Micromantled, Drug-eluting Stent and Study of a Model Therefrom

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Statement of Purpose: Percutaneous transluminal coronary angioplasty was introduced as a less invasive alternative to coronary artery bypass grafting for treating coronary atherosclerosis using expandable, metallic stents to maintain patency and prevent restenosis. Without drug intervention, restenosis occurred in more than 30 percent of the patient population mainly as a result of uncontrolled proliferation of vascular smooth muscle cells (SMCs) at the stent site. With the recent introduction of drug-eluting stents (DES), the rate of restenosis has decreased to about 10 percent. However, the commercially available DESs suffer from (1) initial mechanical incompatibility associated with direct, high contact pressure between the lumen and the stent struts; and/or (2) less-than-optimum balanced effect of drugs in preventing SMC proliferation while supporting the growth of the luminal endothelium. Meanwhile, investigators in this laboratory have been studying (1) a new family of absorbable polyaxial polyesters as compliant microfibrous fabrics made by electrostatic spinning (electrospinning); (2) the direct formation of a fibrous mantle (or cover) on metallic stents; and (3) the effect of composition of the electrospun polyaxial polymers and drug structure on release profiles.[1-5] Recognition of shortcomings of commercially available DES and new means to overcome them provided an incentive to pursue the present study to determine the feasibility of using drug-loaded, absorbable, electrospun, microfibrous, compliant fabrics on the outside surface of a metallic stent for development of a controlled release system of one or more antiproliferative agents to achieve, in part, the sought balanced effect on SMCs and luminal endothelial cells (ECs). The preliminary part of this study is designed to use a typical electrospun fabric similar to those to be deposited on the metallic stent as a model substrate to study the controlled release of paclitaxel as an established antineoplastic/anti-proliferative and leflunomide as an anti-arthritic agent with suspected anti-inflammatory/ immunosuppressive activities.

Methods: Six polyaxial copolyesters (PAX-2, -6, -10, -11, -12, and -13) were prepared as described in earlier reports.[1-3] The polymers were characterized for molecular weight by GPC and inherent viscosity (I.V.) and thermal prperties (T_m, ΔH_f) using DSC.

A concentrated solution of paclitaxel or leflunomide in ethanol was added to select polymer solutions to produce a drug-loaded solution with the drug representing 1% or 10% (by weight) of polymer. The individual solutions were electrospun under practically constant processing conditions similar to those described earlier and characterized for drug release.[2,4]

In a separate experiment, a drug-free, 0.1 mm thick microfibrous fabric of PAX-10 was prepared as above. Tensile testing was performed to determine the ability of the electrospun construct to deform similarly to an expanding stent without failure.

Results: Molar ratios of monomers used in preparing the polymers and their properties are summarized in Table I. Two representative polymers (PAX-10 and PAX-12) were used to produce drug-loaded microfibers, with average microfiber diameter of about 5μm as determined by SEM. Drug release testing was performed and indicated controlled release of both paclitaxel and leflunomide through 10 days, as summarized in Table II.

Tensile test specimens of the fabric exhibited an ultimate elongation of about 380%. The ability to electrospin PAX-10 and PAX-12, as typical microfiber precursors, directly on commercial metallic stents was also demonstrated. The amount of microfibers deposited on a stent weighing about 35 mg varied between about 0.5 and 1 mg. Expansion of the mantled stents using a standard inflatable balloon was easily achieved and shown to be equivalent in terms of expandability to a mantleless stent.

Table I. Monomer Ratios and Polymer Properties

Poly-mer PAX-	Monomer Ratios[a] LL/CL/TMC/G	DSC Data T_m, °C	DSC Data ΔHf, J/g	I.V. ($CHCl_3$) dL/g	M_w, kDa	% Mass Loss[b], 9 Wks.
2	**39** / 33 / 28 / **0**	159	25	1.02	129	<8
6	**40** / 30 / 26 / **4**	146	12	1.42	141	9
10	**36** / 34 / 16 / **14**	121	8	1.45	144	25
11	**42** / 32 / 16 / **10**	149	16	1.49	142	17
12	34 / **35** / 14 / **17**	109	7	1.45	146	42
13	32 / **35** / 14 / **19**	101	5	1.23	135	45

[a]LL=*l*-lactide; CL=ε-caprolactone; TMC=trimethylene carbonate; G=glycolide.
[b]Tested in the form of molded disc

Table II. Cumulative *In Vitro*[a] Drug Release Data

Controlled Release System[a]	% Cumulative Release of Paclitaxel on Day 1	2	5	10	% Cumulative Release of Leflunomide on Day 1	2	5	10
1% Drug in PAX-10								
% Released	1.6	3.0	5.8	7.2	25	45	78	83
1% Drug in PAX-12								
% Released	1.0	2.1	4.2	5.4	15	42	67	88
10% Drug in PAX-12								
% Released	--	--	--	--	23	45	73	92

[a]Using a phosphate buffer at pH 7.2 and 37°C

Conclusions: The results of the preliminary study demonstrate (1) the ability to deposit a microfibrous mantle on a typical metallic stent; (2) a typical and atypical drug can be loaded into the polymers which can be converted to active microfibrous fabric; and (3) the two examined drugs exhibit different release profiles.

References:

[1]Taylor, M.S. et al., *Trans Soc. Biomater.*, 27, 1042 (2004).
[2]Shalaby, S.W. et al., U.S. Pat. Appl. Ser. No. 11/175,635 (2005).
[3]Shalaby, S.W., U.S. Patent No. 7,129,319 (2006).
[4]Taylor, M.S. et al., *Trans Soc. Biomater.*, 30, 295 (2007).
[5]Shalaby, S.W., U.S. Patent No. 7,416,559 (2008).