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A Generalized Bulk-Degradation Model for Hydrogel Networks Formed from Multivinyl Cross-linking Molecules

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A theoretical model has been developed to describe the degradation behavior of hydrogels formed from multivinyl cross-linking molecules. Kinetic information was incorporated into the model to predict the cleavage of the cross-links and structural information was included to describe the mass loss from the network. Mass loss from the networks was shown to depend on many parameters, such as the number of vinyl groups on the cross-linking molecule and the average number of cross-linking molecules reacted into each kinetic chain. Other parameters that influenced the mass loss profile are the weight fraction of the network that is contained in the cross-linking molecule, the propensity to form primary cycles, and the hydrolysis kinetic constant. Two other macroscopic properties, volumetric swelling ratio and compressive modulus, were examined as a function of the average number of cross-links per kinetic chain. Through this modeling approach, the degradation of many realistic systems can be understood and predicted, providing insight into the design of degradable hydrogel networks with the desired properties.

Introduction

Hydrogels are water swellable, cross-linked polymer networks synthesized from a large variety of hydrophilic monomers; these characteristics give hydrogels many unique properties that are useful for numerous applications. For example, the ability to imbibe large quantities of water makes hydrogels useful as superabsorbent materials,[1] whereas the high water content and elastic nature allows for their use in biomedical applications, such as contact lenses, controlled release matrices, and bioadhesives.[2,3] For many other biomedical applications, such as orthopedic implants and internal tissue adhesives, it is desirable to use hydrogels that are hydrolytically or enzymatically degradable. In any application where a degradable system is desired, the degradation behavior and resulting macroscopic properties must be predictable and well understood for a variety of conditions. A more complete understanding of all the parameters that influence the degradation behavior of a hydrogel facilitates a better understanding of how to design the initial polymer system.

A theoretical model to describe the bulk-degradation behavior of hydrogels formed from PLA-b-PEG-b-PLA diacrylate macromers was previously developed[4] that accounts for both structural and kinetic parameters of the degrading copolymer networks. For example, the mass loss of the systems was predicted as a function of degradation time for many different parameters, including the number of cross-links in the kinetic chain and the hydrolysis rate constant. Incorporation of numerous nonidealities associated with the network structure and the degradation allowed the model to predict swelling, compressive modulus, mass loss, and drug release successfully.[4] However, the application of this model has been limited to hydrogels with degradable cross-links where the cross-linker was a divinyl molecule. A more general model capable of predicting the degradation behavior of hydrogels formed from a multivinyl cross-linking molecule would be extremely advantageous. Although the structure and degradation behavior of such hydrogels could be very different from that seen for the PLA-b-PEG-b-PLA gels, the same statistical-kinetic approach to predicting their behavior is applicable.

Thus, a more generalized bulk-degradation model was developed for multivinyl hydrogels containing degradable cross-links. This model is capable of accounting for variations in many parameters including the number of vinyl groups on the cross-linking molecule and the weight fraction of the system that is contained in the cross-linking molecules. In addition, network parameters such as information about the kinetic chain length and the likelihood of cyclization are included. Mass loss profiles for the entire network, as well as the kinetic chains and the cross-linking molecules, were predicted as a function of these many parameters. In addition, the average number of cross-links per kinetic chain was calculated throughout the degradation and related to volumetric swelling and compressive modulus to provide insight into other macroscopic properties.

Generalized Cross-linked Network

The cross-linked networks to which the generalized bulk-degradation model applies are formed by the polymerization of multivinyl cross-linking molecules. The cross-linking molecules that form the foundation of the gels consist of three units: (1) a core structure with multiple terminal functional groups to which the degradable units can be grafted, (2) oligomeric degradable units of materials such as poly(lactic acid) (PLA) or poly(glycolic acid) (PGA) attached to the core functional groups, and (3) radically polymerizable vinyl functionalities such as acrylates or methacrylates attached to each of the degradable segments. Examples of core cross-linking molecules include poly(ethylene glycol) (PEG), which has one reactive hydroxyl group on each chain-end, and poly(vinyl

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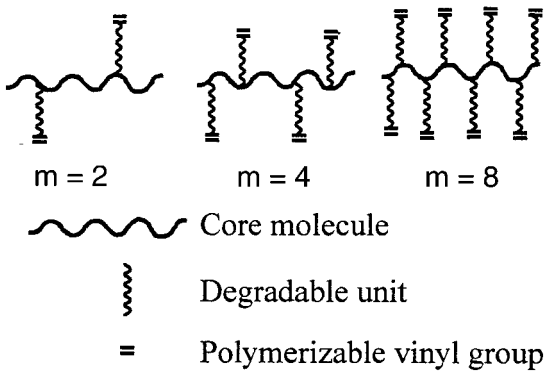

Figure 1. Generalized structure of multivinyl cross-linking molecules that are polymerized to form degradable hydrogels. The degradation of the resulting hydrogel networks formed from these molecules is described by the model developed here.

alcohol) (PVA), which contains a reactive hydroxyl group along each repeat unit of the chain. Polysaccharides, such as dextran or amylose, which contain multiple hydroxyl groups per repeat unit, can also be used.[5] For cross-linking molecules with functional groups at each repeat unit, the final functionality of the molecule can be controlled either by varying the molecular weight of the core structure or by limiting the degree of substitution.

The general structures of the multivinyl, degradable cross-linking molecules are shown in Figure 1. In all cases, functional groups on the core structure are systematically derivitized with degradable units followed by subsequent derivitization with radically polymerizable groups. The final number of double bonds on the cross-linking molecule is *m*. Examples of cross-linking molecules of increasing vinyl functionality are shown in Figure 1.

Cross-linked, degradable gels are formed by the chain polymerization of the multivinyl molecules through their vinyl groups, typically acrylates or methacrylates. The ideal result of such a polymerization is a degradable hydrogel consisting of two distinct structures: (1) polyacrylate or polymethacrylate kinetic chains formed through the polymerization reaction and (2) the cross-linking molecule, which includes the core structure and the degradable segments. The mass fraction of the network residing in each block is determined by the molecular weight of the original cross-linking molecule relative to the type and number of polymerizable groups.

Cleavage of cross-links in these networks leads to changes in the physical and mechanical properties of the gels. As degradation occurs, degradable linkages in each "arm" of the multivinyl cross-linking molecules are cleaved systematically, lowering the average number of cross-links per kinetic chain with time and causing eventual mass loss. Upon complete hydrolysis and erosion, only three species remain from the originally cross-linked gel: (1) the core structure, (2) monomeric or oligomeric degradable units, and (3) the kinetic chains formed from the radically polymerized groups of the cross-linking molecules. The rate of mass loss from these systems, as well as the overall mass loss behavior, is governed by the degradation kinetics and by the network structure of these multivinyl hydrogels.

Development of Generalized Bulk-Degradation Model

The chosen modeling scheme is a generalized form of a statistical, mean-field approach developed earlier[4] and predicts the total mass loss of the system and the average number of cross-links per kinetic chain, as well as the fraction of kinetic chains and cross-linking molecules that are released. All of the cross-linking molecules are assumed fully reacted during network formation, implying that all degradable segments exist as either cross-links or cycles between the kinetic chains. All chain lengths within the gels are assumed to be monodisperse, and chain transfer reactions are neglected. Each degradable "arm" from the multivinyl cross-linking molecule is considered as a single, degradable block, which is necessary to capture the true degradation behavior of these systems. All of the modeled networks are highly swollen, and therefore, the hydrolysis of the degradable units is assumed to occur homogeneously. Pseudo first-order hydrolysis kinetics are assumed because of the high water content, although more complex kinetic mechanisms could be incorporated into the model. The diffusion of degradation products out of the cross-linked systems is assumed to occur much more rapidly than the degradation. Thus, once all of the linkages connecting a certain chain to the network are broken, the chain is considered to be released and no longer contributes to the network mass. Only homopolymerizations of these degradable cross-linking molecules are discussed here, although the model is equally applicable for copolymer networks. In addition, it is always assumed that there are more cross-linking molecules per kinetic chain, *n*, than there are vinyl groups on the cross-linking molecule, *m*.

Two other elements of the network formation and degradation were also considered, cyclization and reverse gelation. Primary cyclization within the network can be quite extensive and occurs when two vinyl groups from a cross-linking molecule react into the same kinetic chain. Primary cyclization results in many nonidealities in the network that affect the mass loss profiles, as well as many other network properties. Reverse gelation is also incorporated into the model and occurs when there are, on average, two cross-links per kinetic chain. Reverse gelation results in the final, complete degradation of the hydrogel.

Degradable blocks within the network are assumed to hydrolyze according to pseudo first-order kinetics. Therefore, the probability that any random degradable unit has been hydrolyzed, *P*, equals the fraction of total units hydrolyzed and is written in terms of the overall degradation time, *t*:

$$P = 1 - \frac{[\mathrm{DU}]}{[\mathrm{DU}]_o} = 1 - e^{-k't} \qquad (1)$$

Here, k' is the pseudo first-order kinetic rate constant for the hydrolysis reaction of the degradable blocks; [DU] is the number of degradable blocks at time *t*; and $[\mathrm{DU}]_o$ is the original number of degradable blocks within the undegraded hydrogel.

In combination with eq 1, structural information about the hydrogel must be incorporated into the model to relate bond degradation to hydrogel erosion. Neglecting any mass loss due to the degradable units themselves, the generalized mass loss equation from these gels is written as a function of the two types of molecules that are released:

$$\%\ \text{mass loss} = (W_{xl}F_{xl} + W_{kc}F_{kc}) \qquad (2)$$

Here, F_{xl} is the fraction of cross-linking molecules that are extractable from the gel, while F_{kc} is the corresponding fraction of kinetic chains that are extractable. Similarly, W_{xl} is the mass percent of the original cross-linked network contained in the cross-linking molecules, whereas W_{kc} is the mass percent in the kinetic chains. W_{xl} and W_{kc} are ascertained based on the chemical structure of the starting macromers. Determining the time-dependent erosion profiles of these cross-linked gels, therefore, depends on calculating F_{xl} and F_{kc} as functions of degradation

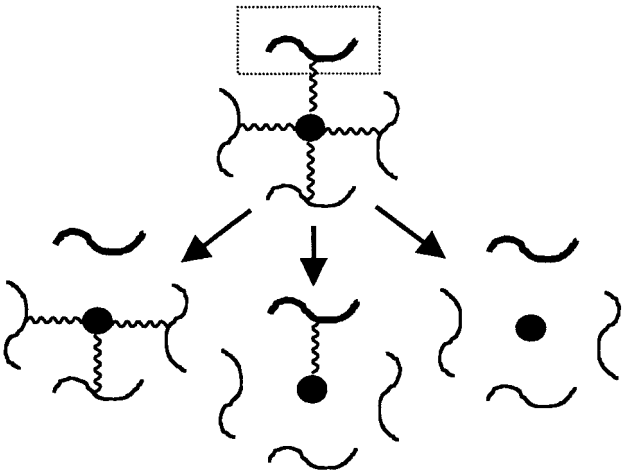

Figure 2. Schematic showing the three possible paths to releasing a kinetic chain from the rest of the network through a tetravinyl cross-linking molecule.

time. Relationships describing each of these parameters will first be described for the degradation of hydrogels with no cycles present within their cross-linked structures and subsequently for the significantly more complicated, but also more realistic, case of hydrogels with cycles. Reverse gelation is incorporated into both analyses.

Erosion Without Cyclization. Without cyclization, each m-vinyl cross-linking molecule within the network is attached to m kinetic chains. This structure implies that each degradable arm of the multivinyl cross-linking molecule is attached to a different kinetic chain. The fraction of releasable kinetic chains (F_{kc}) is related to P, the fraction of degradable linkages degraded, using an understanding of the structure. Examining a particular kinetic chain, each repeat unit of the kinetic chain will be attached to a cross-linking molecule through one of the degradable arms of the cross-linking molecule. The other $m - 1$ arms will each be connected to other kinetic chains. Prior to reverse gelation, a particular kinetic chain is only releasable when it is connected to no other kinetic chains in the network. As shown in Figure 2, this happens in one of three different ways: (1) degradation of the arm attached to that kinetic chain, (2) degradation of the arms connected to all of the other kinetic chains, and (3) complete degradation of the cross-linking molecule.

Summing the probabilities of all three degradation pathways yields the probability that a particular repeat unit of a kinetic chain is releasable. The fraction of releasable kinetic chains (F_{kc}) is then given by this probability raised to the nth power:

$$F_{kc} = [P + (1 - P)P^{m-1}]^n \quad (3)$$

Here, n represents the average number of cross-linking molecules originally attached to each kinetic chain and also equals the number of repeat units in each kinetic chain when there is no cyclization.

Once the fraction of releasable kinetic chains (F_{kc}) is known, the fraction of releasable cross-linking molecules (F_{xl}) is calculated. The fraction of releasable cross-linking molecules is the sum of the two pathways in which these chains may be released and is given by eq 4.

$$F_{xl} = [P^m + F_{kc}(1 - P)P^{m-1}] \quad (4)$$

The terms on the right-hand side of eq 4 represent the probability that a cross-linking molecule is released by complete degradation

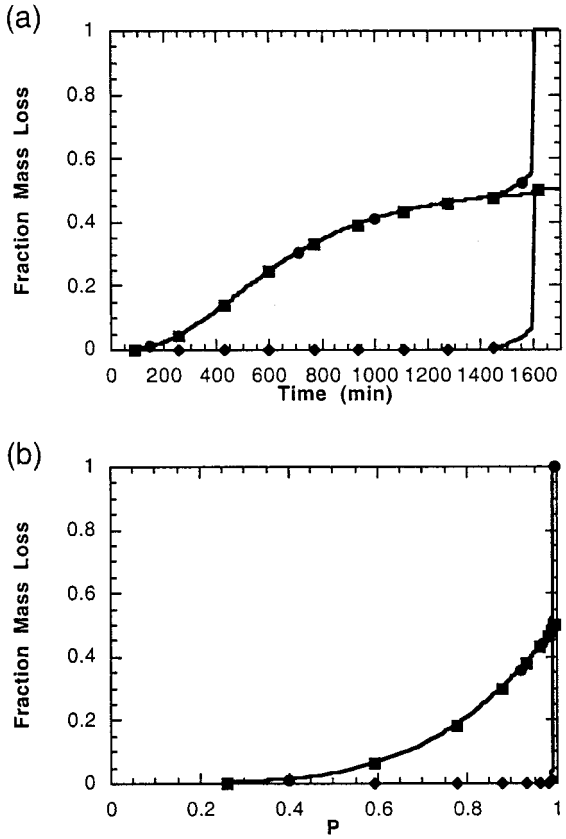

Figure 3. Mass loss predictions for a tetravinyl cross-linking molecule as a function of (a) degradation time and (b) the fraction of total linkages degraded: (◆) kinetic chains, (■) cross-linking molecules, (●) total mass loss. Other model parameters: $m = 4$, $n = 10\,000$, $W_{xl} = 0.5$, $k' = 0.003$ min^{-1}. No cyclization is present.

of all degradable linkages (P^m) or through degradation of all but one degradable arm on the cross-linking molecule when the one remaining arm is attached to a releasable kinetic chain [$F_{kc}(1 - P)P^{m-1}$].

The final element of the mass loss that must be incorporated is the reverse gelation effect. Gelation of a polymer network occurs when an infinite network is formed by the cross-linking of the polymer molecules.[6] Reverse gelation occurs when the infinite network no longer exists, which happens when there are two cross-links per kinetic chain. To understand when reverse gelation will occur, the average number of cross-links per kinetic chain must be known. When there are, on average, exactly two cross-links per kinetic chain, reverse gelation occurs and the entire network becomes soluble.

$$\mathrm{xl} = n(1 - P)(1 - P^{m-1}) \quad (5)$$

Here, xl is the average number of cross-links per kinetic chain at any point throughout degradation. If xl $\leq$ 2, then there are no more than two cross-links per kinetic chain, on average, and reverse gelation occurs. When reverse gelation occurs, there is complete mass loss, as the remainder of the polymer network becomes soluble.

Equations 3 and 4 are combined in eq 2 to predict the mass loss profile in the absence of cyclization for hydrogels formed from any functionality cross-linking molecule. The mass loss of the kinetic chains and the cross-linking molecules, as well as the resulting total mass loss profile for a network of 50 wt % cross-linking molecules and 50 wt % kinetic chains, is shown in Figure 3. Figure 3a is fractional mass loss as a function of

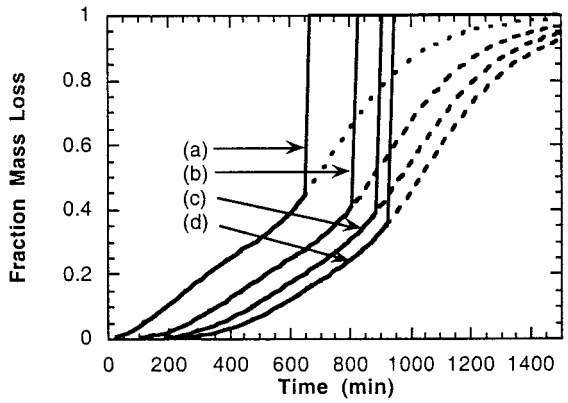

Figure 4. Mass loss predictions from networks with an increasing number of vinyl groups on the cross-linking molecule: (a) $m = 2$, (b) $m = 4$, (c) $m = 6$, and (d) $m = 8$. The solid lines are the model predictions with reverse gelation occurring, and the dashed lines are the model predictions without reverse gelation. Other model parameters for all curves: $n = 100$, $W_{xl} = 0.5$, $k' = 0.003$ min^{-1}. No cyclization is occurring.

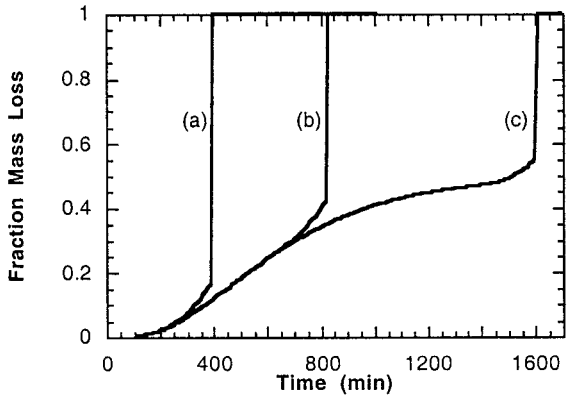

Figure 5. Mass loss predictions for networks with increasing kinetic chain lengths: (a) $n = 10$, (b) $n = 100$, (c) $n = 10\,000$. Other model parameters for all curves: $m = 4$, $W_{xl} = 0.5$, $k' = 0.003$ min^{-1}, and no cyclization.

degradation time for the specified kinetics, and Figure 3b is fractional mass loss as a function of the probability of the degradable linkages being degraded, P. In both cases, the lower functionality of the cross-linking molecules in comparison to the number of cross-linking molecules in the kinetic chains (i.e., $m = 4$, $n = 10\,000$) results in the mass loss profile being dominated by the release of cross-linking molecules. It is not until almost all of the degradable linkages are broken ($P > 98\%$) that any significant fractions of kinetic chains are released. This release contributes to the change in the slope of the total mass loss curve only after 1450 min. The sharp increase in all three curves at the end is the point at which reverse gelation occurs, and the entire network becomes soluble.

The predictions described in this section are comparable to those developed previously for divinyl systems when the number of vinyls on the cross-linking molecule, m, is two. These comparisons yield identical predictions for the two models. The generalized bulk-degradation model can also be used to predict the mass loss from hydrogels formed from cross-linking molecules with more than two vinyl groups. Figure 4 shows the influence of increasing the number of vinyl groups on the cross-linking molecules. As the number of vinyl groups on the cross-linking molecule increases, additional degradable units must be broken to release the cross-linking molecules. This effect results in longer inhibition times for the mass loss profiles of cross-linking molecules with an increasing number of vinyl groups. In addition, the fraction of the total mass loss at the time of reverse gelation decreases with an increase in the number of vinyl groups attached to a cross-linking molecule, i.e., a smaller amount of the network is released prior to reverse gelation. This result is expected because an increased number of linkages on the cross-linking molecule will need to be degraded before the cross-linking molecule is releasable and results in fewer chains being released before reverse gelation. In addition, Figure 4 compares the model predictions for systems with reverse gelation (solid lines) and systems without reverse gelation (dashed lines). This comparison illustrates how including reverse gelation influences the mass loss profiles.

The reverse gelation time is also strongly influenced by the total number of cross-linking molecules in the kinetic chain, n. Similar to increasing the number of vinyl groups on the cross-linking molecule, if the total number of cross-linking molecules in the kinetic chains increases, more degradable linkages must be broken to release the kinetic chains, thus delaying the onset of reverse gelation. When no cyclization occurs, n represents the initial number of cross-links in the kinetic chains (or number of repeat units). When cyclization does occur, n no longer represents the actual number of cross-links, but rather the number of cross-linking molecules in the kinetic chain. Figure 5 illustrates the differences between three systems with increasing kinetic chain length and, therefore, increasing number of cross-links per kinetic chain. As can be seen in Figure 5, all three curves collapse into a single curve initially. The curves deviate from each other when the kinetic chains begin to release, which occurs later in networks with an increasing number of cross-linking molecules in the kinetic chain, n.

Erosion with Cyclization. In networks with cyclization, an m-vinyl cross-linking molecule does not necessarily link m kinetic chains. Each cross-linking molecule can link anywhere from 1 to m kinetic chains, and there will be several possible configurations. A tetravinyl cross-linking molecule, for example, can be attached to one, two, three, or four different kinetic chains. The case of the tetravinyl cross-linking molecule will be used for illustrative purposes in all examples and explanations in this paper, although the model has been completely developed for cross-linking molecules with up to nine vinyl groups. In addition, there are two different configurations of this cross-linking molecule when linking two kinetic chains, either both kinetic chains have two vinyl groups reacted into them, or one kinetic chain has one vinyl reacted and the other kinetic chain has three vinyl groups reacted into it. All of the configurations possible for trivinyl and tetravinyl cross-linking molecules are presented in Figure 6.

The basic equations that describe the hydrogel mass loss from highly functionalized cross-linking molecules with cyclization are very similar to those for networks without cycles. Once the fractions of releasable kinetic chains (F_{kc}) and releasable cross-linking molecules (F_{xl}) are known, eq 2 is used to determine the overall mass loss as a function of the fraction of degradable linkages that are degraded, P, or degradation time, t. The hydrogel structure, and therefore the degradation behavior of the gel, will vary significantly with the extent of cyclization. The number of kinetic chains a cross-linking molecule is connected to is designated by the model parameter i and affects not only the average number of cross-links per kinetic chain within these networks but also the mass loss profile during degradation.

In networks with cyclization, the cross-linking molecules are found in a number of different configurations, and the fraction of cross-linking molecules in each structural configuration, Y_{i_k},

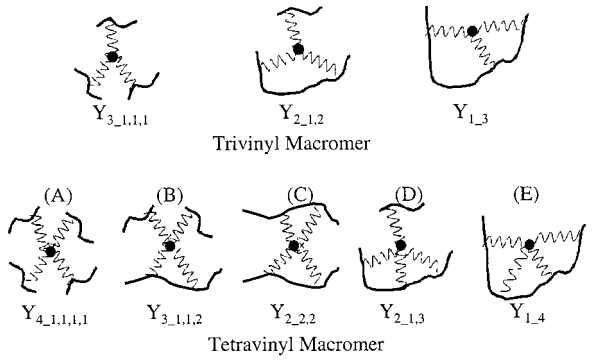

Figure 6. Possible configurations for trivinyl and tetravinyl cross-linking molecules when cyclization is present. There are a total of three unique configurations for the trivinyl and five unique configurations for the tetravinyl cross-linking molecules. Each configuration depends on the number of kinetic chains the cross-linking molecule is attached to and the number of vinyl groups reacted into each kinetic chain.

must be computed. Each of these configurations is specified by the number of kinetic chains the cross-linking molecule is attached to, i, and the number of vinyl groups reacted into each kinetic chain, k. For example, $Y_{2\text{—}1,3}$ is the probability that a tetravinyl cross-linking molecule connects two kinetic chains, and one of those kinetic chains has one of the vinyl groups reacted into it and the other kinetic chain has reacted with the other three vinyl groups. In Figure 6, $Y_{2\text{—}1,3}$ is represented by configuration D of the tetravinyl case.

$Y_{i\text{—}k}$ is determined based on the probability of cyclization, Ψ_x. The subscript x refers to the number of *unreacted* vinyl groups on a cross-linking molecule. After the first vinyl group of a tetravinyl cross-linking molecule is reacted into the network, the probability that the next vinyl group to react will form a primary cycle is Ψ_3. Hence, the probability that the last remaining vinyl group forms a primary cycle is Ψ_1 and has been calculated for many cross-linking monomers.[7] Values for the remaining cyclization probabilities are approximated by relating them to Ψ_1:

$$\Psi_2 = 1 - (1 - \Psi_1)^2 \tag{6}$$

$$\Psi_3 = 1 - (1 - \Psi_1)^3 \tag{7}$$

$$\Psi_x = 1 - (1 - \Psi_1)^x \tag{8}$$

These results assume that cyclization reactions occur with similar mechanisms and kinetics, independent of the number of unreacted vinyls, and also assumes equal reactivity of all double bonds during polymerization of the network. Thus, to determine the fraction of cross-linking molecules in each structural configuration, $Y_{i\text{—}k}$, when cyclization is present, the cyclization probability must be considered. For example, in a tetravinyl cross-linking molecule, the cross-linking molecule can be attached to one, two, three, or four different kinetic chains due to cyclization. The fraction of cross-linking molecules in each of the five different configurations (see Figure 6) is given by:

four kinetic chains (A): $Y_{4\text{—}1,1,1,1} = (1 - \Psi_3)(1 - \Psi_2)(1 - \Psi_1)$ (9)

three kinetic chains (B): $Y_{3\text{—}1,1,2} = \Psi_3(1 - \Psi_2)(1 - \Psi_1) + (1 - \Psi_3)(1 - \Psi_2)\Psi_1 + (1 - \Psi_3)\Psi_2(1 - \Psi_1)$ (10)

two kinetic chains ($k = 1,3$) (C): $Y_{2\text{—}1,3} = (1-\Psi_3)\Psi_2\Psi_1 + \Psi_3\Psi_2(1 - \Psi_1)$ (11)

two kinetic chains ($k = 2,2$) (D): $Y_{2\text{—}2,2} = \Psi_3(1- \Psi_2)\Psi_1$ (12)

one kinetic chain (E): $Y_{1\text{—}4} = \Psi_3\Psi_2\Psi_1$ (13)

Equations 10 and 11 contain multiple terms because more than one way exists to achieve this configuration, and each possible way of forming this configuration must be accounted for. The fraction of cross-linking molecules in each structural configuration for cross-linking molecules of other functionalities is calculated in a similar fashion.

Once the various configurations of the multivinyl cross-linking molecule are known, the fraction of releasable kinetic chains (F_{kc}) is calculated using an approach similar to that developed for eq 3. Each repeat unit of the kinetic chain is examined for the probability that it is releasable. However, in the case with cyclization, the cross-linking molecule can have more than one linkage intact and still allow the release of the kinetic chain if the links are cycles. Specifically, the probability of release of the kinetic chain is the probability that *all* repeat units along a chain are releasable and is written as

$$F_{kc} = \Pi(\chi_{ij}^{\,nY_{i\text{—}k}/i}) \tag{14}$$

Here, χ_{ij} is the probability that a cross-linking molecule in the $Y_{i\text{—}k}$ configuration is broken in a manner that allows the kinetic chain to be released; $Y_{i\text{—}k}$ is the fraction of cross-linking molecules attached to the kinetic chain in a specific structural configuration (i.e., a multivinyl cross-linking molecule connected to i different kinetic chains with k vinyl groups reacted into each kinetic chain); and j is the number of vinyl groups reacted into a specific kinetic chain. χ_{ij} is for a specific cross-linking molecule in the kinetic chain and it is raised to the quantity $(nY_{i\text{—}k}/i)$, which is the average number of cross-links of the considered configuration in each kinetic chain. A cross-linking molecule in the $Y_{i\text{—}k}$ configuration can be broken in two different manners that allow the kinetic chain to be released. Therefore, χ_{ij} is the sum of the probability of separating the cross-linking molecule from the kinetic chain in question, and the probability of separating the cross-linking molecule from all other kinetic chains but remaining attached to the kinetic chain of interest. The five different structural configurations used for a tetravinyl cross-linking molecule (see eqs 9−13) correspond to seven different equations for χ_{ij} in this system:

$$Y_{4\text{—}1,1,1,1}: \ \chi_{41} = P + (1 - P)P^3 \tag{15}$$

$$Y_{3\text{—}1,1,2}: \ \chi_{31} = P + (1 - P)P^3 \tag{16a}$$

$$\chi_{32} = P^2 + (1 - P^2)P^2 \tag{16b}$$

$$Y_{2\text{—}1,3}: \ \chi_{21} = P + (1 - P)P^3 \tag{17a}$$

$$\chi_{23} = P^3 + (1 - P^3)P \tag{17b}$$

$$Y_{2\text{—}2,2}: \ \chi_{22} = P^2 + (1 - P^2)P^2 \tag{18}$$

$$Y_{1\text{—}4}: \ \chi_{14} = P^4 + (1 - P^4) = 1 \tag{19}$$

These seven equations relate to the probability of releasing a specified kinetic chain, attached to a cross-linking molecule in a specific configuration, from the rest of the network. If no

cyclization is present, then Ψ_1 equals zero and only one configuration is possible ($Y_{4\text{—}1,1,1,1}$). Equation 14 simplifies in this case to eq 3, i.e., the relationship obtained when cyclization was not considered.

The fraction of releasable cross-linking molecules, F_{xl}, in a multivinyl system with cyclization is again calculated by summing over the cross-linking molecules released by complete degradation of all attachments (P^m) and those cross-linking molecules attached to kinetic chains that are released ($F_{kc}\Phi_{ij}Y_{i\text{—}k}$). The general equation is written as

$$F_{xl} = P^m + F_{kc}\sum(\Phi_{ij}Y_{i\text{—}k}) \tag{20}$$

Here, Φ_{ij} is the probability that a cross-linking molecule in a certain structural configuration (similar to χ_{ij}) is attached to a releasable kinetic chain. Φ_{ij} is multiplied by the probability of being in a particular configuration, $Y_{i\text{—}k}$, and the fraction of kinetic chains that are releasable, F_{kc}. Φ_{ij} is the probability that a cross-linking molecule is attached to only the kinetic chain of interest divided by all possible states of degradation, i.e., the cross-linking molecule is not completely intact. This probability is written as

$$\Phi_{ij} = \frac{(1 - P^j)P^{m-j}}{1 - (1 - P^{m-j})(1 - P^j)} \tag{21}$$

Again, for a system without cyclization, only one configuration of the cross-linking molecule is possible and eqs 20 and 21 simplify to eq 4.

The point at which reverse gelation occurs is also influenced by cyclization. The definition of reverse gelation remains unchanged; however, the final equation is significantly more complex. Reverse gelation occurs when the average number of *cross-links* remaining per kinetic chain, xl, is 2. Since cyclization is present, many structural configurations result, and the calculation of the cross-linking density must incorporate all of the different configurations and their probabilities.

$$\mathrm{xl} = \sum(1 - \chi_{ij})\left(\frac{Y_{i\text{—}k}n}{i}\right) \tag{22}$$

Because χ_{ij} is the probability that a certain cross-linking molecule is releasable, $(1-\chi_{ij})$ is the probability that it is not releasable, i.e., it is still attached and functioning as a cross-link.

To predict the mass loss profile of hydrogels formed from multivinyl cross-linking molecules with varying degrees of cyclization, eqs 14 and 20 were substituted into eq 2. Figure 7 illustrates the effect of cyclization on the mass loss predictions for a hydrogel polymerized from a tetravinyl cross-linking molecule where Ψ_1 is varied from 0.2 to 0.8. Cyclization effectively lowers the average functionality of the cross-linking molecules within the hydrogels, causing increased mass loss rates and reduced degradation times.

To understand the differences in the three curves in Figure 7 fully, the overall fraction of cycles present in the networks was calculated. The fraction of cycles, F_c, is defined as the relative number of cycles in the system compared to the number of cross-links. This fraction was calculated from

$$F_c = \sum Y_{i\text{—}k}\left(\frac{m - i}{m - 1}\right) \tag{23}$$

For the three systems in Figure 7, (a) has approximately 35% cyclization, whereas (b) and (c) have 71% and 92% cyclization, respectively. Thus, as the tendency to cycle with only one vinyl group left, Ψ_1, increases, the total cyclization in the system also increases and is significantly greater than Ψ_1.

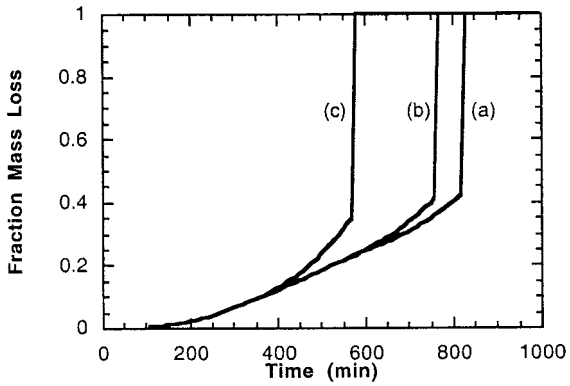

Figure 7. Predicted mass loss versus degradation time from three hydrogels with increasing degrees of cyclization: (a) $\Psi_1 = 0.2$, (b) $\Psi_1 = 0.5$, and (c) $\Psi_1 = 0.8$. Model parameters for all three curves: $m = 4$, $n = 100$, $k' = 0.003$ min^{-1}, and $W_{xl} = 0.5$.

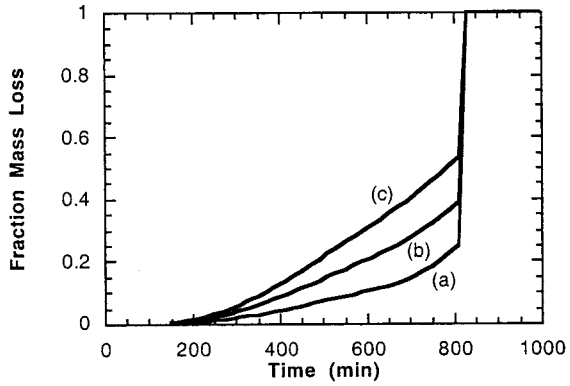

Figure 8. Theoretical predictions of mass loss for networks with increasing weight percentage of the network contained in the cross-linking molecules: (a) $W_{xl} = 0.25$, (b) $W_{xl} = 0.5$, (c) $W_{xl} = 0.75$. Other parameters for all three systems: $n = 100$, $m = 5$, $\Psi_1 = 0.5$, and $k' = 0.003$ min^{-1}.

Two other model parameters that are adjustable are (1) the weight percent of the network contained in the cross-linking molecules, W_{xl}, relative to the kinetic chains, and (2) the pseudo first-order kinetic rate constant, k', for the hydrolysis of the degradable units. The effect of the weight percent of the cross-linking molecule on the theoretical mass loss predictions is shown in Figure 8. Physically, the weight percent in the cross-linking molecules versus kinetic chains can be varied by synthesizing a higher molecular weight cross-linking molecule while leaving the number of vinyl groups the same, or copolymerizing the cross-linking molecule with varying amounts of monovinyl monomer.

The three curves in Figure 8 have one distinct similarity: all three systems undergo reverse gelation at the same time. The reverse gelation time is a function of only the initial number of cross-links per kinetic chain and the kinetic rate constant. Both of these elements are held constant in the systems shown in Figure 8, so it would be expected that reverse gelation would be independent of W_{xl}. Prior to reverse gelation, however, there are significant variations in the mass loss profiles of these three systems. Referring back to Figure 3, at short times the mass loss profiles of the systems are dominated by the release of the cross-linking molecule. Thus, as W_{xl} increases, greater mass loss occurs at earlier times due to a higher fraction of cross-linking molecules in the system.

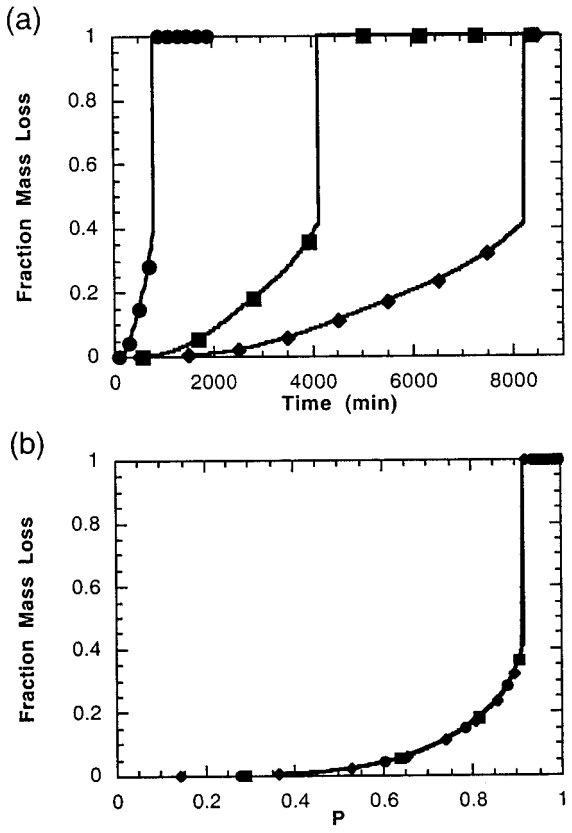

Figure 9. Mass loss predictions for hydrogels with varying hydrolysis rate constants as a function of (a) degradation time and (b) the probability of the linkages being degraded: (●) $k' = 0.003$ min^{-1}, (■) $k' = 0.0006$ min^{-1}, (◆) $k' = 0.0003$ min^{-1}. Other parameters: $n = 100$, $m = 5$, $W_{xl} = 0.5$, $\Psi_1 = 0.5$.

The effect of the hydrolysis rate constant, k', on the mass loss predictions is shown in Figure 9. Figure 9a demonstrates that this parameter most significantly affects the total time required for network degradation. Recall that the pseudo first-order rate constant, k', includes the true kinetic rate constant along with the water concentration within the system due to the high degree of swelling that is assumed for these systems. Because this parameter dictates the rate at which the degradable linkages are hydrolyzed, it follows that as k' is increased so is the overall rate of mass loss. Note that k' affects the time that reverse gelation occurs, but does not have an effect on the mass loss profiles plotted as functions of the probability of degradation, P (Figure 9b). This result follows from the reasoning that if everything else in the networks remains the same, changing the rate at which the bonds are degraded will affect only the time for degradation and not how many linkages must be degraded before reverse gelation occurs. A change in k' can be achieved in real systems by varying conditions such as the temperature or pH at which the degradation occurs.

This model also has the capability of looking at macroscopic properties other than mass loss, such as volumetric swelling ratio, Q, and compressive modulus, K. In many applications it is strongly desirable to understand and predict how both of these properties change as the hydrogels degrade. These properties were predicted by comparing them to a normalized number of cross-links per kinetic chain, xl/xl_o. The normalized number of cross-links allows for easy comparisons between different systems. The Flory−Rehner equation predicts the molecular weight between cross-links for a system as a function of swelling.[8] From this relationship, a correlation between Q and xl is obtained by neglecting chain ends and assuming a highly swollen gel. Similarly, the compressive modulus is related to xl through the rubber-elasticity theory.[8,9] The resulting relationships are

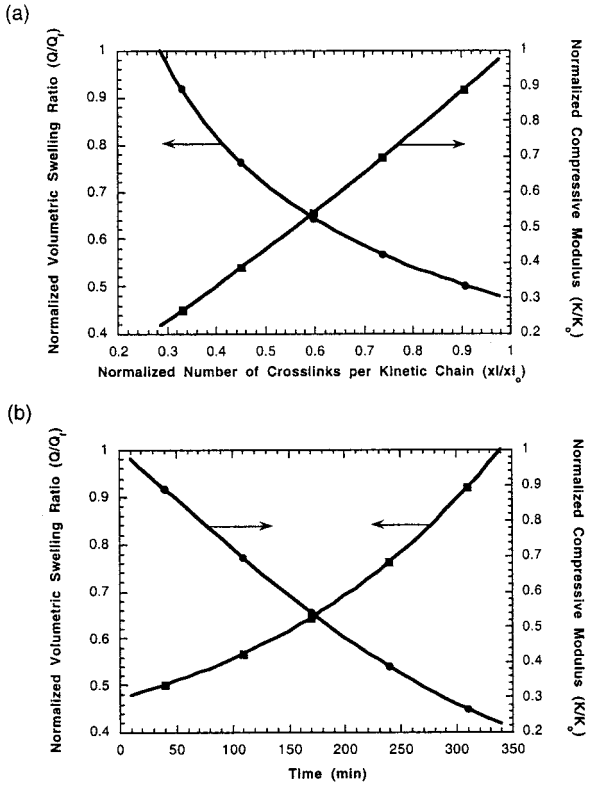

Figure 10. Predicted volumetric swelling ratio profile and compressive modulus profile as a function of (a) the normalized number of cross-links per kinetic chain, xl/xl_o, and (b) degradation time: (●) volumetric swelling ratio, (■) compressive modulus. Network parameters include: $m = 4$, $n = 10$, $\Psi_1 = 0.5$, $W_{xl} = 0.5$, and $k' = 0.003$ min^{-1}.

$$Q \propto [xl]^{-3/5} \tag{24a}$$

$$K \propto [xl]^{6/5} \tag{24b}$$

Normalized volumetric swelling ratio and compressive modulus are plotted in Figure 10. The normalized volumetric swelling ratio, Q/Q_f, is the ratio of Q at any point during the degradation to the final value of Q before reverse gelation occurs. Similarly, the normalized compressive modulus, K/K_o, is the ratio of the compressive modulus at any point to the initial compressive modulus.

Conclusions

A model to describe the bulk degradation of hydrogel systems formed by radical polymerization of degradable multivinyl cross-linking molecules was developed. This model has the flexibility of being applicable to many systems with multivinyl cross-linking molecules. The model is based on a statistical, mean-field approach. Cyclization and reverse gelation, two important structural elements, were also incorporated into the model. Both of these structural elements were shown to have dramatic effects on the mass loss profiles. Reverse gelation determines when complete mass loss is achieved, and an increase in cyclization results in a decrease in time required to reach complete degradation. Due to the generalized nature of this model, many parameters can be adjusted to predict degradation under a variety of circumstances. Predictions for systems with different cross-linking functionalities, as well systems with an increasing

number of cross-linking molecules per kinetic chain, were calculated, and mass loss was shown to depend on these parameters. Increasing either of these parameters results in a longer time for degradation of the system. The effects of two additional model parameters, the weight percentage of the network contained in the cross-linking molecules and the hydrolysis rate constant were also characterized and shown to influence the mass loss profile. The average number of cross-links per kinetic chain was calculated as a function of the degradation time and was related to other macroscopic gel properties. Relationships between the average number of cross-links per kinetic chain and the volumetric swelling ratio and the compressive modulus were identified, and normalized predictions for the macroscopic properties were made. Through a combination of these parameters, the degradation of many realistic systems could be predicted and subsequently controlled. Overall, this model incorporates five different parameters, of which two are inherent to the polymer system being used, the number of vinyl groups on the cross-linking molecule, and the weight percentage of the system that is the cross-linking molecule. A third parameter, the hydrolysis rate constant, can be obtained directly from the volumetric swelling profile for the system. The fourth parameter, the amount of cyclization, can be estimated from previous work.[7] This leaves just one parameter, the number of cross-linking molecules in each kinetic chain, which can be adjusted to fit the experimental data.

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