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Preparation of controlled release systems by free-radical UV polymerizations in the presence of a drug

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Abstract

UV free-radical polymerization techniques are often used to synthesize hydrogels for controlled release applications. Numerous techniques exist for immobilizing drugs or solutes in the gel. This work focuses on the entrapment of solute in a hydrogel by conducting a photopolymerization in the presence of the monomer and the solute. A kinetic gelation model has been developed to examine the effect of the solute material on the polymerization process and the ensuing network structure. Kinetic experiments have also been conducted of the polymerization of poly(ethylene glycol) methacrylate in the presence of theophylline. It was found that the presence of the solute led to a more heterogeneous network with numerous microgel regions present. The effect of the size of the solute on the polymerization was also investigated. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Photopolymerization; Entrapment; Kinetic gelation model

1. Introduction

Free radical, network-producing polymerizations are used in a variety of applications including coatings, information storage systems, films, and aspherical lenses [1–3] and biomaterials [4–10]. There are several advantages to using the photo-

polymerization technique, particularly in biomaterials. In general, the process is benign and the polymers can be fabricated at temperatures and pH values near physiological ranges and even in the presence of biologically active materials. The process also proceeds very rapidly at these conditions for most monomers and conventional initiators. In addition, the ability to direct the exposure of UV light and time of incidence to achieve temporal control is particularly advantageous for the formation of complex devices [5].

One of the primary applications of UV polymerizations in the biomedical field is in the synthesis of hydrogels. Hydrogels are insoluble, water-swollen networks composed of hydrophilic homo- or co-

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polymers [11]. They are desirable for biomedical applications because of their high water content and rubbery nature, similar to natural tissue [12]. In addition, hydrogels may be responsive to their environment. Because of these properties, hydrogels have been investigated extensively for their application as carriers in swelling-controlled release devices.

In this type of device, a drug or protein is incorporated into the system and then released in response to a change in the environment. Depending on the nature of the material of the hydrogel, it swells or collapses in response to a pH or temperature change in the environment. For example, in a cationic hydrogel, a decrease in pH causes the gel to swell, while in an anionic hydrogel the opposite occurs in that the gel mesh size decreases in response to a lower pH. Custom devices can be fabricated to release the drug or protein at a specific condition as the drug/protein diffuses out of the gel when it swells.

Numerous techniques exist for immobilizing drugs on and within a hydrogel, including physical entrapment, electrostatic attraction, physical adsorption, and chemical bonding [13]. The method used depends on the type of hydrogel and drug, and there are advantages and disadvantages to each technique.

Entrapment is probably one of the easiest and simplest methods for developing a controlled release device. In this method, the solute is contained within the hydrogel, which has a tight enough structure to inhibit diffusion of the solute into the surroundings. There are several ways to entrap the molecule. In imbibition, a previously prepared hydrogel is placed in a solution containing the solute for an extended period of time. Eventually, the solute diffuses into the hydrogel. There must be sufficient crosslinking or entanglements to ensure that the solute remains in the hydrogel. Kim et al. [14] review the compositional and structural effects of polymers on loading and release of drug. Numerous researchers have used the method of imbibition in their controlled release studies [15–17]. Lee [18] discusses the subsequent release of the drug from the hydrogel matrices.

Another method for entrapping the drug is to polymerize the hydrogels in the presence of the solute in order to form a network around the solute

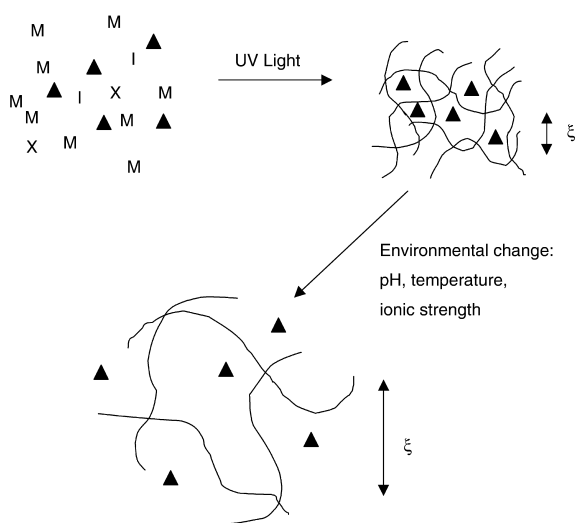


Fig. 1. UV free-radical polymerization of a hydrogel in the presence of a biomolecule (\blacktriangle) and subsequent swelling in response to a change in the environment. Here, M is monomer, X is the crosslinker, I is initiator and ξ is the mesh size.

[4,5,19]. Solute diffusion out of the system occurs when the hydrogel is placed in an environment causing it to swell and the mesh size to increase. Fig. 1 provides a description of this process. Free-radical polymerizations are often employed in this technique because of the benefits described previously. However, before using this technique, the solute must be investigated to ensure that it can withstand the polymerization and will not react with the monomers in the system. It is also important to ensure that the polymeric system is not too crosslinked as the solute will not be able to diffuse out of the system.

In the previously mentioned controlled release studies, an emphasis was placed on the loading of the solute and subsequent release and not necessarily the effect of solute on the polymerization and synthesis of the device. Therefore, in this work, we investigate the effect of solute on the polymerization process by developing a kinetic gelation model and through kinetic experiments. In this paper, the word inert will be used to describe any solute that does not polymerize with the functional groups in the monomer and therefore is not chemically bonded to the polymer.

2. Free-radical polymerization modeling

We consider the case of preparing a swelling-controlled release system by free-radical polymerization in the presence of an inert drug finely dispersed in the form of microparticles. A kinetic gelation model was developed to more closely examine this network formation.

2.1. Background

Manneville and de Seze [20] proposed the first kinetic gelation model to more accurately explain free radical polymerization. They studied the gelation process of a solution of bifunctional and tetrafunctional monomers in the absence of solvent. Sites on a lattice were randomly assigned to the bifunctional unit or the tetrafunctional unit. Reaction occurred by randomly selecting an active site and linking it to a randomly selected first or second neighbor with an available functional group. The active site was then transferred to the neighboring site. Termination occurred when an active site reacted with another active site.

This model was the first of its type to account for growth and steric hindrance effects. The resulting structure was very different from that obtained by standard percolation or by the Bethe lattice of Flory and Stockmayer [21]. The large clusters formed on the lattice were often entangled with each other. Even though these clusters were not linked chemically, the entanglements affected the mechanical properties of the gel.

The kinetic gelation model developed for this study is based on the model proposed by Bowman and Peppas [22,23] and Anseth and Bowman [24]. They improved the original model of Manneville and de Seze [20] by incorporating a more realistic initiating mechanism and monomer and polymer movement. This model was chosen because it provides structural information of the evolving polymer structure. Though it lacks molecular interactions and accurate modeling of molecular movement, it has proven very efficient in describing the network formation process and has shown agreement with experimental techniques in describing the same trends observed in free-radical polymerizations.

2.2. Kinetic gelation model details

To begin the modeling process in the computer program, first the monomers and initiators were randomly distributed on the lattice. The lattice used in this study was a face centered cubic lattice with a length of 31. Therefore, every site on the lattice had 12 nearest neighbors. In all of the simulations, 15% of the sites remained vacant to allow for reasonable mobility of the monomer molecules. In addition, periodic boundary conditions were implemented in order to neglect edge effects.

Initiators occupied two neighboring sites in the lattice. Monomers occupied a specified number of neighboring sites depending on their relative size. In addition, either one end (bifunctional monomer) or both ends (tetrafunctional monomer or crosslinking agent) of the monomer were specified as reactive functional groups. The amount of crosslinking agent was varied between 10 and 33 mol%. After randomly placing the initiators and monomers on the lattice, simulation of the polymerization process was started. During a single step in the model, three different actions took place: initiation, polymerization, and monomer and chain segment movement.

Initiation of the polymerization began with the decomposition of the initiator molecules into radicals, as shown by Eq. (1):

$$\frac{[I]}{[I]_0} = e^{-kt} \quad (1)$$

where $[I]$ is the initiator concentration, $[I]_0$ is the initial initiator concentration, t is time step and k is the decay constant. Upon decomposition, the initiator split into two radicals, each occupying one site. For all of the results presented here, k was set to 0.02 (units of inverse time step) unless otherwise noted. For photopolymerizations, a larger k corresponds to a higher UV intensity, resulting in more radicals introduced into the system in a shorter time period. The value of 0.02 was chosen based on the work of Anseth and Bowman [24].

After Eq. (1) was evaluated, all of the radicals in the system were examined. Reaction occurred if a radical was a nearest neighbor to either a reactive group or to another radical. If the radical reacted

with a functional group end of a monomer, propagation occurred. In this case, a bond was formed between the radical and the monomer and the radical was transferred to the functional group. If the radical reacted with another radical, termination occurred. In this case, a bond formed between both radical sites and the radicals were terminated.

One of the key steps in this model was the movement of the molecules of monomer, initiator, and polymer. The movement allowed for the possibility of reactive ends becoming nearest neighbors. Movement of species occurred at every step.

First, 33% of the occupied sites were selected at random. Because the monomers, initiators and polymers occupied multiple sites, only a single site within the molecule was chosen. Next, a nearest neighbor of each site was also selected at random. If that neighboring site was empty, an attempt was made to move the previously selected occupied site. A move was accepted as long as all bonds remained intact. A bond could not be broken or lengthened, and all occupied sites within an initiator, monomer, or polymer had to remain nearest neighbors. Only 33% of the occupied sites were chosen to save simulation time. Simulations took considerably longer if it was attempted to move every occupied site as movement of the molecules took most of the computer time. The value of 33% was decided upon as an optimum in moving species and finishing a simulation in reasonable time.

The inert drug particles were incorporated in the models by randomly placing them on the lattice in the initial step and specifying that they occupy a certain number of neighboring sites. The more neighboring sites the inert material occupied, the larger the solute. Corresponding to a larger radius. The incorporation of this solute was different than incorporating more void spaces because the solutes occupied a finite space on the lattice. Thus, the monomers and polymers in the system were forced to move around the solute.

The model was coded in MATLAB and simulations were performed on a Sun Ultra 5 workstation. Each simulation took approximately 12 h to run. All results reported here were an average of three to five runs at the exact same conditions, just different random numbers used for the configuration and movement of molecules. Ideally, an infinite number

of simulations should be run and averaged, but it was found that running more simulations did not significantly change the average.

3. Experimental

3.1. Materials

The monomers examined in this study were poly(ethylene glycol)200 methacrylate (PEG200MA) and poly(ethylene glycol)400 methacrylate (PEG400MA) and the crosslinking agent was poly(ethylene glycol)200 dimethacrylate (PEG200DMA). All monomers were used as received (Polysciences, Warrington, PA, USA). The drug used as an inert solute was theophylline ($M_w = 180$, $r_h = 0.23$ nm) (Aldrich, Milwaukee, WI, USA). Solutions were prepared with either PEG200MA or PEG400MA, the crosslinking agent PEG200DMA, theophylline and 0.1 wt% of the initiator, 2,2-dimethoxy-2-phenylacetophenone (DMPA, Aldrich). The crosslinking agent concentration was varied from 2.5 to 30 mol%. Nitrogen was bubbled through the mixture to remove any dissolved oxygen. Solutions were also prepared without the theophylline present.

3.2. Kinetic experiments

Kinetic experiments were conducted with a differential scanning photocalorimeter (DPC, DPC930, TA Instruments, New Castle, DE, USA). The UV light source was a 200 W mercury arc lamp and the intensity was set to 1.2 mW/cm². A small amount of the monomer mixture (2–6 mg) was placed in a small aluminum pan and covered with a thin polyethylene film to minimize evaporation. Experiments were conducted at 30°C and the sample was allowed to equilibrate for 1 min at 30°C before irradiation. An empty aluminum pan with a polyethylene cover was used as a heat flow reference.

The DPC measured the heat flow per unit mass as a function of time. The theoretical enthalpies of each mixture were calculated based on the known enthalpy of -13.1 kcal/mol [25] for methacrylate double bonds. The rate of polymerization, R_p , was calculated by dividing the measured heat flow per unit mass by the theoretical enthalpy. The units of R_p

are fractional double bond conversion per second. Integration of the polymerization rate data gave the double bond conversion. The presence of the theophylline was accounted for in the calculations, as it did not participate in the polymerization reaction.

Experiments were easily reproduced. It was found that the greatest source of error was in the calculations of the rate of polymerization and conversion with the assumed enthalpy for methacrylate double bonds. For these studies, the enthalpy was assumed to have an error of $\pm 5\%$.

4. Results and discussion

4.1. Modeling

During a simulation, every monomer was tracked. Records were kept regarding its position, reactivity and where it was in a polymer chain. Both functional groups of the crosslinking agent were tracked. For these network-producing polymerizations, the pendent double bond reactivity was extremely important and was used to characterize the network. A pendent double bond was formed when one end of a crosslinking agent reacted in a polymer chain leaving the other reactive end dangling from the polymer chain and free to react. When this pendent double bond reacted, a cycle formed. Fig. 2 illustrates the three

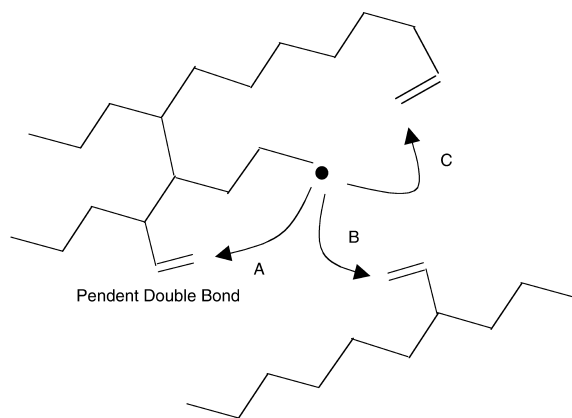
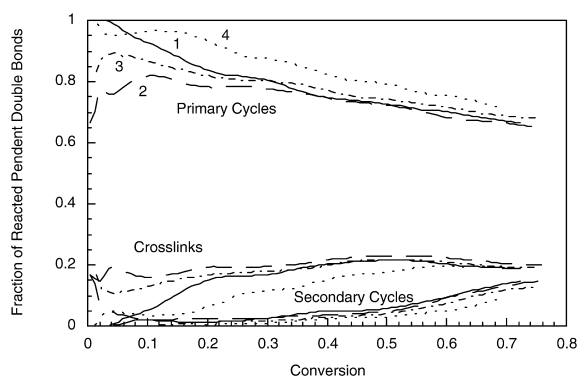


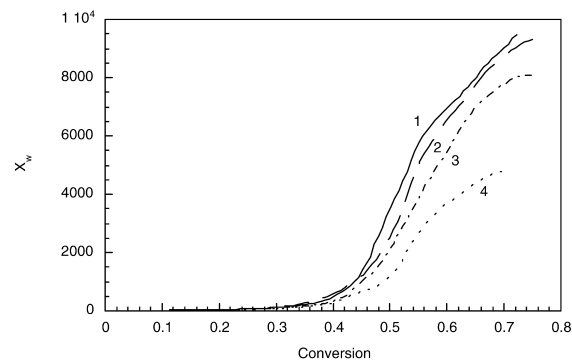
Fig. 2. Three types of cycles can form in a polymer network when a pendent double bond reacts with a free radical. Primary cycles are formed according to reaction (A), crosslinks are formed according to reaction (B) and secondary cycles are formed according to reaction (C).

types of cycles: primary cycle, secondary cycle and crosslink. Numerous primary and secondary cycles result in a very heterogeneous structure with microgel regions. These cycles do not contribute to the overall structure of the polymer as only the formation of crosslinks leads to an expansion of the polymer network.

In the first set of polymerizations, the effect of increasing the amount of solute was studied. Fig. 3a displays the pendent double bond reactivity as a function of conversion for polymerizations of 10% crosslinking agent (2-sites, both ends reactive) and 90% bifunctional monomer (2-sites, only one end reactive). In the first polymerization, there was no



(a)



(b)

Fig. 3. Pendent double bond reactivity (a) and weight average number of sites occupied by the polymers, X_w , (b) as a function of conversion for polymerizations with 10% crosslinking agent and (1) no solute, (2) 5% of the space occupied by solute, (3) 10% of the space occupied by solute, and (4) 20% of the space occupied by solute.

drug present. The amount of drug was then increased to 5, 10 and 20% of the lattice sites. For these polymerizations, all of the solute occupied just one site on the lattice, simulating an inert material that is smaller than the monomers and crosslinking agent.

The results indicated that early in the polymerization (<10% conversion), as the amount of solute was increased, more primary cycles formed except for the case where there was no solute. After about 10% conversion, there was a definite trend that more solute led to an increase in the formation of primary cycles and a decrease in crosslinks and secondary cycles. The solute was acting as a hindrance for diffusion of the monomers and polymer chains. The easiest reaction to occur was the primary cycle because the pendent double bond was in close proximity to the radical on the same primary chain. As the amount of solute was increased, diffusion became increasingly difficult. This led to the formation of microgel regions instead of an extended, crosslinked polymer network. It is believed that the high amount of primary cycles at less than 10% conversion for the polymerization without solute was an effect of a more rapid polymerization due to the lack of solutes hindering any diffusion.

The simulations followed the polymer network evolution and calculated chain lengths. Fig. 3b shows the weight average number of sites occupied, X_w , for the polymers during the polymerization. Since there was crosslinking agent present in these polymerizations, X_w diverged at what was known as the gel point. This was when the polymer formed a network of essentially one molecule and expanded across the entire lattice. The presence of the solute delayed the gel point due to the formation of microgel regions. Small polymer networks were forming around the solute and these molecules were not able to diffuse and react with each other to form one molecule until a higher conversion. At this point, enough monomer had reacted that the microgel regions were able to connect around the solute. As the amount of solute was increased, the gel point was delayed to a higher conversion.

In the next set of polymerizations, the amount of crosslinking agent was increased. Fig. 4a shows the pendent double bond reactivity for polymerizations with 33% crosslinking agent conducted with and without solute. Here, there was a drastic increase in

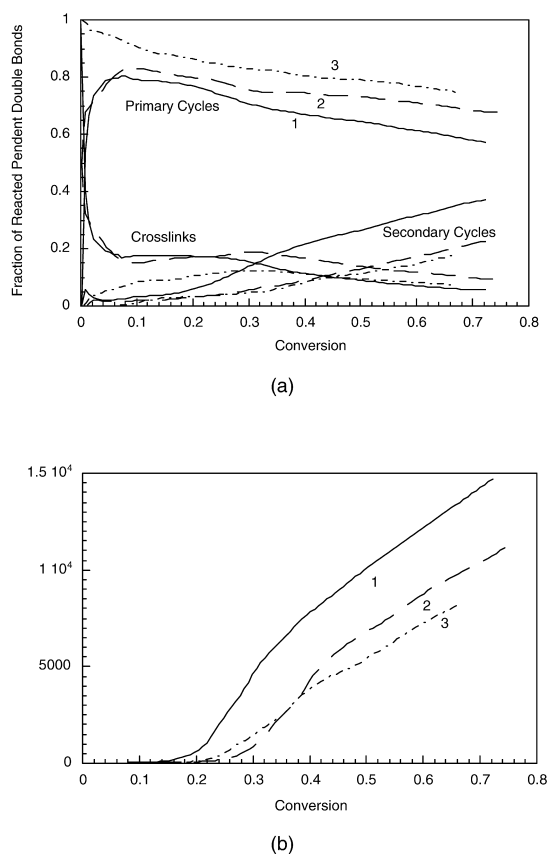


Fig. 4. Pendent double bond reactivity (a) and X_w (b) as a function of conversion for polymerizations with 33% crosslinking agent and (1) no solute, (2) 20% of the space occupied by solute and (3) 33% of the space occupied by solute.

the formation of primary cycles as the amount of solute was increased. In addition, Fig. 4b shows the resulting delay in the gel point from the introduction of solute to these polymerizations. Overall, the gel point for a polymerization with 33% crosslinking agent occurred earlier than for the polymerization with 10% crosslinking agent. The polymer expanded the lattice faster because there was more crosslinking agent to act as bridges between polymer molecules.

There was a more dramatic effect from the presence of solute for the polymerizations with more crosslinking agent because of the increased diffusion limitations. Since there was more crosslinking agent, the viscosity of the system increased faster due to the formation of larger polymer molecules. This hindered diffusion of the longer chains and favored

diffusion of the smaller monomers. Diffusion and movement of the molecules is easier when the concentration of crosslinking agent is decreased and there are more smaller, linear polymer molecules. After solute was added to the more highly cross-linked polymerization, diffusion became even more hindered for all molecules. The solute did not have as much of an effect on the more loosely crosslinked polymerizations.

In the next set of polymerizations, the effect of the size of the solute was examined. Fig. 5a shows the pendent double bond reactivity for polymerizations with only 10% crosslinking agent. Here, the solute occupied 10% of the total lattice and were either of size 1-site or 5-sites. This is analogous to increasing the hydrodynamic radius of the solute. There appears little difference in the formation of cycles. However,

the larger solutes resulted in slightly more primary cycles after 20% conversion. This led to a delay in the gel point, as evident in the X_w data presented in Fig. 5b. Increasing the size of the solute delayed the gel point from 40% conversion to 50% conversion.

The effect of the solute size in a more highly crosslinked polymer was also examined. Fig. 6a shows the pendent double bond reactivity for polymerizations with 33% crosslinking agent and 20% of the sites on the lattice occupied by solute. The solute size was varied between 1-site, 2-sites and 5-sites. There was little effect of increasing the size of the solute at the higher crosslinking agent concentration. There was only a slight difference at a conversion of less than 5%. Very early in the reaction, the largest solute caused slightly more primary cycles to form because of diffusion limitations. However, this had

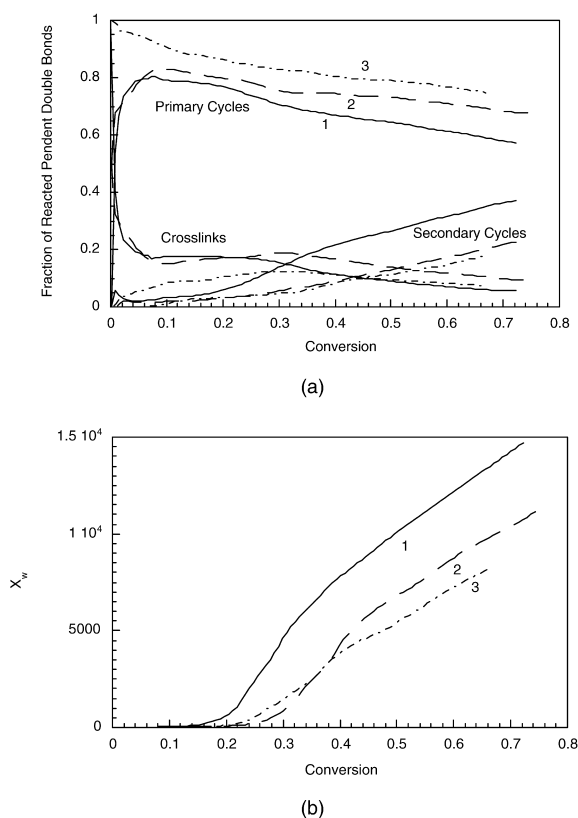


Fig. 5. Pendent double bond reactivity (a) and X_w (b) as a function of conversion for polymerizations with 10% crosslinking agent and 10% of the space occupied by solute. The solute occupied (1) 1-site or (2) 5-sites.

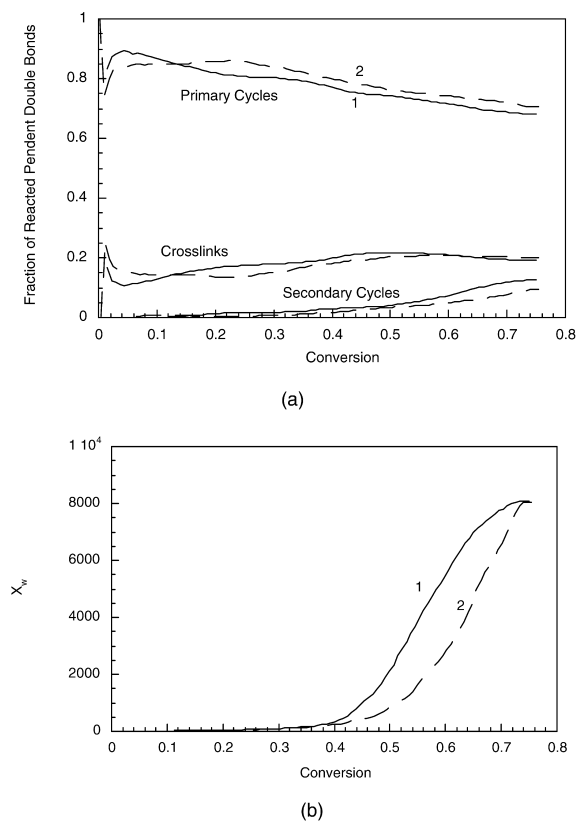


Fig. 6. Pendent double bond reactivity (a) and X_w (b) as a function of conversion for polymerizations with 33% crosslinking agent and 20% of the space occupied by solute. The solute occupied (1) 1-site, (2) 2-sites, or (3) 5-sites.

no effect on the gel point and X_w , as shown in Fig. 6b. Here, the polymerization resulted in such high molecular weight polymers early in the reaction that the size of the solute had little effect on diffusion. The size of the polymers had become very large in comparison with the solute. However, as Fig. 4 indicates, the presence of solutes, no matter what the size, does alter the polymerization and the network formation process.

After completion of the modeling, the kinetics of the polymerization was examined experimentally in order to compare with the model.

4.2. Experimental studies

Results from the polymerization in the presence of theophylline can be seen in Figs. 7 and 8. Fig. 7 shows the polymerization rate as a function of conversion for the copolymerization of PEG200MA with the crosslinking agent PEG200DMA. As the concentration of PEG200DMA was increased, the maximum of the polymerization rate R_p increased and there was a stronger autoacceleration effect. This same trend was observed in polymerizations without theophylline. The autoacceleration effect occurs when the rate of polymerization increases with decreasing monomer concentration. The rate of termination is decreased during this period of the polymerization because of diffusion limitations. It is

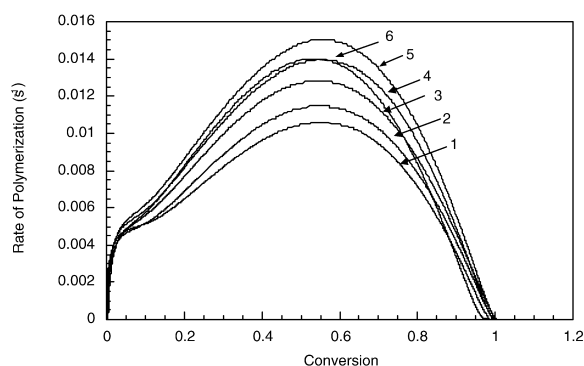


Fig. 7. Rate of polymerization as a function of conversion for the copolymerization of PEG200MA with the crosslinking agent PEG200DMA in the presence of theophylline. The different runs correspond to different amounts of the crosslinking agent PEG200DMA: (1) 2.5 mol%, (2) 10.0 mol%, (3) 15.0 mol%, (4) 20 mol%, (5) 25 mol% and (6) 30 mol%.

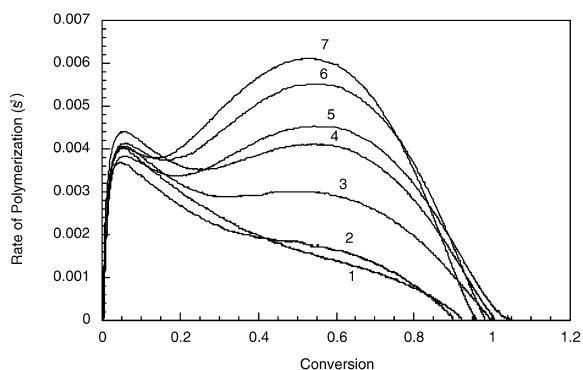


Fig. 8. Rate of polymerization as a function of time for the copolymerization of PEG400MA with the crosslinking agent PEG200DMA in the presence of theophylline. The different runs correspond to different amounts of the crosslinking agent PEG200DMA: (1) 2.5 mol%, (2) 5.0 mol%, (3) 10.0 mol%, (4) 15.0 mol%, (5) 20 mol%, (6) 25 mol% and (7) 30 mol%.

difficult for the two long propagating chains to diffuse and terminate and much easier for propagation to occur. Eventually, the rate of termination drastically increases and R_p decreases.

Fig. 8 shows the polymerization rate as a function of conversion for the copolymerization of PEG400MA with the crosslinking agent PEG200DMA. A similar trend of increasing PEG200DMA concentration causing an increase in the autoacceleration effect was observed. It was also observed that the copolymerizations with the smaller PEG200MA reached higher polymerization rates than the copolymerizations with PEG400MA. The PEG200MA monomer is smaller and more mobile; therefore the rate of polymerization was increased.

Fig. 9 shows a side-by-side comparison of the polymerization rates with and without the drug present. From Fig. 9a, it is evident that the presence of the drug significantly increased the polymerization rate and the autoacceleration effect for both loosely crosslinked systems (2.5 mol% PEG200DMA) and for more tightly crosslinked systems (30 mol% PEG200DMA). It is believed that, in the presence of the drug, the polymerization was forced to produce a network around the solute, which in turn increased the formation of microgel regions. The propagating chains were reacting with functional groups that had been forced into less space due to the presence of the solute. Since the functional groups were closer to

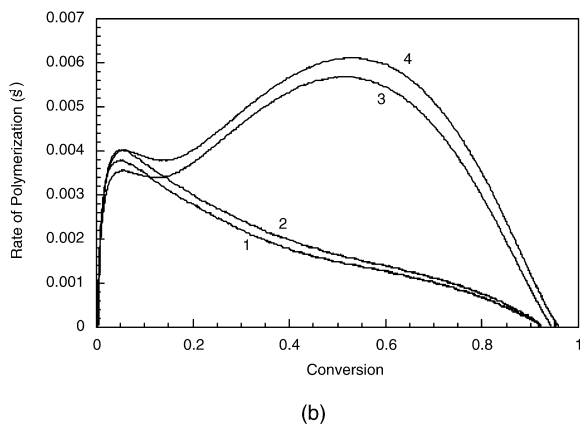
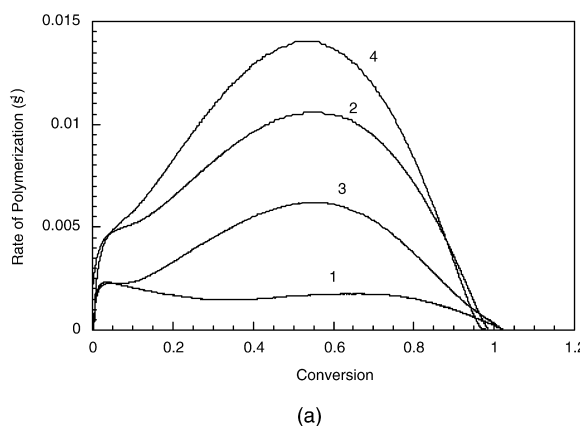


Fig. 9. The rate of polymerization as a function of conversion for PEG200MA (a) and PEG400MA (b) with 2.5 mol% PEG200DMA without drug (1) and with drug (2) and with 30 mol% PEG200DMA without drug (3) and with drug (4).

each other, propagation proceeded at a much faster rate.

These data agree with the kinetic gelation modeling results. In the model, it was shown that the presence of a solute during a polymerization with a crosslinking agent resulted in more primary cycles and a delay in the gel point. This would lead to an increased autoacceleration period because primary cycles occur at a faster rate due to the close proximity of the radicals and the functional groups. Anseth et al. [26] noted a similar observation in their work examining reaction diffusion in PEGDMA polymerizations. Due to the close proximity of the radicals and the limited diffusion of monomers in the

network, termination was limited by reaction diffusion.

For the system with the longer PEG400MA monomer, the presence of the drug did not have such a significant effect in either the loosely crosslinked system or the more tightly crosslinked networks. However, there was still the observed trend of an increased R_p in the presence of the solute. The rate of polymerization increased by about 5% in the presence of the drug. In this case, the longer PEG chain hindered the propagation of radical chains more than the PEG200 chains. Even though the functional groups were in less space, radicals were not able to propagate faster due to the presence of the long PEG chains.

5. Conclusions

In this study, the effect of a solute (drug) on the polymerization kinetics was studied. A kinetic gelation model was used to examine the network formation for polymerizations in the presence of a crosslinking agent. From these studies, it was determined that the presence of a solute will result in more microgel regions, a more heterogeneous material and a delay in the gel point. Kinetic experiments were also conducted to examine the photopolymerization of PEG200MA and PEG200DMA in the presence of the drug theophylline. These studies showed that the presence of a low molecular weight solute increased the rate of polymerization. The kinetic experiments agreed with the kinetic gelation modeling. The formation of primary cycles and microgel regions will generally occur at a faster rate because the functional groups are in closer proximity to each other. Polymerizations with the longer monomer PEG400MA were not affected as much by the presence of a solute because the longer PEG chain hindered polymerization.

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