Controlled Nitric Oxide Releasing Dendronized Poly(vinyl chloride) for Improving Biocompatibility of Implantable Devices

Sean Hopkins, Megan Frost
Michigan Technological University

Statement of Purpose: There is huge potential to improve patient treatment by obtaining physiological measurements of important analytes (i.e., PO_2, PCO_2, pH, glucose, etc.) in real-time data using implantable sensors. Although miniaturized sensors have existed for several decades, most of this technology never becomes widely used due to unreliable analytical data from implanted sensors. This is due primarily to the biological response from the body when a foreign material is introduced to that environment. A possible option to overcome this complication with blood contacting devices is through the utilization of nitric oxide (NO). NO is a free radical gas that is produced in our body that has a variety of important functions. A specific example demonstrating the importance of NO is seen in endothelial cells that line our vasculature where NO is produced continuously at an estimated flux of 1 x 10^{-10} mol cm^{-2} min^{-1}, which prevents platelets from becoming activated and maintains vascular tone [1]. The objective of this research is to develop a high capacity, controlled NO releasing material by covalently linking hyperbranched polyamidoamine (HPAMAM) molecules to the backbone of poly (vinyl chloride) (PVC) to create a dendronized polymer with high functionality. The structure is then further modified to release NO either catalytically or through hemolytic cleavage using light.

Methods: PVC (M_w = 233,000 g mol^{-1}, M_n = 99,000 g mol^{-1}) was used as the base polymer to be modified. The synthesis of HPAMAM was done through the Michael Addition reaction between methyl acrylate and ethylenediamine. Entire HPAMAM molecules can then be directly grafted to the back of the PVC or directly grown on PVC using the same Michael Addition. Once covalently linked onto the backbone of the PVC chains, the resulting dendronized PVC has the capability of containing a large quantity of primary amine sites, where each primary amine is able to be derivatized into an NO donor site. The NO donor used is *N*-acetyl-*D*-penicillamine, which can be nitrosated after reacting with a primary amine site to create *S*-nitroso- *N*-acetylpenicillamine (SNAP). To demonstrate the versatility of the synthesized dendronized PVC, a light-emitting diode (LED) with a 110 ohm resistor variable power supply was used to control the light emitted from the LED which thereby controlled the level of NO released by the functionalized PVC.

Results: The synthesis procedure of creating HPAMAM was successfully developed and the structure of HPAMAM was verified through ^1H NMR spectroscopy. ATTO-TAG™ FQ Amine-Derivatization testing was also done to the synthesized polymer to show the amount of primary amine sites on the backbone of the polymer as the branching of the HPAMAM progressed. The dendronized PVC was created by doing two alternate methods of attaching HPAMAM to the backbone of PVC. Both synthetic procedures resulted in a polymer that was able to release a large amount of controlled NO at varying light intensities used to trigger NO release as shown in figure 1. Growing HPAMAM directly onto the PVC backbone allows better control on what exact structure of the pendant HPAMAM is obtained.

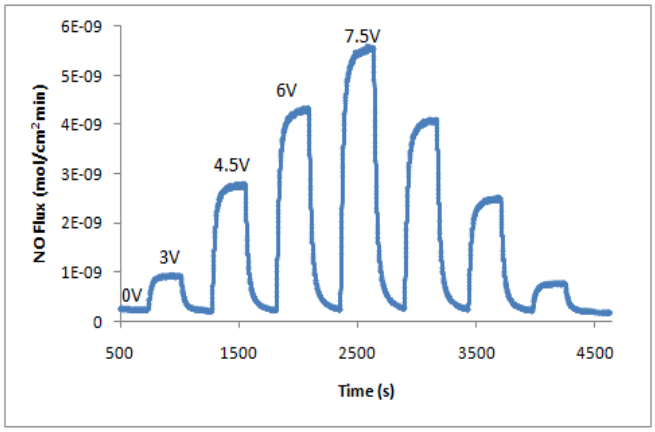

Figure 1 – NO release from dendronized SNAP PVC films with a diameter of 5.5 mm and average thickness of 0.10 mm.

Conclusions: With polymeric coatings that are able to demonstrate controlled NO release, implantable blood contacting devices would be able to inhibit platelet adhesion and prevent fibrin clots formation. The next step is to demonstrate exactly how long the coatings would be able to emit NO at the same level as vascular endothelial cells and to optimize storage and processing conditions.

References: [1] Frost, M. et. al. *Biomaterials*, 2004, 26, 1685-1693.