Biodegradable Polymer-Coated Drug-Eluting Stents with Improved Coating Stability Using Biodegradable Nano-Brushes

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Statement of Purpose: Drug-eluting stents (DES) are currently applied to patients to treat the cardiovascular diseases such as restenosis. However, the commercially available stents suffers from weak adhesion between stent surface and polymer coatings. This weakness causes the polymer layer to detach or peel-off that in turn lead to a series of adverse and inter-related events such as non-uniform local drug distribution, local inflammation, and thrombosis [1]. In this area, we have currently focused on using biodegradable nano-brushes to enhance the adhesion of the polymer coating with the underlying stent surface in order to prevent the stent from the delamination and to control the drug release [2]. The aim of this study was to investigate the preventive effect of the nano-brushes on delamination of the polymer coating through Co-Cr substrate modification by biodegradable PLLA brushes.

Methods: Cobalt-chromium (Co-Cr) plate (1×1 cm^2) was obtained from Han Kook Vacuum Metallurgy (Korea). Poly(D,L-lactide) (PDLLA; 75:25, Mol. Wt. = 115K) was purchased from Boehringer Ingelheim (Germany). (2-{2-[2-hydroxy-ethoxy]-ethoxy}-ethyl) phosphonic acid (PA) was supplied from SIKEMIA company (France). Prior to the piranha treatment, Co-Cr specimens were mechanically polished, cleaned in ethanol and dried under argon gas. PA was grafted on the Co-Cr surface and the hydroxyl group in the PA self-assembled monolayer (SAM) initiates the ring opening polymerization (ROP) of the L-lactide forming PLLA brushes. Sirolimus-in-PDLLA matrix was ultrasonically coated to the control and the modified samples. The modification steps were characterized by several analyses including ATR-FTIR, XPS, and water contact angle. The drug release profiles were studied for 4 months under a physiological condition. The morphology of the coating after 4 month of release was imaged using SEM.

Results: PA SAM was used to initiate the ROP of L-lactide to give PLLA brush on Co-Cr stent surface. The formation of the SAM and the successive PLLA brushes was proved by FTIR, XPS and contact angle. The FTIR spectra showed the characteristic peaks of the PA that appears at 3600-3400 cm^{-1}, 1260 cm^{-1} and 1095 cm^{-1}. After ROP, new peak at 1760 cm^{-1} was attributed to carbonyl groups of the PLLA brush as shown in Figure 1. Table 1 presents the XPS elemental compositions as well as the water contact angle that systematically proved the formation of SAM and the PLLA brush on the Co-Cr surface. Figure 2 presents *in vitro* drug release profiles. The modified stent showed a sustained release as compared to the control (no treatment). After 4 months of drug release as presented in Figure 3, the morphology of polymer coating on the control DES sample presented delamination, cracking, and peeling. On the other hand, the nanocoupled samples (NCS) did not show any sign of cracking or delamination. Our results clearly demonstrated that the nano-brush layer at the interface effectively increased the durability of the polymer coating on the stent surface. Further *in vivo* studies are ongoing.

Table 1. XPS elemental compositions and water contact angle measurements of the control and nanocoupled Co-Cr specimens

Specimen	Elemental compositions					Contact angle
	C%	O%	P%	Cr%	Co%	
BMS	32.90	47.72	0	13.78	5.60	61.4±1.8
BMS (piranha)	34.69	53.52	0	9.34	2.44	30.8±0.9
NCS-P-OH	45.25	39.79	4.57	6.71	3.69	37.8±2.3
NCS-P-PLLA2D	48.19	38.57	2.39	8.02	2.85	65.9±2.8

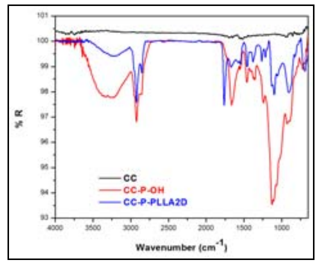

Figure 1. ATR-FTIR spectra of the Co-Cr (control) and after each modification step

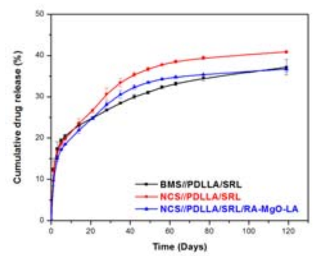

Figure 2. Sirolimus release profile of different specimens

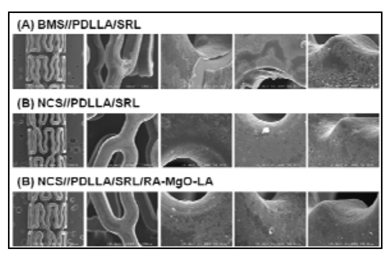

Figure 3. Coating morphologies after 4 month of drug release

Conclusions: PLLA brush as an interfacial layer between the stent surface and polymer coatings could enhance coating stability and sustain the drug release. This nanocoupling technology will be promising tool to be applied to biodegradable-coated DESs.

References:

[1] Basalus, MWZ., et al., Eurointervention 2009;5: 505-510.

[2] Bedair TM, *et al.*, *Langmuir* 2014;30:8020-8028.