Co-Delivery of Paclitaxel and Nitric Oxide from Abluminal and Luminal Surfaces of a Coronary Stent

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Statement of Purpose: The implantation of stents to open up the narrowed coronary artery causes neointimal hyperplasia (NH).[1] NH is the growth and migration of smooth muscle cells (SMCs) inside the lumen, which re-narrows the artery after stent implantation. Drug-eluting stents (DES) which release anti-proliferative drugs to inhibit the growth of SMCs are currently implanted to treat NH.[1] Although the release of anti-proliferative drugs in the abluminal (towards vessel wall) direction is beneficial for controlling the growth of SMCs, the release of these drugs in the luminal (towards lumen) direction inhibits the growth of endothelial cells (ECs).[2] Delayed or impaired endothelialization on luminal stent surfaces causes late stent thrombosis,[2] which results in heart attack or death. Hence, the main objective of this study is to co-deliver an anti-proliferative agent (paclitaxel – PAT) and an endothelial cell promoting agent (nitric oxide – NO) from abluminal and luminal stent surfaces, respectively. Since some polymer-based drug delivery carriers cause adverse reactions in patients,[3] a polymer-free platform using phosphonoacetic acid (PAA) molecular coatings was used to co-deliver the drugs from stents.

Methods: Co-Cr alloy stents were chemically cleaned and immersed in 1mM solution of PAA in deionized (DI) H_2O for 24h. The PAA coated stents were then heated at 120°C for 18h to stabilize the coating. PAT was spray coated on the abluminal surface of the stent. A nitric oxide donor drug, diethylenetriamine diazeniumdiolate (DETA NONOate), was coated on the luminal stent surfaces as follows: a mandrel was immersed in a 5mM solution of DETA NONOate in DI-H_2O. The stent was then placed on the DETA NONOate wetted mandrel such that the luminal surface was in close contact with DETA NONOate. This transferred the DETA NONOate from the mandrel to the luminal stent surface. The co-coated stents were characterized using scanning electron microscopy (SEM), Fourier transform infrared spectroscopy (FTIR), 3D optical surface profilometry (OSP), and contact angle goniometry (CAG). The co-coated stents were immersed in PBS/Tween-20 (pH 7.4) at 37°C for up to 28 days. The PBS/T-20 solutions collected at different points were used to determine the amount of PAT and NO released using high performance liquid chromatography and Griess reagent, respectively.

Results: FTIR spectra strongly confirmed the co-coating of PAT and DETA NONOate on the abluminal and luminal stent surfaces, respectively. The fingerprint region of PAT (IR peaks at 690, 1071, and 1229 cm^{-1}) was observed on the abluminal stent surface (Fig 1A) while the fingerprint region of DETA NONOate (IR peaks at 667, 870, 935, and 1183 cm-1) was observed on the luminal stent surface (Fig 1B). SEM showed that the PAT coating was present only on the abluminal stent surface (Fig 2A) while the DETA NONOate was present only on the luminal stent surface (Fig 2B). The OSP images (Fig 3A and B) were also in excellent agreement with the results of FTIR and SEM. PAT and DETA NONOate are hydrophobic and hydrophilic drugs, respectively. Hence, the CAG showed hydrophobic abluminal (82.9 ± 6.3°) and hydrophilic luminal (69.7 ± 11.2°) surfaces. *In vitro* drug release studies showed that PAT was released from the abluminal stent surfaces in a biphasic manner (an initial burst followed by a sustained release, Fig 4A) while the NO was released from the luminal stent surfaces in a burst manner (Fig 4B).

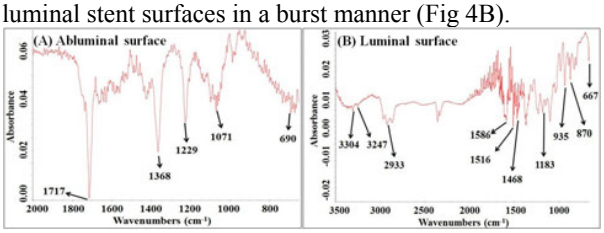

Fig 1. FTIR spectra of (A) PAT and (B) DETA NONOate

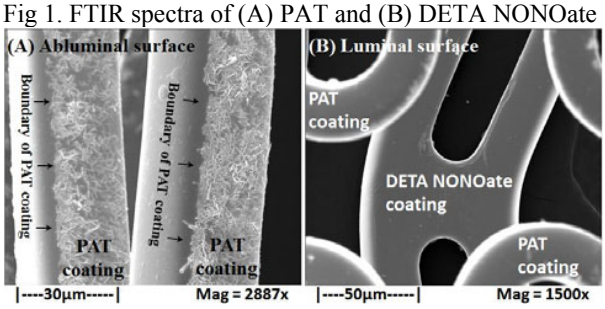

Fig 2. SEM images of (A) abluminal, (B) luminal surfaces

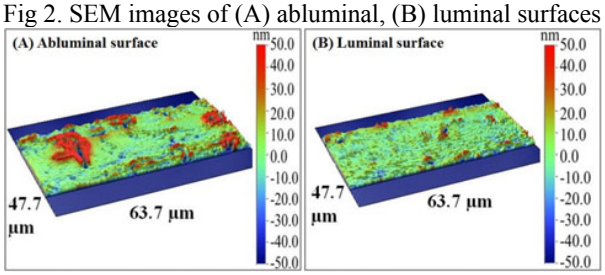

Fig 3. OSP of (A) abluminal and (B) luminal surfaces

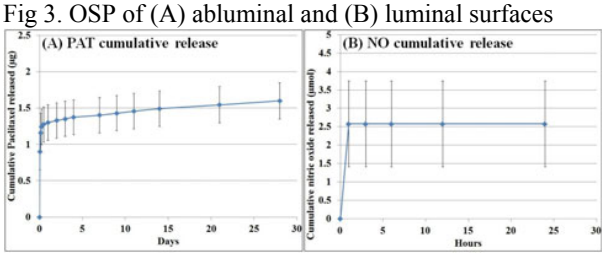

Fig 4. Release profiles of (A) PAT and (B) NO

Conclusions: A dual drug-eluting coronary stent was successfully prepared to co-elute PAT and NO from abluminal and luminal stent surfaces, respectively. This stent has potential applications in inhibiting neointimal hyperplasia as well as encouraging endothelialization to prevent late stent thrombosis.

References: (1) Mani G. Biomaterials 2007; 28: 1689-1710; (2) Finn AV. Circulation 2007; 115: 2435-41; (3) Virmani R. Circulation 2004; 109: 701-5.

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