Nanoporous Metal Surface via Selective Plasma Etching for Application of Polymer-Free Drug Eluting Stent

Sung-Won Kim, Tae-Sik Jang, Ju-Ha Song and Hyoun-Ee Kim*

Department of Materials Science and Engineering, Seoul National University, Seoul, 151-742, Korea

Statement of Purpose: Drug eluting stent (DES) has been developed by coating the stent surface with drug-loaded polymer layers in order to reduce restenosis. However, the coated polymer layers of DES are often found to cause late stent thrombosis because they induce hypersensitivity and inflammatory responses [1]. To solve this problem, polymer-free DES through crystallized drug coating has been proposed, proving the significant suppression of polymer-related adverse effect [2]. In this study, we have introduced a selective plasma etching (SPE) process to create nanoporous stent surface and have evaluated the newly modified surface as a drug loading carrier for the application of polymer-free DES.

Methods: The Co-Cr substrate was selectively etched using direct current (DC) sputter with a Ta target under Ar-rich ambient condition and extremely high negative bias up to 800V. Both non-treated and treated Co-Cr samples were immersed in ethanol solution with 10wt% paclitaxel inside a vacuum chamber for 20 min. Surface and cross-sectional morphology of all samples was characterized by FE-SEM and FIB. The amount of drug loading per sample was measured after loaded drug was fully dissolved in ethanol under sonification for 2 hr. The drug release test of drug-loaded samples were performed in 8:2 mixture of PBS/ethanol solution at 37 ℃. The amount of drug in a solution was determined using a UV spectrophotometer.

Results: After sputtering, elongated and curved nano pores with the dimension of 100 nm (width) and 800 nm (length) were uniformly created on the Co-Cr surface with the saw-tooth shaped morphology in cross-section with an average pore depth of 380 nm (Fig. 1a, b). Paclitaxel was found to cover the porous Co-Cr surface (Fig. 1c), but also fill the most depth of pores (Fig. 1d). The quantified amount of drug loading for both non-treated and treated Co-Cr samples clearly show that nano pores on the roughened surface significantly enhance drug loading capability by 80 % as compared to the bare smooth surface (Fig. 2). Drug release behavior of nanoporous Co-Cr surface was compared to that of bare Co-Cr surface as shown in Fig. 3. Both exhibit the burst effect for initial two days after the test, releasing significant amount of drug from their surface. However, nanoporous samples were found to continuously release drug up to ~ 3 weeks, whereas bare samples almost stop releasing drug after a week (Fig. 3a). The gap between the total cumulative drugs of two samples shows good agreement with the difference shown in Fig. 2. Moreover, the surface morphology of both samples after the release test indicates that nanoporous surface is more capable of sustainable drug release because of observed drug within the pores after three weeks (Fig.3b).

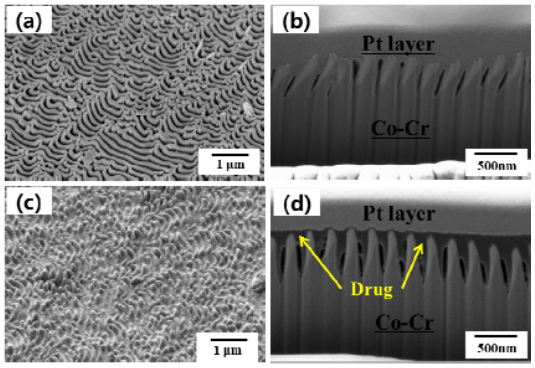

Figure 1. (a) Surface and (b) cross-sectional morphology of the Co-Cr substrate after sputtering, and (c) surface and (d) cross-sectional morphology of nanoporous layer after drug loading

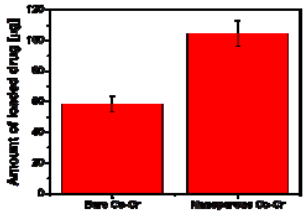

Figure 2. Amount of drug loaded on bare and nanoporous Co-Cr surface

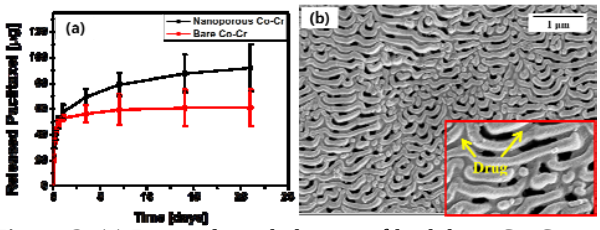

Figure 3. (a) Drug release behavior of both bare Co-Cr and nanoporous Co-Cr in PBS/ethanol mixed solution up to 21 days, and (b) surface morphology of nanoporous Co-Cr after 21 days of drug release

Conclusions: Nanoporous surface of Co-Cr via selective plasma etching successfully carried the remarkably increased amount of polymer-free drugs, exhibiting enhanced drug eluting behavior as compared to non-treated Co-Cr surface. By varying the pore density or surface chemistry, nanoporous Co-Cr has great potential for the application of controllable polymer-free DES.

References:

[1] H. Jia et al. J Biomed Mater Res A. 2011;98A:629-637

[2] W. Khan et al. J Control Release. 2013;168:70-76

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