Biomaterials and Biomechanics in Bioengineering, *Vol. 1, No. 3 (2014) 131-150*
(Formerly, Biomaterials and Biomedical Engineering)
DOI: http://dx.doi.org/10.12989/bme.2014.1.3.131

Coating defects in polymer-coated drug-eluting stents

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(Received September 18, 2014, Revised September 22, 2014, Accepted September 23, 2014)

Abstract. Vascular stenting has a great attention as a treatment for coronary arteries diseases as compared with percutaneous balloon angioplasty. In-stent restenosis and thrombosis are side effects resulting from using bare metal stent (BMS). Employing platelet therapy allowed to reduce the rate of thrombosis, however, the rate of restenosis remains a major problem. In 2002, drug-eluting stents (DESs) were introduced as an effort to reduce the restenosis. The commercially available DESs continue to suffer from coating defects that might lead to a series of adverse effects. Most importantly, multiple concerns remain regarding the polymer coating integrity on metal surfaces or the relation of polymer irregularities to long-term adverse events.

Keywords: drug-eluting stent; thrombosis; restenosis; coating defects; durability

1. Introduction

The coronary arteries are the vessels that supply the heart with rich-oxygen blood. If the artery was narrowed or blocked by plaque, the amount of the oxygen that reaches the heart muscle will reduce leading to coronary artery disease (CAD). This narrowing is known as stenosis. CAD is a serious disease that leads to the death of millions of patients around the world.

The most common way to treat this blockage is to use percutaneous transluminal coronary angioplasty (PTCA). The major limitations of PTCA are early abrupt closure, late restenosis, constrictive remodeling, and intimal hyperplasia. Restenosis, re-narrowing of the artery, occurs up to 6 months after the initial procedure (Serruys *et al.* 1988). Therefore, bare metal stent (BMS) was developed as a promising solution.

BMS is a small mesh tube which is pre-loaded on a catheter and that is guided forward from the aorta to the blocked area. At the lesion site it is expanded within the vessel. After expansion, the

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http://www.techno-press.org/journals/bme&subpage=7 ISSN: 2288-3738 (Print), 2288-3746 (Online)

BMS serves as a scaffold to leave the artery open. The initial clinical results were interesting as the restenosis rate decreased from 40% to 20% (Fischman *et al.* 1994, Serruys *et al.* 1994). The re-narrowing of the artery after using stent is called in-stent restenosis (ISR). ISR results mainly from neointimal hyperplasia, increase the vascular smooth muscle cells (VSMCs) proliferation, migration, extracellular matrix and collagen synthesis triggered by vessel injury during implantation (Tesfamariam 2007). Drug-eluting stents (DESs) were developed to limit such problems (Alfonso *et al.* 2009, Butt *et al.* 2009, Martin and Boyle 2011).

DES devices are tubular mesh scaffolds made from metallic platform coated with thin polymer film containing anti-proliferative drug. The anti-proliferative drug prevents the overgrowth of VSMCs in the artery, and therefore reduces the incidence of ISR. Clinical results demonstrated a sustained suppression of neointimal proliferations and decreased the ISR rates after DES deployment as compared to BMS (Martin and Boyle 2011, Sousa *et al.* 2001).

Different generation of DESs was developed to improve performance. The first generation included thick stent strut coated with non-biodegradable polymers such as Cypher (sirolimus-eluting stent, Johnson & Johnson) and Taxus (paclitaxel-eluting stent, Boston Scientific). The early results were promising in reducing the restenosis rate. However, late stent thrombosis is still a major drawback, especially after the arrest of dual antiplatelet therapy. The second generation of DES was developed with thinner strut such as Endeavor (zotarolimus-eluting stent) and Xience V (everolimus-eluting stent) (Doostzadeh *et al.* 2010, Joner *et al.* 2008, Lange and Hillis 2010, Lopez *et al.* 2010, Sheiban *et al.* 2008). The permanent contact of these polymers with tissue and blood led to sever inflammation and endothelial dysfunction (Byrne *et al.* 2009, Cook *et al.* 2009, Virmani *et al.* 2004). This justified the large efforts undertaken to develop biodegradable reservoirs. Biodegradable polymer-coated DESs, polymer-free DESs, and fully bioabsorbable DESs were proposed as relevant alternatives. Even though all of the previously mentioned DESs have their limitations to be an excellent medical implant, one of the most serious problems in all types of DESs is coating defects.

Recently, the commercially available DESs, especially first generation, continue to suffer from irregularities in polymer coating leading to cracking, delamination, and peeling. These defects and irregularities increase the roughness of the stent surface and promote thrombus formation (Mani *et al*. 2007). Research in this area is currently focusing on developing safe stents on a longer term. The aim of this paper is to review the types of coating defects in several DESs and to summarize the efforts undertaken to diminish theirs impact.

2. Methods

The drug-eluting stents were made from metallic or inorganic scaffolds coated with a polymer and drug matrix. The metallic or inorganic framework in the stent provides the mechanical properties. It is used to maintain the artery open and prevent the elastic recoil. The therapeutic drugs are used to treat the disease locally. The polymers are used as a drug reservoir in order to control the drug release for a period of time.

2.1 Stent platform

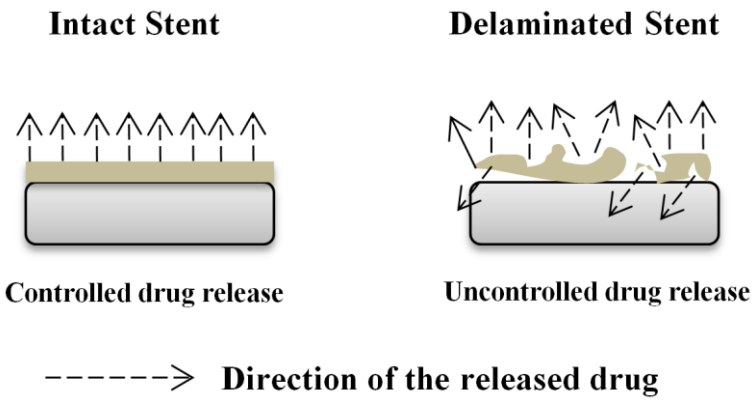
Stents were firstly made from biologically inert metal such as stainless steel. Recently, the cobalt-chromium alloy proved its superiority over steel as stent scaffold. This alloy possesses

Table 1 List of materials used for the platform strut of DESs

Stent material	Stent name	Reference
Stainless Steel	Cypher, Taxus, ZoMaxx, Supralimus, Excel stent, Biomatrix, NOBORI, Infinium stent, JACTAX HD, CORACTO	(Chevalier *et al*. 2008, Costa *et al*. 2009, Costa *et al*. 2008a, Danzi *et al*. 2010, Davlouros *et al*. 2011, Gao *et al*. 2008, Ge *et al*. 2007, Grube and Buellesfeld 2006, Grube *et al*. 2010, Guagliumi *et al*. 2010, Martin and Boyle 2011, Mehilli *et al*. 2006, Reifart *et al*. 2010, Waseda *et al*. 2011, Waseda *et al*. 2010, Wykrzykowska *et al*. 2009)
Cobalt-Chromium	Endeavor ZES, Endeavor Resolute, Xience V, Custom NX, NEVO, Elixir Myolimus, Elixir novolimus	(Basalus *et al.* 2010, Costa *et al*. 2008b, Garg and Serruys 2010, Jain *et al*. 2010, Martin and Boyle 2011, Parker *et al*. 2010, Stella *et al*. 2008)
Platinum-Chromium	Promus, ION stent	(Kereiakes *et al.* 2011, Parker *et al*. 2010)
Nickel-Titanium	Axxess	(Verheye *et al*. 2009)

Table 2 List of drugs used for the coating layer of DESs

Drug	Stent name	Reference
Paclitaxel	Taxus, ION stent, Infinium stent, JACTAX HD	(Davlouros *et al*. 2011, Grube *et al*. 2010, Guagliumi *et al.* 2010, Kereiakes *et al*. 2011, Martin and Boyle 2011, Wykrzykowska *et al*. 2009)
Sirolimus	Cypher, Supralimus, Excel stent, NEVO, CORACTO	(Biondi-Zoccai *et al*. 2008, Gao *et al*. 2008, Ge *et al*. 2007, Martin and Boyle 2011, Wykrzykowska *et al*. 2009)
Zotarolimus	Endeavor ZES, Endeavor Resolute, ZoMaxx	(Basalus *et al*. 2010, Chevalier *et al*. 2008, Jain *et al*. 2010, Martin and Boyle 2011, Parker *et al*. 2010, Waseda *et al*. 2011, Waseda *et al*. 2010)
Everolimus	Promus, Xience V	(Martin and Boyle 2011, Parker *et al*. 2010)
Biolimus A9	Axxess, Custom NX, BioMatrix, NOBORI	(Danzi *et al*. 2010, Grube and Buellesfeld 2006, Martin and Boyle 2011, Stella *et al*. 2008, Verheye *et al*. 2009)
Myolimus	Elixir myolimus	(Garg and Serruys 2010)
Novolimus	Elixir novolimus	(Costa *et al*. 2008b)



Scheme 1 Schematic illustration of the drug release behaviors from intact and delaminated stents

Table 3 List of polymers used for the coating layer of DESs

Polymer		Stent name	Reference
Non-biodegradable polymer	Polyethylene-*co*-vinyl acetate	Cypher	(Martin and Boyle 2011, Wykrzykowska *et al*. 2009)
	Poly-*n*-butyl methacrylate	Cypher, Xience V, Elixir novolimus	(Costa *et al*. 2008b, Martin and Boyle 2011, Parker *et al*. 2010, Wykrzykowska *et al*. 2009)
	Poly(styrene-*b*-isobutylene-b-styrene)	Taxus, Promus, ION stent	(Kereiakes *et al.* 2011, Martin and Boyle 2011, Parker *et al*. 2010, Wykrzykowska *et al*. 2009)
	Polyvinylidene fluoride-*co*-hexafluoropropylene	Xience V	(Martin and Boyle 2011, Parker *et al*. 2010)
Biological polymer	Phosphorylcholine	Endeavor ZES, ZoMaxx	(Chevalier *et al*. 2008, Guagliumi *et al*. 2010, Jain *et al*. 2010, Martin and Boyle 2011, Waseda *et al*. 2011, Waseda *et al*. 2010)
Biodegradable polymer	Polylactide	Axxess, Custom NX, Excel stent, BioMatrix, NOBORI, Elixir Myolimus, Infinium stent, JACTAX HD	(Danzi *et al*. 2010, Davlouros *et al*. 2011, Gao *et al*. 2008, Garg and Serruys 2010, Ge *et al*. 2007, Grube and Buellesfeld 2006, Grube *et al*. 2010, Guagliumi *et al*. 2010, Martin and Boyle 2011, Stella *et al*. 2008, Verheye *et al*. 2009)
	Polyvinyl pyrrolidone	Supralimus, Infinium stent	(Davlouros *et al*. 2011, Martin and Boyle 2011)
	Polylactide-*co*-caprolactone	Supralimus, Infinium stent	(Davlouros *et al*. 2011, Martin and Boyle 2011)
	Polylactide-*co*-glycolide	Supralimus, NEVO, Infinium stent, CORACTO	(Davlouros *et al*. 2011, Martin and Boyle 2011, Reifart *et al*. 2010)

higher strength value and x-ray attenuation that help to design thinner stent strut as compared to steel. The commonly used metals for stent manufacture and name of the corresponding stent are summarized in Table 1.

2.2 Drugs

DESs provide both the mechanical and biological solution to treat the stenosis and prevent the ISR. Three important factors should be taken into account for DESs design: (a) employing the most appropriate drug, (b) optimizing the local dose of the drug, and (c) employing an appropriate biocompatible vehicle to deliver the drug (Kavanagh *et al.* 2004, Teomim *et al.* 1999).

Four classes of drugs are used in DES including: (a) anti-inflammatory, (b) anti-thrombogenic, (c) anti-proliferative, and (d) immunosuppressive drugs. These drugs are used to inhibit the pathways leading to restenosis and to inhibit proliferation of endothelial cells (Axel *et al.* 1997). The drugs that strongly interfere with re-endothelialization may lead to thrombosis and restenosis. A list of such drugs and name of the corresponding stents are summarized in Table 2.

2.3 Polymers

The polymer used for stent reaction should verify some requirements including biocompatibility, non-thrombogenicity, non-inflammatory reaction, non-toxicity to cells, and re-endothelializations process. Additionally, polymer coating on DES surface should be able to stretch without cracking, delaminating, or flaking and be able to sustain (control) the drug released (Levy *et al.* 2009a, Parker *et al.* 2010).

The polymers can be classified as: a) durable (non-biodegradable) polymers such as polyethylene-co-vinyl acetate, poly-n-butyl methacrylate, poly(styrene-b-isobutylene-b-styrene), (b) biodegradable polymer e.g. polylactide (PLA), polyglycolide (PGA), and their co-polymers, and (c) biological polymers e.g. phosphorylcholine (PC) and hyaluronic acid (HA) (Mani *et al.* 2007). The polymer is mixed with drug carefully in order to govern the elution of the drug to the arterial tissue. The polymers for various DES types are summarized in Table 3.

3. Coating defects

DESs are made of metallic scaffold coated with a mixture of polymer and desirable drug in order to prevent the in-stent restenosis that mainly occurs after BMS deployments. The polymer matrix must be firmly attached to the stent scaffold to maintain high stent quality during handling, crimping, deliverability, expansion, and throughout the device life cycle. Additionally, the polymer coating must control the pharmaceutical compound release and prevent peeling or flaking that accompanies the stent deployment. Joung *et al.* (2014) tried to identify the optimal conditions for polymer coating and drug release profile on DES (Joung *et al.* 2014).

Table 4 Coating defects categories of durable polymer-coated DESs

Category	Type	Stent name
I. Irregularities with reduced thickness	IA. Small or big areas with aspect of bare metal (Fig. 1(a) and 1(b))	Xience V and Endeavor Sprint
	IB. cracks (Fig. 1(c))	Endeavor Resolute
	IC. Reduced thickness at strut crossings (Fig. 1(d))	Taxus Liberté
II. irregularities with increased thickness	IIA. "Auricle-shaped" excess of coating (Fig. 1(e))	Taxus Liberté
	IIB. Ridge-shaped excess of coating (Fig. 1(f))	Xience V
	IIC. Small round structure of excess coating (Fig. 1(g))	Xience V
III. Irregularities with inhomogeneous coating	IIIA. Crater-shaped with metal exposure (Fig. 1(h))	Endeavor Resolute
	IIIB. Crater-shaped without metal exposure (Fig. 1(i) and 1(j))	Xience V and Endeavor Resolute
	IIIC. Small crater-shaped irregularity (Fig. 1(k))	Taxus Liberté
	IIID. Wrinkles i.e., shallow minimal linear irregularities (Fig. 1(l))	Xience V
	IIIE. Flatten coating (Fig. 1(m))	Endeavor Resolute
IV. irregularities with displacement of coating	IVA. Webbing with metal exposure (Fig. 1(n))	Taxus Liberté
	IVB. Webbing without metal exposure (Fig. 1(o))	Taxus Liberté
	IVC. Fragments of coating i.e., detached piece of coating (Fig. 1(p))	Xience V

Due to different physical and mechanical properties between the stent scaffold and the polymer matrix, polymers do not adhere firmly to the stent substrate. If the coating is not adhering well to the stent scaffold, it may induce a series of adverse and interrelated events including non-uniform local drug distribution that may increase the accidence of neointimal hyperplasia, local inflammation, and thrombosis (Hwang *et al.* 2005).

3.1 Durable polymer-based DES

Several kinds of coating defects happen due to mechanical stress and the instability of the coating on the substrate. Otsuka *et al.* (2007) studied the morphology of the polymer on three commercially available polymer-coated stents after balloon expansion in saline solution at 37^{o}C.

The BiodivYsio stent showed no irregularities on the outer surface, but polymer was peeled off from the inner surface. An excess of polymer was also present on the stent edges. The Taxus stent also did not display any irregularities on the outer surface, but there was polymer bridging across the strut and linear cracking across the bridges, as well as bare-metal exposure on the inner surface.

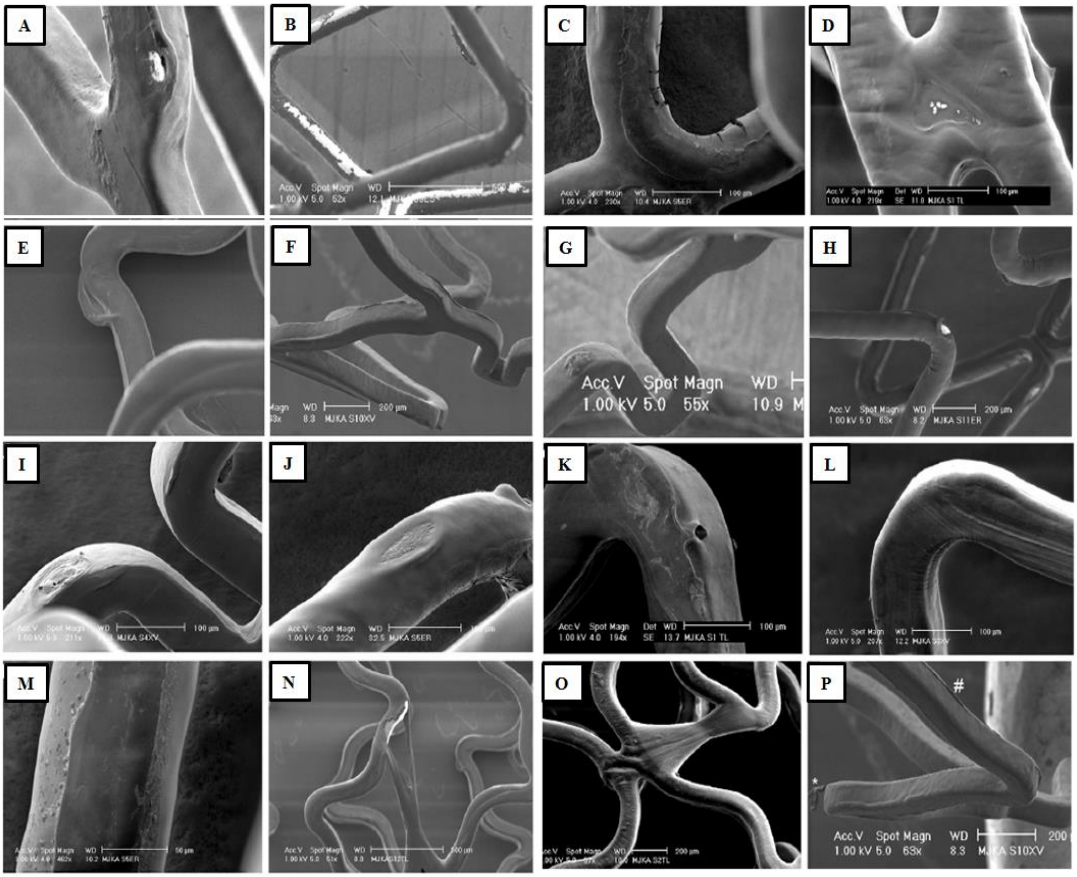


Fig. 1 SEM images of various coating irregularities of (i) Xience V (Fig. a, f, g, i, l, and p); (ii) Endeavor Sprint (Figure b); (iii) Endeavor Resolute (Fig. c, h, j, and m); and (iv) Taxus Liberté (Fig. d, e, k, n, and o)

The Cypher stent showed a rough surface with irregularities and waving on the outer surface. The balloon expansion on BiodivYsio stent in air didn't indicate any change with that expanded in saline solution. However, expanded Taxus and Cypher demonstrated more bridging and cracking after expansion in air (Otsuka *et al.* 2007).

To evaluate the shape and size of the coating irregularities, Basalus *et al.* (2009a) employed a quantitative analysis of coating irregularities on the durable polymer-based DESs using SEM images captured from both luminal and abluminal sides. Four different stents, Xience V™, Endeavor Sprint™, Endeavor Resolute™, and Taxus Liberté™, were examined. All the images showed coating irregularities with different damage ratios. Based on the thickness and/or displacement of the polymer coating, the coating irregularities were classified into four categories: (I) reduced coating thickness, (II) increased coating thickness, (III) inhomogeneous thickness of coating, and (IV) displacement of coating as summarized in Table 4 and Fig. 1 (Basalus *et al.* 2009a). Cracks in the coating were found only in Endeavor Sprint and Endeavor Resolute, while Taxus Liberte was the only DES type that showed webbing with and without bare-metal exposure. On the other hand, Xience V displayed wrinkles exclusively. The exposure of bare-metal area was largest on Endeavor Sprint, while the incidence on Xience V was particularly low (Basalus *et al.* 2009a).

Denardo *et al.* (2012) employed bright field microscopy to define the coating defects on Xience V, Taxus Liberte, Cypher, and Endeavor stents as: (I) delamination, complete detach of the polymer from the stent surface; (II) webbing, distortion of the polymer between stent struts; (III) peeling, partially but incomplete detach of the polymer from the surface; (IV) ridging, dislocation without delamination but accumulation of the polymer to make an elevated mass on the stent surface; and (V) cracking, fracture through entire polymer thickness as described in Fig. 2 (Denardo *et al.* 2012).

Calcifications are a common problem in coronary artery disease. Almost 58% of patients with documented coronary artery diseases suffer from calcifications (Gianrossi *et al.* 1990). It was interesting to investigate if calcified lesions can damage drug eluting stent coatings. Wiemer *et al*.

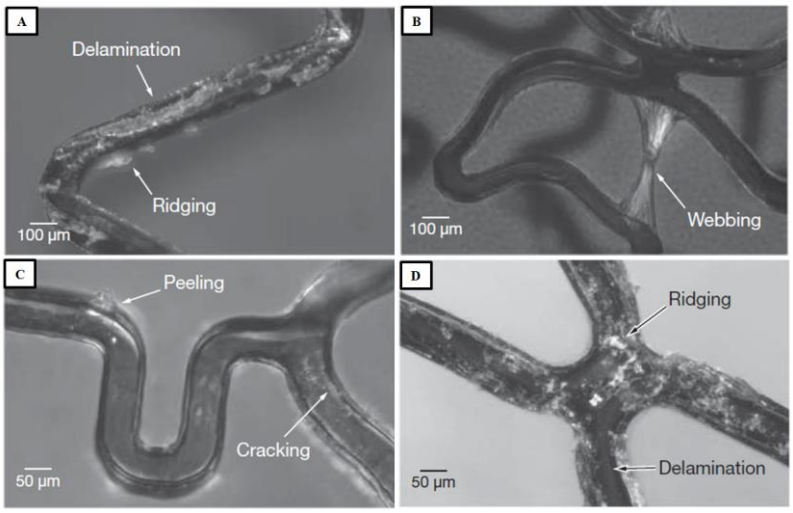


Fig. 2 The optical microscopic images that explain the coating defects in various polymer-coated DESs: (a) Xience V, (b) Taxus Liberte´, (c) Cypher, and (d) Endeavor

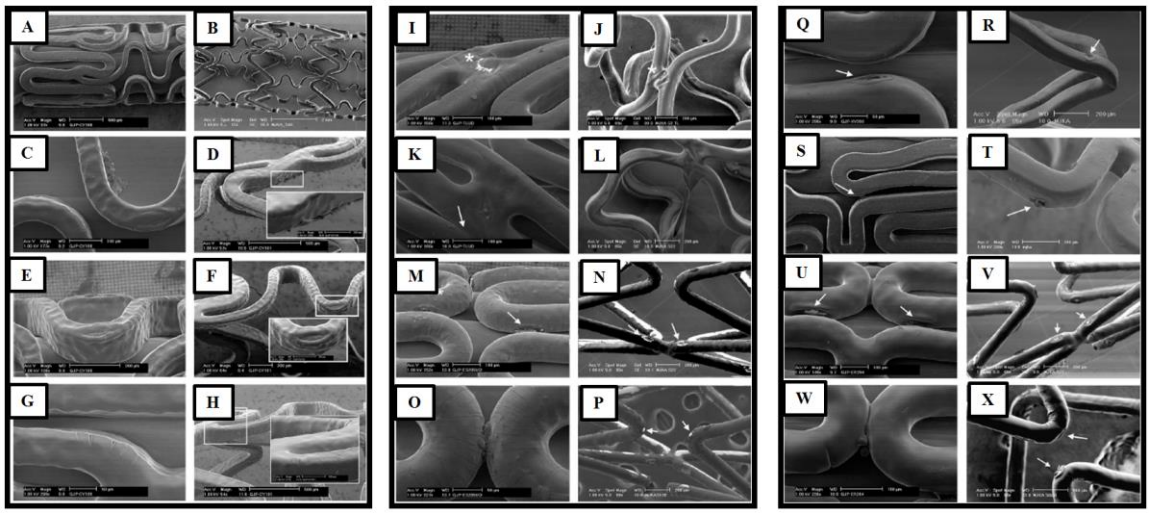


Fig. 3 The SEM images of Cypher selected stents (a-h) [(a) unexpanded stent; (b) expanded stent; (c) precursor of peeled polymer; (d) peeled polymer; (e and f) crater lesions on unexpanded and expanded stents; (g and h) mild crack present on unexpanded and expanded stent], Taxus Liberte´ stensts (i-l) [(i and j) thinning of polymer at strut crossing for unexpanded and expanded stents; (k) adhesion of polymer coating on unexpanded stent; (l) Webbing on expanded stent], Endeavor Sprint stents (m-p) [(m) small bare metal area and crater lesion on unexpanded stent; (n) Crater lesions on expanded stent; (o) mild crack and adhesion on unexpanded stent; (p) crater lesion on expanded stent], Xience V stent (q-t) [(q and r) crater lesions on unexpanded and expanded stents; (s) A precursor of crater lesion on unexpanded stent; (t) crater lesions on expanded stent], and Endeavor Resolute stents (u-x) [(u) crater lesion on unexpanded stents; (v) crater lesions on expanded stents with cracks at the inner curvatures; (w) A precursor of crater lesion on unexpanded stent; (x) crater lesions on expanded stent with some cracks at the inner curvatures]

studied the morphology of the polymer coatings on different DESs in tortuous vessels and/or calcified lesions (Wiemer *et al.* 2010). The polymer coating on Taxus^{TM}, Cypher selected^{TM}, and Xience V^{TM} DES showed a slightly damaged area (less than 3% of surface area), whereas the EndeavorTM stent showed up to 20% damaged surface area after failed implantation in calcified lesion in the artery. They concluded that the placement of DES in calcified lesions or tortuous vessels could cause major coating defects by scratching and scraping the polymer, even before implantation (Wiemer *et al.* 2010).

Recently, the origin of coating irregularities on unexpanded and expanded durable polymer-based DESs such as Cypher Select Plus, Taxus Liberte´, Endeavor Sprint, Xience V, and Endeavor Resolute were assessed and quantified by SEM analysis (Basalus *et al.* 2012). The coating irregularities on the unexpanded stent were identified and compared with the expanded one. The unexpanded Cypher stent showed small crater lesions and cracks together with precursor of peeling (Figs. 3(a)-(h)). "Precursor" refers to the coating irregularities on unexpanded stents that differed morphologically from those observed on the corresponding expanded samples while sharing the same location. Unexpanded Taxus Liberte stent revealed thinning of polymer, small area of bare-metal, wrinkles, and one type of precursor (Figs. 3(i)-(l)). Unexpanded Endeavor Sprint stents displayed cracks, small area of bare-metal, crater lesions, and their precursor (Figs. 3(m)-(p)). The unexpanded Xience V (Figs. 3(q)-(t)) and Endeavor Resolute stents (Figs. 3(u)-(x)) mainly exhibited crater lesions and their precursors. There is no difference between the

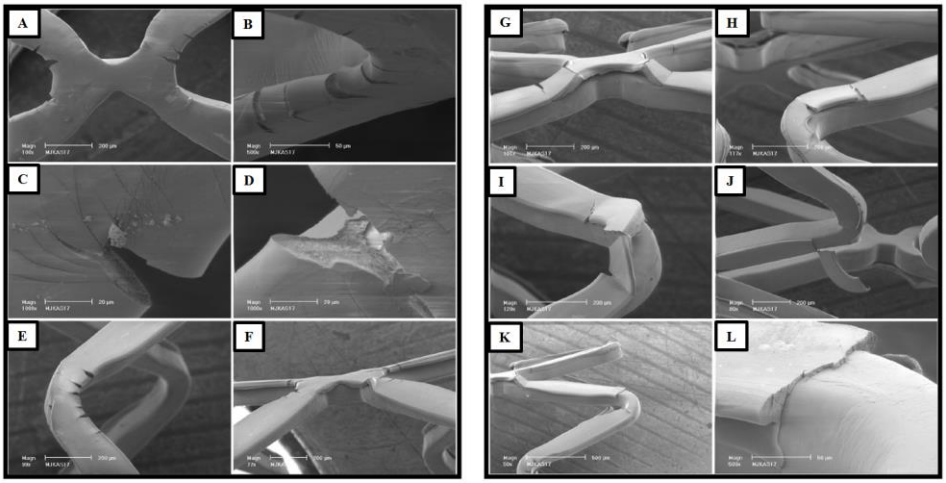


Fig. 4 SEM images of biolimus-eluting stents (BioMatrix stent) at different ballooning conditions: (a-f) expanded in air at 14^{o}C and 14 atm without post-dilatation; and (g-l) expanded in water at 37^{o}C and 14 atm without post-dilatation

unexpanded and expanded stents in the frequency of coating irregularities. However, they only differ in the area of the bare-metal exposure especially on the expanded Taxus Liberte. Most of the coating irregularities on the expanded stents are inherent to the unexpanded DES. This means that balloon do not play any role in the coating irregularities. The design of stent and physical properties of the coatings may be the important determinants of the formation of coating irregularities (Basalus *et al.* 2012).

3.2 Biodegradable polymer-based DES

Earlier research on expanded DES demonstrated loosely attached polymer particles of wide size of 30 μm on durable polymer-based DES versus up to 300 μm on biodegradable polymer-based DES (Basalus *et al.* 2009a, Basalus *et al.* 2009b). Basalus *et al.* (2009b) also suggested a relatively low elasticity of the biodegradable coating on BioMatrix stent. At nominal pressure, stents showed mild cracks, while cracks increased after slightly overstretch (Basalus *et al.* 2009b). Moreover, the incidence of the polymer cracking increased in BioMatrix stents expanded in water as compared to air as shown in Fig. 4 (Basalus *et al.* 2009b). These results were in agreement with Yazdani's study (Yazdani *et al.* 2011). These authors analyzed integrity on various types of stents after in vitro and in vivo expansion. They demonstrated polymer coating defects on the abluminal surface of all DESs including polymer crack (BioMatrixTM), bridging (Taxus LiberteTM), round-small defects (Cypher SelectTM), and flaking (Xience VTM) after seven days in healthy swine coronary arteries. The in vitro results showed the greater cracking and lifting of the polymer on the BioMatrixTM stent as compared to in vivo implanted stents (Yazdani *et al.* 2011).

4. Methods to determine the coating defects

To the best of our knowledge, there are only three devices which can determine the coating

irregularities qualitatively and/or quantitatively. The stability of coating over long period of time could be examined through these devices: light microscopy, scanning electron microscope, and micro-balance (Levy *et al.* 2009a).

4.1 Light microscopy

Light microscopic images show the coating defects qualitatively as the reflected light from the metallic surface appears as white spots. However, mild defects such as minor peeling or cracking cannot be resolved because of reflection from the metallic surface (Levy *et al.* 2009a).

4.2 Scanning electron microscopy

SEM is a technique which allows shedding electron on the origin of DES coating irregularities after carefully inspection of the coating before and after mechanical stress including crimping, deliverability, and stent expansion (Levy *et al.* 2009a). It can closely examine the above-mentioned defects, not only qualitatively but also quantitatively. Two methods could be used to quantify the coating defect. Quantified defects (QD) index in obtained when using the following method: five of two different areas on stent were chosen randomly - the maximum stress areas and the flexible curves - to give ten images. The total number of defects (e.g., cracking, webbing, delamination, and/or peeling) are counted and summed to generate a score ranging from zero to ten. The average score of four stents is recorded and the percentage (%) is calculated. Higher the values of QD index mean lower stability. It is derived from the more defects of the coating (Levy *et al.* 2009a). Another method to determine the coating defect quantitatively is based on calculating the size and dimensions of the coating defect from SEM images. The defect areas identified are translated into number of pixels per image. The number of pixels is multiplied by the surface area presented by single pixel. The total defect area, S_{DA}, is the sum of defect areas measured for each image. The defect area is presented as, % defect area, R_{DA}, according to [$R_{DA}=(\Sigma S_{DA}/S_{SA})*100$] where, S_{SA}, is the visible stent surface area (Balss *et al.* 2012).

4.3 Micro-balance

Micro-balance is used to determine the weight loss of the coating. This quantitatively estimates the extent of degradation, drug release as well as the coating particulates. This method cannot evaluate the coating defect directly but it reflects the stability of the coating that in turn related to coating defects. This method could be used especially when the durability of the coating is studied in buffered media for specific time. The stent are weighted at time zero. The stent is then taken out, dried, and weighted at regular time intervals. The differences represent the degraded product and the delaminated amount. Higher values of weight loss mean faster degradation and release rates.

5. Methods of surface modification

It is essential that the adhesion strength of the coating on the substrate must be higher than the cohesion strength between the polymeric matrixes. A method to improve the adhesion strength would be beneficial. This could be done by using an adhesion promoter or primer at the interface

Table 5 Standard adhesion test, QD index, and weight loss results of the control and electro-modified stainless steel plate

Incubation time (days)	Peeling (%, S.D)		QD index (%)		Weight loss (μg)	
	Control	Electrocoated	Control	Electrocoated	Control	Electrocoated
0	0 (0)	0(0)	3±5	3±5	0	0
3	86.6 (13)	24.2 (11.2)	58±18	10±12	9±1	8±2
15	90.6 (4.2)	30.4 (22.1)	-	-	-	-
30	94.3 (3.6)	66.1 (30.2)	95±5	8±10	59±6	32±6

between the polymer/drug coating and the underlying stent frameworks. Such primer should be biocompatible, stable, easy to process and able to promote good adhesion between the stent surface and the coating. Several methods to meet these assumptions are summarized below.

5.1 Durable polymer-coated DES

To improve the durability of the coated layer, Parylene C, a non-degradable polymer, has been widely used for coating of DESs. However, side effects from permanent contact of this polymer with blood arise and cause inflammation and late thrombosis. A very stable thermoplastic phenoxy resin, acts as a bridge primer between the stent framework and the drug-in-polymer matrix, was also used. This resin showed good adhesion properties to the metals and the polymer/drug mixture. Also, this resin is tough and flexible. This primer could be optionally crosslinked using isocyanate to control the hardness. The phenoxy resin contains both hydroxyl and ether groups. These groups have the ability to bind strongly to the underlying stent framework and to the polymer coating as well. The phenoxy resin is dissolved in organic solvent such as chloroform, and then the stent is dipped in phenoxy resin solution, dried, and further coated with drug-in-polymer matrix. The thickness of the primer is between 200-600 nm and the weight is ranging from 20 to 70 μg (Cheng *et al.* 2004).

Levy *et al.* (2009a) demonstrated the relation between the modification of stent surface and the durability of polymer/drug coating in both physiological and accelerated conditions according to single and dual layer coating models (Levy *et al.* 2009a). A nano-layer of 4-dodecyloxyphenyldiazonium tetrafluoroborate was electro-coated on the stent surface to generate a chemically grafted basecoat of aliphatic aryl groups (Levy *et al.* 2009a, Levy *et al.* 2009b). These substances undergo a cleavage of carbon-nitrogen bond upon reduction producing a reactive free radical species that covalently bound to several metal surfaces and carbonaceous materials with 5 to 10 nm thickness (Adenier *et al.* 2001, Pinson and Podvorica 2005). The biocompatibility study of the basecoat showed inert properties (Levy *et al.* 2009b). The quantitative results of standard adhesion test, QD index, and weight loss demonstrated that nano-layer of this substance significantly enhanced the adhesion and the stability of the polymer/drug coatings on the metallic stent as shown in Table 5 (Levy *et al.* 2009a, Levy *et al.* 2009b). Additionally, the modified stent didn't show any defects for the coating whereas the control stents displayed several kinds of coating defects such as peeling, cracking, and delamination. In summary, the durability of coatings was higher on the electro-coated stent when compare to the control. Moreover, the improved durability exhibited a stabilized drug release (Levy *et al.* 2009b). The electro-grafting of diazonium salts on the metallic implants allows diverse surface modification with various

functionalities.

A few studies reported on the polymerization of N-substituted pyrrole by electrochemical oxidation. Okner *et al.* (2007) reported the copolymerization of *N*-(2-carboxyethyl)pyrrole (PPA) and a butyl ester of PPA (BuOPy) on glassy carbon and stainless steel substrate (Okner *et al.* 2007). The rate of BuOPy electro-polymerization was higher than that of PPA due to more hydrophobic nature of BuOPy that enhances electron transfer on this hydrophobic surface. The electrochemical oxidation of the hydrophobic BuOPy on stainless steel plate has a higher roughness value as compared to the hydrophilic PPA compound. Therefore, the surface roughness can be controlled by using different BuOPy:PPA ratio. A primer of three different pyrrole derivatives was coated on stainless steel stent by an electrochemical deposition. This primer improved the stability, adhesion, coating morphology, and paclitaxel release profile on methyl and lauryl methacrylate coated DES. This primer possesses good adhesion to the stent platform surface and the polymer coating. This primer roughened the stent surface providing excellent morphology to enhance the adhesion with the polymer coating (Okner *et al.* 2009).

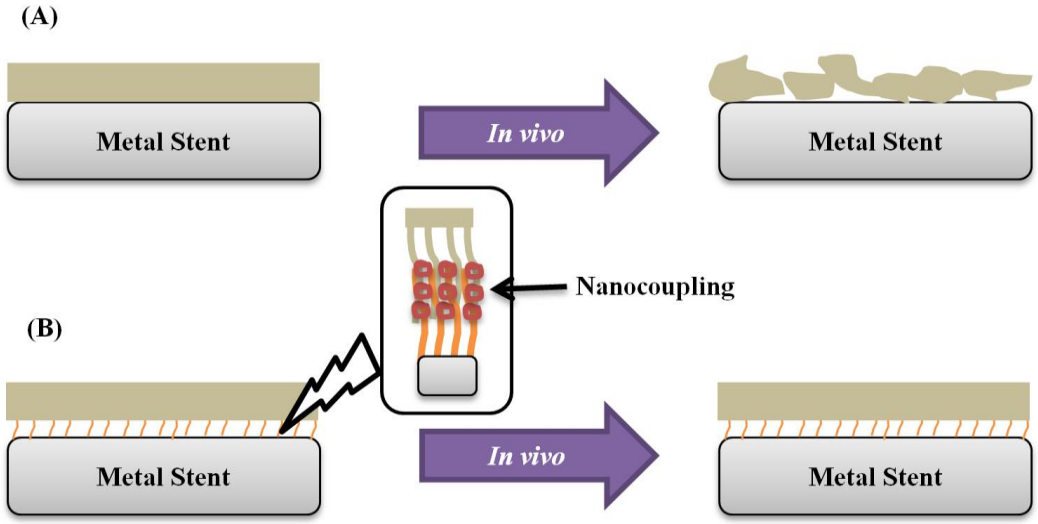
Polymer brushes have attracted a great deal of attention over the past few years. They can provide the metallic surface with a variety of properties such as hydrophobic and/or hydrophilic characteristics. These polymer brushes could enhance the adhesion of the coating to the metal substrate and thereby prevent the coating delamination. The interactions that could form as a result of polymer brush at the interface might be hydrophobic interactions, physical interactions, and entanglement between the polymer brushes and the coated polymer. Therefore, some researchers suggest that, these polymer brushes might be the best way to prevent the coating defects. The schematic illustrations of the polymer brush function at the interface are explained in Scheme 2.

Shaulov *et al.* (2009) successfully modified the stent surface with 4-(2-bromoethyl) benzenediazonium tetrafluoroborate by electrochemical reduction method. The bromide end diazonium salt initiates the polymerization of methyl methacrylate through atom-transfer radical polymerization. The schematic illustration for the cardiovascular surface modification was presented in Scheme 3. These poly(methyl methacrylate) brushes significantly improved the durability of the drug-in-polymer matrix on DES surface as well as controlled the paclitaxel release (Shaulov *et al.* 2009).

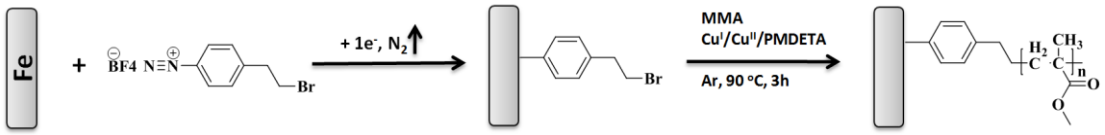
5.2 Biodegradable polymer-coated DES

Biodegradable polymers coating DES are hydrolyzed slowly and degraded into small molecules. The molecules are metabolized into natural products such as carbon dioxide and water that are released from the body through metabolic pathways. It was hypotheses that after complete degradation of these polymers, only BMS remains in contact with the artery wall. Several studies have been performed to improve the adhesion, durability, control the drug release, and remove the adverse events from using a non-biodegradable primer.

Hanefeld *et al.* (2006) studied the adhesion of poly(lactide)-poly(ethylene oxide)-poly(lactide) triblock copolymers (PLA-PEO-PLA) and PLA polymer on poly(p-xylylene) (PPX-N) coated stainless steel substrate. The PPX-N coating was prepared by vapor phase pyrolysis of [2.2]-paracyclophane and subsequent chemical vapor deposition (CVD) of quinodimethane according to the Gorham process (Miesserov 1966). From the blister test, the triblock copolymer showed excellent adhesion property to the prewetted PPX-N surface, whereas the PLA coated samples showed week adhesion property. Mechanical expansion of the PLA coated stent showed a lot of defects. On the other hand, the PLA-PEO-PLA coated stent showed a smooth coating after



Scheme 2 Schematic illustration of the nanocoupling strategy (enhance the durability of polymer-based DES). (a) The polymer coated on metal stents without modification results in uncontrolled degradation and easy delamination; (b) The polymer coated on polymer brush modified stent results in controlled degradation and no delamination [the red rings refer to the entanglements that occur between the brushes and the coating polymer]

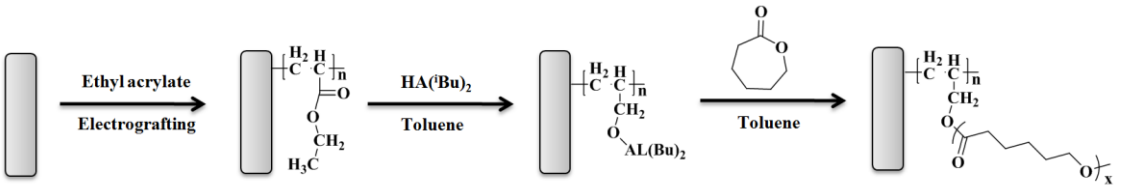


Scheme 3 Schematic illustration of the successive modification steps of the stainless steel (SS) stents [MMA, methyl methacrylate]

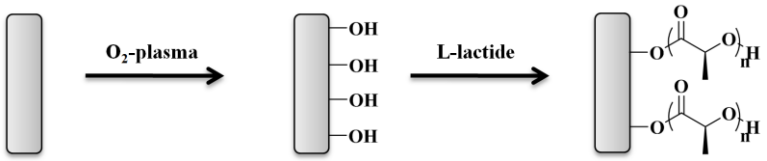
expansion with very few small cracks (Hanefeld *et al.* 2006). Unger *et al.* (2007) proved that the prewetted PPX-N coating allows good adhesion to poly(ethylene carbonate) (PEC), a rubber like, biodegradable polymer and helps it to withstand expansion better than PLGA. The tensile testing for the PEC showed a stress to strain more than 600% (Unger *et al.* 2007). This shows that the interfacial ultrathin layer modification could be beneficial for some polymers and has no effect on others.

Electrochemical grafting is employed for grafting a polymer coating conductive substrates such as steel, stainless steel, tantalum, Nitinol, and transition metals. This interesting method can produce a variety of covalently grafting polymers (Bertrand *et al.* 2002). The strongly adhered biocompatible and biodegradable polyester brushes were grafted on cardiovascular stents through two steps. The first step includes an covalent electro-grafting process of poly(ethylacrylate) (PEA) by cathodic reduction. In the second step, the ester groups of the PEA were reduced by diisobutylaluminum hydride forming aluminum alkoxide terminal groups that are able to initiate the ring opening polymerization of D,L-lactide (LA) or ε-caprolactone (CL) as shown in Scheme 4.

The PDLLA or PCL brushes that formed on the stent surface could act as anchoring layer for



Scheme 4 Schematic illustrations of surface modification on tantalum and stainless steel stents through a combination of electro-grafting and ring-opening polymerization (ROP)



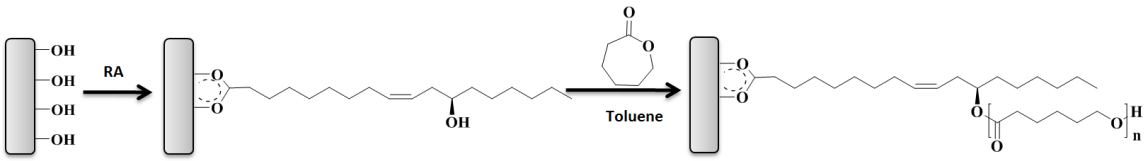
Scheme 5 Surface modification of stainless steel by using SI-ROP to produce PLLA brushes at the surface

the subsequent drug-in-polymer matrix layer (Jerome *et al.* 2006). After complete degradation of the biodegradable polymer coating and brushes, the covalently attached polymer will be remained on the stent surface that might has adverse hazardous events. Therefore, researchers decide to use a biodegradable polymer brushes as a primer to achieve their goal and also degraded with time leaving BMS without adverse events.

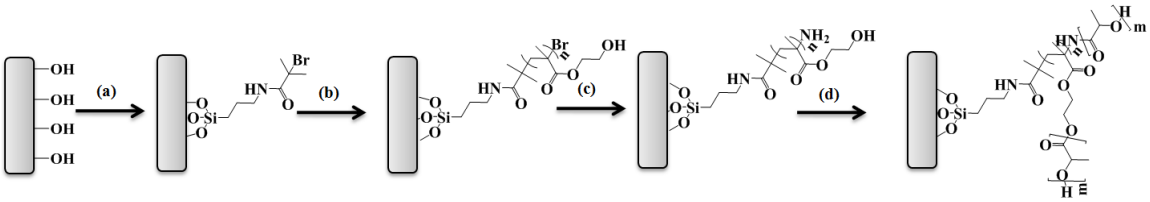
The biodegradable polymer brushes were proved their ability to improve the interfacial adhesion between the biodegradable polymer coatings and metal substrates (Bedair *et al.* 2014b, Choi *et al.* 2011). Choi *et al.* (2011) tried to modify the surface of stainless steel with 4 nm thickness of PLLA brushes through direct surface-initiated ring-opening polymerization (SI-ROP) of L-lactide as illustrated in Scheme 5. From the adhesion tests and the degradation behavior, it was demonstrated that the nanocoupling affects not only the adhesion strength, but also the degradation behavior of the polymer coating.

Recently, the Co-Cr alloy was successfully modified with two different thicknesses of poly(*ε*-caprolactone) (PCL) brushes that was 10 and 16 nm in thickness. This was accomplished using a spacer of ricinoleic acid (RA) that initiates the ROP of caprolactone for 3 and 6 days as shown in Scheme 6. They studied the effect of the thickness on the adhesion stability and drug release profile. It was noticed from the scratch test analysis that increasing the thickness of the PCL brushes increases the adhesion force between the biodegradable coating and the Co-Cr alloy surface and decreases the drug elution. In fact, there is no report about the optimal thickness of the polymer brushes that achieve the best coating stability (Bedair *et al.* 2014b). In addition, Cho *et al.* (2014) suggested strongly the nanocoupling strategy to address the cracking issue of polymer coating on DES by introducing the RA-PCL brush on the surface of Co-Cr stent (Cho *et al.* 2014).

Bedair *et al.* (2014a) also studied the effect of polymer brushes on the durability of the polymer/drug coating. The surface modification steps of Co-Cr were shown in Scheme 7. The durability of the coating was tested on modified and control Co-Cr plates under physiological conditions. It was noticed that PLLA brushes at the interface improve the durability of biodegradable coatings. SEM images showed a smooth coating morphology of the PDLLA coating on brush modified sample. On the contrary, the control sample showed complete detachment of polymer coating after 4 weeks at the same conditions. Also, the blood compatibility test exhibited



Scheme 6 Surface modification steps of Co-Cr with 10 and 16 nm thickness of PCL brushes [RA=ricinoleic acid]



Scheme 7 The modification steps of Co-Cr including (a) silanization step; (b) ATRP of HEMA; (c) azide formation and reduction step; and (d) ROP of L-lactide

that the nanocoupled modified sample contains a fewer number of platelet adhered on the surface as compared to the unmodified Co-Cr plate or coated sample. Moreover, the elution of sirolimus from the PLLA brush-modified sample showed a control release (Bedair *et al.* 2014a).

6. Conclusions

The drug-eluting stents suffers from irregularities of polymer coating that follow balloon expansion or even during coating methodologies. These defects could be the reason for hazardous clinical events such as late thrombosis. Therefore, the treatment of these defects is in great interest. Several methods including thin layer organic coating at the interface were developed through simple coating method or polymer brush technique. These methods prove its ability to enhance the adhesion of the coating on the metallic implant. Also, it could affect the degradation behavior of the coating and drug release. Additionally, it could enhance the durability of the coating on metal substrate as well as prevent cracking during the balloon expansion. Especially, the introduction of biodegradable polymer brushes or coatings on the surface of metallic DESs could be one of strategy to address the coating defects.

Acknowledgments

This work was supported by the Cell Regeneration Program (2012M3A9C6049717) of the National Research Foundation of Korea funded by the Ministry of Science, ICT & Future Planning (MSIP), Industrial Strategic Technology Development Program (10048019) and Advanced New Materials (Fiber) Development Program (R0002647) funded by the Ministry of Trade, Industry and Energy (MOTIE), Republic of Korea.

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