Hyaluronic Acid Enhancement of Polyethylene Terephthalate for Blood Contacting Applications

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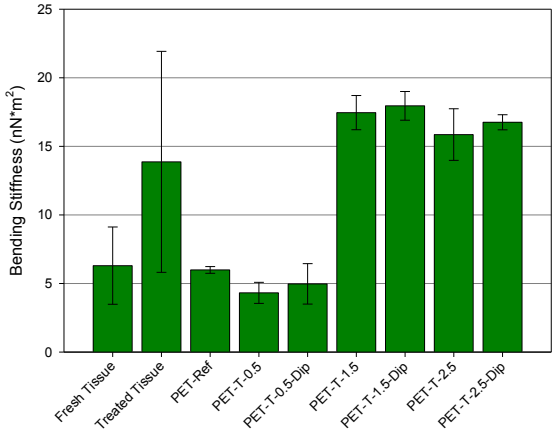
Statement of Purpose: There is an ongoing need for hemocompatible, durable, synthetic plastics in blood-contacting medical devices, particularly small diameter vascular grafts that remain patent long term, and flexible heart valve leaflets that are hemocompatible, durable, avoid *in vivo* calcification and can be folded into a catheter for less-invasive delivery. While treatment with heparin increases the patency of small diameter vascular grafts, concerns about the durability and long term action of the heparin coating remain[1]. Recently, researchers have shown the promise of flexible leaflet polyethylene terephthlate (PET or Dacron) heart valves; yet, still struggle with PET hemocompatiblity and *in vivo* calcification[2,3]. Hyaluronan (HA) has been used as a coating to reduce platelet adhesion in small diameter vascular grafts[4] and to help mitigate calcification in bioprosthetic materials[5]. This purpose of this study was to develop methods for enhancing PET fabric with HA and perform preliminary mechanical and hemocompatibility testing to determine the feasibilty of using such materials in blood-contacting medical devices and implants.

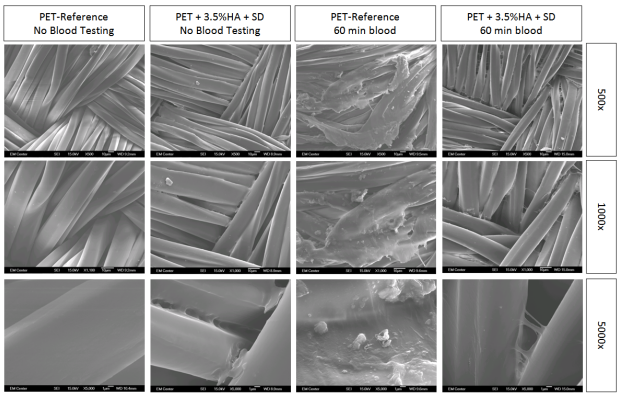
Methods: PET fabric (Style 6010) was purchased from BARD Peripheral Vascular OEM Products (Tempe, Arizona). The Dacron fabric was immersed in a silylated HA (silyl HA-CTA)/xylenes solution (0.5, 1.5 or 2.5% w/v) for 15 minutes and after drying the samples were immersed in a 2% (v/v) poly (hexamethylene diisocyanate) or HMDI xylenes solution (i.e. HA crosslinking solution) for 15 minutes, and then cured at 50°C in a vacuum oven for ≥3 hours. Samples were hydrolyzed to revert the silylated HA back to native HA and half of the samples were given an additional HA surface dip (1% HA w/v aqueous solution) wherein the additional HA was crosslinked to the HA molecules already entangled and crosslinked into the Dacron fabric[6]. Thermogravimetric analysis (TGA) was used to determine the HA content of treated samples. Bending stiffness was determined by ASTM D1388-08, and differential scanning calorimetry (ASTM D3418-03) was used to determine if the treatment altered the percent crystallinity of the PET. Preliminary thrombogenicity testing was performed by incubating 6µl of whole blood on the surface of each specimen for 60 minutes, and then fixing for imaging with a scanning electron microscope.

Results: As shown below, the samples treated with higher concentration silylated HA solutions had higher HA compositions, and the additional surface dip added substantially more HA to those samples. The samples treated with the two highest concentration solutions also exhibited significantly increased bending stiffness, but not due to an increase in crystallinity as determined by DSC (no significant differences between any treatment group and untreated PET). The samples treated with the two highest concentrations also showed reduced thrombogenicity relative to untreated PET.

Table 1: HA compositions. PET-T-0.5-D = 0.5HA% treatment solution and with additional surface dip (D).

Treatment Group	Bulk Weight % XL HA	Surface Weight % XL HA
PET-T-0.5	0.242 ± 0.02	n.a.
PET-T-1.5	0.973 ± 0.18	n.a.
PET-T-2.5	1.228 ± 0.07	n.a.
PET-T-0.5-D	1.260 ± 0.26	1.018 ± 0.002
PET-T-1.5-D	1.996 ± 0.13	1.023 ± 0.002
PET-T-2.5-D	3.510 ± 1.21	2.283 ± 0.012





Conclusions:

The PET samples with the higher HA compositions showed a higher bending stiffness, and reduced thrombogenicity. Future studies will quantify thrombus formation and platelet activation. While these preliminary results are promising, the durability of the enhancement needs to be investigated, as well as the propensity for the HA treatment to reduce *in vivo* calcification. For some applications additional treatments to prevent leakage will be investigated.

References: [1] Xue, L. J Vasc Surg 2003;37:472-80. [2] Heim, F. J Biomed Mater Res B Appl Biomater. 2010 92(1):68-77. [3] Heim F. J Heart Valve Dis. 2013, 22 (3); 361-367. [4] Kito H, J Biomed Mater Res. 1996;30:321-330. [5] Vyavahare N, J Biomed Mater Res. 1999;46:44-50. [6] Dean HC. Col. State Univ.; 2011;M.S. Thesis.