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DRUG DISTRIBUTION AND STENT RETENTION OF DRUG ELUTING STENTS

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Abstract: *In this paper the examinations of drug eluting coronary stents are shown, such as the morphology of the coatings before expansion, drug distribution, the methodology and the value of stent retention. Surface qualities of drug coatings were examined with stereo-microscope, metallographic microscope and scanning electron microscope. Examinations with confocal microscope show drug distribution in the coatings. Stent retention is a very important property of the stent system. Stent retention is a force, needed to the stent slip down from the balloon. Three drug eluting coronary stents were tested with our method.*

Keywords: *drug eluting coronary stent, stent retention, drug distribution*

1 INTRODUCTION

The illnesses of the cardiovascular system are among the most frequent diseases of the adult population in Europe. Inside of these, the atherosclerosis and the consequences of the occlusions of the arteries (e.g. thrombosis, heart attack and stroke) are the main causes of death, especially in the adult men population. The stent implantation is one of the most important treatments in the correction of the narrowed vessels [1,2].

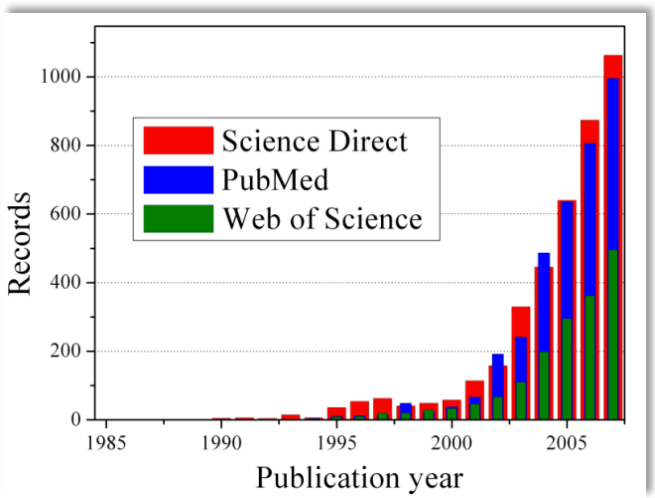

Fig. 1 Number of papers containing the keyword "coated and drug eluting coronary stent"

Figure 1 shows the results obtained from three well known scientific publication databases. The results, which are indicated by the year of publishing, show that there is a dynamic development in this field possibly due to increased morbidity.

2 COATING STRATEGIES

In this paper examination of drug eluting coronary stents are shown. The application of coating is a possible way to combine the favourable properties of different materials. Stent coatings can be active or passive. While passive coatings work as a separate layer between the stent and the surrounding tissue due to their high biocompatibility, the active coatings inhibit directly the hyper-proliferation of intima. Active coatings work by the effect of the applied drug [3]. There are several methods to control drug release and release time for stent coatings. The kinetics of drug elution is a very important factor and to control it, usually some kind of polymer matrix were used [4,5].

It is possible to simple dip the stent into the agent, without polymer matrix [6]. It seemed useful to leave the polymer matrix because it caused inflammation. However, the experiments have shown that with dipping large percentage of the agent was lost during implantation. Another method is to apply the agent on the polymer layer, or the active substance can also be coated with an additional biodegradable polymer layer. This outer, drug-free polymer layer is very important to control the drug release because after implantation, in the first few days the exaggerated drug release can be very disadvantageous. A common method is mixing the drug with the polymer (matrix) and then coating the stent with this mix (Fig. 2). In these matrix devices, a drug is usually dispersed inside the polymer matrix, and the drug is released into the environment without any rate-controlling barrier layer [5]. A unique method is cutting special slots into the outer surface of the stent and these carry the drug (Fig. 3) [7]. The slots can carry drug or drug/polymer mix. Its drug eluting properties are five times better than the other stents with similar size [5,8,9]. In the reservoir devices, the drug reservoir is covered with a thin polymer layer (Fig. 4), which functions as a rate-controlling membrane [5]. Another solution to produce a ceramic or polymer coating is when the entire coating or its outer layer has pores in it (Fig. 5), and the drug is applied into the pores by dipping [10]. Ion exchange based drug release can be used for controlled release of ionized drugs which binds to the matrix through electrostatic interactions.

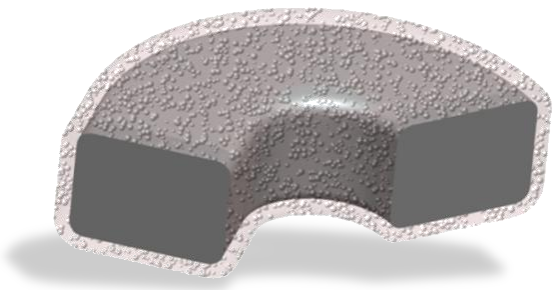

Fig. 2 Release by diffusion

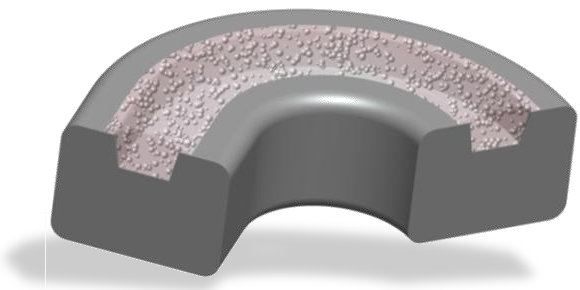

Fig. 3 Slots filled with polymer and drug

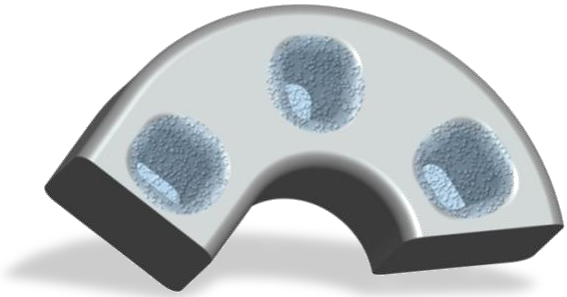

Fig. 4 Drug loaded in stent reservoirs

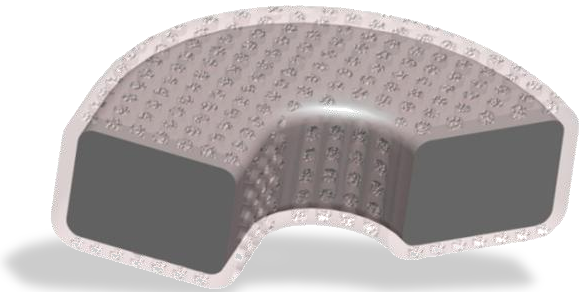

Fig. 5 Porous coating with drug

3 TESTING METHODS

The investigations and the order of them have to be planned to ensure the highest possible number of test can be performed with a stent because coronary stents are very expensive tools. In our order of testing, first the destruction free methods (stereo- or metallographic microscopy and imaging) were used, these were followed by the destruction examinations, experiments (expansion, stent retention, etc.). Subsequently another destruction free method was applied (SEM, EDS-analysis) to study the change of the coatings. Test results were processed by computer and on the pictures the measurements were done by image analyser programs. Local microanalyses were done by energy dispersive x-ray detector mounted on the scanning electron microscope.

Fig 6 Stent retention test

Confocal microscope was used to study drug distribution. The tested stents were not marked with fluorescent material because these are complete coatings; thus we tried to use the possible autofluorescent properties of the coatings. In our sample autofluorescent reactions were found mostly at the wavelengths of 405 nm, 488 nm and 514 nm.

Stent retention is a force, needed to the stent slip down from the balloon. To test stent retention, the balloon-mounted stents were fixed with an adhesive layer and placed into the upper clamp of the tensile equipment. In the lower clamp of the tensile equipment, the catheter was fixed. During the movement of the upper and lower jaws of the tensile equipment, the stent was pulled off from the balloon (Fig. 6).

4 COATING EXAMINATIONS

4.1 TAXUS Express^2 stent (3.5×24 mm)

The material of TAXUS Express^2 stent is 316L, austenitic stainless steel (Fig. 7). The stent is coated with a proprietary polymer called Translute, which was developed specifically for the TAXUS stent. The Translute polymer is also known as SIBS [poly(styrene-*b*-isobutylene-*b*-styrene)]. The polymer controls the release of paclitaxel, which may allow for consistent drug release and more uniform drug distribution. Paclitaxel's multi-functional effects, stabilize microtubules and inhibit activities that contribute to restenosis [11]. Paclitaxel is highly lipophilic, which may contribute to more uniform drug distribution [12]. This paclitaxel/polymer coating exerts its effect primarily in the wall of the arteries and only minimal amount of drug gets into the blood stream. The applied dose of drug is small but very effective, and it mostly effects when the restenosis appears. A portion of the drug remains in the coating. And experiments have found no measurable volume of drug in the body [13,14].

Fig. 7 The design of TAXUS Express^2 stent

In metallographic microscopic images it was observable that the coating has specific waving in the surface of the whole stent (Fig. 8) and polymer films between the connecting struts (Fig. 9). Confocal microscopy (Fig. 10) shows homogenous drug distribution. The green and red areas on the surface of the stent are very likely the drug particles.

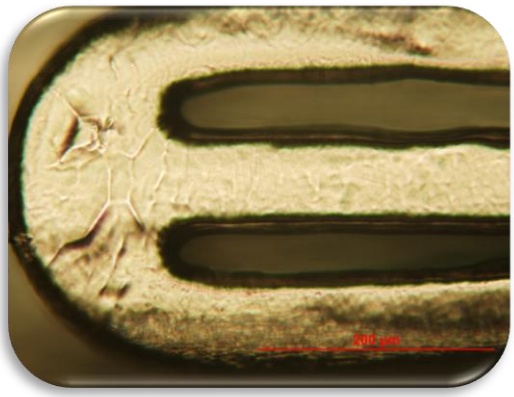

Fig. 8 The waviness of the coating of TAXUS Express^2 stent

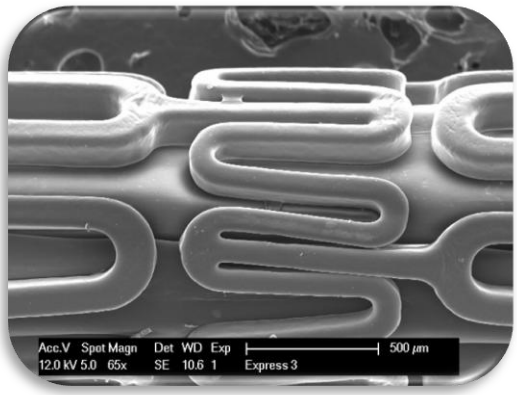

Fig. 9 Films between the struts of TAXUS Express^2 stent

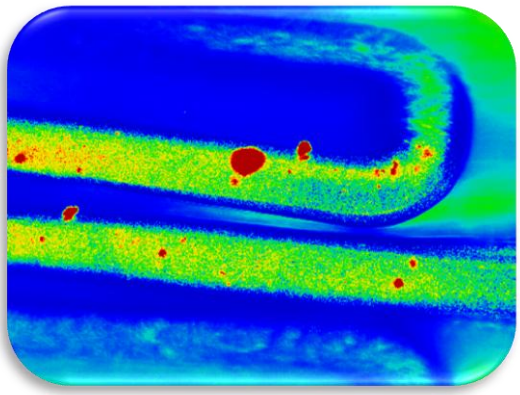

Fig. 10 Drug distribution of TAXUS Express^2 stent

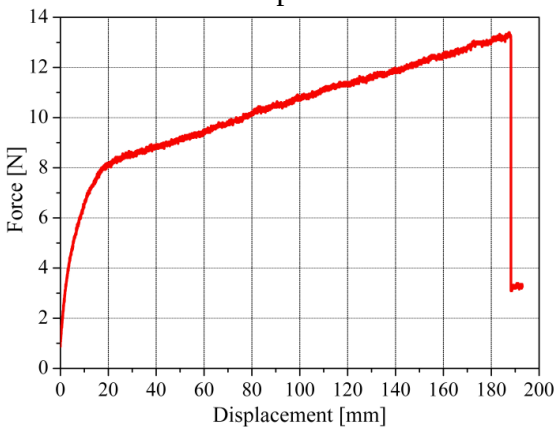

Fig. 11 Retention diagram of TAXUS Express^2 stent

After these destruction free examinations the retention of the stent was measured. The speed of this test was 5 mm/min. The stent did not slip down from the balloon during this experiment, the maximum force 13.6 N when the catheter was break away but the stent remained on the balloon. Figure 11 shows the force in function of the displacement.

4.2 TAXUS Liberté stent (3.5×20 mm)

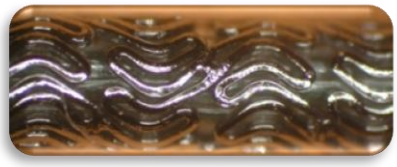

Fig. 12 The design of TAXUS Liberté stent

TAXUS Liberté coronary stent has the same coating as TAXUS Express^2 but the design of this stent is a result of development (Fig. 12). This stent has special design with flexible cells and cell distribution better simulating the anatomy of the artery [13,14].

In metallographic microscopic images it was observable that the coating has specific waving in the surface of the whole stent, like TAXUS Express^2 stent (Fig. 13). The coating shows continuous films between the struts in several places and there were some sections where the coating lost its homogeneity (Fig. 14). The superficial alteration at the connections of the struts is easily observable and at these sites the coating is adhered more unevenly as well. The distribution of the drug was uniform (Fig. 15). After these destruction free examinations the retention of the stent was measured. The speed of this test was 5 mm/min. The stent did not slip down from the balloon during this experiment, the maximum force 10.9 N when the catheter was break away but the stent remained on the balloon. Figure 16 shows the force in function of the displacement.

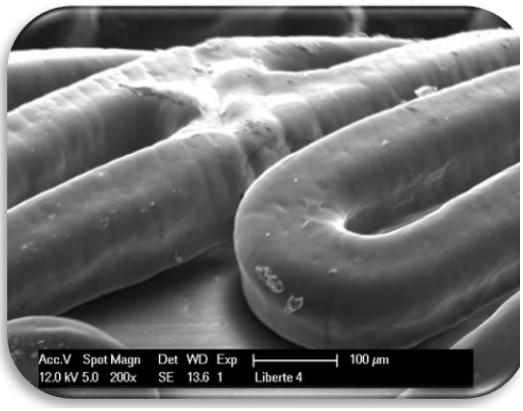

Fig. 13 The waviness of the coating of TAXUS Liberté stent

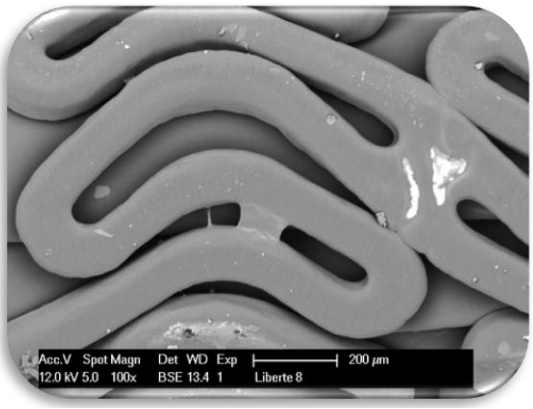

Fig. 14 The polymer film between the struts of TAXUS Liberté stent

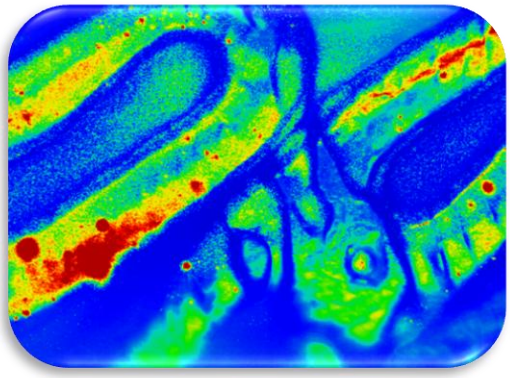

Fig. 15 Drug distribution of TAXUS Liberté stent

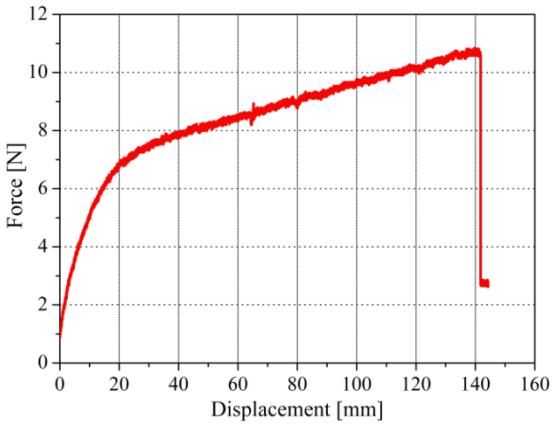

Fig. 16 Retention diagram of TAXUS Liberté stent

4.3 Examination of Conor CoStar (2.5×16) stent

The Conor CoStar stent is made of cobalt-chromium alloy. Due to the higher strength, the stent has thin struts and smaller profile diameter that promotes easier passing through the arteries. This stent design incorporates small holes, each acting as a reservoir into which drug-polymer compositions can be loaded (Fig. 17). This design allows greater control of release kinetics. Conor CoStar stents are different from conventional surface-coated stents and have been designed specifically for drug delivery. The stent incorporate special structural elements called "ductile hinges" which absorb the mechanical stresses that occur during expansion. This stress absorption mechanism allows for other structural elements of the stent including the drug/polymer containing reservoirs to remain relatively deformation-free. Thus the reservoirs are largely non-deforming during stent expansion, and it is possible to use polymers in the reservoirs which do not have the level of elasticity, adhesion and other properties required in surface coatings [15]. This unique reservoir design platform contains the PLGA matrix with paclitaxel. Paclitaxel efficiently interferes with the proliferation of neointima hyperplasia. The PLGA matrix ensures the controlled drug release and drug eluting kinetics.

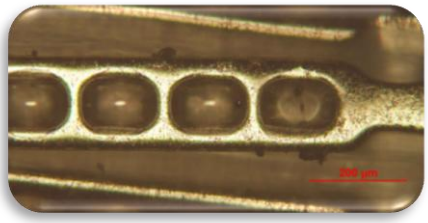

Fig. 17 Reservoires of Conor CoStar stent

In vitro studies have shown that the matrix and drug are absorbed within 180 days [16,17]. A piezoelectric microdispenser was used to coat the reservoirs, with repeated application. The release of paclitaxel can be controlled easily by changing the degradation kinetics of the matrix [5].

The tested stent has a nominal diameter of 2.5 mm and a nominal length of 16 mm. Subsequently to the opening the sterile packing the stent was examined by stereo and metallographic microscopes. The next test was done by a confocal microscope. The green and red areas on the pictures are likely to show the drug (Fig. 18).

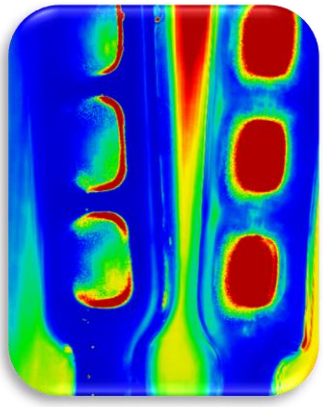

Fig. 18 Drug distribution and ductile hinges of Conor CoStar stent

Then the stent were expanded in air to their nominal expansion pressure (9 bar). The changing of the stent and mainly the surface of its coating influenced by the expansion was studied. The stent has three reservoirs each with different shape and size. The coating in the reservoirs of Conor CoStar stent remained uniform after expansion (Fig. 19).

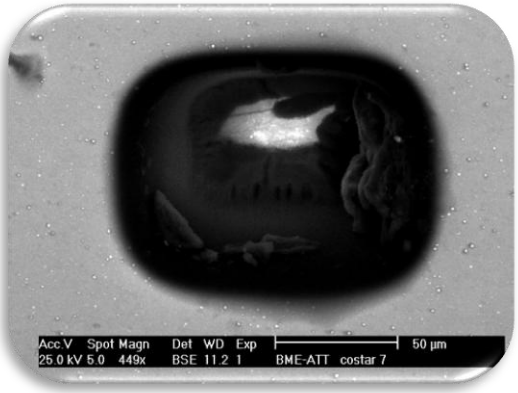

Fig. 19 Square shaped reservoir of Conor CoStar stent, after expansion

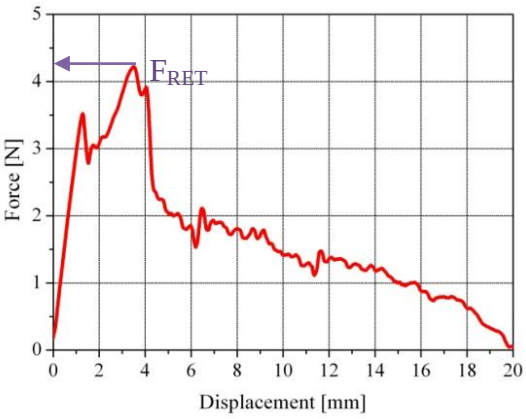

Fig. 20 Retention diagram of Conor CoStar stent

Another, but same sized stent was used to stent retention. Subsequently to opening the sterile packing the stent was tested by metallographic microscope and then the retention was measured. The speed of this test was 5 mm/min. The maximum force required was F_{RET} = 4.3 N. Figure 20 shows the force in function of the displacement.

5 CONCLUSIONS

The polymer coating of TAXUS Liberté and TAXUS Express[2] stents were damaged or uneven already before expansion. The drug dissolved uniformly on the whole surface of the stent but small spots with higher concentrations were also found. The waviness of the coating did not influence the drug distribution based on confocal microscopic images.

The coating of Conor CoStar stent was uniform after expansion as well, although the cells were expanded variously. Thanks to the flexible bridges, reservoirs maintain their original shape even after expansion. The confocal- and electron microscopy showed that the drug was located mostly in the reservoirs but small spots were found on the surface as well.

The measured value of stent retention of Conor CoStar was 4.3 N which was influenced by the type of coating, the material (cobalt-chromium alloy) and stent geometry. The two other stents did not slip down from the balloon, due to the material of the stents (316L) and the crimping technology.

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