Hemocompatible Polymeric Coatings with Sulfonated Polyurethanes as Matrix for Sustained Nitric Oxide Release

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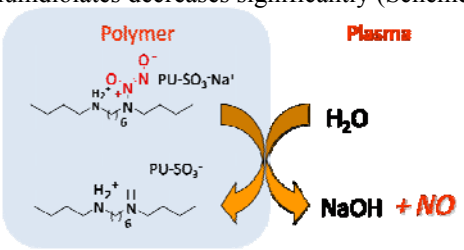
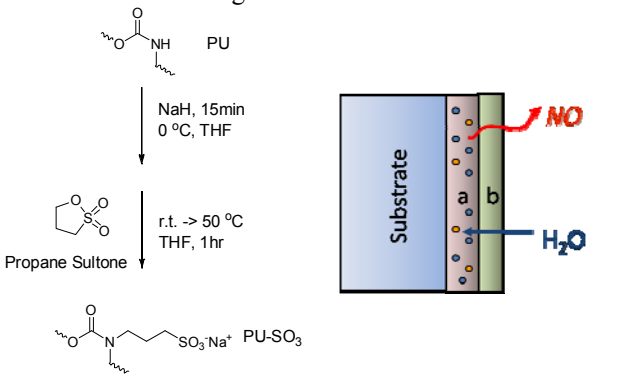
Statement of Purpose: Nitric oxide (NO) is a potent antiplatelet agent produced endogenously by endothelial and other cells. NO is also known to facilitate the migration and proliferation of endothelial cells (EC) while simultaneously inhibiting the growth of smooth muscle cells (SMC) (Jun HW Biomacromolecules 2005;10:838-844). A number of NO donor compounds have been studied that spontaneously decompose to release NO, and such molecules can potentially be used to create thromboresistant and anti-SMC proliferation polymeric coatings. Notably, diazeniumdiolates, which contain the $[N(O)NO]^-$ functional group, have been extensively examined for such applications. *In vivo* studies have shown that the use of these NO donors in polymer coatings provides enhanced thromboresistance for a variety of medical applications including vascular grafts (Batchelor MM. J Med Chem. 2003;46:5153-5161), intravascular sensors (Schoenfisch MH. Anal Chem. 2002;74:5937-5941), extracorporeal circuits (Zhang HP. J Am Chem Soc. 2003;125:5016-5024), etc. The decomposition of the intramolecular zwitterionic diazeniumdiolates is proton-driven, and as the pH of the environment within the polymer becomes more basic, the rate of decomposition to liberate NO decreases. Indeed, as water diffuses into the film, initiating NO release, secondary amine sites result. This basic microdomain environment within the polymer, in turn, slows further decomposition of the remaining diazeniumdiolates that could generate NO.

To overcome this problem, we have chemically tethered sulfonate groups onto the backbones of two commercially available biomedical grade polyether polyurethanes (Tecophilic® and Tecoflex®). The incorporated sulfonate groups provide anionic sites that can serve as counterions to the organic ammonium cations. In this way, the sodium cation and hydroxide ion can diffuse from the polymer matrix to the surrounding aqueous phase and NO release is maintained at a more constant rate until the total concentration of diazeniumdiolates decreases significantly (Scheme 1).



Scheme 1. Proton-driven decomposition of diamine diazeniumdiolates and buffering effect sulfonate groups in the polymer matrix.

Methods: Sulfonation of the polyurethanes (PUs) was described in a paper published by Cooper's group (Grasel TG. J. Biomed. Mater. Res. 1989;23:311-338) (Scheme 2). Diazeniumdiolated *N,N'*-dibutyl-1,6-hexanediamine ($DBHD/N_2O_2$) was synthesized as described previously (Batchelor MM. J Med Chem. 2003;46:5153-5161). A cocktail containing well-suspended $DBHD/N_2O_2$ in the THF solutions of $PU\text{-}SO_3$ was used to cast the NO releasing layer. DMAc/THF solution of PurSil™ was used to cast a top layer as a diffusion barrier to achieve controlled NO release (Scheme 2). Control coatings without NO release were made by only casting PurSil layer or by casting $PU\text{-}SO_3$ as the bottom layer and PurSil as the top layer ($PU\text{-}SO_3$/PurSil). NO release kinetics were measured at 37 °C in PBS (10 mM, pH 7.4) by NO analyzer (NOA™ 280, Sievers Instruments, Inc.) in a continuous monitoring mode.



Scheme 2. Synthesis of $PU\text{-}SO_3$ (Left) and bilayer NO release coatings (Right). b: $DBHD/N_2O_2$ doped $PU\text{-}SO_3$ NO release layer; c: PurSil top layer.

Results: Tecophilic® and Tecoflex® were sulfonated via the reaction between the deprotonated urethane nitrogen atom and propane sultone. The SO_3^- concentration is ca. 500 μmol/g in Tecophilic (SP-93A-100) and ca. 400 μmol/g in Tecoflex (PU-60D-20). The sulfonate groups on the polymer backbones were able to buffer the pH change within the polymer matrix, allowing NO to be released stochimetrically from $DBHD/N_2O_2$ (>93%). The NO flux could sustain for at least 23 days at a constant flux of ca. 1×10^{-10} mol·cm^{-2}·min^{-1}, comparable to a healthy endothelium (Vaughn MW. Am J Physiol. 1998;274:H2163-H2176).

Conclusions: Two biomedical grade polyether PUs were successfully sulfonated. Sustained and stoichimetric NO release was achieved by using such sulfonated polymers as the matrix for diazeniumdiolated NO donors. Future research will focus on examining the effects of NO release on vascular endothelial and smooth muscle cell proliferation and differentiation as well as on the anti-platelet activation/adhesion/aggregation properties of the new coatings.