-links must be hydrolyzed for the kinetic chain to be released from the gel. PLA-*b*-PEG-*b*-PLA segments that form cycles, however, do not have to degrade for the polyacrylate chain to be released because the cycles do not contribute to the connectivity between the chain and the rest of the network. Mathematically, the fraction of polyacrylate kinetic chains that can be released from the network at any point in the degradation process ( $F_{PA}$ ) is given by the

fraction of cross-links in State 2 and 3, raised to the  $N$ th power, where  $N$  is the number of cross-links originally attached to each kinetic chain:

$$F_{PA} = (y_2 + y_3)^N = [1 - (1 - P)^2]^N \quad (8)$$

Once  $F_{PA}$  is known, the fraction of PLA-*b*-PEG-*b*-PLA segments released from the network ( $F_{PEG}$ ) can also be calculated. PLA-*b*-PEG-*b*-PLA segments can be eroded from the gel while in any of the three states given by eqs 5–7. Individual PEG chains are simply released when the PEG-*b*-PLA segment exists in the third state with both PLA units hydrolyzed. PLA-*b*-PEG-*b*-PLA segments in the other two states can be released only if the polyacrylate chain(s) they are attached to are eroded from the gel. Therefore, combinatorial statistics must be used once again to determine the probability that a polyacrylate chain is released and that the PLA-*b*-PEG-*b*-PLA segment is still attached to that chain. At this point a distinction should be made between PLA-*b*-PEG-*b*-PLA cross-links and cycles since they attach differently to the backbone chain (one attachment point for the cross-link and two attachment points for the cycle). It was determined, however, during the course of model development that  $F_{PA}$ ,  $F_{PEG}$ , and the resulting mass loss profiles are not sensitive to the number of cycles per backbone chain. Therefore, for all results presented in this work, cycles are neglected to simplify model calculations.  $F_{PEG}$  is then composed of two terms: independent, fully degraded PLA-*b*-PEG-*b*-PLA segments and dangling PEG segments attached by only one PLA unit to the polyacrylate backbone chain:

$$F_{PEG} = P^2 + F_{PA} \left( \frac{y_2}{2} \right) \quad (9)$$

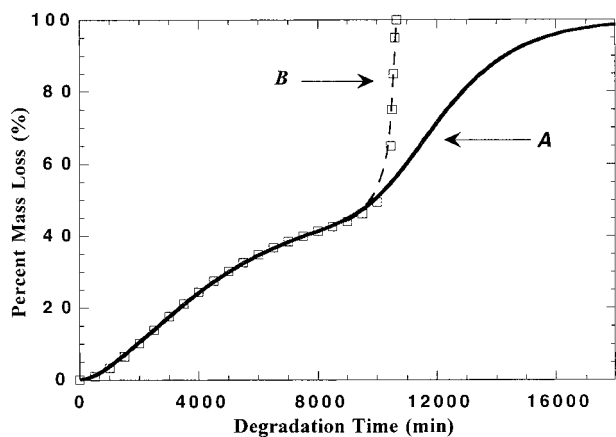
Once the fraction of each building block released is known, the calculation of mass loss from the degrading hydrogel is relatively straightforward:

$$\% \text{ mass loss} = (W_{PA} F_{PA} + W_{PEG} F_{PEG}) \quad (10)$$

Here,  $F_{PEG}$  is the fraction of PLA-*b*-PEG-*b*-PLA segments within the network that have been eroded from the gel while  $F_{PA}$  is the corresponding fraction of polyacrylate chains that have been eroded. Similarly,  $W_{PEG}$  is the mass percent of the cross-linked network contained in the PLA-*b*-PEG-*b*-PLA segments while  $W_{PA}$  is the mass percent in the polyacrylate chains.

Using eq 10, the mass loss from a degrading hydrogel is calculated as a function of time in Figure 4 (Curve A). Although the initial mass loss is primarily a result of the release of single PEG chains that originally were cross-links, the increase in the rate of erosion at approximately 50% mass loss is generated by the release of the backbone polyacrylate chains. The inclusion of three types of erosion products into the model, however, does not predict every trend in the experimental data. Despite capturing several critical aspects of the early stages of degradation, the late-stage erosion profile predicted by Curve A in Figure 4 does not agree with experimental mass-loss data.

The increased rate of mass loss during the final stage of degradation in cross-linked PLA-*b*-PEG-*b*-PLA systems (Figure 3) can be accounted for by incorporation of even higher molecular weight erosion products into the model. For example, during the later stages of degradation, the probability of releasing degradation products composed of several backbone polyacrylate chains becomes significant. In essence, a critical point exists wherein enough PLA units have broken such that the once cross-



**Figure 4.** Theoretically predicted mass loss of a PLA-*b*-PEG-*b*-PLA hydrogel versus degradation time (**Curve A**) without reverse gelation and (**Curve B**) with reverse gelation. Model parameters:  $W_{PA} = W_{PEG} = 50$  wt %;  $N = 1000$  cross-links per backbone chain; and  $k' = 0.0003$  min<sup>-1</sup>.

linked gel becomes a collection of highly branched, water soluble polymer chains. At this critical point, the material is assumed to be water-soluble, and therefore, an erosion product.

To address this issue by calculating the statistical probability for the release of every possible branched-chain configuration within a bulk-degrading network would be a very daunting task.<sup>15,16</sup> However, an easier and equally effective method is to examine the limit where the remaining chains in a bulk-degrading system no longer combine to form a gel with an infinite weight-averaged molecular weight ( $\bar{M}_w$ ). This event is essentially the opposite of the gel point conversion that occurs during cross-linking polymerizations.<sup>12</sup> When enough cross-links are broken, all that remains of the three-dimensional network are highly branched, yet uncross-linked and soluble chains. The dissolution of these chains into the surrounding buffer solution media results in a nearly instantaneous loss of the remaining network mass, a characteristic seen in Figure 3.

According to Flory, macroscopic gelation occurs when there is an average of two cross-links attached to each kinetic chain in the network.<sup>12</sup> At the gel point, the weight average degree of polymerization diverges, and the critical extent of reaction at the gel point ( $X_c$ ) can be calculated from the Carothers Equation:

$$X_c = \frac{2}{f_{\text{avg}}} \quad (11)$$

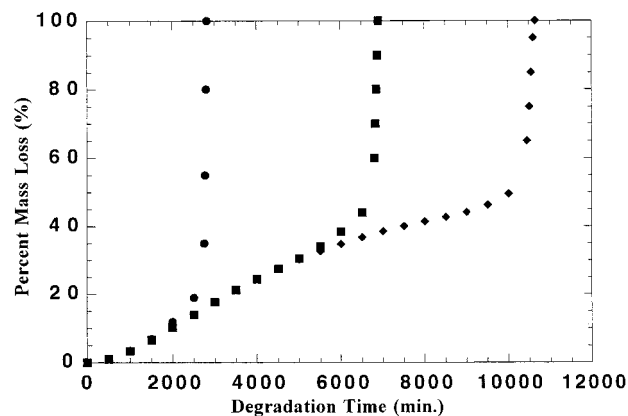
Here,  $f_{\text{avg}}$  is the average functionality of the monomer used in the polymerization system.

Eq 11 can also be used to determine when reverse gelation of a cross-linked, bulk-degrading system occurs (i.e., when the chains no longer form an infinite, three-dimensional network). For this specialized case,  $f_{\text{avg}}$  now becomes equal to the functionality of the backbone chains within the network or, in other words, the number of functional cross-links attached to each backbone chain ( $N$ ), and  $X_c$  is the critical conversion of cross-links along the backbone chains when a gel is first formed.

The fraction of cross-links that remain unbroken (i.e., in State (1), neither PLA unit along the PLA-*b*-PEG-*b*-PLA segment has been broken),  $X(t)$ , can be calculated from:

$$X(t) = [1 - P(t)]^2 \quad (12)$$

where  $P(t)$  is the fraction of PLA units hydrolyzed from eq 4. Reverse gelation occurs when  $X(t)$  is less than or equal to  $X_c$ , or the conversion of cross-links is less than or equal to the



**Figure 5.** Percent mass loss as a function of degradation time for hydrogels with an increasing number of PLA-*b*-PEG-*b*-PLA cross-links per backbone chain: (●)  $N = 10$ ; (■)  $N = 100$ ; and (◆)  $N = 1000$ . Other model parameters for all curves:  $W_{PA} = W_{PEG} = 50$  wt % and  $k' = 0.0003$  min<sup>-1</sup>.

critical conversion needed to form an infinite gel. Combining eqs 11 and 12, the critical degradation conversion at which reverse gelation occurs, ( $P_c$ ), becomes a simple function of the number of cross-links per kinetic chain ( $N$ ):

$$P_c = 1 - \left[ \frac{2}{N} \right]^{1/2} \quad (13)$$

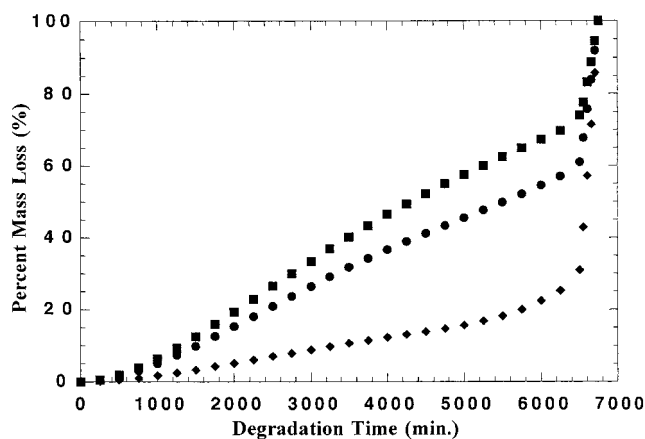
Since  $P(t)$  is a function of PLA hydrolysis kinetics, the time at which reverse gelation occurs ( $t_c$ ) can also be predicted:

$$t_c = \frac{\ln(1 - P_c)}{-k'} = \frac{\ln\left(1 - \left[1 - \frac{2}{N}\right]^{1/2}\right)}{-k'} \quad (14)$$

$P_c$  is a function of a single network parameter, the number of cross-links per backbone chain ( $N$ ), whereas  $t_c$  is a function of  $N$  and a kinetic parameter, the pseudo first-order hydrolysis rate constant ( $k'$ ).

The effects of incorporating reverse gelation into the mass-loss predictions for the model are shown in Figure 4 (Curve B). Initially Curve B appears the same as Curve A. With reverse gelation included, however, the predicted fractional mass loss reaches 100% much sooner. The final stage of degradation in Curve B is characterized by a sudden increase in the mass-loss rate until none of the original cross-linked structure remains. The general shape of this mass-loss curve very closely resembles the experimental data in Figure 3, supporting the reverse gelation mechanism during the final stage of hydrogel degradation.

**Evaluation of Theoretical Model.** The effects of the single network parameter, the number of cross-links per kinetic chain, on mass-loss predictions are shown in Figure 5. Three major steps in the degradation of the PLA-*b*-PEG-*b*-PLA hydrogel networks are readily observed from the three curves in this plot. First, because the PEG chains are bound to the network by only two PLA units, they are released first, producing identical results for all three curves. As more cross-links continue to degrade, a greater fraction of backbone chains with PLA-*b*-PEG-*b*-PLA segments attached are released, resulting in an increase in the degradation rate. This step occurs at an early time when there are only 10 cross-links per chain, and at progressively later times as the number of cross-links per chain increases. The third and final stage of degradation occurs soon after the onset of the second step and is characterized by a reverse gelation of the cross-linked network.

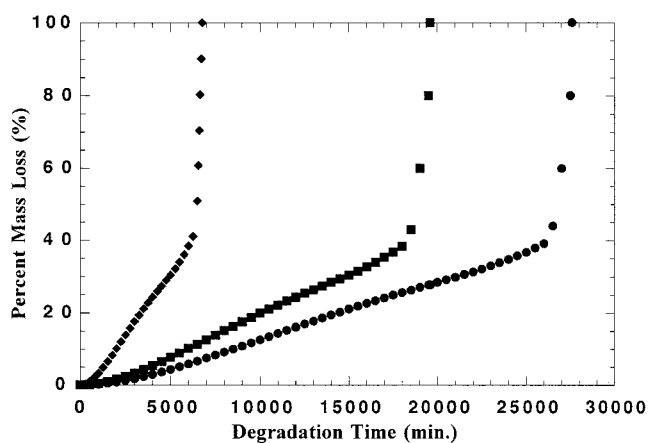


**Figure 6.** Percent mass loss as a function of degradation time for hydrogels with a varying weight percentage in the network backbone chains: (■) 5 wt %; (●) 25 wt %; and (◆) 75 wt %. Other model parameters for all curves:  $N = 100$  cross-links per backbone chain and  $k' = 0.0003 \text{ min}^{-1}$ .

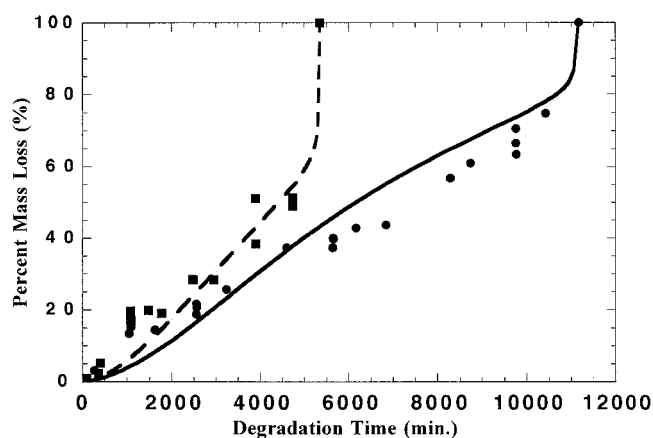
As discussed during the development of the model, there are two other fundamental parameters upon which the statistical model is based. These parameters include (1) the weight percent of the network contained in the polymer backbone ( $W_{PA}$ ) relative to the PLA-*b*-PEG-*b*-PLA segments, and (2) the first-order kinetic rate constant ( $k'$ ) for the hydrolysis of the PLA units. The effect of the backbone weight percent on the theoretical mass-loss predictions is shown in Figure 6. In the physical system, the backbone weight percent could be increased by polymerizing a PLA-*b*-PEG-*b*-PLA macromer with a lower molecular weight PEG chain or by copolymerizing a mono-vinyl species with the divinyl PLA-*b*-PEG-*b*-PLA macromer.

All three erosion profiles in Figure 6 undergo reverse gelation at the same time, since that step depends only upon the number of cross-links per chain and the kinetic rate constant as shown in eq 14. The network mass loss is significantly different, however, before that point. As the backbone weight fraction decreases, a higher fraction of the network mass resides in the PLA-*b*-PEG-*b*-PLA segments. The PEG chains within these segments are released at an early time in the network degradation because they are attached to the gel by only two PLA linkages, as opposed to the backbone polyacrylate chains that are attached through 100 PLA-*b*-PEG-*b*-PLA cross-links for these particular systems. Therefore, the curves with lower backbone weight fractions show higher mass loss percentages at earlier times because a higher fraction of their weight is located within the more easily released PLA-*b*-PEG-*b*-PLA segments.

The effect of the kinetic parameter, the hydrolysis rate constant ( $k'$ ), on mass loss predictions is shown in Figure 7. This parameter has perhaps the strongest effect on the mass loss predictions when plotted versus degradation time. This pseudo first-order rate constant incorporates the true rate constant along with the water and acid concentrations within the system. This parameter determines the rate at which the hydrolysis reaction proceeds and has a direct impact on the rate of mass loss. The three curves in Figure 7 demonstrate that as  $k'$  increases, the observed rate of mass loss also increases when other parameters are held constant. The value for the rate constant also impacts the time at which reverse gelation occurs. The three curves in Figure 8 share the same characteristic sigmoidal shape but over drastically different time scales. The kinetic rate constant ( $k'$ ) therefore influences only the time scale of the network erosion while the structural parameters such as the number of cross-links per kinetic chain ( $N$ ) and the weight



**Figure 7.** Percent mass loss as a function of degradation time for hydrogels with a varying hydrolysis rate constant: (●)  $k' = 0.0007 \text{ min}^{-1}$ ; (■)  $k' = 0.0001 \text{ min}^{-1}$ ; and (◆)  $k' = 0.0003 \text{ min}^{-1}$ . Other model parameters for all curves:  $N = 100$  cross-links per backbone chain and  $W_{PA} = W_{PEG} = 50 \text{ wt } \%$ .



**Figure 8.** Experimental mass loss data ( $\pm 2.0\%$ ) as a function of degradation time for hydrogels polymerized with varying macromer concentrations: (■) 25 wt % and (●) 50 wt %. The solid and dashed lines represent the percent mass loss predicted by the statistical model: (dashed) 25 wt % and (solid) 50 wt %. All model parameters used for both fits are given in Table 1.

fraction of the kinetic chains ( $W_{PA}$ ) determine the characteristic shape of the hydrogel erosion profile.

**Comparison with Experimental Data.** The statistical model that has been developed incorporates the important fundamentals of the bulk-degradation of a cross-linked hydrogel, and, as Figures 5 through 7 show, allows one to investigate the controlling parameters behind the complex process. The measure of an accurate model, however, is how well it can predict the degradation behavior of a real system. In Figure 8, mass loss is again plotted versus degradation time for two PLA-*b*-PEG-*b*-PLA hydrogels polymerized in solution with different concentrations of macromer. These degrading hydrogels, therefore, have the same chemical composition yet different initial cross-linking densities and microstructures.<sup>9</sup> The circles and squares represent experimental data obtained from the degradation of these hydrogels in phosphate buffered solution. The solid and dashed lines represent the mass loss profile predicted by the statistical model. For each system, the backbone weight fraction of the network ( $W_{PA}$ ) was automatically set to match that of the experimental system, approximately 95% in both cases. The kinetic rate constants ( $k'$ ) were calculated using compressive modulus decay data presented in a previous paper for these same degrading gels.<sup>8</sup> The exponential rate constant of the modulus

**TABLE 1. Summary of the Parameter Values Used to Calculate the Erosion Profiles in Figure 9**

macromer concentration (%)	$W_{PA}$ (%)	$k'$ ( $\text{min}^{-1}$ )	N
25	95	$2.8 \times 10^{-4}$	27
50	95	$2.1 \times 10^{-4}$	140

decay data ( $k_{\text{mod}}$ ) can be related to  $k'$  through the decreasing cross-linking density of a degrading gel, which also relies upon  $P$ , the fraction of PLA units hydrolyzed.<sup>8</sup> Using statistical relationships along with rubber elasticity theory to relate the modulus to the cross-linking density of the gel,  $k'$  can be calculated from the modulus data as follows:<sup>8,17</sup>

$$k' = -\left(\frac{5}{12}\right)k_{\text{mod}} \quad (15)$$

Finally, the network parameter of number of cross-links per kinetic chain ( $N$ ) was adjusted for each profile to match the last points in each data set where reverse gelation occurs.

A summary of the parameter values used to predict each erosion profile is given in Table 1. The profiles predicted by the model agree with the experimental data extremely well. In addition, comparing the two erosion profiles and the parameters used to create them indicates that as macromer concentration in the polymerized solution is increased, the degradation rate constant ( $k'$ ) is decreased whereas the number of cross-links per kinetic chain ( $N$ ) is increased. Both of these trends lead to a longer degradation time scale for the hydrogels originally polymerized with a higher concentration of macromer.

Other research efforts investigating the degradation of PLA systems have calculated first-order reaction rate constants for the hydrolysis of PLA anywhere from  $1.7 \times 10^{-6} \text{ min}^{-1}$  to  $2.2 \times 10^{-3} \text{ min}^{-1}$ .<sup>18,19</sup> This wide range of published values indicates how strongly  $k'$  can vary with system conditions. It has been shown, however, that  $k'$  will increase as the molecular weight of the PLA decreases<sup>19</sup> and as the PEG content increases in a PLA-*b*-PEG-*b*-PLA copolymer.<sup>18</sup> Increasing amounts of hydrophilic PEG draw more water into a sample, thereby increasing the reactive water concentration within the network. As mentioned earlier,  $k'$  is a function of water concentration. This effect can be significant when considering that pure PLA films will absorb approximately 1 wt % water, whereas the PLA-*b*-PEG-*b*-PLA hydrogels used in the current study absorb up to 80 wt % water. In addition, using the current approach for calculating  $k'$  based on modulus decay data indicates that  $k'$  effectively represents the kinetic constant for cleavage of a PLA unit, not a single lactide bond. Because of statistical considerations and end-effects, hydrolysis of a PLA unit with multiple ester linkages will always be more probable than hydrolysis of a single ester bond. For these reasons, one would expect the  $k'$  values calculated in this study to be somewhat higher than the rate constant values calculated in other PLA degradation studies.

Similarly, the increasing trend observed in the number of cross-links per kinetic chain ( $N$ ) with initial monomer concentration can also be rationalized through two separate arguments. All else being equal, the parameter  $N$  should increase with an increasing kinetic chain length. From a kinetic point of view, if the pseudo-steady-state assumption is made for the polymerization of these gels, then the kinetic chain length will be

directly proportional to the monomer concentration found in the polymerizing solution. Additionally, other studies have shown that cyclization increases within a network as solvent concentration increases.<sup>20</sup> Since there is a direct tradeoff between forming cycles and cross-links within these gels, both of these factors indicate that  $N$  should increase with monomer concentration as shown in Table 1.

## Conclusion

A statistical, mean-field model based on fundamental parameters has been developed to explain the bulk-degradation phenomenon for a model PLA-*b*-PEG-*b*-PLA hydrogel system. Mass loss from the chemically cross-linked network is shown to depend on network parameters such as the number of cross-links per backbone chain and the mass fraction of the network contained in the backbone as opposed to the rest of the network. Model predictions versus degradation time also depend on reaction parameters such as the order of the hydrolysis reaction and the value of the kinetic rate constant.

With reasonable adjustment of only one of these variables (the number of cross-links per chain), the mass loss predictions of the first-principles based model agree very well with experimental data. The parameter values obtained from fitting the model to experimental data also agree well with their literature values. Beyond the explanation of bulk-degradation behavior for the PLA-*b*-PEG-*b*-PLA system, the theoretical framework developed in this work can be extended to describe any other bulk-degrading system with hydrolyzable cross-links.

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