Naturally Derived Fatty Acid Biomaterials for Local Drug Delivery

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Statement of Purpose: Naturally derived biomaterials offer several advantages over synthetically derived materials. In addition to being made from renewable resources, such materials often offer improvements in the biocompatibility of the material and its degradation products. While naturally derived materials such as cellulose and protein based materials are commonly used in implantable medical devices, materials created from lipids represent an area of further research and opportunity. Omega-3 fatty acids are commonly obtained from fish and plant sources in triglyceride oil form, but can also be converted into ethyl ester form. Oils contain a mixture of saturated, monounsaturated, and polyunsaturated fatty acids which can be used to create biomaterials with different physical and chemical properties. Fatty acids are absorbed and metabolized by cells for energy production and specific fatty acids, such as EPA and DHA, are known to possess anti-inflammatory and pro-resolution properties during healing.

We developed a cross-linked fatty acid material that can be implanted as a film, coating material or gel for drug delivery[1-3]. These materials are created using thermal oxidative crosslinking without the addition of toxic chemical agents. The polarity and hydrolysis rate of these naturally derived fatty acid-based materials can be tailored by modulating fatty acid composition. We hypothesize that these constructs can deliver drugs at a controlled rate based on the material dissolution rate, as drug release from these materials predominantly results from fatty acid compositional properties rather than simple diffusion.

Methods: Fatty acid biomaterials consisting of differing ratios of fatty acid ester (i.e. glyceride and ethyl ester) and chain composition were mixed, applied onto polypropylene mesh substrates, and underwent thermal oxidative crosslinking. Paclitaxel was used as a model anti-proliferative drug. Drug release kinetics of paclitaxel applied to cross-linked fatty acid materials of different composition were measured using radiometric techniques.

Results: Naturally derived fatty acid biomaterials from plant and fish oils were subjected to accelerated alkaline chemical hydrolysis via aqueous sodium hydroxide in order to identify the effects of different ester and fatty acid composition on material dissolution (Figure 1). These studies showed that fatty acid biomaterials formed using 100 % flaxseed plant triglycerides hydrolyzed at a much slower rate than the 100 % fish oil triglyceride coatings. This is theorized to be due to higher material polarity (confirmed using contact angle measurements) and lactone crosslinks (confirmed using FTIR spectroscopy) that form in the fish oil material from the long polyunsaturated EPA and DHA fatty acids flaxseed oil lacks. Addition of enriched fish oil ethyl esters containing high amounts of EPA and DHA resulted in a further decrease in the biomaterial hydrolysis time for both materials, albeit at different rates (Figure 1). The addition of ethyl ester fish oil to either oil increases the lactone crosslinking of both materials, and further accelerates hydrolysis due to the relatively faster hydrolysis rate of ethyl esters versus triglyceride esters. This trend was also observed in preclinical testing[2].

Drug release kinetics of paclitaxel from different fatty acid biomaterials in a biologically relevant media (37% calf serum, 63% DMEM) shows that drug release is more rapid for faster hydrolyzing materials (Figure 2). This trend also holds true when measuring drug release kinetics of other drugs such as triclosan and mTOR derivatives. These results are consistent with a fatty acid mediated drug release rather than a diffusion mediated drug release. Finally, it has been demonstrated that other naturally derived biomaterials, such as carboxy-methyl cellulose can be coupled to fatty acid materials as a further means to control drug delivery and aid in tissue adhesion[4].

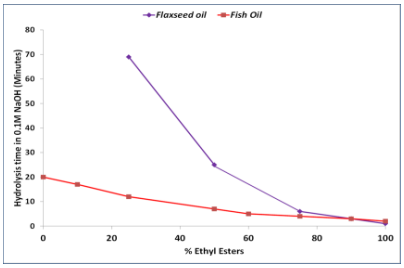

Figure 1: Hydrolysis of naturally derived lipids enriched with fish oil ethyl esters

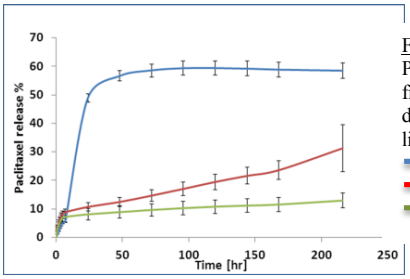

Figure 2: Paclitaxel release from naturally derived lipids & lipid blends
Ethyl ester blend
Fish oil
Flaxseed oil

Conclusions: Naturally derived fatty acid biomaterials show promise as a tailorable absorbable material that can be used to control drug release kinetics. These materials are biocompatible and able to be utilized in a variety of medical applications[1-3].

References:

1. Faucher et al, US Patent 8124127
2. Faucher et al, US Patent Application 20120016038
3. Faucher et al, US Patent Application 20090181937
4. Artzi et al, "Hydrophobic cross-linked degradable materials for local release." Society for Biomaterials Conference Presentation, New Orleans, October 2012.