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Nanostructured Hydrogels via Photopolymerization in Lyotropic Liquid Crystalline Systems

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Much research has focused on the control of material structure on the nanometer size scale. The self assembled, highly organized solutions inherent to lyotropic liquid crystals (LLCs) have recently emerged as promising tools in the synthesis of organic nanostructured materials. In this work highly ordered LLC morphologies have been utilized as polymerization templates to dictate and achieve unique polymer network structure. The influence of nanoscale organization of the monomer is directly related to the physical and diffusive behavior of the resulting polymer. Additionally, LLC ordered solutions have shown great promise in compatibilizing blends of immiscible monomers. To this end, the precise organization of the LLC has been investigated as a means to segregate immiscible monomers into isolated nanoscale domains for the copolymerization of two separate but interconnected networks. The results from this study have demonstrated that the network structure of PEGDA hydrogels or PEGDA/HDDA blends can be directed by LLC templates, and that the physical properties of the templated materials are indeed influenced by the network structure induced by the templating process. This work has established that LLCs are an important tool in the creation of materials with nanoscopic architecture that directly leads to attractive and previously unattainable materials properties.

Keywords: lyotropic liquid crystals; nanostructured polymers; photopolymerization; templated polymerization

I. INTRODUCTION

Over the last two decades, research in nanostructured materials has grown exponentially as nanotechnology continues to alter the ways

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in which materials are fabricated, synthesized, and processed [1]. Most recently, the use of nanotechnology is finding application in the biomaterial arena as a means to engineer the properties of synthetic polymer hydrogels to create highly advanced materials for tissue engineering scaffolds, drug delivery vehicles, and implant devices [2]. Researchers have found that nanostructured biomaterials often possess unique attributes for biomedical applications such as nanotopographic scaffold surfaces that promote cell adhesion and directional growth, or nanoparticles drug carriers that elude immune clearing mechanisms for precisely targeted systemic delivery [3,4].

One of the more promising methods for creating nanostructured materials has been through the use of self-assembling media such as lyotropic liquid crystals (LLCs) [5–7]. LLCs exhibit a number of nanostructured mesophases that are induced by the specific concentration of self-assembling surfactant molecules in aqueous solution. Recent research has explored the use of LLCs as photopolymerization templates, directing the structure of a growing polymer network into the highly ordered geometry of the liquid crystal. It was found that the order of the parent LLC could be used to control the physical properties of the resulting polymer as well as elicit unique material characteristics that are not accessible with isotropic hydrogels [8–13].

This study investigates the use of hexagonal and lamellar LLC mesophases as templates for synthesized photocured biodegradable macromers to fabricate LLC structured biomaterials that possess unique and highly tailorable properties. The physical properties of the LLC templated biomaterials including network swelling, mechanics, and degradation were studied as a function of the parent template used to create each LLC structured gel. It is hypothesized that by understanding the relationship between the physical properties and the induced morphology of the templated materials, advanced nanostructured biomaterials may be fabricated that possess unique and desirable properties that can be precisely tailored for bioapplications.

II. EXPERIMENTAL

Materials

In this study, Poly(ethylene glycol) (MW 2000 Aldrich), poly(ethylene glycol) methacrylate (MW 525, Aldrich), dl-lactide (Polysciences), acryloyl chloride (Aldrich), hexamethylene diisocyanate (Aldrich) were

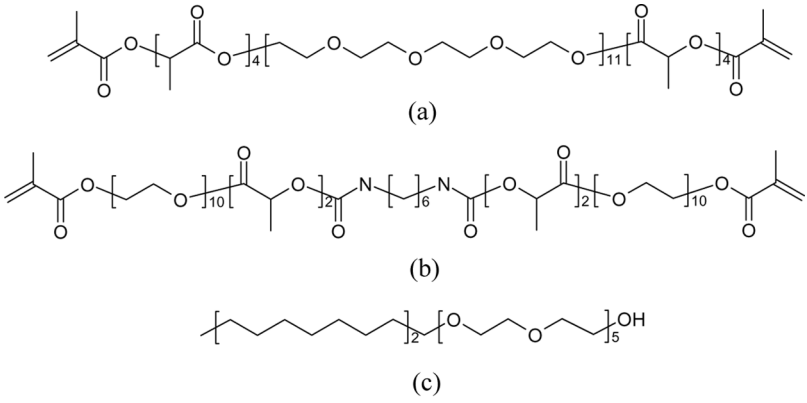

FIGURE 1 Chemical structures of (a) poly(lactic acid)-poly(ethylene glycol)-poly(lactic acid) dimethacrylate (LPLDMA, MW 2900), (b) Poly(ethylene glycol)-poly(lactic acid)-hexamethylene dimethacrylate (PLPDMA, MW 1500), and (c) Brij 56.

used as precursors in the synthesis of the (meth)acrylate PEG-PLA macromers. The biodegradable macromers used in this study were synthesized using previously defined methods [14–16]. The surfactant used was polyoxyethylene (10) cetyl ether (Brij 56, Aldrich). 1-hydroxy-cyclohexyl phenyl-ketone (Irgacure 184, Ciba Specialty Chemicals) was used to initiate the photopolymerizations. The chemical structures of the synthesized monomers and surfactant are shown in Figure 1.

Procedure

Lyotropic liquid crystalline solutions were formulated by mixing specific concentrations of synthesized biodegradable macromer, surfactant, deionized water, and photoinitiator. LLC templated biodegradable hydrogels were synthesized by pipetting the liquid crystal/macromer solutions into a Teflon mold under nitrogen purged conditions. 365 nm UV light was used to polymerize the hydrogels, which were then cut into disks, placed in ethanol to remove surfactant, and then dried under vacuum. A diagram of the templating process using an LLC mesophase is shown in Figure 2.

Polarized light microscopy (PLM) and small angle x-ray scattering (SAXS) were used to determine the LLC phase behavior of the LLC/macromer solutions prior to polymerization. These methods were

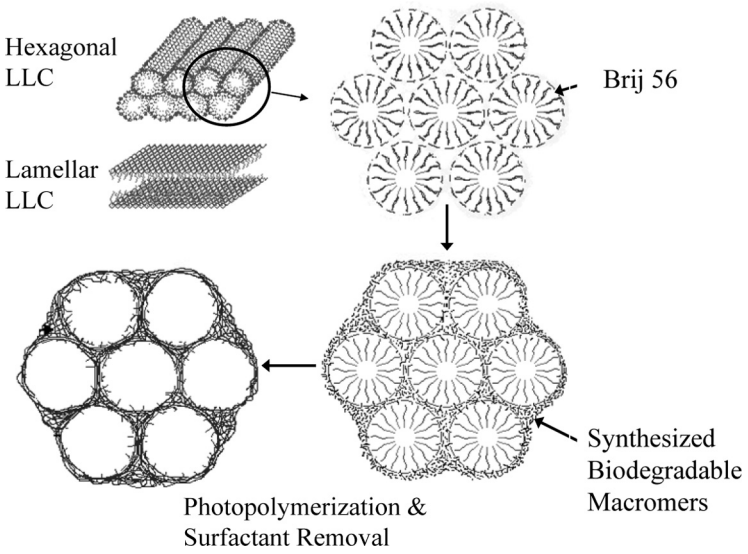

FIGURE 2 LLC templating method clockwise starting from upper left: 3D diagram of hexagonal and lamellar LLC mesophase templates; 2D representation of hexagonal LLC with Brij 56 surfactant; hexagonal LLC with dispersed biomacromers; polymer network post photopolymerization and surfactant removal.

also used to determine the degree of structure retention and presence of LLC structure post-polymerization. The polymerization behavior of LPLDMA (see Fig. 1) was measured using photo-differential scanning calorimetry (pDSC) to determine the polymerization rate and real-time infrared spectroscopy (RTIR) to determine the conversion of vinyl bonds during the polymerization.

Water absorption for the LLC templated biomaterials was measured gravimetrically by placing the dehydrated disks (post surfactant removal) into 37°C PBS solution and recording water uptake at given intervals of soak time. Dynamic mechanical analysis (DMA) was used to determine the compressive modulus of the templated biomaterials using previously established methods [5] with the stress/strain curves from DMA tests. The degradation of the biohydrogels was tracked by placing approximately 40 disks of each sample material in individual vials of PBS solution at 37°C. Disks were removed at predetermined intervals and water uptake and mass loss were recorded and combined to form a transient degradation profile for each templated gel.

III. RESULTS AND DISCUSSION

Previous work using LLC templates to create highly ordered synthetic networks has focused primarily on non-degradable polymer systems. Primary efforts have explored the relationships between the specific morphology of the parent template and the polymerization rate, formation of the LLC polymer network, formation of dual network systems, and the resulting physical properties of the material [6–10]. Specifically, LLC templating was found to have a large influence over the degree of water uptake or swelling, the mechanical strength, and the permeability of hydrogel networks templated with highly ordered hexagonal and lamellar mesophases [6–8]. Similarly, the goal of this study is to template biodegradable macromers and investigate the effects of specific LLC order on the resulting biopolymers in an effort to obtain a degree of control over the physical properties and behavior of these materials.

Inherent of LLCs, the concentration of surfactant (Brij 56) dictates the geometric self-assembling mesophase that forms. Using SAXS and PLM techniques, a phase diagram was created for mixtures of Brij 56, water, and the LPLDMA macromer in Figure 2. With a constant loading of 40 wt% macromer, a lamellar LLC is formed as the Brij 56 concentration is raised above 35 wt%. Below this surfactant concentration, optical isotropy was observed indicating the absence of a highly ordered lamellar or hexagonal LLC. To investigate the effects of the lamellar ordering on the physical behavior of the LPLDMA samples, formulations were created using 40 wt% macromer, 20 wt% water, and 0 or 45 wt% Brij 56 to yield isotropic and lamellar templated networks respectively. Figure 4 shows the degree of swelling and compressive modulus for the lamellar templated LPLDMA relative to the isotropic gel. It was observed that the initial degree of swelling for the lamellar templated LPLDMA gel was approximately 160% of the isotropic hydrogel. Furthermore, the compressive modulus of the swollen lamellar templated hydrogel was approximately 60% of the modulus of the swollen isotropic hydrogel. The drop in modulus is most likely due to the increased amount of water that is retained in the lamellar templated network. By removing the surfactant post photopolymerization, the templated and isotropic biomaterial were compositionally and chemically equal, and therefore, the shifts in both swelling and modulus are solely attributed to the structure of the templated gel, a result of the parent LLC morphology.

In addition to the initial swelling and mechanical assessment of the templated LPLDMA biomaterials, the degradation behavior was studied to determine the influence of LLC order on the breakdown and

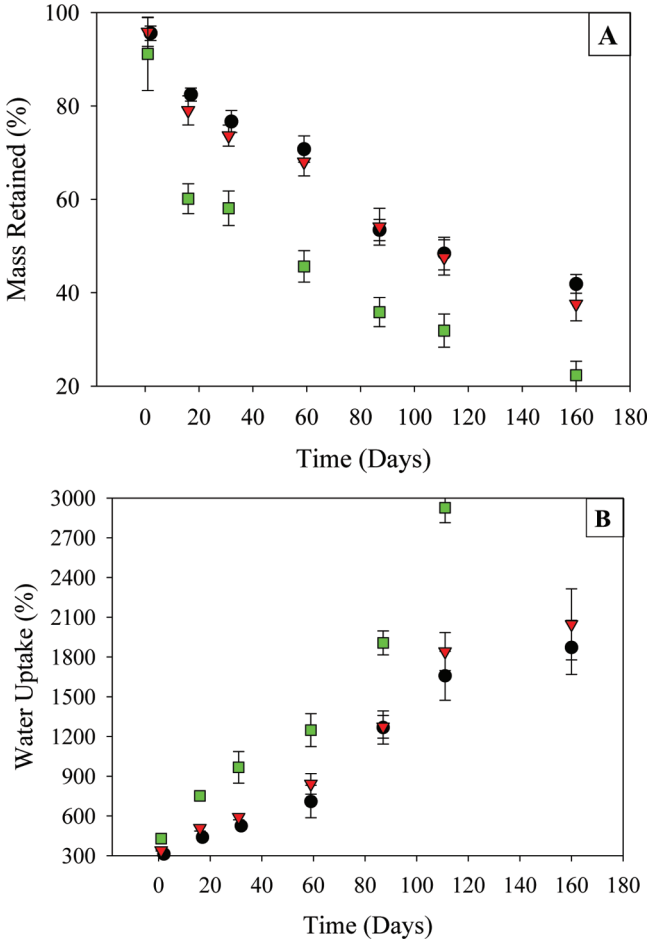

FIGURE 3 (A) Degradation profiles and (B) transient swelling profiles in 37°C PBS solution of 40 wt% LPLDMA templated with 0 wt% Brij 56 (isotropic) (●), 20 wt% Brij 56 (isotropic) (▼), and 45 wt% Brij 56 (lamellar) (■). Surfactant is removed prior to all experiments.

transient swelling of these materials. Due to the mechanism of network breakdown, hydrolysis of ester bonds in the networks crosslinking sections, the increase in swelling observed for the lamellar templated gel is expected to heavily influence the degradation of this system. Figure 3 shows the degradation and transient swelling of LPLDMA templated in both and isotropic and lamellar conditions. It is observed that

the lamellar templated hydrogel degrades more rapidly and swells to a greater degree over the same time frame when compared to the isotropic LPLDMA materials. The increase in swelling and control over the degradation of the biopolymeric scaffold has significant biomedical implications as high porosity and control over degradation rate have been identified as critical parameters in the success of a biomaterial as a tissue scaffold or drug delivery device [15].

In addition to the property and degradation behavior, the polymerization behavior of the lamellar templated LPLDMA was also studied to investigate the structural characteristics of the LLC formed network that might elucidate the observed property dissimilarities between templated and isotropic LPLDMA networks. Using pDSC, it was observed that as LPLDMA is photopolymerized within the highly ordered domains of the lamellar LLC, the polymerization rate is approximately double that of the isotropic polymerization. Furthermore, using RTIR, it was found that the nanotemplated lamellar LPLDMA exhibited approximately twice the degree of double bond conversion as its isotropic counterpart. The results of the polymerization behavior experiments indicate that the observed increase in swelling and degradation rate with the lamellar templated LPLDMA is not due to a disruption of network formation or low conversion from the lamellar LLC. Rather it is theorized that the lamellar templated network structure allows a greater degree of water uptake and greater permeability that, in turn, accounts for the lower mechanics and more rapid degradation when compared to the isotropic LPLDMA hydrogels.

To access additional LLC geometries such as the hexagonal mesophase, a second PEG-PLA methacrylated macromer was synthesized, PLPDMA (Fig. 2). By reversing the location of the PEG and PLA (hydrophilic and hydrophobic) blocks and decreasing the overall size of the PLPDMA macromer, it was observed that the phase diagram of LLC formulations of 40 wt% macromer, Brij 56, and water yielded both a hexagonal and lamellar mesophase at specific concentrations of Brij 56. The availability of both the hexagonal and lamellar LLC mesophases using PLPDMA increases the utility of the LLC templating method over the LPLDMA formulations, as here, two highly ordered LLCs may be used to control the network structure and physical properties of the PLPDMA biomaterials. Figure 4 shows the change in both the compressive modulus and network swelling of the hexagonal and lamellar templated PLPDMA gels relative to an isotropic PLPDMA network. Similar to the lamellar templated LPLDMA gel, the swelling of the lamellar templated PLPDMA material is greater than the isotropic gel while the compressive modulus

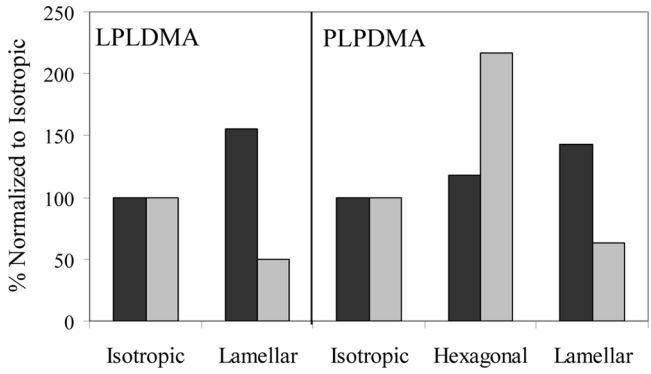

FIGURE 4 Physical properties of 40 wt% LPLDMA and 40 wt% PLPDMA as a function of the parent LLC template used to create each gel. The degree of water uptake (■) and the compressive modulus (■) is listed as a percentage of the isotropic templated sample in each case.

decreases. The decrease in modulus is attributed to the significant increase in the amount of water that is in the lamellar network.

In Figure 4, the hexagonal templated PLPDMA gel also shows a small increase in swelling relative to the isotropic gel. However, a large increase in the compressive modulus of the LLC templated gel is observed that is over twice the modulus of the isotropic gel. This is a significant result as, even with more water in the network, the highly ordered hydrogel network induced from the hexagonal template provides mechanical stability and results in a greater resistance to compression compared to the isotropic network. Typically, hydrogels that have adequate porosity are often too weak for the intended application, and in turn, hydrogels with desired mechanical strength are often not porous enough to allow for sufficient tissue proliferation. Therefore, biohydrogels exhibiting high modulus and high swelling or porosity have long been of interest for use as tissue engineering scaffolds.

IV. CONCLUSIONS

By photopolymerizing synthesized biodegradable macromers within the highly ordered domains of various LLC templates, significant variations in the physical behavior of the resulting templated hydrogels were obtained when compared to isotropic networks of the same macromers. Specifically, an increase in water uptake and degradation

rate was observed as the biomaterial network was templated with the highly ordered lamellar LLC. Furthermore, using a nanostructured hexagonal LLC template resulted in unique material properties including a simultaneous increase in both the swelling and compressive modulus of the templated biomaterial over the isotropic gel, behavior that is not accessible with typical hydrogel engineering methods. The ability to control biomaterial properties using the LLC method to structure the gel, without changing the chemical or compositional make-up of the material, offers significant advantages in the engineering of these gels for biomedical applications.

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