Development of a Porous Poly-L-lactic Acid Dexamethasone Releasing Sleeve for Implantable Glucose Sensors

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Statement of Purpose: Type I diabetes is a chronic condition marked by high glucose levels in the blood. It affects millions of patients each year and is caused by the insufficient production of insulin by pancreatic cells. One of the most promising treatments for this disease is the use of closed loop insulin pumps that continuously monitor blood glucose levels and deliver insulin at adequate rates. Unfortunately, the long-term use of such devices has been hindered by untimely failure, due to an undesirable foreign body reaction (FBR) to glucose biosensors[1]. The formation of a fibrous capsule which is not associated nor supplied with blood vessels leads to a loss of signal at the sensor tip. Users will then have to repeatedly change tips to allow for optimal signal recordings and appropriate insulin delivery. The lifetime of these pumps can be extended by modulating the FBR by applying strategies that prevent biofouling, diminish inflammation and promote angiogenesis.

As part of a multifaceted approach, we have developed a porous dexamethasone (DX) releasing poly-L-lactic acid (PLLA) sleeve. Sleeves were then characterized by Environmental Scanning Microscopy and the DX release was evaluated *in vitro* over a period of 13 days by High Performance Liquid Chromatography (HPLC).

Methods: DX-Free porous sleeves were prepared according to methods described by Koschwanez et al[2]. In short, 0.1 g of PLLA pellets were dissolved overnight at room temperature in 2 ml of dichloromethane (DCM). Previously milled and sieved ammonium bicarbonate porogens (50 -70 μm in size) were added to the polymer solution by manual stirring until a homogenous polymer slurry was obtained. Finally, 1 ml of DCM was added to the polymer slurry and stirred.

DX-Containing samples were prepared following the procedure outlined above. DX was first dissolved in ethanol and then added to the polymer slurry to obtain three different final DX concentrations: 10, 20 and 30 mg/ml.

Copper wire coated with polyurethane/nylon (AWG 22; maximum outer diameter 0.69 mm) mandrels were then dipped into each the polymer slurry to a length of ~1.7 cm. Samples were then submerged into a 90°C DI water for 5 min to drive pore formation. The mandrels were then submerged in 4 °C DI water for 20 min to quench the reaction, removed, air-dried for 2–4 h, and stored in a desiccator.

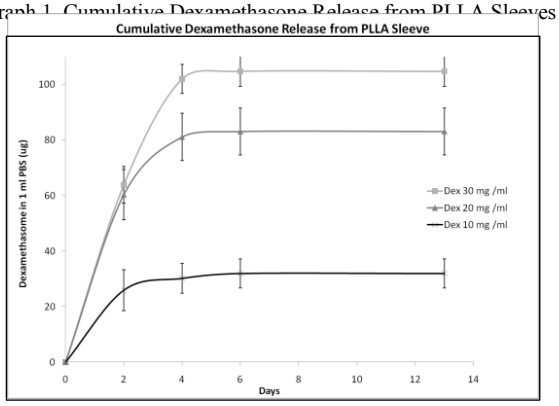
Porogen size, inside and outside pore size, thickness and degradation of the sleeves were assessed by ESEM.

Sleeves were then placed into a microcentrifuge tube containing 1 ml of Phosphate Buffered Saline (PBS). Tubes were then incubated at 37 °C. Every two days samples were collected by removal and replacement of the PBS. Samples were gathered over a 14 day period.

DX release from samples was analyzed by HPLC. The isocratic mobile phase consisted of 42% acetonitrile and 58% water. Each sample was detected using a UV detector at 246 nm. Retention time of DX was 3.7 min [1].

Results: Size of the ammonium bicarbonate leachables showed to be related to final pore size of 62.02 ±15.75 μm. Sleeve thickness was 57.85 ± 17.75 μm. Evaluation after 15 days in PBS showed that porous structure of the sleeves was maintained. DX incorporation into the sleeves did not affect these parameters significantly.

Graph 1. Cumulative Dexamethasone Release from PLLA Sleeves



HPLC analysis showed that sleeves could be loaded with 70% efficiency at all concentrations. As expected, sleeves prepared with higher DX concentration slurries showed a higher net release at the end of the 13 day period. We also observed a burst release of DX, with 90% being released within the first 4 days in all groups. Cumulative Release profiles of DX loaded PLLA sleeves are shown in Graph 1.

Conclusions: Porous structures have been successfully employed for the modulation of the later stages of the FBR. The described salt leaching method yielded an even macroporous structure. This result is consistent with the finding that pore size can be controlled by incorporation of salt particles of a desirable size. We expect that this porous coating will decrease fibrous capsule formation and promote angiogenesis following sensor implantation. Moreover, early and localized release of DX will have an anti-inflammatory effect during the FBR. Unfortunately, the maximum cumulative DX release of our sleeves (104 μg) is almost five times under the reported therapeutic DX dosage that prevents an inflammatory response to sensor implantation[3]. Approaches that will increase DX loading (changing solvent system) and will better control the release (DX microencapsulation) should be explored. Finally, the use of a porous non-degradable dexamethasone releasing sleeve is a promising approach for improving the wound healing response at the tissue-sensor interface.

References:

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2. Koschwanez HE. J Biomed Mat Res A. 2008; 87A:792
3. T. Hickey. J Biomed Mat Res 2. 2002; 61:180-87