Acta Materialia Transylvanica 2/2. (2019) 73–78.
https://doi.org/10.33924/amt-2019-02-02
Hungarian: https://doi.org/10.33923/amt-2019-02-02
https://eda.eme.ro/handle/10598/31507

Examination of Drug-eluting Coatings of Coronary Artery Stents

Lilla ASZTALOS[1], Krisztina HORICSÁNYI[2]

[1] *Budapest University of Technology and Economy, Faculty of Mechanical Engineering, Department of Materials Science & Engineering, Budapest, Hungary, lilla@eik.bme.hu*

[2] *Budapest University of Technology and Economy, Faculty of Mechanical Engineering, Department of Mechatronics, Optics and Mechanical Engineering Informatics Budapest, Hungary, horicsanyi.krisztina@gmail.com*

Abstract

Drug-eluting stents provide a solution for treating restenosis in arteries expanded by using conventional bare metal stents, but there are a small number of publications on the processes of coating damage established due to the various effects that occur during the life cycle of the stent. In the current research damage to the coating was investigated along with the effects of damage on the corrosion resistance of the stent in multiple ways. This research investigates not only traditional drug eluting stents with polymer matrix, but also the new generation of polymer-free types.

Keywords*: coronary stent, drug eluting stent, coating, corrosion.*

1. Drug Eluting Stents

At the beginning of the 2000's the so-called drug eluting stents (DES) were introduced, and were used to reduce neointimal proliferation – the primary cause of in-stent-restinosis – to 5-10%. While optimizing the architecture and mechanical properties of bare metal stents (BMS) has also led to a reduction in restenosis, the use of drug eluting stents has not been neglected **[1].**

Techniques for applying the active agent to the stent surface can be divided into three groups: (a) applying the active agent directly to the metal surface, (b) applying the active agent to the surface pores of the metal stent, (c) bonding the active agent to a polymer and bringing the polymer-drug mixture on the implant surface **[1, 2].** Not only can there be a coating on the surface of the stents which releases the drug, but there are also non-drug coated stents. The firsts are called active stents, the seconds are called passive coatings **[3].** The main advantage of passive stent coatings is that they make the metal device "invisible" to the surrounding tissue. Passive coatings should ensure optimal interaction with blood and arterial wall **[4].** Method (c) is the most widely used coating technique today, however, in order to eliminate longterm problems due to nondegradable polymers and slow drug dissolution, drug-free stents produced by method (a) are appearing in more and more manufacturers **[5].**

The main requirements for stent coatings are proper adhesion and release, but also the basic material of the carrier polymer itself, the quality of the coating surface, etc. are important. Previous research at the Department of Materials Science and Engineering of the Budapest University of Technology and Economics has dealt with studying commercially available coated stents and the development of polyurethane based coatings **[6, 7].** Over the years, coating-specific research has introduced a number of previously untested types of coating, as well as types with biodegradable polymers and the already mentioned polymer free types **[8, 9].** In our previous research, we investigated the coating damage of platinum-chromium-alloyed steel stents containing polyvinylidene fluoride-cohexafluoropropylene (hereinafter PVDF-HFP) containing the active compound everolimus **[10]**, however, a wider variety of base materials and coating types are observed in our current study. Corrosion measurements were also performed on coronary stents [11], and the Department of General and Physical Chemistry at the University of Pécs has supported us in rethinking and evaluating the measurements.

2. Our research

2.1. Examination of coating failures

The coating of drug eluting stents is examined using an electron microscope. So far, however, for scanning electron microscopic examination, the stents have to be fixed to the sample holder with a special double-sided adhesive tape. The problem with the method is that we have to take out the stent from the microscope chamber, remove it from the adhesive tape, and then fix it again after moving it, if we want to change the position of the sample. This process is time-consuming due to vacuuming and the adhesive tape can damage the coating each time the stent is removed.

To overcome this problem, we have developed a clamping and moving device that allows the stent to be rotated without opening the chamber so that the coating of the stent can be examined along its mantle. A prototype was prepared from the designed device (Figure 1). The stent rotator was designed for the chamber of the Zeiss EVO MA 10 type electron microscope on the Department of Materials Science and Engineering of the Budapest University of Technology and Economics. The prototype device fits into the chamber of the electron microscope (Figure 2), the stepper motor for axis movement is mounted on an Arduino free software open source electronics development platform, with a Raspberry Pi programmed single card computer, and this system can be controlled via WiFi, and the network control can function even if the chamber is closed and vacuumed. The development goals of the prototype device include further size reduction and the design of a housing for the electronic components.

In addition to the previously studied PVDF-HFP-coated, platinum-chromium-alloyed steel stents, we also investigated amorphous silicon-carbide-coated, cobalt-chromium-alloyed steel stents, as well as drug-release coated stents without polymeric binding layer.

The amorphous silicon carbide coating, like the PVDF-HFP coating, was broken at several sites already after the expansion in water, the damages was located typically in the curved sections of the struts (Figure 3). Compared to the two coating types, the PVDF-HFP coating was less damaged.

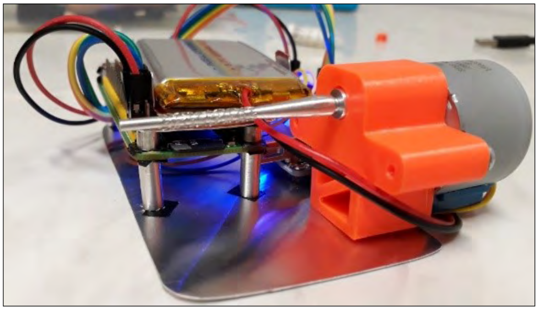

Figure 1. *Prototype of the stent clamping and rotating device*

Figure 2. *Placement of stent clamping and rotating prototype in the chamber of a Zeiss EVO MA 10 scanning electron microscope*

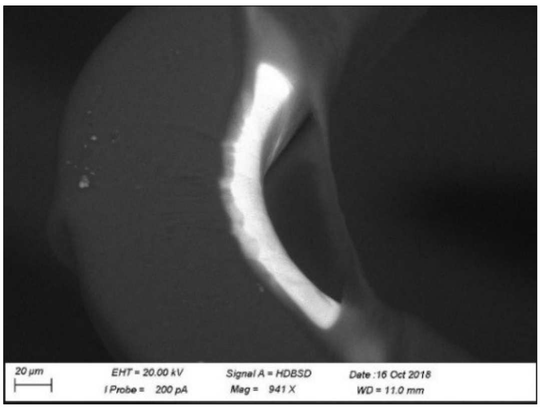

Figure 3. *Damage on a strut of an amorphous silicon carbide coated drug eluting cobalt-chromium stent after expansion*

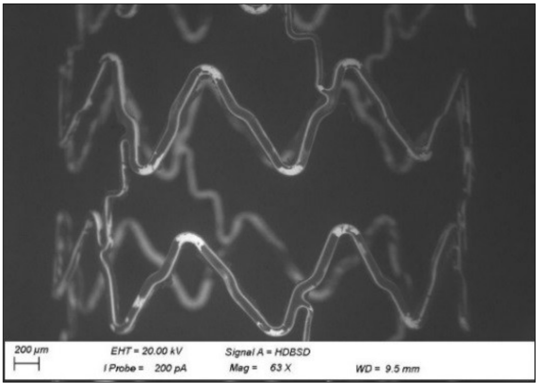

Figure 4. *Electron microscopic image of two rings of a polymer-free drug eluting stent after expansion*

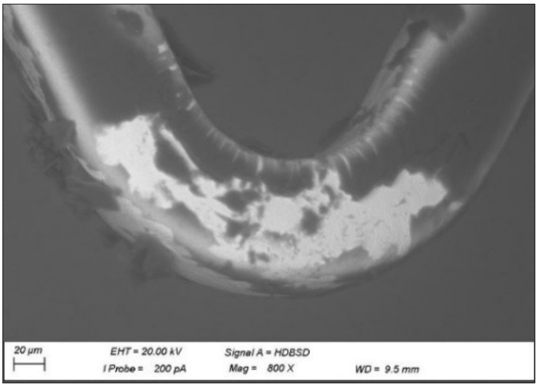

Figure 5. *A large crack and peeling of the coating can be observed at the peaks of the strut curves on the examined polymer-free drug eluting stent after expansion*

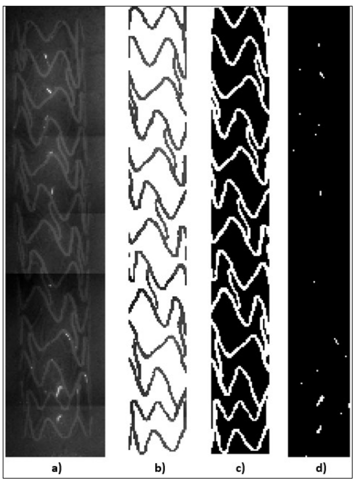

Figure 6. *Steps of the image processing process: a) Composition of the electron microscope images. b) Circumcision of the stent. c) Binarization and complementation of the image. d) Location of coating damage on stent surface.*

A much greater degree of damage can be observed for polymer-free coated drug eluting stents. This is partly due to the fact that some parts of the coating were dissolved from the stent surface prior to dilation in the fluid medium (water), and the coating thickness is also much smaller on these types (Figure 4 and 5.).

2.2. Rating system for classification of coating damage

Based on the above, it can be concluded that the damage to stent coatings is mainly manifested in the separation from the metal surface. Based on this, for an objective evaluation system, we need to examine how much of the coating's total surface area has been removed from the metal. In order to be able to compare stents of different sizes, it is advisable to form a measure based on the ratio of damaged surface to total surface but at least on a given projection.

With the scanning electron microscope, we cannot take a picture at such a low magnification that the entire length of the stent can be seen in a single image, so we photograph the stent in sections and compose the stent using an image editing program.

By backscattered electron detection, coating defects can be well distinguished, since the intact polymer coating is darker and the metal base at the damaged sections appears lighter in the images (Figures 3–5). This can be exploited to determine the amount of damage to the stent surface using appropriate software. For image analysis, we first cut a stent from the rest of the image with a MATLAB code so that the dark background does not cause any problems with image analysis. The images are binarized and pixels of different darkness are calculated to give a measure of the ratio of the damaged surface to the observed projection. The image processing steps are shown in Figure 6. The illustrations were made prior to the availability of the stent clamping and rotating device. By developing this device, it will be possible to determine the extent of coating damage over the entire outer surface of the stent.

2.3. Corrosion test: measurement of open circuit potential

Using open circuit potential (OCP) the thermodynamic tendency of a material to undergo electrochemical oxidation can be characterized. During the OCP measurement, no current is applied to the working electrode, so the development of a so-called equilibrium or open circuit potential can be recorded between the metal and the electrolyte solution. The change in open circuit potential as a function of time may indicate:

- oxidation, in which case the open circuit potential shows a decreasing tendency;
- for the formation of a passive oxide layer, in which case the OCP shows an increasing tendency; as well as
- inhibitor, the potential is constant [12].

The advantage of the measurement method is that it is independent of the size of the specimens, so stents of different diameters and lengths are easier to compare than by other electrochemical measurements. Determining the size of stent surfaces is also a complex process, so it is worthwhile to prioritize methods that exclude this factor. OCP measurements should be performed in standard 2-electrode cells. Phosphate buffer solution (PBS) was used for the electrolyte measurement in a composition as follows: 800 g H_2O 8 g NaCl; 0.2 g KCl; 1.44 g Na_2HPO_4; 0.24 g KH_2PO_4, with a pH value set for 7.4. The reference electrode was a Hg/Hg_2Cl_2 standard calomel electrode. During the measurements, the electrolyte temperature was maintained at 37 ± 1 °C and stirred at low speed (80 rpm). The measurement layout is shown in Figure 7. Marked in the picture:

1. Potentiostat (Biologic SP-150);
2. Heated magnetic stirrer (IKA RCT basic)
3. Working electrode
4. Reference electrode
5. Holder

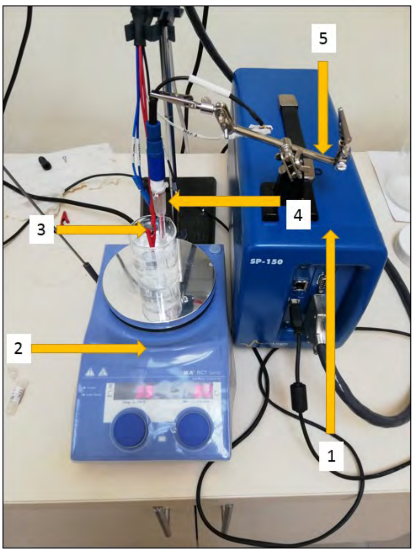

Figure 7. The two electrode cell and its parts used for the open circuit potential measurements

The main characteristics of the stents examined during the measurements: base material, coating material, expansion pressure (EP), manufacturer (Man.) are summarized in Table 1, and we will refer to each specimen marked as in the table below.

Table 1. *Summary table of stents tested. For expansion pressure (EP), MP is the maximum allowable pressure, and NP is the nominal pressure. These pressure values are the values specified by the manufacturers and vary by stent type.*

Mark	Material	Coating	EP	Man.
S1	X2CrNi-Mo18-15-3	No	MP	A
S2	X2CrNi-Mo18-15-3	No	NP	A
S3	Co-Cr-W-Ni	No	MP	B
S4	Co-Cr-W-Ni	No	NP	B
S5	Co-Cr-W-Ni	Amorphous SiC	MP	C
S6	Co-Cr-W-Ni	Amorphous SiC	NP	C
S7	Co-Cr-W-Ni	No	NP	D
S8	Co-Cr-W-Ni	Polymer free drug eluting stent	NP	D
S9	Fe-Pt-Cr	No	NP	E
S10	Fe-Pt-Cr	PVDF-HFP	NP	E

The OCP values of the above listed stents after a measurement time of 3600 seconds as well as the changes in the OCP are presented in Table 2.

Table 2. *Open circuit potential values measured at the end of the 3600-second measurement time, as well as changes in OCP from baseline*

Stent	OCP after 3600 seconds	Change in potential value
S1	0.0439	0.1167
S2	0.0424	0.1158
S3	–0.2097	–0.0348
S4	–0.1051	–1.0767
S5	–0.2953	–0.7531
S6	–0.2496	–0.0242
S7	–0.2256	0.1157
S8	–0.2188	0.1344
S9	0.1242	0.0680
S10	0.2173	0.0522

The austenitic stainless steel (X2CrNiMo18-15-3) stents have a positive open circuit potential value and an increasing tendency.

In the case of cobalt-chromium alloys (Co-Cr-W-Ni alloy) the OCP measurement showed a decreasing tendency in 4 cases and an increasing tendency in two cases. **Table 1** shows that the stents made from the similar cobalt-chromium alloy are manufactured by different manufacturers. In the case of bare metal stents, based on material composition results, it was found that although each stent conforms to the material composition according to ISO 5832-5 for the base material, the tungsten content of the stents showing a decreasing tendency is at the upper limit permitted by the standard (16%), for the samples, which showed an increasing OCP this alloy content was close to the lower limit (14%). Scanning electron microscopic images of the stents S3, S4 also show that the tungsten particles are at the edge of the grain (**Figure 8**), while in the case of S7, the distribution is homogeneous, the grain boundaries are not sharply drawn by tungsten (**Figure 9**).

Figures 10. and **11.** show that the surface of stent has much more discontinuities than S7, which may result from different surface treatments used by the manufacturers. A more uneven stent surface can adversely affect the corrosion characteristics. However, the potential value is negative in all 6 investigated cases for the Co-Cr-W-Ni alloy, so the corrosion resistance of this alloy type is weaker than that of the other two alloy types, regardless of the tendency.

Increasing the expansion pressure did not show a clear tendency for any alloy.

The open-circuit potential of the polymer coated Fe-Pt-Cr stent is the highest of the 10 examined stents, followed by the uncoated Fe-Pt-Cr and then the uncoated austenitic stainless steel stents. The polymer free drug eluting coating did not significantly affect the value of the open circuit potential, the primary reason being that some of the coating was dissolved during the measurement

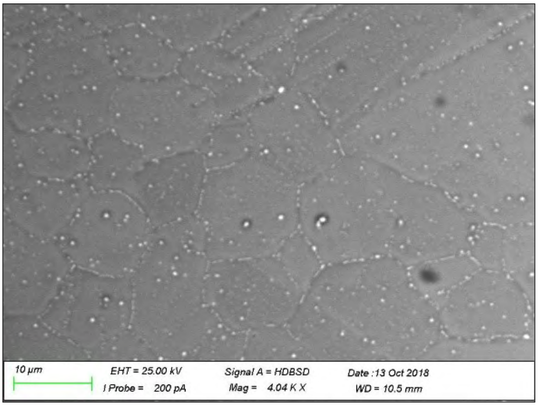

Figure 8. *Electron microscopic image of S3 stent detail before corrosion tests, tungsten particles along the grain boundaries*

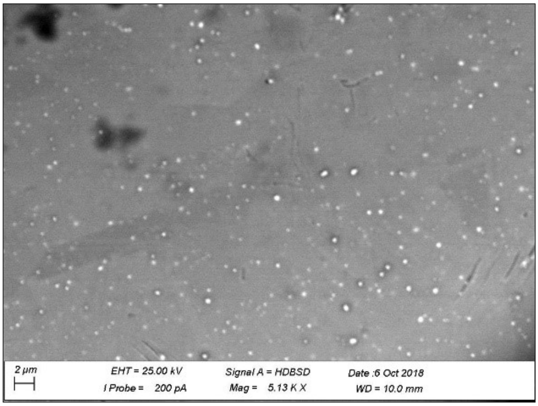

Figure 9. *Electron microscopic image of S7 stent detail before corrosion tests, tungsten grain distribution more homogeneous than in case of the S3 stent showed in Figure 8*

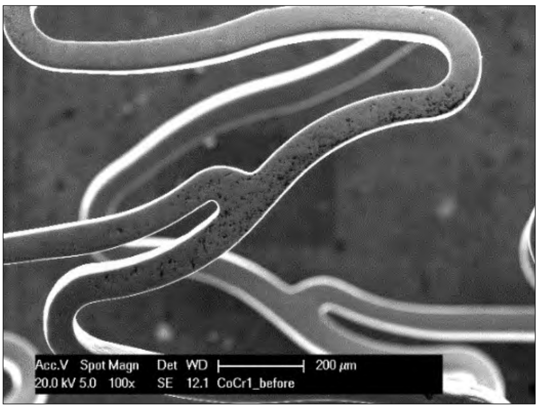

Figure 10. *Electron microscopic image of a detail of the stent S3 before corrosion testing*

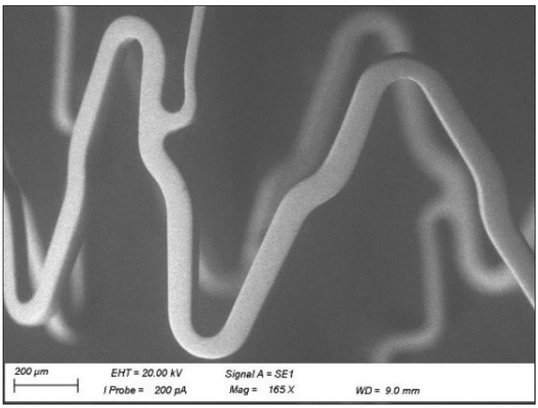

Figure 11. *Electron microscopic image of a detail of the stent S7 before corrosion testing*

and therefore did not exhibit an insulating effect such as the PVDF-HFP coating of the Fe-Pt-Cr stents or amorphous silicon carbide coating in the case of the S5 and S6 samples.

3. Summary

The primary purpose of this study was to develop a method of testing the coating damage of polymer-free and polymer-matrixed drug eluting coated stents in such a way that fixing and removal of the tested devices from the holder does not damage the test piece. To this end, we have created a prototype of a device that allows the stents to be fixed and rotated within the electron microscope chamber so that neither the specimen nor the coating on it is damaged during or after the test. We also created a method for evaluating the electron microscopic images thus prepared, which quantifies the extent of coating damage on the stents tested using MATLAB.

In the second half of our research, open circuit corrosion tests were performed to investigate the effects of coatings on corrosion properties. Based on our measurements, it can be concluded that the resistance of the polymer-matrix drug eluting coated stents to corrosion is better than that of uncoated stents, but the polymer-free coating did not have a significant effect on corrosion resistance. Our results provide a good basis for our new research focusing on coating development.

Acknowledgement

Supported by the ÚNKP-18-3-II New National Excellence Program of the Ministry of Human Capacities. A special thanks to Adam Meisel, student of mechanical engineering, for his help in the development of the stent clamping and rotating device. I owe a debt of gratitude to the staff of the Department of General and Physical Chemistry of the University of Pécs for providing me the measuring equipment.

References

[1] Mani G., et al.: *Coronary stents: A materials perspective.* Biomaterials, 28. (2006) 1689–1710. https://doi.org/10.1016/j.biomaterials.2006.11.042

[2] Wienke H., et al.: *Stent coating with titanium-nitride-oxide for reduction of neointimal hyperplasia.* Circulation, (2001) 928–933. https://doi.org/10.1161/hc3401.093146

[3] Bognár E. et al.: *Investigation of Drug Elutigng Stents.* Materials Science Forum, 589. (2008) 361–366. https://doi.org/10.4028/www.scientific.net/MSF.589.361

[4] Bognár E. et al.: *Investigation of Coated Coronary Stents.* Materials Science Forum, 537–538. (2007) 307–314. https://doi.org/10.4028/www.scientific.net/MSF.537-538.307

[5] Hausleiter J. et al.: *Prevention of restenosis by a novel drug-eluting stent system with a dose-adjustable, polymer-free, on-site stent coating*. European Heart Journal, 26/15. (2005) 1475–1481. https://doi.org/10.1093/eurheartj/ehi405

[6] Selley T. L. et al.: *Development of adhesion test for coated medical device.* Biomechanica Hungarica, (2013) 303–310. https://doi.org/10.1093/eurheartj/ehi405

[7] Ginsztler J. et al.: *Development and Manufacturing of Coronary Stents in Hungary*. Materials Science Forum, 537–538. (2007) 631–638. https://doi.org/10.4028/www.scientific.net/MSF.537-538.631

[8] Khan W. et al.: *Drug eluting stents: Developments and current status.* Journal of Controlled Release, 161/2. (2012) 703–712. https://doi.org/10.1016/j.jconrel.2012.02.010

[9] Park J. K. et al.: *Development of a novel drug-eluting stent consisting of an abluminal and luminal coating layer dual therapy system*. RSC Advances, 5. (2015) 40700–40707. https://doi.org/10.1039/C5RA04270D

[10] Horicsányi K. et al.: *Effect of Expansion Pressure ont he Drug Eluting Coating of Coronary Stents.* Acta Materialia Transylvanica, 1/1. (2018) 37–40. https://doi.org/10.2478/amt-2018-0012

[11] Asztalos L. et al.: *Kobalt-króm ötvözet alapanyagú sztentek korróziós tulajdonságainak vizsgálata.* Műszaki tudományos közlemények, 7. (2017) 79-82. https://doi.org/10.33895/mtk-2017.07. 12

[12] Jiménez Y. S. et al.: *Interpretation of open circuit potential of two titanium alloys for a long time immersion in physiological fluid.* Bulletin of the Transilvania University of Brasov, Series I: Engineering Sciences, 2/51. (2009) 197–204.