FEM Optimization of Sustained VEGF Delivery for Angiogenesis Applications

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Statement of Purpose: Large bioengineered organs such as the heart and kidney need immediate perfusion by the host vascular network to avoid ischemia, support implant survival, and prevent implant failure. Vascularization of new bioengineered-tissues can be stimulated by porous scaffold design and vascular growth factors. However, comprehensive vascularization of thick tissues in vitro remains a formidable challenge. In sharp contrast, luminal hydrogel microchannels providing a biological active concentration of Vascular Endothelial Growth Factor (VEGF) can be used to promote angiogenesis [1]. In this study we compare the microenvironment generated in the lumen of a single channel and multiluminal hydrogel scaffolds for acute and controlled release of VEGF.

Methods: A finite element method (FEM) based model implemented in Comsol Multiphysics using fully scaled geometries for a description of the microenvironment generated in the lumen of a single channel and multiluminal hydrogel scaffolds for acute and controlled release of VEGF. The single channel scaffold consisted of a 1676.4 (μm) channel with an initial load of 100 (ng/ml) of VEGF, the channel walls were made out of polyurethane therefore they were considered as impermeable for the simulation. The multiluminal hydrogel scaffold consisted of seven agarose microchannels of 250 (μm) in diameter. Diffusivity of VEGF in agarose and extracellular matrix were modeled based on literature values taking in consideration the molecular weight of the released molecule and the pore size of the hydrogel. The initial concentration value for acute release was 100 (ng/ml) of VEGF. The simulation was based on the convection diffusion equation:

$$\frac{\partial c_i}{\partial t} + \nabla \cdot (-D_i \nabla c_i + c_i \mathbf{u}) = R_i$$

For the controlled release the multiluminal hydrogel scaffold was loaded with .0625 (mg) of PLGA (75/25) microparticles with a concentration of 184.42 (ng/ml) of VEGF. The release of VEGF from the microparticles was measured by ELISA and the results were utilized to generate a function of release over time that was used to model the microparticles as concentration sources of VEGF. The simulation was run for 30 days with a time step of one 1 hour. In order to decrease computation time only one of the microchannels in the multiluminal scaffolds were simulated.

Results: The single channel scaffold with impermeable walls simulating acute release showed a rapid decrease in the average concentration inside the lumen going from 100 to 7.94 E -7 (ng/ml) over a period of one day. The multiluminal scaffold showing acute released showed a linear decrease of concentration in the lumen over a period of 24 hours going from 100 to 19.87 (ng/ml), but then a much slower rate of decrease from hour 25 to day 30 decreasing only .122 (ng/ml) over time period. Finally the controlled released multiluminal scaffold showed an increase in concentration over time showing a significant increase until day 20, when a linear increase was observed going from 4.61 to 51.23(ng/ml) at day 30.

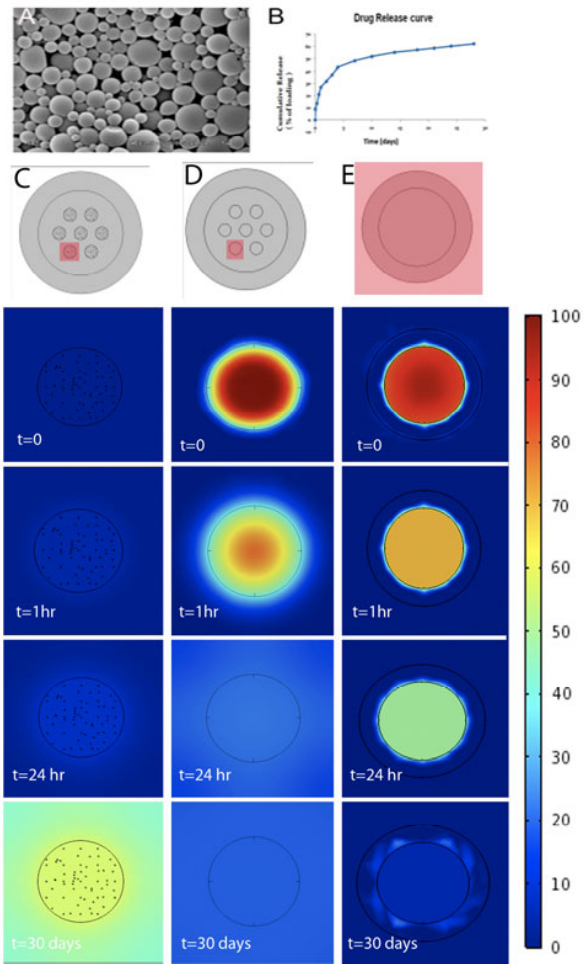

Fig 1. Comparison of lumen concentration of VEGF. A) SEM picture showing morphology of VEGF-encapsulated PLGA microspheres. B) Continued released of VEGF was confirmed by ELISA (mean ± SD; n=4). C) Multiluminal Scaffold with controlled release using PLGA microparticles. Area modeled is highlighted. Concentration over t=0, t=1 hr, t=24 hr and t=30 days are shown. D) Multiluminal scaffold with initial concentration of VEGF. E) Single channel scaffold with initial concentration of VEGF

Conclusions: The simulation help in the prediction of the change over time of the microenvironment in the lumen of the different scaffolds tested. These findings will help in the design and development of a scaffold capable of providing a desired microenvironment taking advantage of combination of acute and controlled release of VEGF to stimulate angiogenesis.

References:

[1] (Nillesen, S. Biomaterials. 2007; 28:1123-1131.)