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Controlling Hydrogel Properties by Crystallization of Hydrophobic Domains

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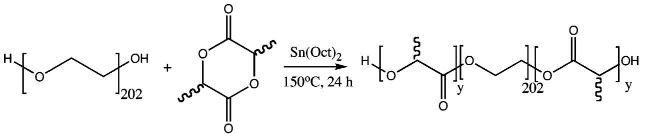
We report the use of crystallinity within the hydrophobic domains of physically cross-linked triblock copolymer hydrogels to control bulk mechanical modulus. Hydrogels have more recently become a topic of great interest due to their potential biomedical applications, including tissue engineering scaffolds and drug delivery.[1−5] Hydrogels have many properties similar to native tissue, including a predominately aqueous environment, similar surface tension, and facile transport of cell metabolites.[1] Unfortunately, many of the hydrogels currently used have limited mechanical properties,[6] and the design principles for controlling these properties have focused mainly on the mesh size and structure. Learning to control mechanical properties by other methods will be essential for developing new hydrogels for advanced applications. For instance, it has been shown that cells can sense their mechanical environment (in both native and polymeric systems) resulting in changes to their gene expression, adhesion, and genotype.[7−10] This report shows crystallinity within hydrophobic domains provides a new handle for controlling mechanical properties.

While previous reports have used crystalline domains[11,12] within the hydrogel structure to improve mechanical properties, there has not been a system where one could directly compare the crystalline system with an amorphous analogue. Poly(vinyl alcohol) [PVA] hydrogels used repeated freeze/thaw cycles to produce more crystallinity and higher modulus gels. For example, a gel of 14.6 wt % PVA had a storage modulus of 20 kPa after seven freeze/thaw cycles.[13−16] In addition, hydrogels with liquid crystalline domains showed significant crystallinity;[17−21] however, these gels have relatively low water content (at least 84.7 wt % polymer). In both cases, there is no amorphous equivalent for comparison. Without any crystallinity in PVA, a polymer solution is produced, and removal of the liquid crystalline domains would significantly change the molecular structure. Herein, we compare two chemically equivalent polymer systems in which *only* the stereochemistry is changed to create amorphous vs semicrystalline hydrogels. This subtle but significant change produces materials for direct comparison.

There are several polymeric hydrogel systems that are now being studied for use in biological applications.[8] Of considerable interest are block copolymers containing poly(lactide) [PLA] and poly(ethylene oxide) [PEO] units due to the biodegradable ester bonds within the PLA blocks and the biocompatibility of the PEO block.[22−24] The PLA blocks represent an ideal system to examine the influence of crystallinity on elastic modulus because the stereochemistry of the lactide segments controls the crystallinity of this block. For example, isotactic poly(L-lactide) [PLLA] or poly(D-lactide) [PDLA] yields semicrystalline materials while atactic poly(DL-lactide) or poly(R-lactide) [PRLA] is amorphous. This allows the preparation of triblock copolymers in which only the stereochemistry of the hydrophobic PLA block is changed while total molecular weight, polydispersity index (PDI), and composition are held constant.

Scheme 1. Reaction Scheme for PLA−PEO−PLA



L-lactide = semi-crystalline
DL-lactide = amorphous
$DP_{LA} = 2y$

We have synthesized PLA−PEO−PLA triblock copolymers using both L-lactide and DL-lactide monomer (Scheme 1) as previously described in the literature.[25] Using this technique, the PLA chain lengths are controlled, and the PDI is typically less than 1.2. The PEO mid-block has $M_n = 8900$, and the PLA block lengths were varied from $DP_{LA} = 40-88$, giving approximate total molecular weights between 11 500 and 15 500. These polymers were dissolved in water at concentration ranges from 10 to 25 wt % polymer, and they were qualitatively divided into two categories: (1) those that pass the vial-inversion test and (2) those that fail.[26] In all cases, the gels containing PRLA failed the vial-inversion test, while gels composed of PLLA passed when the concentration of polymer exceeded ∼16 wt %. To better quantify the gel strength, rheological measurements were performed with a cone and plate geometry that allows the viscoelastic moduli vs frequency to be measured. This study also allows a direct comparison between stereoregular and stereorandom polymers.

We found that the storage modulus is strongly dependent on the stereochemistry of the PLA blocks. When hydrogels were made from polymers with identical degrees of polymerization and at the same concentration, the gels composed of PLLA blocks were significantly stiffer than those containing racemic PLA blocks. A typical example is shown in Figure 1 where a stereoregular sample, $DP_{LA} = 72$, forms a stiff gel while the racemic sample does not. For example, at 1 Hz the stereoregular gel has a storage modulus of 14 kPa while the racemic solution's storage modulus is 0.1 kPa. The gel formed by stereoregular 72L displays an elastic modulus that is independent of frequency as expected for a hard gel while the much softer racemic sample displays the expected frequency dependence.

We speculated that the increased stiffness of the PLLA gels might be due to the formation of long-lived, crystalline, hydrophobic domains. In contrast, the racemic polymer would form short-lived amorphous hydrophobic domains due to the stereo-random structure.[27] This hypothesis is further supported by the wide-angle X-ray diffraction (WAXD) data shown in Figure 2. The peaks in the powder sample (Figure 2A) at $2\theta \approx 19°$ and 23° are characteristic of crystalline PEO.[24] PLLA is also known to exhibit peaks at $2\theta \approx 19°$ and 22°, so there is overlap between the crystalline PEO and PLLA peaks; however, the peak at $2\theta \approx 17°$ is due solely to crystalline PLLA.[24,28−30] This confirms the presence of crystalline PLLA and PEO in neat solid samples of these triblock copolymers.[31] When the sample is hydrated to form the gel, the peaks corresponding to crystalline PEO disappear while those from PLLA remain and

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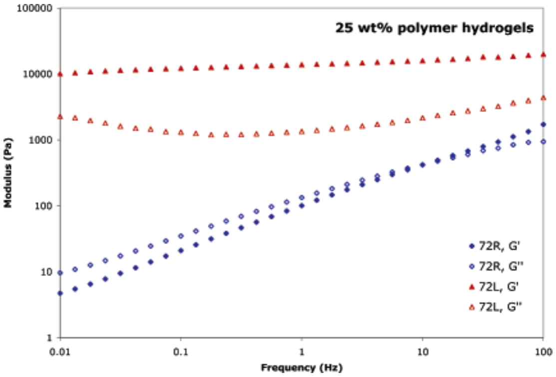

Figure 1. Dependence of the storage modulus on the stereochemistry of the polymer chains is clearly shown. The stereoregular polymer has a storage modulus (*G′*) greater than 10 kPa, while the racemic version is much less stiff. Both materials are 25 wt % polymer in water.

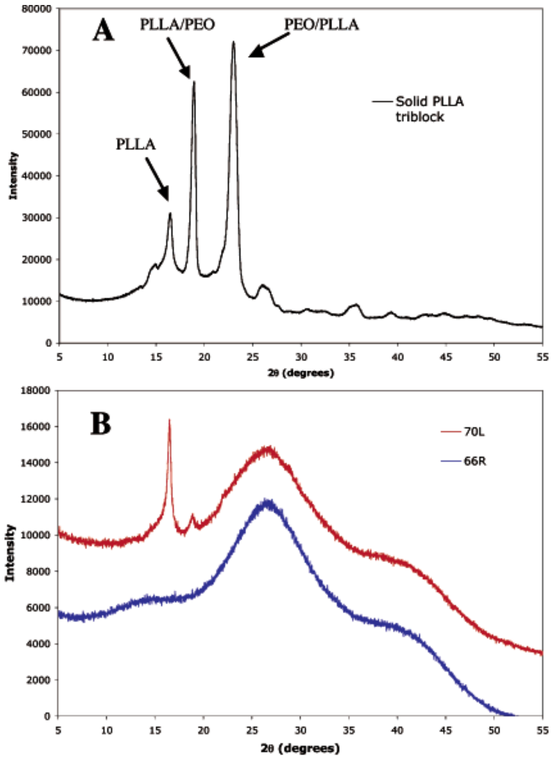

Figure 2. (A) The powder sample shows peaks at $2\theta \approx 19°$ and 23° corresponding to the crystalline regions of both PEO and PLLA and at $2\theta \approx 17°$ corresponding to crystalline PLLA. (B) The PLLA gel sample shows only peaks corresponding to PLLA at $2\theta \approx 17°$ and 19°. The PRLA sample shows no crystallinity as expected.

appear to sharpen upon gel formation. This confirms that the PLLA domains are crystalline in the gel sample and may be more well ordered than in the powder form. Meanwhile, the sample formed from racemic PLA shows no peaks corresponding to crystalline PLA as expected. These WAXD studies confirm the hypothesis that crystalline PLA segments are present in the gels formed by the stereoregular triblock copolymer and that crystallinity of these blocks likely acts to stabilize the hydrophobic domains, resulting in a stiffer hydrogel.

In summary, the stiffness of hydrogels made from PLA−PEO−PLA can be controlled by the stereoregularity of the polymer. This increased stiffness appears to be related to the formation of crystalline hydrophobic PLLA blocks in the gel as evidenced by WAXD. Gels with PLLA hydrophobic domains are considerably stiffer than those with PRLA hydrophobic blocks of identical length. The use of PLA allows perhaps the simplest chemical change, stereochemistry, to be altered while holding all other molecular parameters constant, thus allowing the impact of crystallinity to be determined directly. This tunability is very important in designing hydrogels, and crystallinity, through the control of stereochemistry, is shown to influence gel strength directly for the first time.

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Supporting Information Available: Experimental procedures and characterization for PLA−PEO−PLA triblock copolymer, rheology procedure and data for gels with various molecular weight of polymer, and WAXD procedure and data for gels with various molecular weight of polymer. This material is available free of charge via the Internet at http://pubs.acs.org.

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