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Dual-Layer Coated Drug-Eluting Stents with Improved Degradation Morphology and Controlled Drug Release

Tarek M. Bedair[†,1,2,3]
Wooram Park[†,1]
Bang-Ju Park[4]
Myoung-Woon Moon[5]
Kwang-Ryeol Lee[6]
Yoon Ki Joung[*,2,7]
Dong Keun Han[*,1]

[1] Department of Biomedical Science, College of Life Science, CHA University, 335 Pangyo-ro, Bundang-gu, Seongnam-si, Gyeonggi 13488, Korea
[2] Center for Biomaterials, Biomedical Research Institute, Korea Institute of Science and Technology, Seoul 02792, Korea
[3] Chemistry Department, Faculty of Science, Minia University, El-Minia 61519, Egypt
[4] Department of Electronic Engineering & Institute of Gachon Fusion Technology, Gachon University, Korea
[5] Computational Science Research Center, Korea Institute of Science and Technology, Seoul 02792, Korea
[6] Technology Policy Research Institute, Korea Institute of Science and Technology, Seoul 02792, Korea
[7] Division of Bio-Medical Science and Technology, Korea University of Science and Technology, Gajeong-ro 217, Yuseong-gu, Daejeon 34113, Korea

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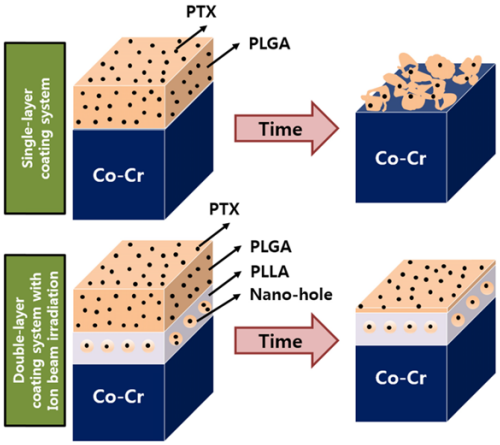
Abstract: Drug-eluting stents (DESs) are used to treat cardiovascular diseases such as atherosclerosis. The anti-proliferative drug released from the DES suppress the proliferation of smooth muscle cells and reduced in-stent restenosis. However, a burst release of the drug in the early stages and degradation morphology of the polymer coating represent major disadvantages, which might increase the incidence of in-stent restenosis and/or thrombosis under *in vivo* clinical studies. To solve these problems, in this study, a double-layer coating system composed of poly(lactide) (PLLA) bottom layer and poly(lactide-*co*-glycolide) (PLGA) top layer are used for the fabrication of DES. PLLA bottom layer was firstly coated on the metal surface followed by oxygen ion beam treatment. It was found that increasing the ion beam exposure time, increased the roughness of PLLA surface with a nanoscale pocket (or hole)-like structure. The top layer coating represented a mixture of PLGA and paclitaxel (PTX) with 5, 10, and 20% PTX contents. The coating was performed through ultrasonic spray technique, and the morphology showed not only a smooth and uniform surface but also no irregularities were observed at zero day. The drug release and degradation morphology for single-layer (PLGA/PTX) and double-layer (PLLA/PLGA/PTX) coatings were compared. The drug release from the double-layer stainless steel (SS) group showed a slower and controlled drug release for all PTX content samples as compared to single-layer SS group. Moreover, the degradation morphology of double-layer SS group presented a smoother and uniform surface after 12 weeks of degradation under physiological conditions. Therefore, an oxygen ion beam technique with double-layer coating system could effectively control the drug release, *i.e.*, prevent initial burst drug release, and improve the degradation morphology of biodegradable polymer-based DESs.



Keywords: drug-eluting stent, paclitaxel, polymer coating, degradation, drug release.

1. Introduction

Over the last decades, various metals and metal alloys such as 316L stainless steel (SS), tantalum, Nitinol, and cobalt-chromium (Co-Cr) alloy have been used for the manufacture of bare metal stent (BMS).[1] The implantation of BMS has many advantages over the use of percutaneous transluminal coronary angioplasty as it could provide the mechanical support of the diseased coronary artery, and effectively prevent acute recoil and negative remodeling of the blood vessel.[2] However, in-stent restenosis remained major drawback and occurred in 30% of patients within 6 months after initial angioplasty.[3] This is mainly due to neointimal hyperplasia caused by the migration/proliferation of smooth muscle cells and extracellular matrix deposition as a response to the vessel injury.[4]

Recently, drug-eluting stents (DESs) have attracted more attention in stent application because it could control the release of anti-proliferative and/or immunosuppressive drugs and prevent in-stent restenosis.[5] Among various anti-proliferative drugs, sirolimus and paclitaxel (PTX), have been widely used in

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***Corresponding Authors:** Dong Keun Han (dkhan@cha.ac.kr), Yoon Ki Joung (ykjoung@kist.re.kr)
[†]These authors contributed equally to this work.

DES platforms since they were approved by the Food and Drug Administration (FDA).[6,7] PTX is a semisynthetic diterpene consists of a rigid taxane ring and a flexible side chain. It has been found that PTX could attenuate stent-induced intimal thickening, and suppress neointimal proliferation.[8,9]

The polymer coating can act as a reservoir for drugs that can be delivered locally over a period of time. The released drug from the polymer coating can inhibit cell proliferation, and inflammation.[10,11] Synthetic non-biodegradable polymers such as poly (ethylene-*co*-vinyl acetate), poly(*n*-butyl methacrylate), poly(styrene-*b*-isobutylene-*b*-styrene), and poly(vinylidene fluoride-*co*-hexafluoropropylene) have been used for the fabrication of DESs.[12] However, permanent contact of these polymers with the tissue may lead to additional inflammatory response and late stent thrombosis.[13,14] Therefore, biocompatible and/or biodegradable polymers were used to avoid these unfavorable adverse effects.[15,16]

It is well-known that biodegradable polymer coating can control the release of anti-proliferative drug over a period of several weeks by biodegradation.[17,18] As a typical biodegradable polymer, poly(lactic acid-*co*-glycolide) (PLGA) is widely used in biomedical fields because of its biodegradability, biocompatibility, and mechanical strength.[19] However, the initial burst release and the morphology of the polymer coating during degradation represented a challenge for the clinical successfulness of stent deployment.[20,21] In this regard, a double-layer coating technique was used for the fabrication of biodegradable polymer-coated SS stent. The drug release and the degradation morphology of single *vs* double-layer biodegradable polymer-coated SS stents were studied under physiological conditions (pH 7.4, 37 °C).

2. Experimental

2.1. Materials

Stent/spring-type stainless steel (SS) (316L SS, 1.8 mm D & 18 mm L) and flat SS disc (10 mm×10 mm) were obtained from Hankook Vacuum Metallurgy Company (Suwon, Korea). Poly(L-lactide) (PLLA, M_w=110,000 g/mol) and poly(lactide-*co*-glycolide) (PLGA 50:50, M_w=40,000 g/mol) were purchased from Boehringer Ingelheim (Ingelheim, Germany). Paclitaxel was obtained from Samyang Genex Corp. (Daejeon, Korea). Chloroform, 1,4-dioxane, and other analytical grade solvents were purchased from Sigma-Aldrich (St. Louis, MO, USA) and used as received.

2.2. Pretreatment of SS spring/stent substrates

The SS springs/stents were cleaned with acetone, ethanol, and water in an ultrasonic bath for 10 min each. The cleaned SS substrates were kept under vacuum until they were used.

2.3. Fabrication of PLLA coated SS spring/stent

PLLA was dissolved in chloroform with a concentration of 0.3 wt% and used to coat SS spring/stent using an ultrasonic atomizing spray system (Sono-Tek Corp., NY, USA) at room temperature. The ultrasonic atomizing system was operated at a flow rate of 0.05 mL/min, and the distance between the substrate and the nozzle was 9 mm. To make a uniform coating layer, the SS spring/stent was rotated at 300 rpm during the coating process. The PLLA coated specimens were kept in a vacuum oven for 24 h prior characterization.

2.4. Oxygen ion beam treatment

The oxygen ion beam treatment of PLLA-coated SS substrates was carried out in a hybrid ion beam system.[22] In brief, the substrates were placed in the ion beam chamber under pressure of 2×10^{-5} mbar. The distance between the ion source and the substrate holder was approximately 15 cm. Oxygen gas from the end-Hall type ion gun was fed to the sample surface at a flow rate of 8 standard cubic cm per min (sccm), and the anode voltage was kept constant at 1 KeV with a current density of 50 mA/cm^2. A radio frequency bias voltage was applied to the substrate holder at -600 V with a corresponding current of 44 mA. The oxygen ion beam exposure time was ranged from 10 to 60 min.

2.5. Fabrication of PLGA/PTX coated spring/stent

Schematic diagram of the double-layer coating was shown in Figure 1. For the second coating, PLGA was dissolved in chloroform/dioxane (2:1, v/v) with concentration of 0.3 wt% and the different weight ratio of PTX was added to the PLGA solution (5, 10, and 20%, w/w based on PLGA). The PLGA/PTX mixture was homogeneously mixed using a bath sonicator (Model: Ultrasonic 2010, Jinwoo Engineering Co., Ltd., Korea) for 30 min. PLGA/PTX solution was coated on SS substrates using the previously described method (*Section 2.3.*). For characterization, flat SS discs were coated with PLGA/PTX mixture using the same ultrasonic atomizing spray system under the same conditions.

2.6. Surface characterization

Chemical elements of PTX-PLGA coating surface on the SS were investigated using X-ray photoelectron spectroscopy (XPS, S-Probe, Surface Science Corp., USA). The relative atomic percentage was calculated from the peak areas. Water contact angle measurements were determined using an optical bench-type contact angle goniometry (Digidrop, GBX Scientific Instrument, France). Surface morphologies of PLLA, oxygen ion beam-treated PLLA, and PLLA/PLGA/PTX coated SS spring samples were observed using field emission-scanning electron microscopy (FE-SEM; Hitachi S-2500C, Tokyo, Japan) at an accelerating voltage of 15 kV.

2.7. *In vitro* PTX release of PLGA/PTX coated SS spring

PTX-loaded SS spring specimens were placed in a vial containing 1 mL of phosphate-buffered saline (PBS, pH 7.4) solution under physiological conditions. At a selected time, the incubation medium was completely shifted to a new vial for analysis and a fresh PBS solution was added to the samples. The amount of PTX released was measured using high-performance liquid chromatography (HPLC, Agilent 1100, USA) consisted of LC-8A solvent delivery

module, SPD-10AVP UV-Vis detector and phenomenax XDB-C18 column (particle size: 5 μm). A mixture of water and acetonitrile (40:60 v/v) was used as a mobile phase with a flow rate of 1.0 mL/min. The elution was monitored using a UV/Vis detector at 227 nm. The release profiles were obtained by measuring the cumulative release percentage of PTX for up to 12 weeks.

2.8. *In vitro* degradation of PLGA/PTX coated SS spring

PLGA/PTX coated SS springs were immersed in 1 mL of PBS solution under physiological conditions. The PBS solution was changed every week to maintain the pH of the solution with 7.4 during the incubation period. After 12 weeks, the samples were taken out, washed with deionized water for three times, and dried under vacuum. The dried samples were sputtered with platinum for 45 s, and the morphologies of the surfaces were visualized by FE-SEM.

2.9. Balloon expansion test for PLLA and PLGA/PTX coated SS stents

PLLA and PLLA/PLGA/PTX coated stents were mounted onto angioplasty balloon and dilated to 3 mm at 10 atmospheric pressure for 40 s. The morphologies of the polymer coating of the expanded stents were examined by FE-SEM as mentioned above.

3. Results and discussion

3.1. Double-layer coating system

The double-layer coating of PLLA/PLGA on SS surface was accomplished through two main steps as presented in Figure 1. In the first step, PLLA was spray coated on the metal surface using an ultrasonic spray coating system. This instrument is widely used to provide a smooth and uniform coating for stent application.[23] Then, the PLLA layer was treated with oxygen ion beam to increase the roughness of PLLA bottom layer and provide a nano-pocket like morphology, which could support the drug-in-polymer matrix top layer coating. According to Koh *et al.*, a change in the morphology of polytetrafluoroethylene from smooth to shallow valley surface due to ion irradiation was reported.[24] In the second step, a matrix of PLGA and PTX was spray coated on PLLA underneath layer. It is expected that PLGA/PTX coating will fill the pores of the ion beam-treated PLLA and consequently, the interaction between both layers will be increased.

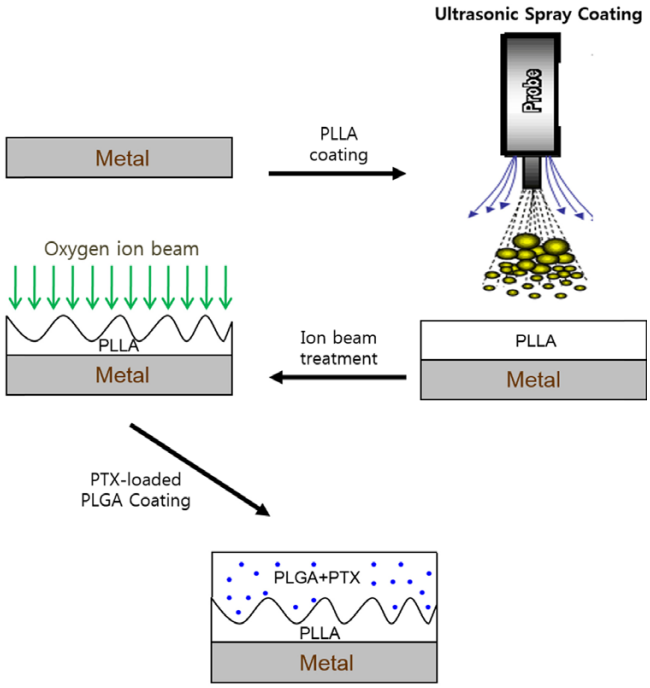

Figure 1. Schematic diagram of double-layer coating on SS spring/stent by an ultrasonic atomizing system.

3.2. Characterization of bottom PLLA layer

To investigate the effect of oxygen ion beam on the morphology of PLLA layer, different exposure times varied between 10 to 60 min were performed. Figure 2 showed SEM images of the top view of PLLA surface coated on flat SS specimens before and after oxygen ion beam-treatment. Before ion treatment, the control PLLA coated SS surface did not exhibit a specific surface pattern and presented a smooth surface morphology (Figure 2(a)), whereas a certain roughness was evolved after 10 min of oxygen ion beam treatment (Figure 2(b)). It was previously reported that the change of the surface morphology of expanded polytetrafluoroethylene was due to ion beam exposure.[25] Increasing the ion beam duration from 10 to 30 min, the roughness increased further (Figure 2(c),(d)). At 40 min duration, nanoscale pocket-like structures were revealed with the size of 200-300 nm in diameter. The size of pocket-like structure increased with more ion beam duration until 60 min and further treatment destroyed the pocket structure. This pocket-like morphology was formed by elastic and inelastic collisions action of the high-speed oxygen ions to PLLA surface.[26] Based on SEM result, the duration time for PLLA treatment of 60 min was selected for this study. The pocket morphology of PLLA bottom layer could increase the interactions with PLGA/PTX coating top layer through the mechanical interlocking mechanism. In addition, the oxygen molecules modified on PLLA surface could also increase the chemical interaction with the PLGA second layer through hydrogen bonds or van der Waals forces.[24] Both of the mechanical interlocking and the chemical interactions could participate in increasing the stability of PLGA/PTX top layer and might affect the drug release.

3.3. Double-layer coating morphology and cross-section thickness on SS spring

The ultrasonic atomizing spray system is a well-known instrument to make a uniform deposition of polymer coating with minimal overspray and applies to the medical implants such as stents and catheters.[27] The surface morphologies of each layer, as well as the thickness of coating layers, were shown in Figure 3. The PLLA layer coating on SS spring displayed a smooth and uniform coating with a thickness of 4.5 μm adjusted by controlling the spray period as determined by cross-sectional SEM (Figure 3(a)). After ion beam treatment, the surface showed sev-

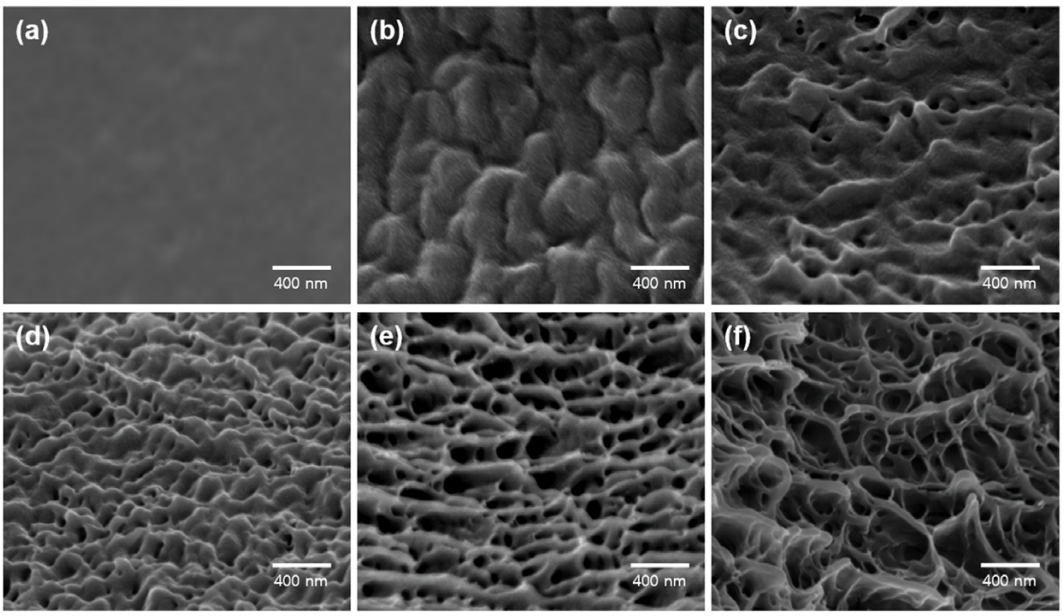

Figure 2. Surface morphologies of PLLA with oxygen ion beam treatment with various durations; (a) control, (b) 10, (c) 20, (d) 30, (e) 40, and (f) 60 min.

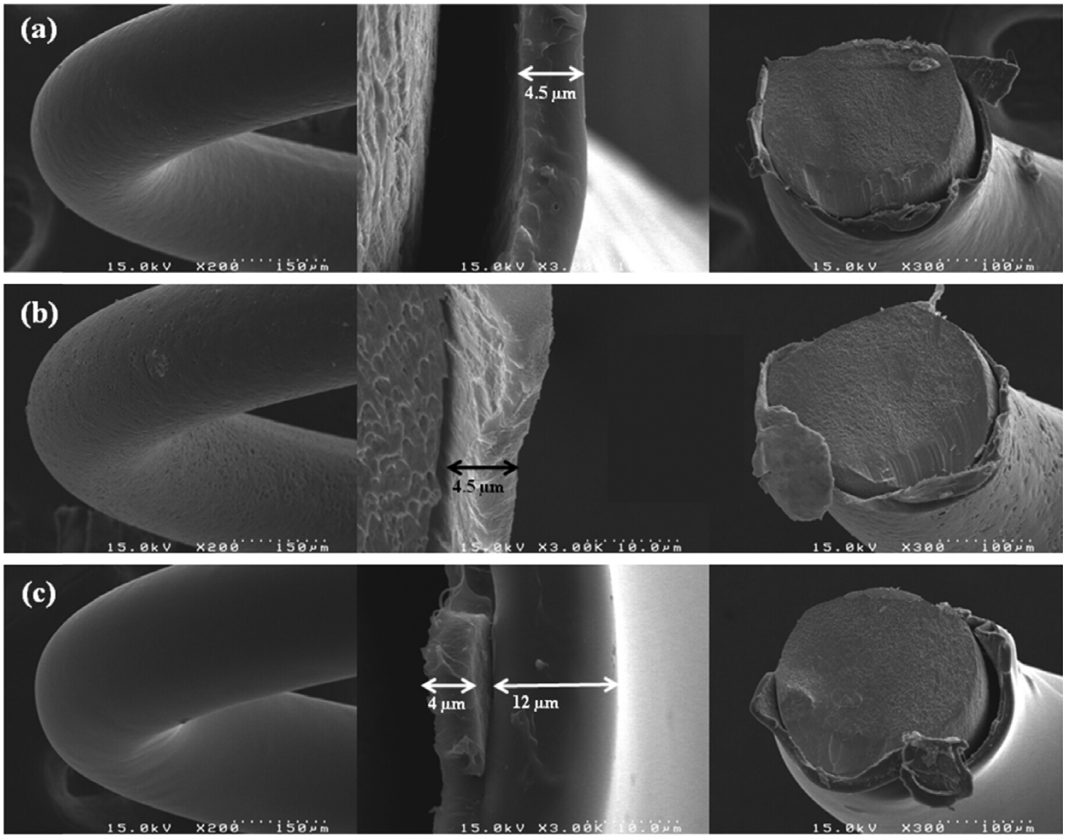

Figure 3. SEM images of (a) PLLA, (b) ion beam-treated PLLA, and (c) PLLA/PLGA/PTX coating on SS spring surfaces.

eral nano-pores with the same coating thickness (4.5 μm) (Figure 3(b)). It is suggested that oxygen ion beam treatment not affect the coating thickness. Unlike the cross-section of pristine PLLA that presented a compact morphology, the ion beam-treated PLLA exhibited a spongy structure, which means that the pores-like structure (Figure 2(f)) was deeply penetrating PLLA coating layer. The morphology of double-layer coating PLLA/PLGA/PTX revealed a very smooth morphology with a homogenous coating without webbing between spring coils. The thickness of PLGA/PTX coating was adjusted to be 12 μm. It is interesting to note that the PLGA/PTX coating filled out the nano-holes of the ion beam-treated PLLA layer as shown in the cross-section SEM image of Figure 3(c). This obviously supports that mechanical interlocking between PLLA and PLGA/PTX took

Table 1. Atomic percentage of elements detected and water contact angle of PLGA-coated SS substrates

Sample	ESCA atomic %			Contact angle (°)
	C1s	N1s	O1s	
PTX	75.90	1.5	22.60	-
PLLA/PLGA	65.42	-	34.58	64.2 ± 0.35
PLLA/PLGA/PTX5	71.26	0.44	28.29	65.6 ± 0.38
PLLA/PLGA/PTX10	69.63	0.53	29.84	67.5 ± 0.45
PLLA/PLGA/PTX20	73.59	0.66	25.75	70.6 ± 0.36

place and consequently increased the chemical interactions and stability.

3.4. Surface characterization of PLGA/PTX coating

XPS allows the determination of elements and chemical compositions of the coating layer at its surface within 5 to 10 nm in depth through measuring the electrons associated with the atoms.[28] Table 1 summarizes the atomic percentage of carbon (C), oxygen (O), and nitrogen (N) contents for 0, 5, 10, and 20% PTX-loaded PLGA surfaces. For pristine PLGA, the main elemental compositions were carbon and oxygen with a percentage of 65.42 and 34.58%, respectively, which was in agreement with the previous report.[28,29] Once PTX was loaded in PLGA, a new peak at ~400 eV was observed which represented N1s peak of PTX molecule. Since PTX contains 47 carbons, it was expected for the carbon content to increase after PTX loading. Interestingly, as the loading amount of PTX in PLGA/PTX layer increased from 5 to 20%, the intensities of N1s and C1s increased, whereas the intensity of O1s decreased.

The hydrophobicity/hydrophilicity of material surface was measured by water contact angle. PLGA is co-polymer synthesized by ring opening polymerization of glycolic acid (hydrophilic property) and lactic acid (hydrophobic property). Based on the ratio between lactide and glycolide in the copolymer, the hydrophilicity and hydrophobicity of the polymer can be appropriately determined. Hence, increasing the lactide ratio give a hydrophobic character while, increasing the glycolide part enhance the hydrophilicity of the polymer.[30] The ratio used in this study was 50:50 and the water contact angle was 64.2°. According to Hasirci *et al.*, the water contact angle of PLGA 50:50 prepared by solvent casting was 67°, similar to our result.[29] The deviation of our results might be due to the presence of PLLA under layer. After the incorporation of lipophilic PTX, the water contact angle increased to 65.6, 67.5, and 70.6° for 5, 10, and 20%, respectively. Based on these results, it was clear that the change in the surface chemistry of the coating due to the addition of PTX had a significant influence on the surface wettability indicating an increase in surface hydrophobicity.[31]

3.5. *In vitro* PTX release profiles of PTX-in-PLGA coating

The cumulative release percentages of PTX from single layer PLGA/PTX and double-layer PLLA/PLGA/PTX coating on SS springs with 5, 10, and 20% PTX contents were monitored by *in vitro* elution test for up to 12 weeks and were summarized in Figure 4(A)-(C).

The release behavior of 5 and 10% PTX contents exhibited a two-phase release pattern including an initial burst release for two weeks followed by sustained release for up to 12 weeks. For 20% PTX content, the release profile presented three phases pattern including an initial burst release for two weeks, a nearly linear slow release phase between 2 and 8 weeks, and a subsequent fast release phase after 8 weeks. Interestingly, the higher-dose PTX samples (10 and 20%) displayed a slower release profile as compared to lower-dose PTX samples (5%). This phenomenon might be due to the higher hydrophobic property of 10 and 20% PTX samples that might prevent the water from penetrating the polymer bulk and therefore delayed degradation. The drug release profile from biodegradable matrix can be divided into an initial burst release phase followed by degradation-controlled phase.[32] Generally, the initial release of the drug from the biodegradable coating is related to the dissolution of the drug near to the surface. Meanwhile, the slow release is related to the hydrolytic degradation of the polymer which is eventually excreted from the body through metabolic pathways.[32]

It is worthy to note that, the amount of the initially released PTX from double-layer coating was significantly lower than from single layer coating between 1 and 7 days (38.7 *vs.* 42.4) for 5% PTX samples, (27.2 *vs.* 30.5) for 10% PTX, and (26.1 *vs.* 30.2) for 20% PTX as shown in Figure 4(C). For 5% PTX samples, the drug released showed no significance between 7 and 84 days. On the other hand, 10% PTX samples still kept a significance in reducing the drug release from PLLA containing samples for up to 84 days, whereas 20% PTX samples kept a significance until 56 days and lost after 56 days. Interestingly, the profile from PLLA/PLGA/PTX10 showed a reduced initial burst with control over the release period. In fact, an initial burst release of the drug is not recommended for stent application as it could cause cells toxicity.[20] In addition, the longer the drug release period of the stent, the lower the in-stent restenosis and the safer the DES is.[20] Several groups have studied the effect of interfacial layer thickness and wettability on drug release of the drug-in-polymer coating.[33,34] They found that hydrophobic or even hydrophilic brushes at the interface between the metal stent and drug-in-polymer matrix coating significantly decreased the degradation rate of the polymer coating and slowed the drug release. Similarly, the existence of PLLA could also affect the degradation of PLGA or poly(D,L-lactide) (PDLLA), and consequently slow the drug release from the matrix accompanied with reduced polymer degradation.[35,36] It is suggested that the existence of PLLA at the interface between spring surface and PLGA/PTX coating was the main reason to slow down PTX release. It is also expected

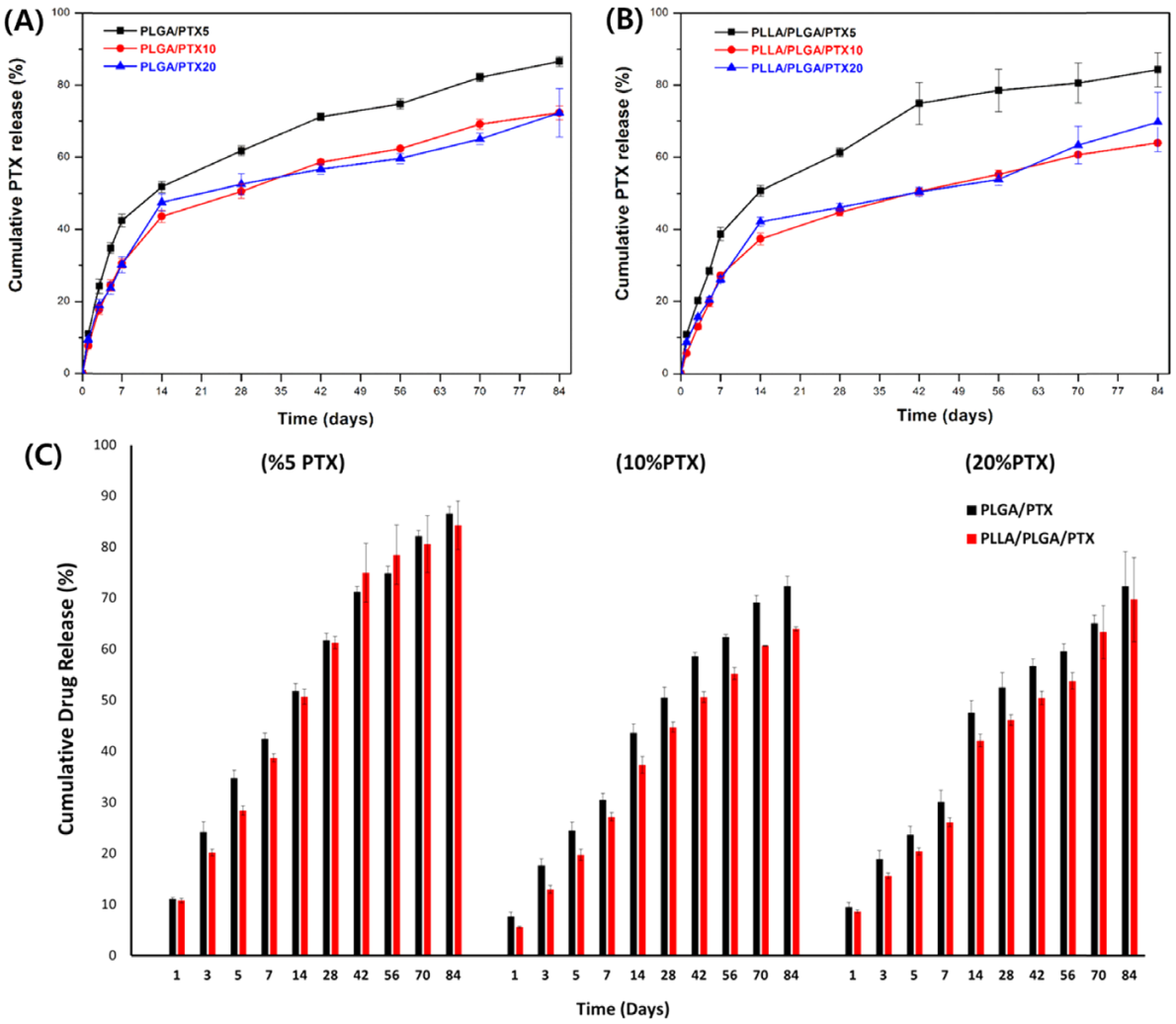

Figure 4. Release profiles of PTX from (A) PLGA/PTX coating, (B) PLLA/PLGA/PTX coating: (■) 5% PTX, (●) 10% PTX, and (▲) 20% PTX, and (C) cumulative release percentage between both samples.

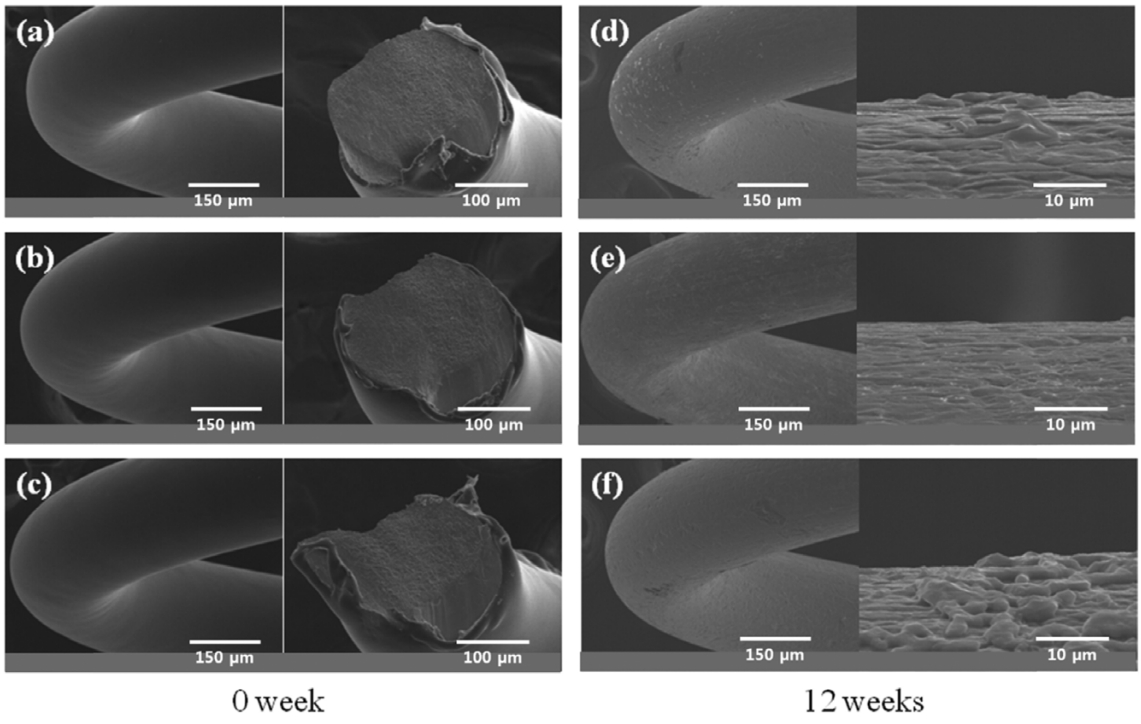

Figure 5. SEM images of PLGA/PTX coating surfaces: 5% PTX (a, d), 10% PTX (b, e), and 20% PTX (c, f) before and after *in vitro* degradation.

that the interaction between PTX and PLLA reduced the diffusion rate of PTX to the release medium.

3.6. *In vitro* degradation morphology of double-layer coated SS spring

The surface morphology of DES played a pivotal role in the success of clinical deployment. Generally, a smooth stent surface would significantly reduce the injury of the blood vessel and consequently reduced the incidence of thrombus formation as compared with rough stent surface.[37] From Figures 5(a-c) and 6(a-c), smooth surface and uniform coating layer for PLGA/PTX and PLLA/PLGA/PTX were obtained, respectively. The degradation of PLGA/PTX coating was also studied under physiological conditions after 12 weeks, and the surfaces morphologies were captured by FE-SEM. It was observed that the morphology of the polymer coating during degradation presented a different behavior. When PLGA/PTX coated directly on control SS spring, somewhat swelling with a rough surface composed of several PLGA debris was observed during degradation (Figure 5(d-f)). This morphology is not recommended for stent application as it could induce thrombosis formation. On the other hand, PLGA/PTX coated on ion beam-treated PLLA presented a smoother surface during degradation as shown in Figure 6(d-f). The hydrolytic degradation of PLGA occurs mainly due to four consecutive steps: (i) Hydration; the penetration of water into the amorphous region of the copolymer which leads to a decrease in glass transition temperature, (ii) initial degradation that involves the breakage of the covalent bonds results in chain length reduction, (iii) constant degradation involves a mass loss due to autocatalytic degradation, and (iv) solubilization; the release of low molecular weight fragment out of the coating matrix results in shrinking of the polymer structure.[38] Several factors could influence the degradation rate of PLGA films such as polymer compositions, crystallinity, molecular weight, drug type and loading, and pH of the media.[30] Moreover, introducing a hydrophobic and semicrystalline polymer to PLGA also affect the degradation rate. According to Fukushima *et al*., the degradation of PDLLA was delayed by blending with poly(ε-caprolactone) (PCL).[39] PCL molecules were able to prevent water diffusion into the bulk of PDLLA leading to the delayed degradation rate of PDLLA. In addition, surface modification of the stent could also influence the degradation rate, and morphology of the biodegradable-polymer coated DESs.[35] PLLA brushes at the interface improve the adhesion of PLGA coating to the surface and slow the degradation rate.[35] Similarly, the existence of PLLA bottom layer with a nano-pocket morphology delayed the degradation of PLGA and improved the degradation morphology.

3.7. *In vitro* ballooning of the double-layer coated SS stent

To investigate whether our double-layer coating technique could be applicable for DESs, PLLA/PLGA/PTX10 was coated on SS stent as previously mentioned and the stent was inflated to 3 mm in diameter. Figure 7 presents the SEM images of PLLA and PLLA/PLGA/PTX coating on stent surface after *in vitro* balloon inflation. Several reports proved the existence of polymer cracks after *in vitro* and/or *in vivo* stent expansion.[40,41] From our results, the double-layer coating protocol did not show any sign of cracks after stent ballooning which suggested the excellent applicability of our protocol to DESs. It is proved that the nano-pores of PLLA layer help PLGA to withstand against crimping and expansion forces. Moreover, the interfacial physical interactions and entanglements between PLLA and PLGA could be the reason for preventing the crack formation. Similar result for crack prevention of PLGA coating through introducing a

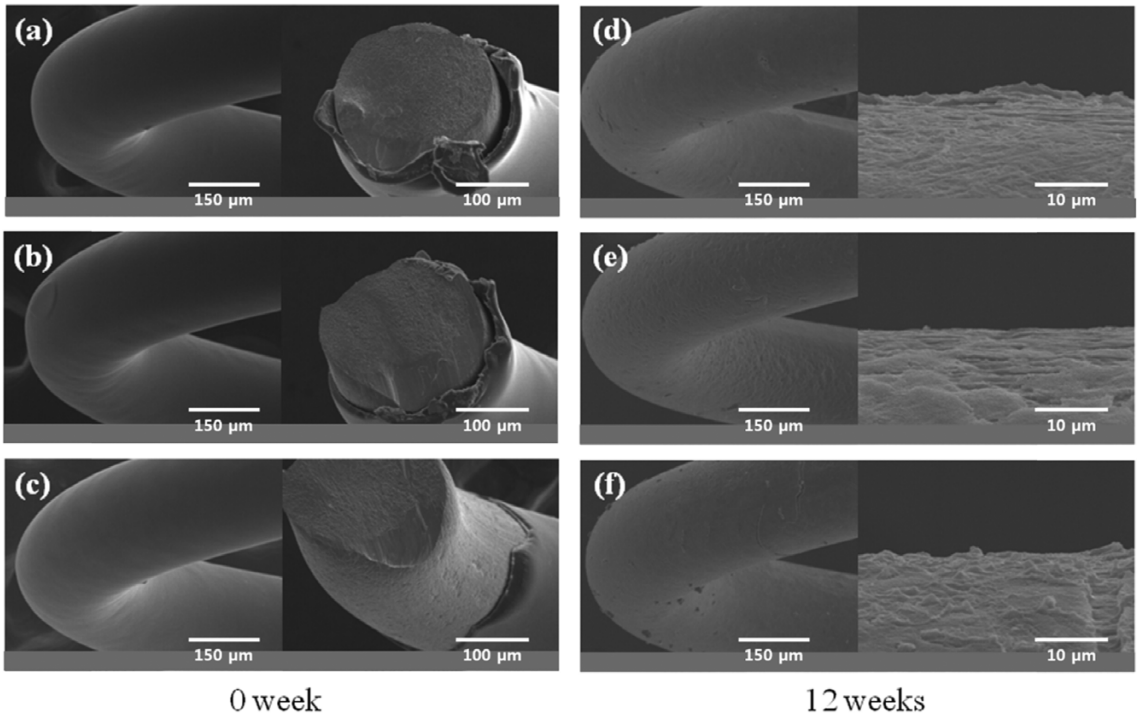

Figure 6. SEM images of PLLA/PLGA/PTX coating surfaces: 5% PTX (a, d), 10% PTX (b, e), and 20% PTX (c, f) before and after *in vitro* degradation.

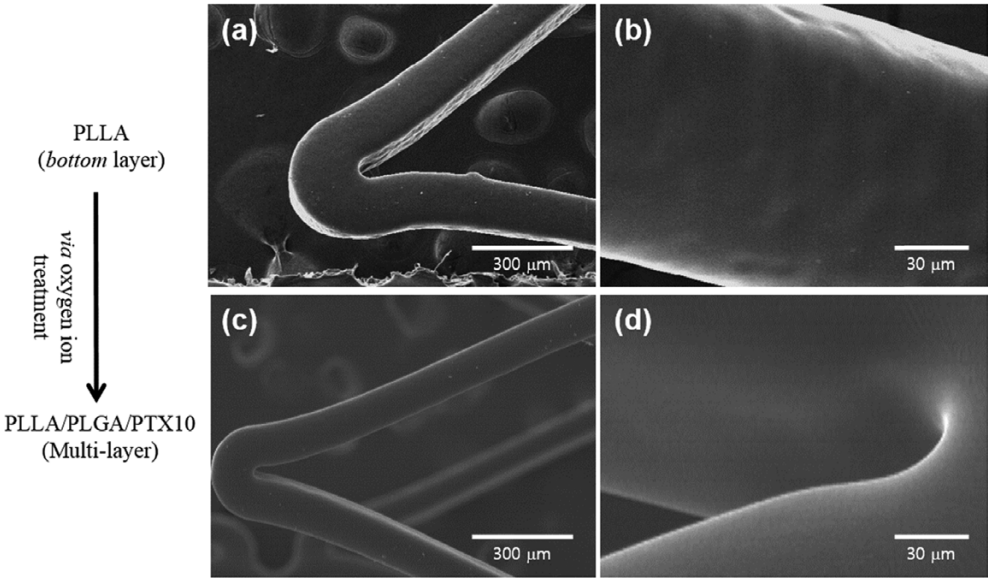

Figure 7. SEM images of SS stents coated with PLLA ((a) low magnification; (b) high magnification) and PLLA/PLGA/PTX10 ((c) low magnification, (d) high magnification) after balloon expansion.

thin layer of PCL brushes at the interface between the metal surface and PLGA coating was reported.[41]

4. Conclusions

Double-layer coating system has been successfully performed on the SS spring/stent surface with a smooth and uniform surface without webbing between stent strut. Ion beam treatment improved the roughness of PLLA bottom layer with a pocket-like morphology that enhanced the stability of the top layer coating. The PTX release from the double-layer containing SS samples exhibited a reduced initial burst release in a controlled manner as compared to the single-layer coated samples. Moreover, the degradation morphology has improved with a smoother surface for the double-layer containing samples. In addition, the crack formation of the double-layer coating was prevented after stent inflation. It is expected that this work could control the drug release, improve the degradation morphology and prevent the crack formation for various kinds of biodegradable polymer-based DESs, which might be promising for clinical study.

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