Impact of Artificial Plaque Composition on Drug Transport

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Statement of Purpose: Drug-eluting stent (DES) implantation is a common treatment for atherosclerosis. The safety and efficacy of these devices will depend on the uptake and distribution of drug into the vessel wall. It is established that the composition of atherosclerotic vessels can vary dramatically with patients’ age and gender. Although it is widely accepted that the composition of atherosclerotic vessels can vary dramatically from patient to patient, these factors are not considered in the design of DES devices, i.e. all patients are treated with the same device. This is largely because existing data on the impact of these variations on drug transport properties, such as diffusivity and solubility, are quite limited. To facilitate in vitro exploration of the impact of plaque composition on drug transport, we have developed artificial tissues that better emulate the composition of atherosclerotic plaque compared with previous efforts. Based on these artificial plaques, we have conducted diffusion experiments to quantify the impact of plaque composition on diffusion (D) and partition coefficients (k) using two different model drugs, and further assessed the relationships between the composition of the artificial plaque and drug hydrophobicity on drug solubility and diffusivity.

Methods: We employed gelatin hydrogels with varying gelatin and lipid concentrations to emulate the observed variations in plaque composition. To fabricate the hydrogels, we started by dissolving gelatin (from bovine skin, type B; Sigma–Aldrich, St. Louis, MO) into deionized water to create aqueous solutions containing 0.025, 0.050, and 0.100 (w/w) gelatin. A small amount (0.005, w/w) of glutaraldehyde (grade II, Sigma–Aldrich) was added to each solution to generate cross-linking. The constituents were selected such that they closely emulate the chemical characteristics of both the matrix and lipid inclusions observed in actual atherosclerotic plaque. Our measurements of tetracycline transport and lipid composition on the mean values of the measured partition coefficients; k, for tetracycline (filled circles) and fluvastatin (open circles). We also found that in the absence of lipid, tetracycline and fluvastatin have comparable diffusivities (D). However, these values diverge as lipid is added to the hydrogel. The presence of the lipids in the artificial plaque significantly reduces the effective diffusivity of fluvastatin through the composite hydrogel, whereas resulting in only a minor increase in the D of tetracycline.

Conclusions: We have estimated the impact of collagen and lipid composition on both diffusion (D) and partition (k) coefficients of two model drugs, tetracycline and fluvastatin, in vitro using gelatin-based artificial plaques. The constituents were selected such that they closely emulated the chemical characteristics of both the matrix and lipid inclusions observed in actual atherosclerotic plaque. Our measurements of tetracycline transport demonstrated that there was essentially no impact of plaque composition on partitioning (solubility) behavior. Although we also found that in the absence of lipid, tetracycline and fluvastatin have comparable diffusivities. However, these values diverge as lipid is added to the hydrogel. The presence of the lipids in the artificial plaque significantly reduces the effective diffusivity of fluvastatin through the composite hydrogel, whereas resulting in only a minor increase in the D of tetracycline.

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References:

Figure 1. The impact of lipid concentration within the artificial plaques on the mean values of the measured partition coefficients; k, for tetracycline (filled circles) and fluvastatin (open circles).

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