# Nanostructured Biodegradable Polymer Composites Generated Using Lyotropic Liquid Crystalline Media

**Jason D. Clapper and C. Allan Guymon***

*Department of Chemical and Biochemical Engineering, The University of Iowa, Iowa City, Iowa 52242*

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ABSTRACT: In tissue engineering applications the physical properties and degradation behavior of the designed synthetic scaffold are crucial for successful growth and function of desired tissue. Combining two or more biodegradable polymers into a single biomaterial composite may provide a pathway toward achieving new and highly tailorable biomaterial properties by taking advantage of the distinct properties from each blend component. In this work, a nanostructured lyotropic liquid crystal (LLC) was used to induce miscibility between blends of two immiscible biodegradable polymer systems, leading to the formation of a compatible composite with advanced properties. The physical properties and degradative behavior of biomaterials made from formulations of PLA-*b*-PEG-*b*-PLA dimethacrylate, caprolactone dimethacrylate, and ethyloxy succinate dimethacrylate were directly controlled using the composition of each material, demonstrating that a high degree of compatibility can be attained from immiscible biopolymer systems using the LLC polymerization template. Specifically, by initially confining the immiscible monomers into the nanometer scale domains of the liquid crystal, composite materials were formed upon cross-linking that demonstrated IPN-type behavior with linear or additive contributions from each biopolymer constituent. The use of a nanostructured LLC to compatibilize immiscible biodegradable monomers represents a significant advancement in the formation of cross-linked biocomposites with highly tailorable properties for tissue engineering applications.

## Introduction

In the design of synthetic biopolymers for tissue engineering applications, a high degree of control over the physical and physiological properties of the biomaterial is necessary for successful growth and function of the desired tissue.[1,2] Ideally, a synthetic degradable matrix will have mechanical properties that match the tissue it is designed to replace. This match can be a considerable design feat with tissues such as cartilage that are multicomponent in nature with both elastic and compressive resistant structures within the tissue.[3,4] Additionally, matching the degradation behavior of a biomaterial to the proliferation of extracellular matrix is often vital in directing the growth and differentiation or function of the desired tissue.[5,6] Thus, numerous polymer chemistries and polymer processing techniques have been explored toward the precise control over the physical properties as well as the degradation behavior of synthetic tissue constructs.[7−10]

In nondegradable polymer systems, copolymerization or blending mixtures of two or more monomer systems offers a simple pathway toward the fabrication of polymer composites with advanced and highly controllable properties. Multicomponent composites will often exhibit the desirable properties of each constituent. By incorporating polymers with significantly different physical properties, a high degree of control over the properties of the composite may be realized simply by altering the ratio of monomers.[11] These same principles have recently been explored in biopolymer systems through blending of biodegradable monomers in pursuit of highly versatile biocomposites for drug delivery and tissue engineering applications. For example, numerous studies have explored controlling the degradation, mechanical properties, delivery of biological agents, and even the degree of cell attachment on biocomposites by blending various biodegradable polymer systems.[7,12−16] In cartilage tissue engineering, for example, blending of both high- and low-modulus biodegradable polymers may allow a composite scaffold that closely matches the mechanics and structure of native cartilage tissue described previously. Furthermore, blends of polymers with varying biodegradation rates have the potential to create scaffolds with temporal and spatially controlled degradation, accessing means by which to influence and direct cell growth and function toward the generation of the complex structures that are important to cartilage tissue function.[3,4]

One of the major complications in monomer blending in biodegradable and nondegradable polymer systems alike is that most multicomponent monomer blends are immiscible due to differences in hydrophobicity, viscosity, polymerization rate, cross-link density, or solvent interactions. This incompatibility will directly lead to materials that are phase separated with poor interfacial adhesion and mechanical stability, negating the usefulness of the material.[17,18] Miscibility in cross-linking biodegradable polymer systems is inherently difficult as polymerization leads to growth in the molecular weight of each polymer, resulting in less compatibility between the two polymers and greater heterogeneity in the material. However, if the cross-linking polymers are confined initially and phase separation is initially restricted, an interpenetrating network (IPN) will often form in which additional cross-linking of each polymer limits further phase separation of the two systems.[19] IPNs have been the focus of recent materials research due to their highly beneficial properties including near homogeneous composite structure as well as behavior in which each cross-linking component contributes additively to the overall properties of the resulting composite.[20]

To create compatible polymer formulations out of immiscible linear or cross-linking components, a great deal of research has been devoted to the use of compatibilizing agents such as surfactants and block copolymers to lower interfacial energy, reducing the phase-separated domains of each monomer.[11,18]

* To whom correspondence should be addressed. E-mail: allan-guymon@uiowa.edu.

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Microemulsions have also received considerable attention due to their ability to compatibilize hydrophilic and hydrophobic monomers by confining them to micron size phase-separated domains, resulting in an intimately mixed composite material.[21] Similar to microemulsions, nanostructured lyotropic liquid crystals (LLCs) have recently been investigated as a possible platform for the compatibilization of immiscible cross-linking monomer systems.[22]

LLCs, formed from the self-assembly of small molecular weight surfactants in aqueous solution, have emerged as promising platform for creating organic nanostructured polymers through their use as structural templates in photopolymerization reactions.[23] To date, researchers have explored the use of LLC templated polymerizations to influence the polymerization rate and physical properties of the forming networks toward applications ranging from nanoscale reactors for chemical catalysis to nanoporous ultrafiltration membranes to name a few.[24−28] The highly ordered arrangement of nanometer scale hydrophilic and hydrophobic domains inherent in LLC geometries is ideal for the compatibilization of immiscible monomer systems, particularly those that are immiscible due to hydrophobicity effects. The nanometer sized domains not only allow for intimate mixing of the immiscible cross-linking monomers on a size scale previously unattainable but also provide an initial restriction to phase separation upon cross-linking, resulting in advanced composite materials. Previous work in our lab has demonstrated the ability of a hexagonal LLC assembly to form nanoscale phase-separated composites from incompatible, nondegradable monomers. These materials were shown to exhibit IPN type behavior in which the physical properties of the composite were directly dependent on the ratio of the two highly cross-linking systems, a characteristic of a highly compatible dual network material.[22]

The present study investigates the use of nanoscale ordered LLCs as a compatibilization platform for immiscible synthesized biodegradable monomers to form biocomposites with a highly controllable degradation rate and physical properties. By incorporating hydrophilic and hydrophobic cross-linking monomers with significantly different physical properties within a LLC geometry, it is hypothesized that a compatibilized IPN composite of the two will be formed that exhibits the desirable properties of each polymer system. In this study, synthesized PLA-*b*-PEG-*b*-PLA dimethacrylate (LPLDMA) was used as the hydrophilic photopolymerizable monomer, while either caprolactone dimethacrylate (CDMA) or newly synthesized ethyloxy succinate dimethacrylate (EOSDMA) was employed as the hydrophobic component in the fabricated biodegradable composites. Simple water-based mixtures of these monomers were found to exhibit low compatibility, and upon polymerization, the composites formed from these pairings were found to have inadequate physical properties for use in materials applications. LPLDMA and CDMA have exceptional promise if compatible composites of the two can be fabricated as both biodegradable polymers have individually demonstrated good cell biocompatibility in our lab and other independent studies.[29,30]

Because of the large differences in the physical properties of LPLDMA, CDMA, and EOSDMA, it is expected that by using the LLC to compatibilize mixtures of the immiscible biodegradable monomers the overall properties of the resulting LLC composites could be directly controlled simply by directing the ratio of the monomer components. The physical properties and degradation behavior of the LLC biodegradable composites were investigated including the network swelling, mechanical properties, thermomechanical properties, and degradation behavior in order to show the degree of miscibility between the biopolymer constituents fabricated in the LLC composite. The purpose of this study is to demonstrate the use of LLC templates as a simple and effective method to attain IPN type behavior within a binary system of cross-linking biodegradable monomers that are not miscible with traditional processing techniques, to allow for the fabrication of highly tailorable biomaterial composites for tissue engineering applications.

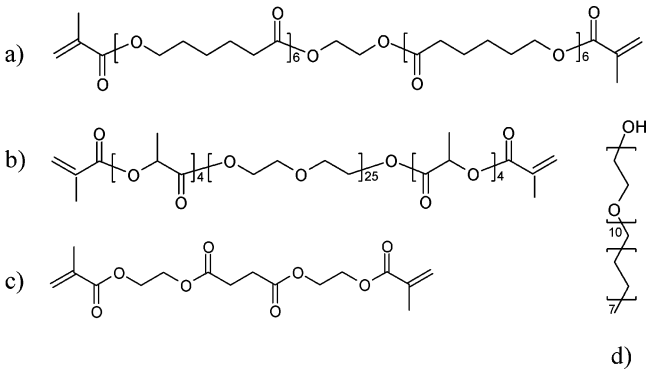


**Figure 1.** Chemical structures of the biodegradable monomers and surfactant used in this study including (a) caprolactone dimethacrylate (CDMA), (b) PLA-*b*-PEG-*b*-PLA dimethacrylate (LPLDMA), (c) ethyloxy succinate dimethacrylate (EOSDMA), and (d) Brij 56 surfactant.

## Experimental Section

**Materials.** Poly(ethylene glycol) (PEG, MW: 2000) was obtained from Aldrich and dried via azeotropic distillation with benzene prior to use. DL-Lactide (Polysciences) was recrystallized in hexanes from ethyl acetate. Stannous octoate, polyoxyethylene (10) cetyl ether (Brij 56), methacryloyl chloride, *N*,*N*-dicyclohexylcarbodiimide, mono-2-(methacryloyloxy)ethyl succinate, and phosphated buffer solution (PBS, pH 7.4) were obtained from Aldrich and used as received. Hydroxyethyl methacrylate and polycaprolactone diol (MW 1250) were obtained from Polysciences. 1-Hydroxycyclohexyl phenyl ketone (Irgacure 184, Ciba Specialty Chemicals) was used as the photoinitiator in all studies.

**Synthesis of Degradable Monomers.** Caprolactone dimethacrylate (CDMA) was synthesized by reacting polycaprolactone diol with methacryloyl chloride and triethylamine in dichloromethane solvent according to techniques described elsewhere.[29] PLA-*b*-PEG-*b*-PLA dimethacrylate macromers were synthesized according to techniques first described by Sawhney et al. using ring-opening addition of lactide onto a central PEG chain followed by capping of the monomer with methacrylate functionality.[30] The PLA-*b*-PEG-*b*-PLA macromer used in this study consists of a 2000 MW central PEG chain with ~4 lactic acid (LA) groups on each end and will be referred to here as LPLDMA. Ethyloxy succinate dimethacrylate, referred to here as EOSDMA, was synthesized by coupling mono-2-(methacryloyloxy)ethyl succinate (MOES) with hydroxyethyl methacrylate (HEMA) using a 2-fold excess of HEMA in a 1 M reaction medium of dicyclohexylcarbodiimide (DCC) in dichloromethane with added base 4-(dimethylamino)pyridine (0 °C, 6 h) following a similar previously reported synthesis.[31] EOSDMA was purified by filtering the DCC salts and passing the product through three consecutive extractions in water to remove excess dichloromethane and unreacted HEMA. The chemical structures of the synthesized biodegradable monomers are shown in Figure 1. FTIR and H NMR were used to confirm the structure of the synthesized monomers, including the addition of methacrylate functionality to the monomers with H NMR peaks at 5.8, 6.1, and 6.4 ppm and IR bands at 1640 and 810 $cm^{-1}$, the coupling of PLA to PEG with H NMR peaks at 1.5 and 5.2 ppm and IR bands at 1750 $cm^{-1}$, and the coupling of HEMA and MOES with the disappearance of the hydroxyl group IR band stretch at 3500 $cm^{-1}$.

**Preparation of LLC Composites.** Formulations with varying ratios of hydrophilic (LPLDMA) and hydrophobic (EOSDMA or

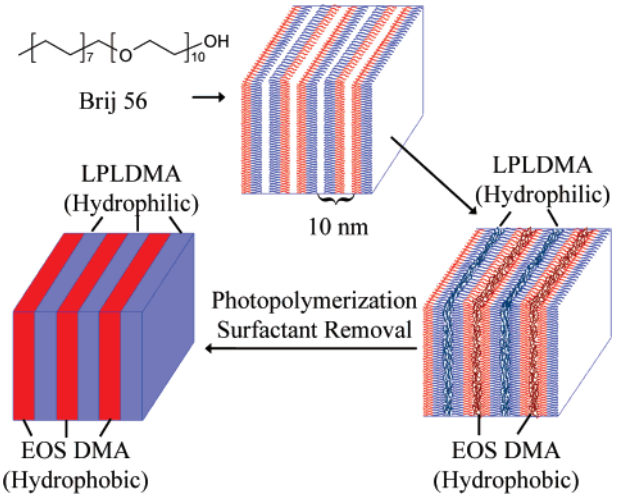


**Figure 2.** Diagram of the use of a lamellar LLC as a compatibilization template for immiscible cross-linking biodegradable polymer composites of LPLDMA and EOSDMA. Clockwise from top; self-assembled Brij 56 lamellar LLC, lamellar LLC with hydrophilic and hydrophobic monomers incorporated, and the photopolymerized LLC composite after surfactant removal.

CDMA) monomers were mixed with 45 wt % Brij 56 surfactant, 14.5 wt % deionized water, and 0.5 wt % photoinitiator. The total monomer content in each formulation is 40 wt %. For isotropic composites, 40 wt % mixtures of the dual component monomer systems were formulated with 59.5 wt % ethanol in place of the water and surfactant above. Formulations were mixed thoroughly for 2 h using heat at 50 °C for the water surfactant blends to ease handling and ensure homogeneity within the solutions. Monomer solutions were poured into both square ($1 \times 1 \times 0.2$ cm) and bar ($1 \times 4 \times 0.2$ cm) Teflon molds and allowed to cool to room temperature in a nitrogen-purged environment (15 min). The samples were then cured for 10 min using UV irradiation (1.8 mW/cm$^2$), removed from the molds, placed in ethanol for 24 h to remove surfactant and unreacted monomer, and then dried overnight under vacuum. Square samples were cut into fourths for the compressive modulus and swelling characterization. The preparation of the LLC composites is illustrated in Figure 2. The nature of the hydrophobic domains of the liquid crystal does not allow for the fabrication of a 100% CDMA or 100% EOSDMA sample within the liquid crystal, and thus no data are available for these points in the following figures.

**LLC Characterization.** Polarized light microscopy (PLM) and small-angle X-ray scattering (SAXS) were used to characterize the LLC mesophase formation in the monomer blends using previously defined methods.[27] SAXS measurements were taken using a Nonius FR590 X-ray apparatus with a standard copper target Rontgen tube radiation source, a camera, a collimation system of the Kratky type, and a PSD 50M position-sensitive linear dectector (Hecus M. Braun, Graz). PLM images were taken using a polarized light microscope (Nikon Eclipse E600W Pol) equipped with a hot stage (Instec, Boulder, CO). In addition, both PLM and SAXS were used to determine the degree of LLC structure disruption that occurs during the photopolymerization of the composite to ensure that phase separation between the growing polymer networks and the liquid crystal was not significant.

**Network Swelling and Mechanical Properties.** Network water uptake was measured gravimetrically by immersing dried polymerized gels in 37 °C PBS solution. At given intervals, samples were removed from the solution and patted to remove surface water, and water uptake was measured. Initial water uptake was determined once the mass of the sample did not change significantly as a function of overall swell time and was calculated using previously defined methods.[26] In the initial swell characterization and all other tests following, three samples of each test material were examined to obtain a standard deviation for the resulting data point represented by error bars in the reported figures.

The compressive modulus of the LLC composite materials was measured using dynamic mechanical analysis (DMA, TA Instruments Q800 series). Post surfactant removal, dehydrated LLC templated composites were incubated in 37 °C PBS solution for 12 h prior to the compressive test to allow the sample to reach a pseudo-equilibrium water uptake before significant degradation of the gel could occur. Square-shaped samples were placed on the compressive clamp of the DMA and compressed to ~90% of their original thickness. Compressive modulus was calculated using the slope of stress/strain curves from the DMA results.

The thermomechanical properties of the LLC compatibilized composite materials were also determined using DMA. Post surfactant removal, dehydrated bar-shaped samples were placed in the single cantilever clamp of the DMA and oscillated at 1 Hz, using a deformation strain of 0.05%, as the temperature was slowly ramped from −90 to 200 °C. Storage modulus and tan $\delta$ were recorded and plotted vs temperature to determine the glass transition temperature ($T_g$) of the material, often recognized as the temperature corresponding to the peak in the tan $\delta$/temperature profile.[32]

**Degradation Characterization.** The degradation profiles for the LLC compatibilized and ethanol compatibilized composites of hydrophilic LPLDMA and hydrophobic EOSDMA or CDMA were determined using ~30 ($1 \times 1 \times 0.25$ cm) squares of each sample material. Squares were dried and weighed after surfactant removal, placed in individual vials filled with 15 mL of PBS, and stored at 37 °C. At selected time intervals, three squares of each material were removed, and both the wet and dry mass were recorded to determine the water uptake and mass loss of the sample. The pH of each vial was also tracked, and if the pH dropped below 6.4, all of the vials for that particular material were replaced with new PBS.

## Results and Discussion

Numerous studies have investigated the use of polymer blending to control and obtain advanced properties in multicomponent formulations of biodegradable polymers.[12−16] Although this is a relatively straightforward process with linear miscible biopolymer systems, the formation of composites from immiscible cross-linking biodegradable polymers represents a significant challenge due to the incompatibility that arises upon polymerization.[17,19] In this work, the use of a nanostructured lyotropic liquid crystal (LLC) as a compatibilizing platform to induce miscibility between dual cross-linking biodegradable polymer systems toward the fabrication of a compatible composite was studied. The physical properties and degradation rate of the LLC biocomposites were analyzed as a function of monomer composition to determine the degree of miscibility with dual network composites as well as to demonstrate the wide range of properties that are available with these systems. In this study, initial results compatibilizing PLA-*b*-PEG-*b*-PLA dimethacrylate (LPLDMA) and caprolactone dimethacrylate (CDMA) within a LLC surfactant based template are discussed. A more in-depth study using blends of LPLDMA and newly synthesized ethyloxy succinate dimethacrylate (EOSDMA) is then described examining water uptake, modulus, glass transition temperature, and degradative behavior of the LLC biocomposites.

**LLC Composites of LPLDMA and CDMA.** Blends of biodegradable LPLDMA and CDMA monomers in simple water formulations exhibit poor mixing and phase separation (observed with optical microscopy) due primarily to the differences in the hydrophobicity of each component. Upon polymerization, the rapid growth in molecular weight of each polymer constituent leads to even greater instability in the system and less compatibility between the two polymers resulting in an unusable composite material. However, blending CDMA and LPLDMA monomers within the nanoscale, self-assembled domains of a lyotropic liquid crystal serves to compatibilize these mixtures

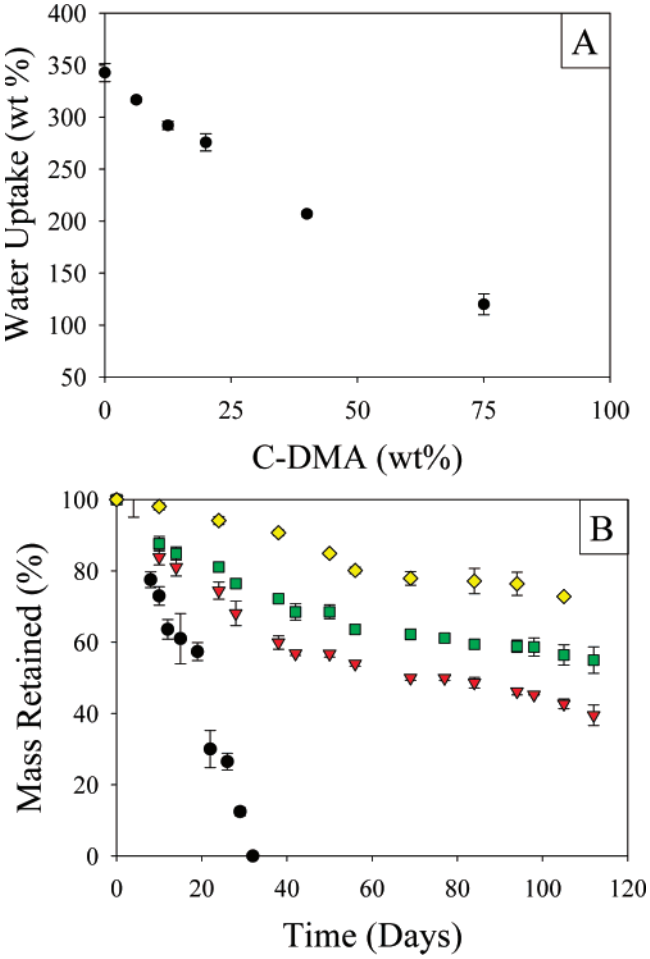


**Figure 3.** Initial water uptake (A) of LLC compatibilized composites of LPLDMA and CDMA as the concentration of CDMA in the composite is increased. Also shown are the degradation profiles (B) of LPLDMA and CDMA composites fabricated within a LLC with CDMA monomer concentrations of 0 (●), 25 (▼), 50 (■), and 75 wt % (◆).

and, upon photopolymerization, results in a composite material with much greater mechanical integrity than the isotropic system. The degree of compatibility between the two immiscible polymers was first investigated through swelling in water of the LLC biocomposites as a function of CDMA and LPLDMA composition. The degree of swelling in cross-linked polymeric materials is dependent on the network structure and the cross-link density of the polymer as well as the chemical interactions between the polymer chains and the solvent, in this case water. Because of the fact that LPLDMA and CDMA have significantly different interactions with water, as LPLDMA is relatively hydrophilic and CDMA is much more hydrophobic,[33] it is reasonable to believe that by blending the two biodegradable monomers into a miscible polymer composite the overall material will reflect the swelling contributions from each polymer system.

Blends of CDMA and LPLDMA monomers were incorporated into a Brij 56 surfactant LLC mesophase geometry in a similar manner to the process diagramed in Figure 2. Once the templating surfactant was removed from the polymerized composites, the dried materials were immersed in PBS solution to measure the degree of water uptake in each system. Figure 3A shows the water uptake in LLC materials of blended CDMA and LPLDMA as the concentration of CDMA is increased. When the percentage of CDMA in the monomer (40 wt % of total formulation) is raised from 0 to 75 wt %, the degree of swelling or water uptake in the polymerized composites decreases by over 200% of the dry material weight. Such behavior is expected due to the hydrophobic contributions of CDMA. More significant is the linear or additive relationship between composition and water uptake in Figure 3A which indicates that a very miscible composite material was formed from the two relatively immiscible biodegradable monomers. Furthermore, this type of behavior is similar to interpenetrating network (IPN) composite behavior, suggesting that the nanophase-separated morphology of the LLC templated materials may result in a biocomposite with highly advanced properties such as direct control over physical properties and synergistic property relationships between the two biopolymers in the composite.[20,34]

Because of the strong relationship between the degree of network swelling and the degradation rate of synthetic biodegradable hydrogels, the degradation rate of the CDMA and LPLDMA composites was also studied as the concentration of CDMA was increased in the material. Figure 3B shows the mass loss of LLC compatibilized blends of the two polymers as they degrade in PBS solution. As the ratio of CDMA to LPLDMA increases in the blend, a significant delay in the degradation rate of the material is observed. The degree of initial water uptake in each LPLDMA/CDMA network has a significant effect on the degradation of that material as the highest swelling LPLDMA network with 0 wt % CDMA degrades fully in ~32 days. As CDMA is blended into the LLC composite at 25, 50, and 75 wt %, the amount of the material remaining after 32 days for these composites is 66, 78, and 92%, respectively, indicating that the hydrophobic CDMA induces less water uptake, thereby resulting in a slower degradation rate compared to the hydrophilic LPLDMA rich composites.

The delay in degradation is not solely due to decreased water uptake in the CDMA rich LLC composites. Polycaprolactone, while considered biodegradable, requires 1−2 years to fully degrade due to high hydrophobicity and low concentration of hydrolyzable ester bonds compared to typical poly(α-hydroxy) polyester degradable polymers.[33,35] Therefore, it is the combination of the slow degradation mechanism and the hydrophobicity of CDMA that serves to limit the degradation rate of the LLC compatibilized LPLDMA and CDMA materials. Similar to the swelling results above, the degradation profiles of the blended materials seem to be directly dependent on the composition of each composite, again suggesting that the LLC compatibilized blends result in a very miscible system between the two constituents that is not available through traditional processing or blending methods. Furthermore, through the use of the LLC as a compatibilization platform, the water uptake and degradation behavior of the biodegradable composites can be significantly controlled simply by manipulating the ratio of LPLDMA to CDMA.

**LLC Composites of EOSDMA and LPLDMA.** The results above, in which two relatively immiscible biodegradable monomers were compatibilized using a LLC template to form a composite biomaterial with direct control over water uptake and degradation behavior, show promise toward the fabrication of versatile biodegradable composites for tissue engineering applications. Although CDMA and LPLDMA have much different hydrophobicities and degradation rates, their molecular weights are similar, and thus it is not expected that the mechanical properties of the biocomposites made from these two systems will demonstrate a direct dependence on polymer composition. To investigate the use of LLC templates to compatibilize biodegradable immiscible systems that will exhibit vastly different cross-link densities and mechanical properties as well as hydrophobicities, a low molecular weight ethyloxy

succinate dimethacrylate (EOSDMA) monomer was synthesized and blended with LPLDMA within a lamellar LLC to form the templated composite system, as diagrammed in Figure 2. EOS was specifically designed to be relatively hydrophobic and have a much higher cross-linking density than LPLDMA due to its low molecular weight. If the LLC template is able to miscibilize the LPLDMA and EOSDMA monomers into a compatible biocomposite, the greater degree of dissimilarity between these constituents could lead to a greater range and more direct manipulation of the physical properties of the combined materials compared to LLC blends of the more similar CDMA and LPLDMA.

Similar to blends of CDMA and LPLDMA, EOSDMA and LPLDMA monomer blends in water also exhibit phase separation and, upon photopolymerization, result in a composite with poor mechanical integrity, reducing its usefulness in any materials application. However, blending the two immiscible monomers within a lamellar LLC results in a composite material with excellent mechanical integrity even after the surfactant of the template is removed from the polymerized material. Again, it is hypothesized that the self-assembled hydrophilic and hydrophobic domains of the nanostructured LLC incorporate the two monomers on the nanometer size scale, restricting gross phase separation and resulting in a nanophase-separated composite that is relatively homogeneous compared to typical composites with micron size phase domains or fillers.

Polarized light microscopy (PLM) and small-angle X-ray scattering (SAXS) were used to characterize the self-assembled lamellar LLC with the surfactant/EOSDMA/LPLDMA monomer formulations. During the photopolymerization of the LLC compatibilized polymer composites, the birefringent textures observed on PLM before and after polymerization are nearly identical. Additionally, the SAXS profiles before and after polymerization also do not change to a significant degree, indicating that the morphology of the lamellar LLC is not significantly disturbed by the polymerization of the two biodegradable systems.

Similar to the templated blends of LPLDMA and CDMA above, the network swelling of the EOSDMA/LPLDMA materials compatibilized using a lamellar LLC was investigated as a function of monomer composition. Figure 4A shows the initial water uptake of the EOSDMA/LPLDMA blended composites as the concentration of EOSDMA is increased. As the percentage of EOSDMA in the composite is raised from 0 to 75 wt %, the degree of swelling or water uptake in the polymerized materials exhibits an almost linear decrease with composition with an overall decrease of over 200 wt %. The decrease in swelling is driven by the increased hydrophobicity and increased cross-linking density of the EOSDMA as the concentration of this component is increased in the composite. Furthermore, the linear relationship between network swelling and monomer composition indicates that both LPLDMA and EOSDMA are making additive contributions to the physical properties of the overall composite. This IPN type behavior with two immiscible cross-linking monomers suggests that a very compatible blended monomer formulation and polymerized material is formed using the nanostructured lamellar LLC as a polymerization template.

To investigate the compatibilizing effect of the LLC, EOSDMA/LPLDMA systems compatibilized using the LLC platform were compared to formulations without the liquid crystal template in which the two monomers were blended in isotropic formulations of 40 wt % monomer and 60 wt % ethanol. Since both monomers are highly soluble in ethanol, mixing in this

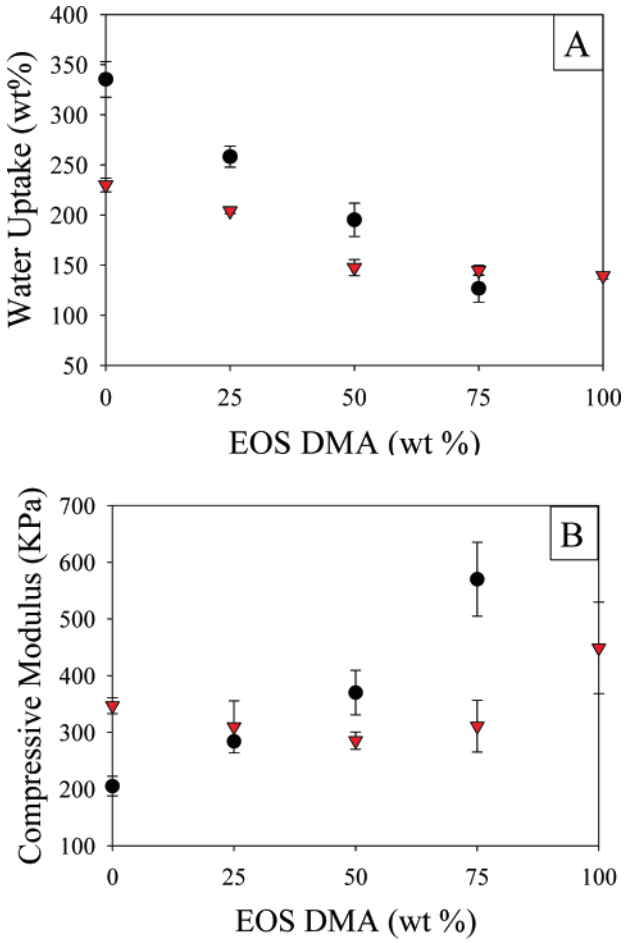


**Figure 4.** Initial water uptake (A) and initial compressive modulus (B) of LPLDMA and EOSDMA biodegradable composites fabricated using either a lamellar LLC (●) or ethanol (▼) to compatibilize the monomer mixture and resulting polymer composite. The physical properties of the composites are shown as a function of the EOSDMA percentage of the monomer (total 40 wt %) in the composite formulations.

solvent leads to miscible monomer formulations as determined by the clarity of the solution and absence of phase separation with optical microscopy. Figure 4A shows the initial water uptake of the isotropic ethanol compatibilized EOSDMA/LPLDMA materials as EOSDMA is increased in the blend. Similar to LLC compatibilized blends, the overall water uptake in the ethanol blended materials generally decreases with increased EOSDMA. However, the trend in the ethanol compatibilized blends is definitely not as linear as with the LLC composites, particularly in blends with greater than 25 wt % EOSDMA, suggesting a decrease in the compatibility between EOSDMA and LPLDMA in this solvent upon polymerization.

The significant differences in cross-link density and water uptake between EOSDMA and LPLDMA will also affect the mechanical properties of composites made from formulations of the two. Figure 4B shows the compressive modulus of water-swollen composites of EOSDMA and LPLDMA, compatibilized using both the lamellar LLC and ethanol solutions, as a function of monomer composition. Again, the composites fabricated within the lamellar LLC demonstrate a very linear relationship between the compressive modulus of the water swollen gels and the monomer composition, indicating additive properties from both the EOSDMA and LPLDMA constituents. Figure 4B shows that by blending in EOSDMA the increase in cross-linking density and decrease in water uptake from this monomer lead to almost a 300% increase in modulus. On the other hand,

the composites polymerized in ethanol do not demonstrate this linear behavior with almost no change in the modulus of the composite until 100 wt % EOSDMA is used as the monomer in the sample.

By removing all solvent and surfactant from each material before testing, both LLC and ethanol compatibilized blends are chemically and compositionally equal with the only difference being the presence of the template during the polymerization of the LLC compatibilized materials. In both the CDMA/LPLDMA and EOSDMA/LPLDMA LLC biocomposites, over 95% of the templating surfactant was removed as determined gravimetrically. Furthermore, no trends are evident between the residual surfactant concentration and the property behavior of these composites. These results reinforce that the composition of the biocomposites is the primary factor in determining property behavior in these systems. Finally, cell biocompatibility tests performed previously in our lab have demonstrated that the small amount of residual Brij 56 in LLC templated LPLDMA hydrogels does not have a significant effect on cell toxicity.

The nonlinear relationship between network modulus and monomer composition in the ethanol compatibilized materials suggests that even though both monomers are very miscible in ethanol, the polymerized composite does not exhibit compatibility between the EOSDMA and LPLDMA and that the networks are phase separated. It seems that the nanostructured hydrophilic and hydrophobic domains of the LLC template are necessary during polymerization to limit phase separation between the two polymers, resulting in an increase in the relative homogeneity of the composite that yields the linear or additive swelling and mechanical properties observed in Figure 4. In addition to greater homogeneity, the linear relationship between the physical properties of the LLC composites and monomer composition directly leads to a high degree of control over the properties of the material, which in turn is an advantageous trait for a biomaterial in which the properties of the material must be finely tuned to meet the demands of a particular biomedical application.[1,2]

In addition to physical properties such as water uptake and modulus, the thermomechanical properties such as the glass transition temperature ($T_g$) profile of a dual polymer composite is often very informative in regards to the miscibility or compatibility between the constituents of the material.[32,36] The monomers in this study, EOSDMA and LPLDMA, have significantly different thermomechanical behavior as EOSDMA should be highly cross-linked and glassy at room temperature, and LPLDMA is rubbery at room temperature due to a long central PEG chain with much less cross-link density than EOSDMA. Dynamic mechanical analysis was used to determine the $T_g$ profiles of the blended EOSDMA and LPLDMA composites compatibilized using either a lamellar LLC or an isotropic ethanol solution. Figure 5A shows the tan $\delta$ profiles as a function of temperature for the LLC templated composites as EOSDMA is blended into the monomer formulations at greater concentrations.

Tan $\delta$ is defined as the ratio of the loss modulus to the storage modulus of the material, and the height of the tan $\delta$ peak during the temperature scan is often used to gauge the ability of a material to absorb energy at its $T_g$. Furthermore, the peak in the tan $\delta$ vs temperature profile is widely recognized as the $T_g$ of the polymeric material.[36] As the highly cross-linked EOSDMA is blended into the composite system, a general shift occurs in the tan $\delta$ profiles to higher temperatures. The shape of the tan $\delta$ profile of a composite system comprised of two

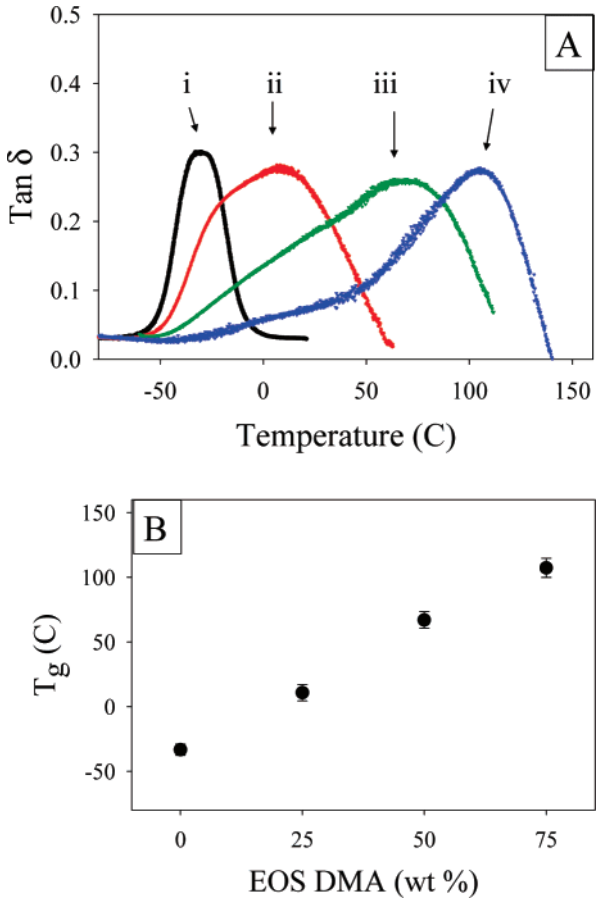


**Figure 5.** Tan $\delta$ vs temperature profiles (A) of LPLDMA and EOSDMA composites fabricated using a lamellar LLC with an EOSDMA concentration of 0 (i), 25 (ii), 50 (iii), and 75 wt % (iv). Also shown is the plot (B) of the $T_g$ of each composite as the EOSDMA concentration is raised in the blended LLC formulations.

polymers of vastly differing $T_g$'s is highly indicative of the compatibility or homogeneity of the system. For example, an incompatible or phase separated composite material typically exhibits two peaks in its tan $\delta$ profile, representing the separate thermomechanical behavior of each phase separated constituent.[36] It should be noted that although LPLDMA and EOSDMA have significantly different $T_g$'s, the LLC composites of these two demonstrate a single tan $\delta$ peak, indicating the high degree of compatibility between the two polymers that is brought about by the LLC template.[32,37]

The broadness of the tan $\delta$ peak is also an indicator of the degree of compatibility in dual polymeric composites. In a highly homogeneous polymer network in which the long-range chain segmental motions will be relatively the same, the motion of all chains in the material will transition within a narrow temperature range, yielding a narrow tan $\delta$ peak. However, phase separation or heavily cross-linked materials will introduce a degree of heterogeneity into the network chains, resulting in a broadening of the temperature range and overall tan $\delta$ profile.[34] In Figure 5, there is a slight broadening of the tan $\delta$ peaks as the concentration of EOSDMA is increased in the composite. However, this general broadening is attributed to small increases in the overall heterogeneity of the material with additions of the highly cross-linked EOSDMA, behavior that has been reported in similar nondegradable compatible blends.[38] A portion of the samples underwent a second temperature ramp in the DMA to ensure that the broadening of the EOSDMA/LPLDMA composites is not due to postcure effects from the temperature ramp. The fact that the profiles in Figure 5A do not decrease in

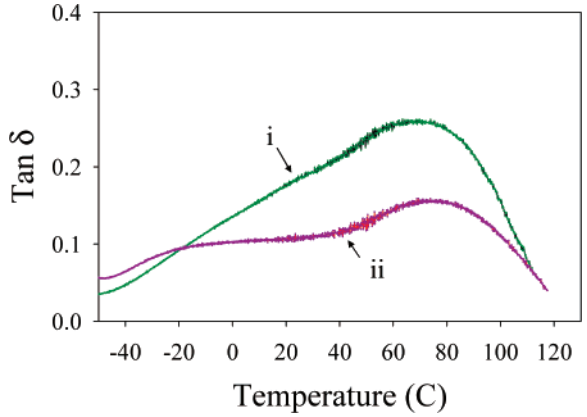


**Figure 6.** Tan $\delta$ vs temperature profiles for a 1:1 mixture (40 wt % total) of EOSDMA and LPLDMA fabricated using either a lamellar liquid crystal (i) or ethanol (ii) to compatibilize the resulting polymer composite.

tan $\delta$ intensity with increasing concentration of EOSDMA further indicates that a high degree of overall homogeneity is present in the blended system, a direct result of the nanoscale arrangement of the two constituents in the composite.[38]

By plotting the $T_g$ of each composite as a function of monomer composition, the contributions from each constituent toward the glass transition temperature can be assessed. Figure 5B shows the $T_g$ of each LPLDMA/EOSDMA composite as the concentration of the latter is increased. In this figure, not only is the $T_g$ of the composite shifted over 160 °C with added EOSDMA, but a direct dependence of $T_g$ on the composition of the monomer is observed, again indicating additive contributions from each constituent and compatibility or miscibility between the two biodegradable polymers in the LLC templated material.

Comparisons between the thermomechanical properties of LPLDMA/EOSDMA composites fabricated either in lamellar LLCs or in isotropic ethanol blended formulations were conducted by directly comparing the tan $\delta$ profiles of each case. Figure 6 shows the tan $\delta$ vs temperature profiles for a 1:1 mixture of LPLDMA to EOSDMA (40 wt % total) compatibilized with either a lamellar LLC (i) or with ethanol (ii). Not only is the $T_g$ (tan $\delta$ peak) of the ethanol compatibilized composite shifted 8 °C higher, but distinct differences are observed in the tan $\delta$ profiles, including nearly a 2-fold decrease in the tan $\delta$ intensity and a more prominent shoulder on the profile of the ethanol fabricated material. The decrease in the intensity of the tan $\delta$ peak coupled with the dual nature of the profile (shoulder at −30 °C and main peak shifted higher to 76 °C) indicates less compatibility and more heterogeneity between the two polymers polymerized in ethanol when compared to networks fabricated using the lamellar liquid crystal template.[37−39] Increased heterogeneity in this case is not unexpected as the phase-separated polymerized regions of each constituent will be more prominent in the isotropic ethanol blended case than with the nanoscale separation associated with the LLC composites. Similar to what was observed in the swelling and modulus tests above, the thermomechanical analysis also demonstrates that the LLC template is necessary not only to create a compatible composite from the immiscible EOSDMA and LPLDMA but also to obtain the advanced IPN type behavior with the composite.

Finally, the degradation behavior of LPLDMA and EOSDMA composites was studied due to the significant and linear control over the physical properties of these materials that was achieved by blending these two monomers within a lamellar LLC (Figure 4). The increase in cross-linking density and hydrophobicity with increased EOSDMA content should have a significant effect delaying the degradation in the LPLDMA/EOSDMA composites. Figure 7A shows the degradation profiles of three LLC templated LPLDMA/EOSDMA composites as a function of both time and the monomer ratio within the materials. As expected, the more hydrophilic and less cross-linked LPLDMA rich materials degrade significantly more rapidly than the other composites. As more EOSDMA is blended into the system, the more hydrophobic and more cross-linked polymer decreases the overall water content in the system and further delays the degradation of these composites. For example, by changing the EOSDMA concentration in the LLC formulation from 25 to 75 wt %, the slope of the degradation profile is reduced over 70%, demonstrating direct control over the rate at which the LPLDMA/EOSDMA composites break down. Again, the significant aspect of these results is that through the use of a LLC template, immiscible EOSDMA/LPLDMA blends can be fabricated into compatible biodegradable composites with a very precise control over the degradation rate of the material.

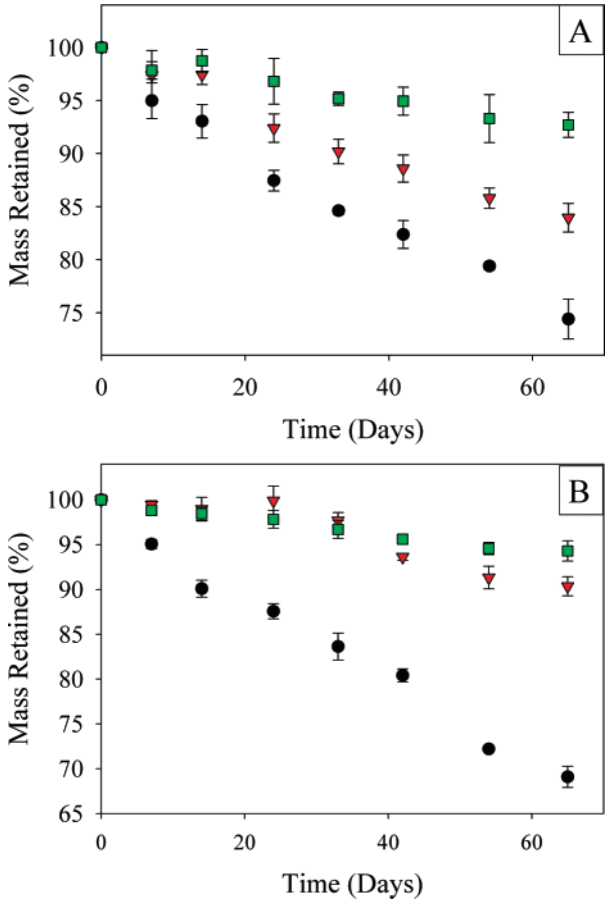


**Figure 7.** Degradation profiles of LPLDMA and EOSDMA composites compatibilized using either (A) the lamellar LLC or (B) an isotropic ethanol solution. The degradation of the various composites are shown as a function of the amount of EOSDMA in the 40 wt % total monomer blend with concentrations of 25 (●), 50 (▼), and 75 wt % (■).

In comparison to the composites in Figure 7A, Figure 7B shows the mass loss or degradation of the LPLDMA/EOSDMA composites compatibilized using an isotropic ethanol solution. Although these samples contain the same composition and EOSDMA/LPLDMA ratios as their LLC counterparts in Figure 7A, there is no LLC formed in these cases as only ethanol is used to miscibilize the monomer formulations. As observed with the LLC templated samples, the degradation rate of these materials can be altered by changing the composition from

LPLDMA to EOSDMA rich composites. However, as the EOSDMA concentration is increased in the ethanol compatibilized formulations, the linear or additive decrease in degradation rate observed with the LLC samples (Figure 7A) is not present here. Instead, there seems to be little to no change in the degradation rate of the 50 and 75 wt % samples even with the large compositional change in these materials. The lack of a direct relationship between the polymer composition and the degradation behavior of the ethanol blended composites in Figure 7B is attributed to the heterogeneity and expected phase separation that is due to the lack of a nanostructured template during polymerization.

Compared to the ethanol compatibilized blends, the lamellar templated EOSDMA/LPLDMA composites previously demonstrated very additive properties in both water uptake (Figure 4A) and mechanical properties (Figure 4B), suggesting that the cross-linking density and water polymer interactions in these systems linearly change with monomer composition. This IPN type behavior is a direct result of the degree of miscibility afforded by the nanostructured LLC template, leading to a relatively homogeneous or compatible composite from the two immiscible cross-linking monomers. Because of the fact that cross-linking density and water uptake directly influence the degradation behavior of typical biodegradable hydrogels,[7,9] the linear changes in degradation rate observed in Figure 7A are then also attributed to the degree of compatibility accessible using the lamellar LLC as a compatibilization platform for the EOSDMA and LPLDMA polymers.

As observed throughout this study, the isotropic ethanol solution, while providing initial miscibility between the incompatible biodegradable monomers, does not provide the structural support or confinement of the monomers within a liquid crystal template and, upon polymerization, results in materials that are phase separated and exhibit poor property/composition behavior. Specifically, the decrease in tan $\delta$ intensity and shoulder in the tan $\delta$ profile as well as the weak relationships between composite composition and the modulus, swelling, and degradation rate of the ethanol blended biocomposites all suggest that these systems are not compatible and are phase separated. One of the main themes of this work is that the lamellar LLC template compatibilizes the two biodegradable monomers on the nanometer scale, resulting in composite materials with IPN type behavior in which the properties of the system are directly dependent and linearly change with the material's polymer composition. Furthermore, through testing of the thermomechanical, physical, and transient (degradative) properties of these composites, it has been repeatedly demonstrated that the ethanol blended formulations do not result in the same degree of compatibility between the EOSDMA and LPLDMA polymer networks and that the LLC template is essential in creating a highly compatible composite from these immiscible dual biopolymer systems.

Throughout this study, a simple processing method has been used to obtain compatible composites from otherwise immiscible biodegradable polymer constituents, resulting in biocomposites with highly versatile and tailorable physical properties. The focus of this study has centered on the introduction of LLC templates as compatibilzation platforms for biocomposites and the advanced properties that result. However, future work will investigate the *in vitro* cell biocompatibility of the templated biocomposites as well as their use *in vivo* in a particular ocular tissue engineering endeavor in which control over the properties and degradation behavior of the composite will be important to the success of the biomedical application.

## Conclusions

In this study, a nanostructured lyotropic liquid crystal was used to induce miscibility between multicomponent formulations of incompatible biodegradable cross-linking polymers. Using the LLC as a photopolymerization template results in material composites that exhibit IPN type behavior with physical properties that are directly dependent on monomer composition. Furthermore, the use of monomer composition to directly control the properties of the LLC composites leads to significant changes in the physical properties and degradation behavior of these materials. For example, as the concentration of highly cross-linking, hydrophobic EOSDMA monomer is increased in a biodegradable composite of EOSDMA and LPLDMA, the water uptake decreases over 60% and the modulus increases 200% compared to the homopolymer of LPLDMA. Additionally, the $T_g$ of this composite can be shifted over a range of 150 °C and the degradation rate delayed up to 70% simply by adding greater concentrations of EOSDMA within the biodegradable LLC compatibilized material. Finally, comparing the LLC templated system to the polymerization of the immiscible biodegradable monomers in water or a good solvent such as ethanol demonstrates that the nanostructured LLC template not only results in a more homogeneous material but also is necessary to attain a composite material with IPN type behavior and advanced properties. Thus, using a LLC template is a simple pathway to compatibilize immiscible cross-linking biodegradable networks into a biocomposite with highly tailorable physical properties.

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