Simvastatin Incorporated Perivascular Polymeric Controlled Drug Delivery System for the Inhibition of Intimal Hyperplasia

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Statement of Purpose: Dialysis access graft failure is a major complication in providing care to patients on hemodialysis therapy. The failure rates have been reported as high as 80% at one year for this procedure. The major cause of failure is intimal hyperplasia (IH). IH is an exaggeration of the normal vascular wall healing response to injury resulting from the migration and proliferation of medial smooth muscle cells. Kanjickal et al., (Kanjickal D. J. Biomed. Mater. Res. 2004; 68A:489-495.) developed a novel polymeric perivascular device, PolyRing (patent application 10/836,787), for the treatment of IH. Our work focuses on evaluating the feasibility of releasing the drug Simvastatin (SV) from the perivascular wrap device to provide localized, site specific, sustained drug delivery for the prevention of IH in vascular tissue.

Method

Materials: Poly (ethylene glycol) (PEG) (M_w 3350), poly (DL-lactide-co-glycolide) (PLGA)(85/15, M_w 3350), Simvastatin (ZOCOR®), poly (vinyl alchohol) (PVA), triphenyl methane triisocyanate (Desmodur RE), dichloromethane (DCM) and acetonitrile (ACN) were used. Distilled-deionized water was used for all purposes.

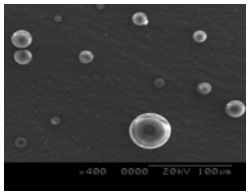
Method: Microspheres were prepared by a standard solvent evaporation oil/water (o/w) emulsion technique. (Jain RA. Biomat. 2000; 21:2475-2490.) PLGA and SV, were dissolved in dichloromethane (DCM) (organic phase) and emulsified, at room temperature, in an aqueous PVA solution (5%) using an impeller at a constant speed of 350 rpm. Further steps included solvent evaporation under atmospheric conditions, centrifugation to collect the microparticles, washing with distilled-deionized water, shell freezing and lyophilization.

The PEG hydrogel was synthesized by chemical crosslinking of poly (ethylene glycol) with triphenyl methane triisocyanate (Desmodur RE). Briefly, 25% (weight) DCM solution of Desmodur RE was added to 25% (weight) solution of 3350 molecular weight PEG. The molar ratio of the hydroxyl group of the PEG to the isocyanate in the crosslinking agent was adjusted to obtain the desired crosslinking ratio of 1:1. SV loaded PLGA microspheres, suspended in DCM, were then dispersed in the solution for the PEG hydrogel synthesis after 30 minutes. The mixture was then transferred into circular aluminum pans resulting in the hydrogel block polymer. Polymeric rings were extracted from this block using drill and plug boring bits.

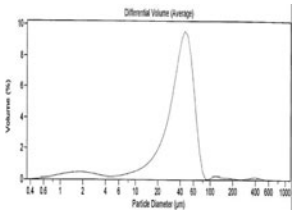
Characterization & Analytical Procedures:

Microsphere surface morphologies, particle sizes and distributions in the PEG hydrogel matrix were analyzed using SEM, laser light scattering and ESEM respectively. Encapsulation efficiency was studied by using ACN: DCM (9:1) as the dissolution media. The drug was detected at a wavelength of 225 nm using a spectrophotometric plate reader.

Results/Discussion: The % yield obtained for the microspheres with 0.1 & 0.2 Drug-to-Polymer (D/P) ratio was approximately, 66% and 85% respectively. The encapsulation efficiency achieved was highest for the microspheres with 0.1 D/P ratio at approximately 81%, The average diameter for the non-drug and drug loaded microparticles was, approximately, 100 µm and 40 µm respectively. Figure 1 shows a scanning electron micrograph of the drug loaded microspheres and their corresponding particle size distribution.



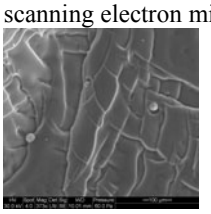
(a)



(b)

Figure 1. (a) Scanning electron micrograph (b) Particle size distribution

The PLGA microspheres appeared to be evenly distributed in the PEG hydrogel network as shown in the environmental scanning electron micrograph (Figure 2).



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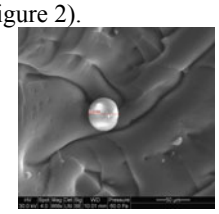

(b)

Figure 2. Environmental scanning electron micrographs (a) Magnification: 373X (b) Magnification: 868x

Conclusions: The results indicate that microspheres with a drug-to-polymer ratio of 0.1 produced maximum encapsulation efficiency of around 81%. The loading of the drug affects the particle size by significantly reducing the diameter of the microspheres but has minimal effect on the surface morphology. Future work will include synthesis of Simvastatin Acid (SVA) - (pharmacologically active form of SV) (Prueksaritanont T. Drug Met. and Disp. 1997; 25:1191-1199.) loaded microspheres by a double emulsion w/o/w technique and studying the loading efficiency of these microparticles. Cell culture studies will be conducted to evaluate the efficacy of the SV and SVA based PolyRing systems in preventing the proliferation of smooth muscle cells. The best system will undergo additional *in vitro* drug release studies and *in vivo* safety and biocompatibility studies.

References: Cited in parentheses (see text) as instructed.