Synthesis and Characterization of Poly (triethylene glycol methyl acrylate-*co*-α-tocopheryl acrylate): a Water Soluble Antioxidant Polymer Derivative to Enable Localized Neuroprotection

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Statement of Purpose: Implantable microelectrode arrays (MEAs) hold enormous hope for individuals with sensory and/or motor deficits. However, long-term functioning of MEAs remains a critical hurdle.[1] Besides extensively studied strategies of mitigating neuroinflammation, protecting neurons from oxidative stress, which is the other key mechanism underlying neuronal death, could further improve functional reliability of MEAs. The objective of this study was to synthesize an antioxidant polymer derivative that can be delivered to the neural tissue around the implant, and present a pharmacological depot to combat the injurious oxidative stress. This report summarizes the synthesis, characterization, controllable surface deposition, and cytotoxicity of this derivative.

Methods: A common antioxidant α-tocopherol (vitamin E, Ve) was selected for this study. The antioxidant polymer derivative (PVT) was synthesized using monomers of triethylene glycol methyl acrylate (TEGMA), and α-tocopheryl acrylate (VeAc), a synthetic derivative of Ve. Chemical composition of the PVT polymer was characterized with ^{1}H NMR and UV-Vis spectroscopy. To demonstrate that the polymer can be integrated with the MEAs in a controllable fashion, a layer-by-layer (LBL) approach based on hydrogen bonding was applied. Using silicon substrates to represent the MEA, an antioxidant containing film was prepared on the surface by alternating incubation of the substrates at pH = 3 in solutions of antioxidant derivative (PVT) and polyacrylic acid (or tannic acid). The thickness of the film was characterized by ellipsometer. Quartz crystal microbalance (QCM) was further used to monitor the deposition process. Cytotoxicity of PVT was studied on primary cortical neuron using an MTT assay.

Results: Structure of the antioxidant polymer derivative was shown in Figure 1. The drug loading capacity can be achieved by adjusting the feeding ratio of monomers. In this study, two derivatives with different compositions of Ve were synthesized. The weight percentages of Ve for the two derivatives were found to be 7% and 14%, respectively, based on the results of ^{1}H NMR. While Ve is insoluble in water, the derivative was soluble in water at 3.1 mg/mL (equivalent to 500 μM Ve), which dramatically increased the solubility of Ve in water for potential therapeutic effect.

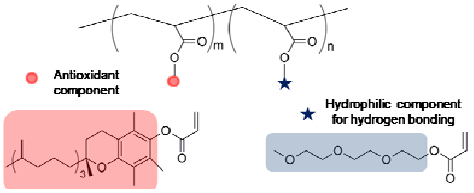

Figure 1. Structure of the antioxidant polymer derivative PVT.

The rationale of using TEGMA is two-fold, (1) to improve water solubility of the polymer, and (2) to enable LBL assembly of the polymer with polyacrylic acid (PAA) or tannic acid (TA) based on hydrogen bonding with the pendant ethylene glycol unit. PAA was used to allow multilayer films dissociation at physiological pH. Furthermore, TA was chosen to form stable LBL films with PVT due to a high pKa value of TA,[2] and the film could delaminate from the surface in vivo and remain as an antioxidant depot at the implant-tissue interface (Figure 2). Ellipsometric measurement showed that 8 bilayers of PAA/PVT and TA/PVT were 277 nm and 114 nm thick, respectively.

Figure 2. Scheme of engineered layer composition on implant.

Details of the multilayer growth were further studied using QCM. Figure 3 showed that layer deposition on the gold crystal resulted in a gradual decrease of resonance frequency. The QCM data revealed that each PVT layer deposition corresponds to 4 μg/cm^2 of PVT. Furthermore, the PVT/PAA layers quickly disintegrated (within 1 min) upon exposure to physiological buffer (pH = 7.4) at 250 min, while the PVT/TA combination remained stable under the same condition. In vitro study showed the PVT polymer is not cytotoxic to neurons at 500 μM (equivalent to Ve).

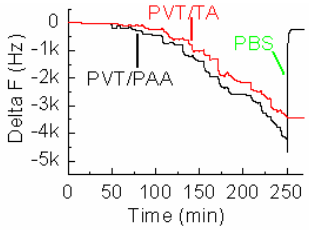

Figure 3. QCM data of LBL deposition of $(PVT/TA)_8$ and $(PVT/PAA)_8$.

Conclusions: A new water soluble and biocompatible antioxidant polymer derivative was synthesized and can be applied to neural implants using the versatile LBL process. By rationally engineering the layer composition, one can potentially achieve sustained localized neuroprotection. Ongoing study includes the therapeutic antioxidative effect of the polymer PVT using primary neurons.

References:

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