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Network Model for the Swelling Properties of End-Linked Linear and Star Poly(ethylene oxide) Hydrogels

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ABSTRACT: The Cima−Lopina equation for swelling in hydrogel networks with a bimodal distribution of cross-link densities is modified slightly for an end-linked system. The revised equation is verified with a controllable series of poly(ethylene oxide) hydrogels synthesized from linear and star PEO molecules cross-linked with a triisocyanate linker. Cross-link density in the gels is independently analyzed from elastic modulus and swelling equilibrium. Good correlation between these two methods confirms the accuracy of the revised Cima−Lopina equation.

Introduction

Hydrogels, water-swollen polymer networks, are finding increasing use in biomedical applications, including absorbents and controlled release agents. Poly(ethylene oxide) (PEO), also known as poly(ethylene glycol) (PEG), has many properties which make it particularly attractive as a biomaterial. PEO is soluble in water and several organic solvents including methylene chloride, toluene, acetone, and ethanol.[1] PEO is nontoxic and has been approved for use in biomedical applications by the Food and Drug Administration.[2] Numerous studies have shown that PEO resists protein adsorption and cell adhesion and does not incite the immune system.[3,4] PEO is available in the traditional linear form and in a relatively new star form, where PEO arms emanate from a central core. The presence of numerous functional groups in a compact volume is an attractive feature for star polymers applied to pharmaceutical and biomedical applications. Biologically active molecules can be immobilized onto the functional groups at the end of the PEO arms.

Recently, there has been a growing interest in applications of hydrogels in medicine and pharmacy, specifically in exploiting the unique properties of star polymer hydrogels in the area of controlled release technology and in tissue engineering. As indicated in an excellent review by Graham,[5] PEO hydrogels can be made by the following methods: (i) free radical or radiation cross-linking; (ii) entanglement cross-linking of high molecular weight PEO; (iii) copolymerization of PEO with other polymers; (iv) molecular complexation by hydrogen bonding between high molecular weight PEO and other polymers; (v) end-linking by reaction of the hydroxyl groups on the ends of the PEO. Gel properties, such as permeability to solutes, elastic modulus, and the average length of dangling chain ends that are to be functionalized for biomolecule immobilization, are functions of the network structure.

Flory developed an elegant theory of network structure swelling,[6] which, together with its modifications,[7−9] provides a suitable basis for predicting the molecular weight between cross-links (M_c) based on the polymer−solvent interaction parameter (χ_1) and equilibrium swelling measurements for gels with homogeneous cross-link functionalities made from linear polymers:

$$\frac{1}{M_c} = \left(\frac{F}{F-2}\right)\frac{1}{M_n} - \frac{[\ln(1-v_{2,s}) + v_{2,s} + \chi_1 v_{2,s}{}^2]\dfrac{\bar{v}}{V_1}}{\left[\left(\dfrac{v_{2,s}}{v_{2,r}}\right)^{1/3} - \dfrac{2}{F}\left(\dfrac{v_{2,s}}{v_{2,r}}\right)\right]v_{2,r}} \qquad (1)$$

where M_n is the number-average molecular weight of a single polymer strand in the cross-linked network, V_1 is the molar volume of the solvent, $v_{2,r}$ and $v_{2,s}$ are the volume fractions of polymer in the solution during cross-link formation and following equilibrium swelling, respectively, and $\bar{v}$ is the specific volume of the polymer. The cross-link functionality (F) is the number of chains emanating from a cross-link, 4 in most cross-link systems. When hydrogels are formed from star polymers, there are two cross-link functionalities present, one from the cross-link between stars (F_1), and a second effective cross-link from the core of the star (F_2). The Cima−Lopina modification[10] of the Flory equation accounts for the biomodal distribution of cross-link functionalities found in star polymer hydrogels.

$$\frac{1}{M_c} = \frac{1}{M_a} - \frac{\bar{v}}{V_1 v_{2,r}}\,\frac{[\chi_1 v_{2,s}{}^2 + \ln(1-v_{2,s}) + v_{2,s}]}{\left[\left(\dfrac{v_{2,s}}{v_{2,r}}\right)^{1/3} - \left\{\dfrac{2}{F_1} + \dfrac{1}{\left(\dfrac{M_a}{M_c} - 1\right)F_2}\right\}\dfrac{v_{2,s}}{v_{2,r}}\right]} \qquad (2)$$

The model was developed and verified by studying hydrogels made from radiation cross-linking of many-armed ($F_2 > 35$) PEO stars in aqueous solution.[10] In radiation cross-linking, cross-links are formed randomly along the length of the polymer arms, leaving one free end and one end attached to the star core. Therefore, the number of free terminal ends in the hydrogel would be equal to the number of ends of star arms in the original solution. This led to the inclusion of the molecular weight of the star arms (M_a) in eq 2 rather than the polymer molecular weight (M_n).[10] The biomodal distribution of cross-link functionality discussed in this work is to be distinguished from the biomodal distribution of chain lengths, which also has implications in

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elasticity theory, as discussed in the excellent reviews by Mark[11] and Kloczkowski.[12]

In this work, the Cima–Lopina equation is verified with hydrogels produced by end-linking PEO stars with four or six arms, using a triisocyanate linker. This method produces hydrogels with two cross-link functionalities, either $F_1 = 3$ and $F_2 = 4$ or $F_1 = 3$ and $F_2 = 6$. The effect of a biomodal distribution of cross-link functionalities is more pronounced when the functionality is small. There are also advantages to using an end-linked hydrogel to test the model. The end-linked systems are well-defined whereas a radiation cross-linked system may lead to loop formations and other network uncertainties due to the random nature of their formation. Also, the molecular weight between cross-links (M_c) and its distribution are the same as those of the linear chains or star arms prior to their being end-linked. Although extensive research has been done on radiation cross-linked systems, little has been done with the end-linking method discussed here. As opposed to the hydrogels formed from radiation cross-linking, the number of free terminal ends in the end-linked system cannot be assumed equal to the number of star ends. The Cima–Lopina equation was modified to reflect that fact:

$$\frac{1}{M_c} = \frac{1}{M_n} - \frac{\bar{v}}{V_1 v_{2,r}} \frac{\lfloor \chi_1 {v_{2,s}}^2 + \ln(1 - v_{2,s}) + v_{2,s} \rfloor}{\left[\left(\frac{v_{2,s}}{v_{2,r}}\right)^{1/3} - \left\{\frac{2}{F_1} + \frac{1}{\left(\frac{M_n}{M_c} - 1\right)F_2}\right\}\frac{v_{2,s}}{v_{2,r}}\right]} \tag{3}$$

The cross-link structure of a network can also be elucidated from the elastic modulus, giving an independent measure of the molecular weight between cross-links. The elastic behavior of networks falls between two idealized limits, affine and phantom, which relate the network structure to the elastic deformation under applied stress.[13] In the affine model, cross-links are assumed to be affine with respect to macroscopic strain and fluctuations of the junctions are completely suppressed. The mathematical expression becomes[10]

$$\frac{1}{M_{c,\text{affine}}} = \left(\frac{F_1}{F_1 - 2}\right)\frac{1}{M_n} + \frac{G_{\text{aff}}\bar{v}}{RTv_{2,r}}\left(\frac{v_{2,r}}{v_{2,s}}\right)^{1/3} \tag{4}$$

where G_{aff} is the measured elastic modulus. In the phantom model, chains are considered immaterial or "phantom" and can freely cross each other. The chains exert forces on the cross-links, which can move independently from the applied stress. The resulting mathematical expression is[10]

$$\frac{1}{M_{c,\text{phantom}}} = \left(\frac{F_1}{F_1 - 2}\right)\frac{1}{M_n} + \frac{G_{\text{ph}}\bar{v}}{RTv_{2,r}\left\{1 - \left(\frac{2}{F_1} + \frac{1}{(M_n/M_c - 1)F_2}\right)\right\}}\left(\frac{v_{2,r}}{v_{2,s}}\right)^{1/3} \tag{5}$$

Experimental Techniques

The experimental protocols include the preparation of linear and star PEO hydrogels followed by their separate characterization by swelling and rubber-elasticity methods. The linear and star PEO precursors used for the cross-linking were characterized by gel permeation chromatography (GPC). The GPC results were used to determine the actual M_n values and the polydispersity index (PDI) of these precursors.

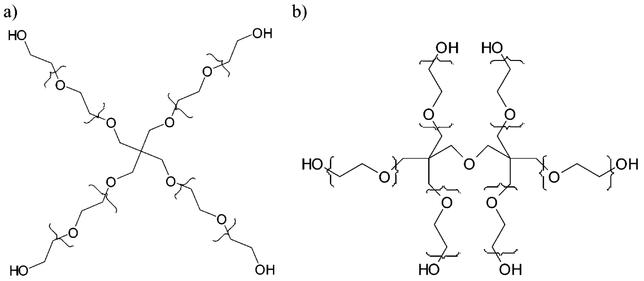

Figure 1. Structure of PEO Stars: (a) four-armed star; (b) six-armed star.

Table 1. Star Polymer Characteristics[a]

polymer designation	no. of arms	arm MW	PDI[b]
4 × 1850	4	1850	1.06
4 × 5000	4	5000	1.10
6 × 1833	6	1833	1.16
6 × 3333	6	3333	1.15

[a] As provided by Polymer Source, Inc. [b] Polydispersity index = M_w/M_n.

Table 2. Molecular Weight Analysis of Linear PEO

nominal MW	measured M_n (GPC)	PDI[a]
1000	980	1.09
3400	3220	1.15
8000	7380	1.10
10 000	11 200	1.11
20 000	18 500	1.11

[a] Polydispersity index = M_w/M_n.

Polymers and Reagents. Linear PEO with nominal MW of 1000, 3400, 8000, 10 000, and 20 000 was purchased from Polysciences as a powder containing approximately 1% silica added as a flowing agent. The PEO stars (four and six arms) with hydroxyl terminals were purchased from Polymer Source, Inc. (Figure 1). Characteristics of the polymer stars are shown in Table 1. The cross-linker triphenylmethane triisocyanate (Desmodur RE) was purchased from Bayer as a 27 wt % solution in ethyl acetate and monochlorobenzene. All other reagents were reagent grade and used without further purification. All aqueous solutions were made with deionized water.

Synthesis of PEO Hydrogels. The hydrogel membranes were prepared by cross-linking PEO chains having narrow molecular weight distribution with a triisocyanate cross-linker. PEO membranes having different water content and permeability were synthesized by varying the molecular weight of the PEO precursor in different batches. Linear PEO of molecular weights ranging from 1000 to 20 000 and star PEO as described above were used for synthesizing linear hydrogels. The molecular weights of the linear PEO chains were confirmed by gel permeation chromatography (GPC) analysis and are summarized in Table 2.

A 20–25 wt % dichloromethane (DCM) solution of triphenylmethane triisocyanate (Desmodur RE) was added to 20–25 wt % PEO in DCM. The molar ratio of hydroxyl groups and isocyanate moieties was adjusted to 1:1. The cross-linking reaction was carried out at 70 °C for 24 h in a flat Petri dish. The resulting xerogel (gel in the relaxed state) was cut into uniform cross sections. These cut samples were separately swollen in DI water with numerous solvent exchanges, and the resulting hydrogel was subsequently removed from the dish for further analysis. All the membranes were air-dried and kept in the dried state after analysis to prevent the degradation of the network structure over a period of time.

Characterization of Cross-Linked Gels. The molecular weight between cross-links was calculated from hydrogel swelling measurements. The xerogel weight was obtained

Table 3. Elastic Moduli for Water-Swollen PEO Gels[a]

polymer MW	% swelling	elastic modulus (kN/m^2)
1000	83.3 ± 0.6	98.0 ± 7.4
3400	91.5 ± 2.3	68.3 ± 5.8
8000	93.7 ± 2.7	38.0 ± 3.3
10 000	94.3 ± 2.9	28.1 ± 3.2
20 000	95.5 ± 4.0	13.6 ± 2.1
4 × 1850	91.9 ± 2.3	91.5 ± 6.4
4 × 5000	93.1 ± 1.8	68.5 ± 3.6
6 × 1833	89.2 ± 1.9	93.2 ± 7.3
6 × 3333	92.5 ± 2.1	72.4 ± 4.2

[a] All measurements done in triplicate.

Table 4. Network Structures Derived from Swelling and Elasiticity Data

nominal MW	M_n	MW before cross-linking	$M_{c,affine}$	$M_{c,phantom}$	$M_{c,swelling}$
1000	3550	980	1060	885	822
3400	10 100	3220	2640	1850	2710
8000	25 000	7380	6030	3880	6460
10 000	85 500	11 200	11 700	5370	13 000
20 000	97 800	18 500	19 400	10 700	20 000
4 × 1850	8000	1850	2100	1360	2760
4 × 5000	18 000	5000	4190	2420	5140
6 × 1833	8700	1833	2310	1560	2120
6 × 3333	10 500	3333	2590	1620	3060

immediately after cross-linking reaction from disks of uniform cross-section (approximately 2.0 cm in diameter). The xerogel was subsequently immersed in DI water for a period of 5−10 days to obtain the swollen hydrogel, exchanging the swelling media twice per day. The sample was blotted with filter paper to remove surface water and weighed. To obtain the dry polymer weight, the swollen hydrogel was placed with desiccant in a vacuum oven at 40 °C for a period of 24 h, or until a constant weight was obtained. The sample was removed and weighed immediately to avoid absorption of atmospheric moisture. For each set of conditions, three samples prepared in identical fashion were evaluated. Elastic moduli of fully swollen gels, in the form of 2.0 cm diameter disks, were determined using a dynamic shear rheometer (DSR) in the creep zone wherein a command stress in the range of 0.1−100 g cm was applied. The number of free ends in the cross-linked hydrogels (and the resultant M_n value) was obtained via elemental analysis completed at the Microanalysis Laboratory at the University of Illinois.

Results and Discussion

The experimental swelling and elastic modulus measurements from both linear and star PEO hydrogels are shown in Table 3. The percentage swelling is defined as the weight percent of water in the fully swollen hydrogel. The M_c values calculated from these results using eqs 3−5 are shown in Table 4, along with the molecular weight of the chains measured before cross-linking. Since we used an end-linking system, the M_c value should be the same as the precursor MW. The M_n values shown in the tables represent the average molecular weight between two free ends in the cross-linked hydrogel, calculated from elemental analysis measurements.

The molecular weight between cross-links calculated from elastic moduli and swelling measurements closely matches the values predicted from a priori knowledge of the length of the PEO chains. An earlier study of model PEO networks synthesized by end-linking linear PEO chains with plurifunctional cross-linking reagents ($F = 2-9$) deomonstrated that the elastic behavior of such networks approaches the affine limit with long chains, and the phantom limit with short chains ($M_c <$ 4000).[14] With the exception of the 3400 MW linear PEO hydrogel, our data correspond well with the earlier result. In the earlier work on the network structure of radiation-cross-linked star PEO hydrogels, the star hydrogels behaved differently than linear hydrolgels.[10] With the multiarmed stars ($F > 35$), it was surmised that approximately 25% of the cross-links formed from the radiation dosing occurred between adjacent star arms, leading to unproductive "loops" in the network and fewer effective cross-links.[10] Loop formation is less likely to occur with the present end-linking system using four- and six-armed stars.

The value of M_c calculated from equilibrium swelling measurements is sensitive to the value of the Flory−Huggins polymer−solvent interaction parameter (χ_1). The interaction parameter theoretically comes from the enthalpy of mixing of polymer segments and solvent molecules.[15] As the only arbitrary parameter in the theoretical description of the free energy of mixing of a binary solution of polymer and solvent, χ_1 also compensates for deficiencies in the theoretical description of the entropy of mixing when fitting data.[15] The interaction parameter for linear, un-cross-linked PEO, has been measured at 0.426 ± 0.01 in the volume fraction range 0.04−0.13.[16] Gnanou and co-workers[14] reported χ_1 values in the range of 0.45−0.58 for water-swollen PEO networks created from plurifunctional isocyanates. They attributed the increased value to the hydrophobic urethane linkages.[14] Likewise, in the study of radiation cross-linked PEO stars,[10] the value of 0.48 was used for χ_1. The increased value was attributed to both the hydrophobic divinylbenzene core of the stars, and entropic factors.[10] In this work, the core of the stars would not contribute a hydrophobic effect to the interaction parameter, and the entropic effect would be minimized with only four- and six-armed stars. This is reflected in the χ_1 parameters used. A value of 0.426 was used for the linear hydrogels, while values of 0.434 and 0.446 were considered optimal for the four- and six-armed stars, respectively. As expected, the values for the star hydrogels are close to that of linear PEO, where the slight increase for the six-armed star might be attributed to entropic effects.

Conclusions

The Cima−Lopina modification of the Flory swelling equation was verified with a system end-linked linear and star PEO hydrogel networks. The end-linked network was well-defined in that loop formation was minimized and the molecular weight between cross-links was known a priori. Five different linear PEO hydrogels and four different star PEO hydrogels were synthesized and characterized by swelling and elasticity measurements. The Cima−Lopina equation was modified slightly for the end-linked hydrogel system. The experimental data confirmed the theoretical predictions for both swelling and elasticity measurements.

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