MODELING OF POLY(ETHYLENE GLYCOL) HYDROGEL MULTILAYERS BY SURFACE INITIATED PHOTOPOLYMERIZATION

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INTRODUCTION

Hydrogels have been increasingly popular since they were discovered due to their high water content and tissue-like physical and mechanical properties. Photopolymerization reaction is one method to covalently crosslink liquid prepolymer solutions in the presence of a photoinitiator and light.[1,2] Due to their biocompatibility, hydrophilicity, and permeability, crosslinked poly(ethylene glycol) (PEG) based hydrogels[3] have been used as immunoprotective barriers in tissue engineering for therapeutic cell transplantation to prevent the rejection of transplanted cells by the host's immune system.[4] They have also been used for the development of cell based biosensing devices,[5] to photoencapsulate mesenchymal stem cells,[6] and as barriers for the sustained release of drugs to the arterial media.[7] These applications of hydrogel membranes often involve single layers and this makes it difficult to obtain membranes that possess all the properties requested for a successful application.[8] Some applications may require the gel to possess several properties such as pH sensitivity or high water absorption. Since it is difficult to obtain multiple properties with a single composition, the formation of multilayers of hydrogels is necessary and beneficial. Multilayers of hydrogels may provide much more precise permeability which may be achieved by varying the composition and concentration of the precursor solution. Also, they may retain specific responsive properties that will change their physicochemical properties with external stimuli, such as pH,[9] temperature,[10] and solvent composition.[11]

In this work we have developed a mathematical model based on the Numerical Fractionation (NF) technique for hydrogel multilayers formed by interfacial photopolymerization of PEG diacrylate/VP. The Numerical Fractionation technique (NF) developed by Teymour and Campbell[12] refers to the numerical isolation of various polymer generations based on the degree of complexity of their microstructure. This technique segregates the polymer into two distinct phases, a soluble (sol) phase and a gel phase. Isolation of the sol from the gel makes it possible to predict polymer properties in the post-gel region. The sol fraction is subdivided into generations that are composed of linear and branched chains. The growth profile, crosslink density, and weight average molecular weight for each layer of hydrogel membrane is determined.

This study combines an experimental approach to multilayer formation that could help form membranes with different properties and a mathematical model of the system that could help explain the properties of those multilayer hydrogel membranes.

EXPERIMENTAL SECTION

Multilayer Hydrogel Formation Through Photopolymerization. Silica surfaces were cleaned and functionalized with photoinitiator eosin based on a procedure described earlier.[13] A prepolymer solution incorporating PEG amino acrylate and PEG diacrylate (formed initially from 20% w/v PEG-DA where one out of every ten acrylate group was modified through a coupling reaction using cysteamine) was placed onto the eosin modified glass surface and the substrate was illuminated with an argon ion laser for 2 minutes (λ=514 nm). To facilitate visualization of the layers, 0.1 mg/ml of fluorescein o-acrylate was incorporated into the precursor solution of the first layer. The precursor solution for the second layer was prepared with 225 mM triethanolamine, 25% (w/w) PEG diacrylate (MW=575 Da), and 37 mM 1-vinyl 2-pyrrolidinone. The glass slide that had the first layer of hydrogel with pendant amine groups was immersed in eosin and the peptide coupling reagent, Woodward's reagent K (WRK), solution for 5 minutes to allow reaction of amine groups present in the PEG structure with the carboxyl groups present in the eosin structure. The slide was then rinsed off and 20 μL of the PEG diacrylate

precursor solution were placed onto the surface of the first layer that had immobilized eosin. The substrate was illuminated with an argon ion laser for 2 minutes (λ=514 nm).

Mechanism of Polymerization. We consider the polymerization system consisting of initiation, propagation, chain transfer to triethanolamine, and radical termination by combination and reaction through pendant double bond. We assume that a terminal model of copolymerization is applicable and we consider copolymerization of A (N-vinyl-pyrrolidinone, VP) and B (PEG diacrylate). The details of the reaction mechanism as well as the population balance equations were described elsewhere.[14]

RESULTS

The interfacial photopolymerization process employed by functionalizing glass, silicon or hydrogel surfaces with eosin Y resulted in the formation of a hydrogel layer at the surface. To aid in demarcation between the different hydrogel layers, fluorescein o-acrylate was added to the precursor solution used for the first layer, while the hydrogel precursor solution used for the second layer did not contain fluorescein. The fluorescent microscope images recorded for bilayers do illustrate distinct, yet cross-linked, layers of hydrogel (Figure 1). Polymerization of the first hydrogel layer occurs at the interface, as the photosensitizer (eosin Y) was present only on the glass or silicon surface. Polymerization of subsequent layers however, resulted in the intrusion of layers due to the presence of the photosensitizer throughout the previous hydrogel layer. Covalent bonding and/or chain entanglement between layers occurs through the reaction of free radicals coming from the previous layer with the acrylate groups in the subsequent layer. In these multilayer samples the first layer was formed with PEG amino acrylate while the second layer was formed using PEG diacrylate only. The use of PEG amino acrylate rather than PEG diacrylate for the inner layer allowed for functionalization of eosin Y on the inner layers, which promoted formation of covalent bonds between the layers.
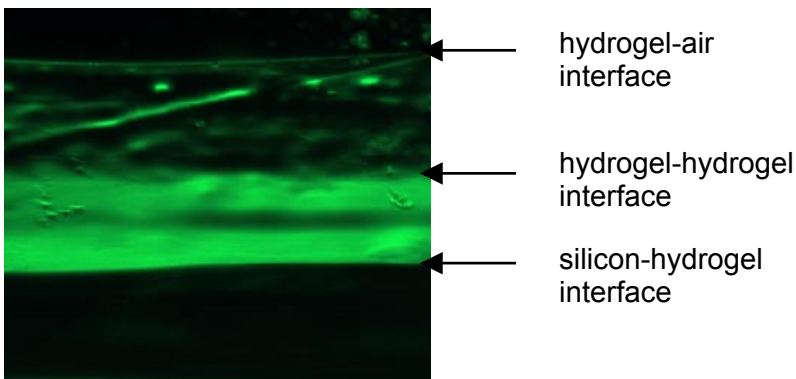

hydrogel-air interface

hydrogel-hydrogel interface

silicon-hydrogel interface

Figure 1. Representative micrograph of a bilayer hydrogels on a silicon surface.

The properties of these multilayers can be predicted by expanding our previous work on modeling the properties of single layers. For this, the following assumptions were made: 1) for subsequent layers initiation reaction takes place only at the hydrogel surface, 2) the intrusion between layers is negligible, thus diffusion of monomers and interpenetration to previous layers is neglected in the model. The validity of the mathematical model developed in this study was established through comparison with experimental results of single layers. Values for the constants used in the model were obtained from the literature and those that were not available were obtained by using a nonlinear least square parameter estimation technique. The estimation was done by comparing experimental measurements with the model predictions (Figure 2). Figure 3 shows the thickness profile for two hydrogel layers. Our model predicted that a thickness of about 164 μm was reached at around 90 seconds of photopolymerization for the first layer, and a total thickness of about 340 μm was reached after the formation of second layer.

The mathematical model can predict the properties of hydrogel multilayers. The process of hydrogel formation by photopolymerization of PEG diacrylate in the presence of VP leads not only to branching but also a crosslinked polymer structure. The fraction of units on a chain that contain
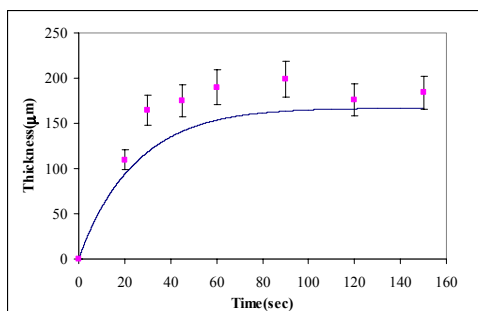
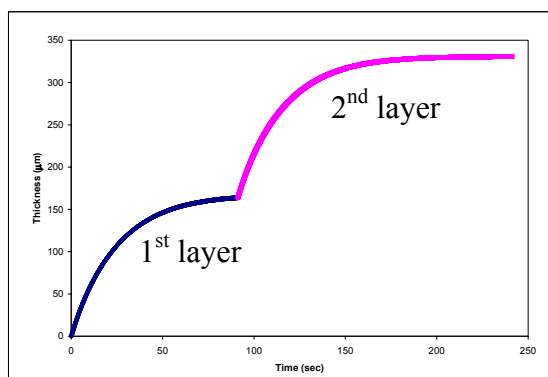**Figure 2.** Membrane growth Profile versus time

Figure 3. Hydogel thickness profiles based on theoretical model.

quaternary branch points (QBP) is used to quantitate the crosslink density of that chain. Figure 4 shows the crosslink densities for the sol, branched sol, gel and overall hydrogel plotted versus time at various locations for two layers of hydrogel. The region for the first layer shows the crosslink density profiles at a point 91 μm away from substrate surface (a point within the first layer, and the total thickness that model predicts for the first layer is about ~164 μm), while the region for the second layer displays the crosslink density profiles at a point 185 μm away from the substrate surface (21 μm away from the first hydrogel layer). For both regions, the figure shows that the values of overall crosslink density (ρ) and sol crosslink density (ρ_S) coincide up to the gel point. At the gel point, the first gel molecule appears with a crosslink density about twice that of the sol at the cell surface. This result is consistent with the prediction of Flory[15] that gel crosslink density becomes twice that of the sol at the gel point. After the gel point, both gel and overall crosslink density increase, while sol crosslink density decreases as high chain length sol molecules get incorporated into the gel phase. At the same time, branched sol crosslink density increases rapidly up to the gel point, and then decreases slowly before achieving a relatively constant value. Figure 4 also shows that the crosslink density values at a point 21 μm away from the first layer surface are higher than the values obtained at a point 91 μm away from substrate surface. This is due to the fact that the point considered for the second layer is closer to the surface of the first layer and thus has higher radical concentration than the point considered for the first layer.

CONCLUSION

We have described a theoretical and experimental model for the photopolymerization of PEG diacrylate hydrogel multilayers on surfaces. The experimental approach is based on the incorporation of the photoinitiator, eosin Y, within the previous layer. The mathematical model uses the NF technique to determine overall crosslink density, sol gel crosslink density and sol fraction of the gel. The theoretical prediction allows determining permeability and thickness profile at different polymerization conditions for each layer without the need to perform numerous experiments, while
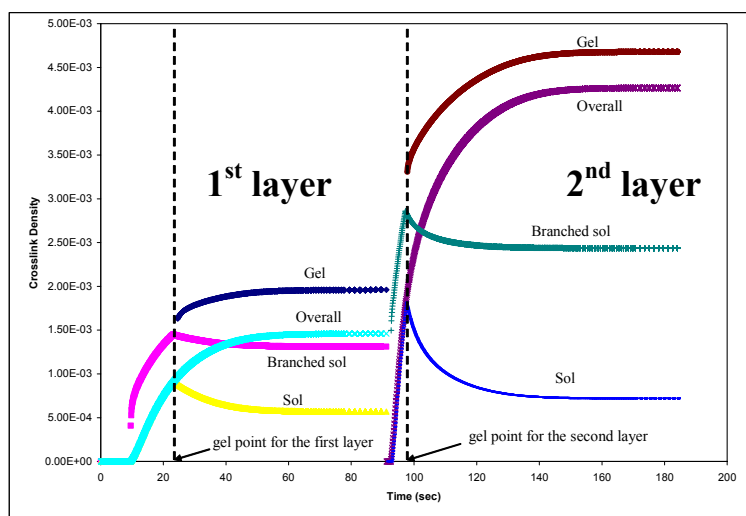
Figure 4. Crosslink Density versus time for bilayers of hydrogel.

the experimental approach for multilayer hydrogel fabrication could be utilized to form multifunctional for immuno-suppression of transplants with more than one layer through cell encapsulation layers or 3D structures for multifunctional biosensors or tissue engineering applications.

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