Hyaluronic Acid Enhancement of Polyethylene for Cardiovascular Applications

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Introduction: The overall goal of this work is to create anti-thrombogenic hyaluronan (HA) enhanced polymers for use in cardiovascular applications such as flexible heart valve leaflets and small diameter vascular grafts. Several studies have shown that increasing the hydrophilicity of materials and HA-modification can decrease thromboembolism and calcification[1, 2, 3]. Linear low density polyethylene (LLDPE) was chosen for HA enhancement in this pilot study because its mechanical properties are comparable to fixed tissue heart valve leaflets. Technology developed to enhance polyethylene with HA for orthopedic applications[4] was adapted for use with LLDPE. The prior work showed that HA can be made nonpolar through silylation, dissolved in xylene and diffused into other polyethylene materials. The present study investigated the swelling kinetics of the LLDPE in the solvent, and the effect of swelling on the mechanical properties of the LLDPE. Hemocompatibility of the HA enhanced materials was then compared to controls.

Methods: The effects of swelling in xylenes were characterized for 0.08mm films blown from three LLDPE resins: Dowlex 2344, 2056 and 2036G (Flex-Pack Engineering, Inc., Uniontown, Ohio). The effect of swelling on crystallinity (ASTM D3418-03) and tensile properties (ASTM D882-10) was investigated. For thrombogenicity testing, 6µl of whole blood was placed onto the surface of each specimen. At each time point, the red blood cells that were not trapped in a thrombus were lysed, and the concentration of free hemoglobin assessed. For platelet activation, plasma (centrifuged from whole blood) was pooled and incubated on the samples. Untreated LLDPE samples and LLDPE enhanced with HA via the swelling process were used for both studies. Samples were fixed for imaging with a scanning electron microscope (SEM).

Results: Xylenes resulted in the greatest degree of swelling in the Dowlex 2056 film (Figure 1). At 50°C and higher, the Dowlex 2056 film had the highest degree of swelling, while swelling of the other two films was inconsistent. Thus, the Dowlex 2056 film was chosen as the base polymer. The crystallinity changes (data not shown) in the 2056 were largest at the highest temperatures.

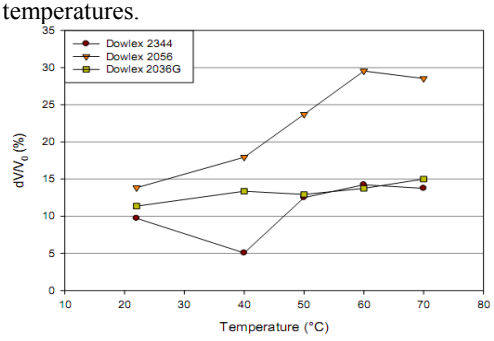

Figure 1. *The percent volume change of LLDPE films in xylenes at various temperatures.*

High degrees of swelling could be achieved at 50 °C with relatively small increases in crystallinity and modulus of elasticity (Figure 2); thus, swelling at 50°C for 60 min was chosen for LLDPE-HA material synthesis. These swelling parameters were used to enhance LLDPE with HA while maintaining the bending stiffness of the films within the range of natural HV leaflets[5].

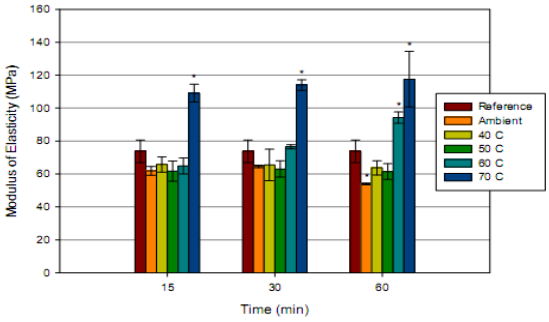

Figure 2. *Modulus of 2056 after swelling. An (*) indicates significant difference ($p<0.05$) from reference.*

Samples with 0.5-1.5% HA with and without an optional surface dip of HA were made. Whole blood clotting was dramatically and significantly reduced on all HA enhanced materials, with the best clotting results for the 1%HA sample with the optional surface dip, demonstrating virtually no clotting at 30 and 60 minutes. Similarly, SEM images (Figure 3) indicate a decrease in platelet activation on LLDPE films treated with 1% HA.

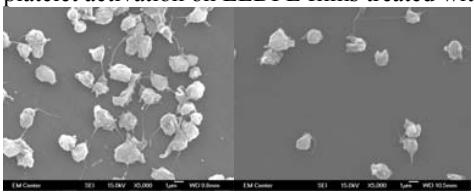

Figure 3. *SEM images of untreated LLDPE (left) and treated LLDPE with 1% HA (right).*

Conclusions: The Dowlex 2056 was selected as the base polymer, with a swelling temperature of 50°C because of the limited increase in crystallinity and modulus of elasticity with swelling. HA enhanced LLDPE made with these parameters exhibited excellent anti-thrombogenecity and significantly decreased platelet adhesion and activation. Future studies will explore complement activation, endothelial cell and immune response to these materials, which show promise for applications in flexible heart valve leaflets and small diameter vascular grafts.

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