Polyether Urethane With Covalently Attached Di-Tert-Butylphenol and Cholesterol Resists Oxidative Degradation

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Introduction: Good mechanical properties and blood compatibility make polyurethanes frequently used components of cardiovascular implants. However, polyurethane vascular devices are subject to oxidation initiated surface degradation, which leads to cracking and contributes to device failure. Prior formulations by others to mitigate oxidative degradation involved a number of innovations including the development of polycarbonate soft segments, incorporation of silicone segments, and co-dissolving antioxidants in polyurethane solvent cast films. The present studies examined a novel strategy involving covalent attaching antioxidant moieties to the urethane nitrogens via bromo-alkylation reactions.

Previously we reported a bulk modification of polyether polyurethanes (Tecothane TT 1074A, Thermedics, Waltham, MA) using a chemical reaction that involved bromo-alkylation of the urethane nitrogens followed by reactive binding of thiol-containing cholesterol moieties to the active bromine residues. This novel cholesterol derivatized polyurethane demonstrated significantly enhanced endothelial cell retention under arterial and valvular levels of shear. However, endothelialization of polymeric surfaces remains to be optimized and in the present studies we investigated a novel modification of the bromo-alkylation chemical strategy just described in order to covalently attach the anti-oxidant, di-tert-butylphenol (DBP), to the urethane nitrogen groups to hypothetically promote resistance to oxidative degradation. We test herein the hypothesis that covalently attaching DBP via functionalization of urethane segments would result in resistance to oxidative attack.

Methods: 4-Mercapto-DBP was reactively combined with bromobutylated PU Tecothane TT 1074A with a net result (for Tecothane TT 1074A) in a series of studies of 3% to 21% of urethane sites modified with DBP. This modification was done alone (DBP-PU) or in a combination with cholesterol-modified polyurethane (DBP-PU-Chol), and changing the ratio of the two reacting thiols (4-mercapto-DBP and thiolated cholesterol) controlled the ratio between the two modifiers. NMR characterization confirmed the presence of DBP and/or cholesterol in the expected amounts. Modified polyurethane was solvent cast and stored at 0°C until use.

A series of comparative oxidative degradation studies involved H_2O_2-$CoCl_2$ exposure, for 15 days at 37°C, to cause accelerated oxidative degradation. Control films were exposed, for the duration of the study, to sterile water. At the conclusion of the study, films were washed with copious water and vacuum dried and stored in a desiccator at 0°C. The extent of degradation was assessed by attenuated total reflectance Fourier transformation infrared spectroscopy (FTIR), scanning electron microscopy (SEM), contact angle analysis, and uniaxial strain testing. These experiments compared PU, PU-DBP, PU-Chol, PU-Chol-DBP, and two commercially available medical grade polycarbonate polyurethanes that were not modified.

Results: The FTIR spectra showed minimal changes between the PU modified with DBP/Chol and water exposed controls. FTIR data further showed that both the Chol and DBP modification confirmed significant resistance to oxidative degradation as evident by the absence of an 1170 cm^{-1} FTIR spectral peak that is characteristically due to polyurethane oxidation and the SEM data. The combined formulation, PU-Chol-DBP gave the best results per this endpoint. Additional FTIR analysis of soft segment loss, as measured by 1110 cm^{-1} peak intensity, showed all modified polyurethane configurations retained 90% of their polyether soft segments. In contrast, FTIR spectral analysis confirmed that unmodified polyurethanes were extremely susceptible to oxidative degradation. Scanning electron microscopy confirmed the strong oxidation resistance of these formulations, demonstrating no major surface changes in any of the covalently modified PU's compared to the marked surface deformation seen in the control PU results. Uniaxial mechanical tests revealed that between 50% and 200% strain no significant differences in stress levels between PU and PU+/- DBP/Chol. All polyurethane configurations had a reduction in surface energy as a result of oxidation. The greatest differences in contact angle were seen in the PU-Chol samples. This loss of surface energy strongly suggests that the cholesterol modification was damaged as a result of oxidation. These studies also compared oxidation results with commercially available polycarbonate polyurethanes, known to resist oxidative degradation, Bionate and CarboSil, (Polymer Technology Group, Berkeley, CA). PU-DBP, and PU-DBP-Chol demonstrated equivalent or better oxidation resistance with these materials in terms of an absence of PU-degradation per FTIR and scanning electron microscopy assessment.

Conclusion: These data demonstrate the efficacy of preventing PU oxidative degradation by covalently attaching DBP and/or Chol via bromoalkylation to polyether urethanes.

Acknowledgement: This research was supported by RO1-HL 59730, T32-HL 07915, and the William J. Rashkind Endowment of the Children's Hospital of Philadelphia.