In vitro characterization of highly porous poly-L-lactic acid coatings for subcutaneously implantable glucose sensors

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Introduction: The long-term reliability of implantable glucose sensors is hindered by wound healing and the resulting membrane biofouling foreign body capsule formation. The overall effect of the foreign body response is impedance of glucose perfusion and diffusion to the sensor surface, thus compromising the reliability of chronically implanted sensors. Textured implants with open-architecture pore structures result in thinner and less dense foreign body capsule formation and more blood vessel formation adjacent to the implant than solid, smooth implants. [1,2,3] We propose that textured coating placed at the tip of glucose sensors will improve their in vivo performance by creating a more desirable sensing environment in the tissue that encapsulates the sensor.

Highly porous tubes of poly-L-lactic acid (PLLA) were fabricated on wire mandrels using ammonium bicarbonate as the gas foaming salt. The porous tubes were removed, slipped over the sensing tip of glucose sensors and secured with medical grade epoxy. Tubes were examined for pore size diameter, % porosity and cytotoxicity. Soaking studies were used to assess polymer degradation and rates of hydration. In vitro testing against glucose standards showed that the porous tubes minimally affected sensor accuracy and response rate.

Methods: PLLA (Mw 300 000) pellets, were dissolved in dichloromethane overnight. Ammonium bicarbonate (NH_4HCO_3) was manually stirred into the dissolved polymer solution to form a polymer slurry.[4] NH_4HCO_3 particulate diameters ranged from 50-75um for "small" pore tubes and from 250-425 um for "large" pore tubes.

Wire mandrels were dipped into the NH_4HCO_3 doped polymer slurry, followed by immersion into hot water to leach out the salt particulates and evolve gaseous ammonium and CO_2, creating highly interconnecting porous tubes. Porous tubes were removed from mandrels, slide over Medtronic MiniMed SOF-SENSOR™ glucose sensors and secured to the sensor shaft using medical grade epoxy.

ISO 10993-5 guidelines were followed to evaluate porous tube and epoxy cytotoxicity. Environmental scanning electron microscopy (ESEM) was used to monitor changes in pore morphology and tube thickness over 6 weeks soaking in phosphate buffered saline. Liquid displacement was used to calculate % porosity and apparent density of the tubes. Diffusion lag times associated with the porous tubes were evaluated by challenging bare and porous PLLA coated sensors to step changes in glucose concentrations ranging from 0 to 400mg/dL glucose in unstirred phosphate buffered saline at 37^0C.

Results/Discussion: Highly porous PLLA tubes for glucose sensors were successfully fabricated using NH_4HCO_3 as the gas foaming/particulate leaching agent.

Porous PLLA tubes and epoxy are non-cytotoxic. The "small" pore tubes had 91% porosity, apparent density of 0.11 g/cm^3; "large" pore tubes had 86% porosity, apparent density of 0.15 g/cm^3.

Based on ESEM images, no appreciable degradation was observed, for both tubing thickness and pore morphology. Polymer hydration slightly reduced pore diameter in the tube lumen while increased pore diameter on the tube exterior. The "large" pore tubes were 12 fold thicker than the "small" pore tubes, to accommodate for the larger NH_4HCO_3 particulates. The additional thickness contributed to the extra 18 hours required to fully hydrate the polymer coating and the increased diffusion lag time in sensor response (Figure 1). No difference in sensor response to challenges from 0 to 400mg/dL glucose solution was noticed between uncoated sensors and sensors coated with the "small" pore, thin tubes (Figure 1).

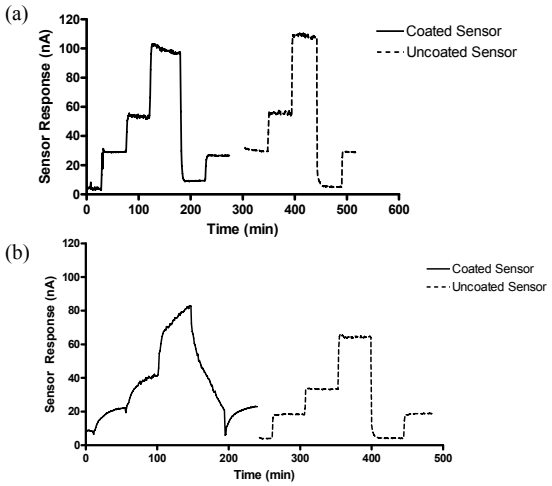

Figure 1 (a) Response of sensor with and without (a) "small pore" tube (b) "large pore" tube. (representative of collected data, n=12)

Conclusions and future work: PLLA tubes maintained their porous structure after 6 weeks in PBS. While thin, porous tubes did not affect in vitro sensor performance, diffusion lag time significantly increased with the thicker tubes, retarding sensor response to glucose challenges. In future work, sensors with porous tubes will be implanted into the epididymal fat pads of rats. The porous tubes are expected to induce vascularization. Improved vascularity may improve sensor longevity and sensitivity compared to uncoated sensors.

References:

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