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[1-2]. 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 lipid mixtures were added to the gelatin solutions in varying amounts up to 0.034 (w/w).

The D coefficient and solubility of our model drugs in the artificial plaques were measured using an established approach[3]. Tetracycline (>98%, Sigma–Aldrich) or fluvastatin (sodium salt; Toronto Research Chemicals, Toronto, Ontario, Canada) were used as target drugs. The analytical solution gave results of drug diffusivity D and partition coefficient k, following Fick's second law as a function of position and time for a one-dimensional, semi-infinite medium in contact with infinitely large volume of solution at constant concentration.

Results: We have estimated the impact of collagen and lipid composition on both diffusivity and solubility of model drugs, tetracycline and fluvastatin, *in vitro* using artificial plaques. Tetracycline solubility was found to be independent of lipid concentration in the hydrogels, as shown in Figure 1. In contrast, lipid concentration has a substantial impact on the measured solubility of fluvastatin, suggesting the lipid-rich phases in the artificial plaque have a strong chemical affinity for fluvastatin relative to the gel matrix.

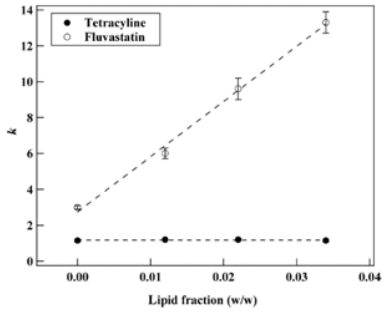

Figure 1. The impact of lipid concentration within the artificial plaques on the mean values of the measured partition coefficients; *k*, for tetracycline (filled circles) and fluvastatin (open circles).

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 no substantive impact of lipid concentration on D for tetracycline, we did observe a significant reduction in D for tetracycline with increasing gelatin content.

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References:

1. Holmes, D. R., *J. Am. Coll. Cardiol.* **2007**; 50(2): 109-118.
2. Mautner, L.N., *J Amer Coll Cardiol.*, **1993**; 21 (6): 1312-1318.
3. Brounéus, F.; *J of Control Release*, **1999**, 59(3): 391-400.