Release Kinetics of FITC-Dextran Particles from Bioerodible Multi-layered Fibrin Matrices: A Study of Peripheral and Local Diffusion

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Statement of Purpose: Fibrin is a natural biopolymer derived from the coagulating reaction between fibrinogen and thrombin. Biochemically, fibrin has been shown to promote cell growth and proliferation in a variety of cell model systems[1]. Mechanically, the open-network structure of the fibrin matrix provides for structural support as well as the uptake and release of nutrients and waste products. The use of fibrin as encapsulation materials for microparticles such as growth factors and drug for delivery has gained interest in recent years; however, the relationship between the fibrin structure and diffusion of particles have yet to be described. In this study, we've compared the diffusivity of neutrally charged FITC-dextran particles from multi-layered fibrin matrices of varying compositions. The diffusion of the particles was measured peripherally (from matrix to liquid environment) as well as locally (from matrix to matrix). The effect of bioerosion by plasmin on diffusivity was also investigated.

Methods: For the peripheral diffusion study, FITC-dextran (3000 kDa) were incorporated into fibrin matrices comprising of different formulations of fibrinogen and thrombin (Tisseel®, Baxter Bioscience). For multi-layered systems, an external fibrin matrix was layered over a FITC-loaded fibrin matrix, creating a bi-layer format. The FITC-loaded matrices were formed in 24-well plates and submerged in serum free DMEM. At various time points, the fluorescent optical density was measured. For the local diffusion study, FITC-loaded fibrin matrices (plus or minus 0.1 ug/ml of plasmin) were embedded in an external fibrin matrix of a fixed composition. The local diffusion of the FITC-dextran particles was measured using a novel spectraphotometric using a plate reader.

Results: Peripheral diffusion of FITC-dextran particles from single and multi-layer fibrin matrices correlated to fibrin matrix compositions of fibrinogen and thrombin. Additional fibrin layer slowed down the rate of FITC-dextran particle release into the external medium (Figure 1). Local diffusion of FITC-dextran particles from fibrin matrices embedded in an external fibrin matrix also showed the dependent on fibrin composition. In bioerodible system with plasmin, the diffusion of FITC-dextran particles was delayed with increasing thrombin concentration (Figure 2).

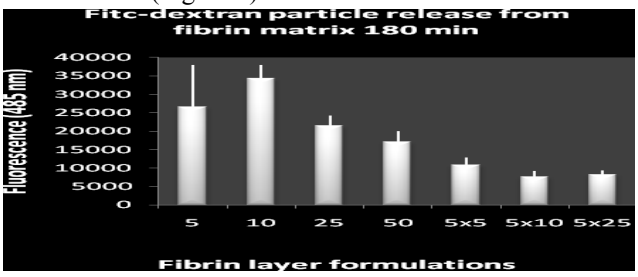

Figure 1

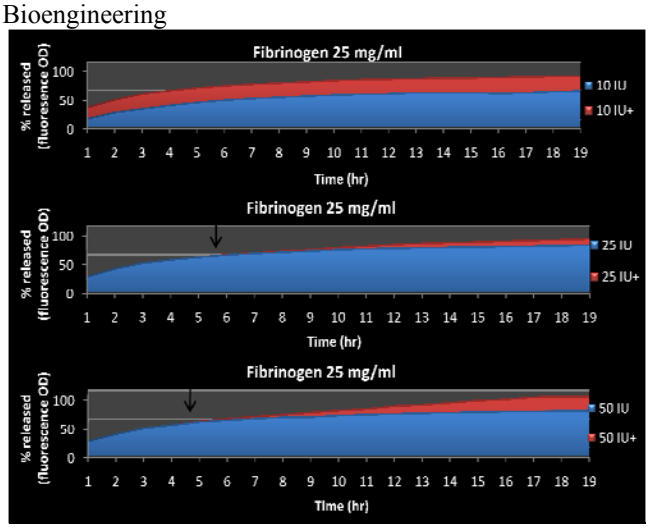

Figure 2

Conclusions: We have previously shown that fibrin composition has significant effects on the mechanical strength of the fibrin matrices.[2] In this study, we've looked at how fibrin composition could mediate the diffusivity of FITC-dextran particles through the porous network of the fibrin matrices. Peripheral diffusion of the particles from the fibrin matrix to a liquid medium may provide insight into how growth factors or drugs may be controlled by changing the fibrin composition or by multi-layering in other fibrin matrices; which could create an additional external fibrin network barrier or network tortuosity that the molecules must travel through. The local diffusion study showed how particles moved from one fibrin matrix into another, and that by changing the fibrin composition, the diffusion of particles could be modulated. Yet, another method to modulate the release of particles from fibrin matrices is the addition of fibrinolytic protease such as plasmin, which could increase the diffusion of embedded particles due to the bulk degradation of the fibrin structure. Understanding the relationship between fibrin composition and the diffusion kinetics of microparticles from the fibrin structures could enable us to design optimal fibrin-based product that are optimized for the controlled delivery of therapeutic such as growth factors or drugs.

References

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Acknowledgements

Funding was provided by NIH R01 AR053250-01A1