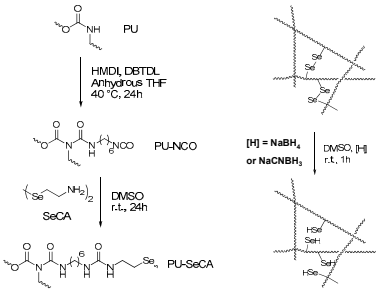
Selenium-Derivatized Polyurethanes – Potential Nitric Oxide Generating Coatings for Stents and Other Biomedical Devices

Wu, Biyun, Mark E. Meyerhoff.
Department of Chemistry, The University of Michigan, Ann Arbor, MI.

Statement of Purpose: Placement of stents by balloon angioplasty represents a major advance in the treatment of obstructive coronary artery diseases. Many drug-eluting stents have emerged as a potential solution for this restenosis problem. However, recent findings have suggested an increased risk of late stent thrombosis associated with these drug-eluting stents.[1] Similar thrombosis issues plague other biomedical devices in contact with blood (e.g., grafts, catheters, etc.).

Nitric oxide (NO), a small molecule that continuously diffuses from the surface of a healthy endothelium to the adjacent blood stream, contributes significantly to the thromboresistance of blood vessels.[2] Recently, some organoselenium (RSe)-derivatized polymers, such as RSe-cellulose and RSe-polyethyleneimine, have been synthesized and shown to generate NO from endogenous S-nitrosothiols species (RSNOs) present in the blood stream [3]

Herein, we report the first RSe-derivatized medical-grade polyurethanes (Tecophilic® and Tecoflex®) that are capable of generating NO from a large RSNO reservoir present within blood to generate continuous surface flux of NO at the polymer/blood interface. Such polymers with prolonged NO-generating ability can potentially be employed as coatings for stents or other intravascular biomedical devices.



Scheme 1. Synthesis of PU-SeH.

Methods: The urethane groups on the Tecophilic and Tecoflex backbones were used to couple with hexamethylene diisocyanate (HMDI) through an allophanate reaction in the presence of a dibutyltin dilaurate (DBTDL) catalyst.[4] The resulting polymer with pendant free isocyanate groups was then reacted with amine groups of selenium cystamine (SeCA),[3] a small diselenide compound, and then reduced with $NaBH_4$ or $NaCNBH_3$ to remove the uncoupled halves of the SeCA molecules (Scheme 1).

FTIR spectra were collected on a Perkin-Elmer BX FT-IR system to characterize the modification of the polymers. The Se concentrations in the polymers were quantified by a Finnigan Element ICP-mass spectrometer. NO fluxes from polymer coatings in the presence of RSNO species were measured by a chemiluminescence NO analyzer (NOA™ 280, Sievers Instruments, Inc.).

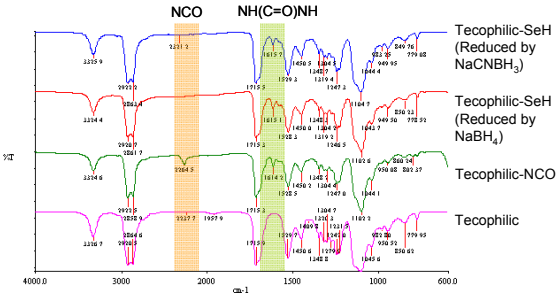


Figure 1. IR spectra of derivatized PUs.

Results: The successful modification of PUs was verified by IR (Figure 1). Elemental analysis showed that the concentrations of Se in the Se-derivatized PUs are approx. 100-150 µmol/g (Table 1). NOA measurements show that RSNOs can be catalytically decomposed to generate NO in the presence of PU-Se (Figure 2).

Table 1. Se concentration in various PU derivatives.

Polymer	Tecophilic-SeCA (unreduced)	Tecophilic-SeH (reduced w/ $NaBH_4$)	Tecophilic-SeH (reduced w/ $NaCNBH_3$)	Tecoflex-SeCA (unreduced)
Se Conc. (µmol/g)	247 ± 12	105 ± 5	157 ± 8	99 ± 5

*Se concentrations are below the detection limit in control PUs.

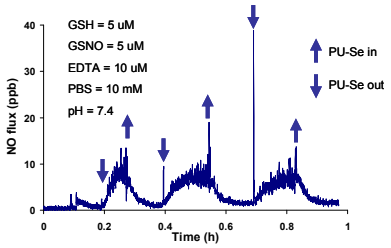


Figure 2. Representative NO generation from Tecophilic-SeH in the presence of GSH and GSNO at 25 °C

Conclusions: Selenium-derivatized medical-grade polyurethanes have been prepared. Such NO generating materials can be used as polymeric coatings for drug-eluting stents and can potentially reduce the occurrence of late stent thrombosis as well as thrombosis on other intravascular biomedical devices.

References:

1) Shuchman, M. *N. Engl. J. Med.* **2006**, 355, 1949.
2) Feelisch, M., Stamler, J.S. *Methods in Nitric Oxide Research*. West Sussex: John Willey and Sons Ltd.; **1996**.
3) Cha, W., Meyerhoff, M.E. *Biomaterials* **2007**, 28, 19.
4) Wu, B., Gerlitz, B., Grinnell, B.W., Meyerhoff, M.E. *Biomaterials* **2007**, 28, 4047.