Electrospun Fiber Matrices for Implantable Glucose Sensors

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Statement of Purpose: Continuous monitoring of physiological glucose concentrations using implantable enzyme-based electrochemical sensors is required to improve clinical measurements and control of diabetes. Even for the few commercially available implantable glucose sensors on the market, sensor failure caused by the inflammatory response and bacterial infection remains a challenge for their successful implantation. The development of controllable nitric oxide (NO) releasing membranes with porous features may: (1) promote tissue integration; (2) mitigate the foreign body response; and (3) improve *in vivo* sensor performance.[1,2] Herein, the development of NO-releasing electrospun fiber matrices as sensor membranes for implantable glucose sensors will be introduced.

Methods: Tecoflex SG-80A (TPU, 12 wt%) was dissolved in a 3:1 mixture of tetrahydrofuran (THF)/ *N,N'*-dimethylformamide (DMF), mixed with a suspension of NO-releasing silica particles in methanol, and placed in a syringe fitted with a 22G blunt tipped needle (0.508 mm ID) atop a syringe pump. An aluminum foil collector and platinum electrode (3 mm dia.) were positioned 10 cm from the tip of the needle and grounded. Electrospinning was performed at an applied voltage of 15 kV under two different flow rates, 15 and 50 μL/min[3]. The resulting electrospun fiber matrix was evaluated in terms of: (1) permeability of hydrogen peroxide (H_2O_2) and oxygen (O_2) by electrochemical methods; (2) film thickness using profilometry; (3) surface morphology and fiber diameter by Environmental Scanning Electron Microscope (ESEM); (4) glucose sensor performances; and, (5) NO release using a chemiluminesence NO Analyzer (NOA). Particle leaching was studied using a Dynamic Light Scattering (DLS).

Results: Due to the general biocompatibility of polyurethanes often employed as glucose sensor membranes, TPU was selected for initial study as membrane system. Fiber matrix structure was investigated as a function of (1) polymer solution concentration; (2) feed rate of polymer solution; and, (3) thickness. The ensuing non-woven mat had random open-pore features (Figure 1). Due to the increased porosity of optimized electrospun fiber matrices, the permeability of H_2O_2 and O_2 were significantly enhanced compared to standard drop-casting techniques, when normalized by thickness of film (Table 1). TPU fibers were next electrospun onto platinum electrodes pre-coated with glucose oxidase sol-gel layer. The resulting glucose sensors were characterized by glucose sensitivity and response time ($t_{95\%}$) of 0.92±0.18 μA/mM and 172.3±51.0 sec, respectively, whereas drop-cast films had no response to glucose. As introducing NO-releasing capabilities, *S*-nitrosothiol silica particles doped electrospun fiber matrix (16.7 wt% particles/fiber matrix) released NO total amount of 0.475 μmol·mg^{-1} over one week. The incorporation of diazeniumdiolate or *S*-nitrosothiol modified silica nano-particles randomly dispersed into this fibrous matrix will be discussed as a means to enhance tissue biocompatibility.

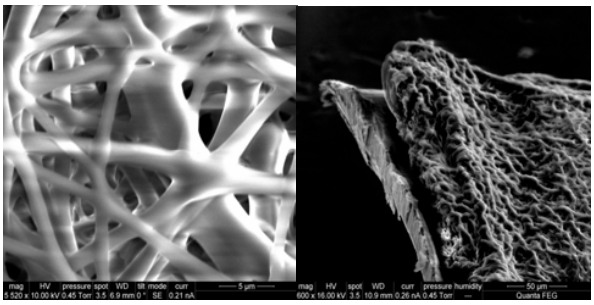

Figure 1. ESEM image of electrospun TPU fiber matrix (12 wt%).

Table 1. Properties of electrospun fiber matrix as a candidate model of glucose sensor membrane.

Glucose sensor membrane	Electrospun 12 wt% TPU	Drop cast 6 wt% TPU
Permeability of O_2*	0.18	N/A
Permeability of H_2O_2*	0.53	1.49×10^{-4}
Film thickness (μm)	44.00±6.02	53.48
Fiber diameter (nm)	1525.9±647.5	N/A

* Permeability is electrochemically determined by peak current ratio of film coated electrode (ΔI_x) and bare platinum electrode (ΔI_b) response at; (1) 0.788 mM H_2O_2; (2) air saturated PBS (oxygen)

The NO-releasing silica particles embedded within fiber matrices coated glucose sensor will be presented in terms of: (1) Glucose sensor performances (e.g., sensitivity, response time, selectivity, and dynamic range); (2) NO-releasing; and, (3) silica particle leaching.

Conclusions: The electrospun polyurethane sensor membrane presented enhanced bench-top sensor performance due to the inherent porosity of the electrospun coatings. Current studies aim to investigate combining this strategy with NO release. Our previous work suggest that the introduction of NO-releasing capabilities will mitigate foreign body response, while maintaining required in vivo glucose sensor performance[4].

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References: (1) Shin, J. H. et al., *Anal. Chem.* **2004**, *76*, 4543-4549. (2) Huang, Z.-M. et al., *Compos. Sci. Technol.* **2003**, *63*, 2223-2253. (3) Ren, G. et al., *React. Funct. Polym.* **2006**, *66*, 1559-1564. (4) Hetrick, E. M. et al., *Biomaterials* **2007**, *28*, 4571-4580.