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Research paper

Drug eluting stents based on Poly(ethylene carbonate): Optimization of the stent coating process

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ABSTRACT

First generation drug eluting stents (DES) show a fivefold higher risk of late stent thrombosis compared to bare metal stents. Therefore, new biodegradable and biocompatible polymers for stent coating are needed to reduce late stent thrombosis. In this study, a reproducible spray-coating process for stents coated with Poly(ethylene carbonate), PEC, and Paclitaxel was investigated. PEC is a biocompatible, thermoelastic polymer of high molecular weight. The surface degradation of PEC is triggered by superoxide anions produced by polymorphonuclear leukocytes and macrophages during inflammatory processes. Stents with different drug loading were reproducibly produced by a spray-coating apparatus. Confocal laser scanning micrographs of fluorescent dye loaded stents were made to investigate the film homogeneity. The abluminal stent site was loaded more than the luminal site, which is superior for DES. The deposition of the layers was confirmed by TOF-SIMS investigations. Referring to the stent surface, the drug loading is 0.32 μg (±0.05) (once coated), 0.53 μg (±0.11) (twice coated), or 0.73 μg (±0.06) (three times coated) Paclitaxel per mm^2 stent surface. The *in vitro* release mechanism during non-degradation conditions can be explained by diffusion-controlled drug release slightly influenced by swelling of PEC, revealing that 100% of the loaded Paclitaxel will be released via diffusion within 2 months. So, the *in vivo* release kinetic is a combination of diffusion-controlled drug release and degradation-controlled drug release depending on the presence or absence of superoxide anions and accordingly depending on the presence or absence of macrophages. We conclude that the specific release kinetics of PEC, its biocompatibility, and the favorable mechanical properties will be beneficial for a next generation drug eluting stent meriting further investigations under *in vivo* conditions.

1. Introduction

Percutaneous transluminal angioplasty (PTCA) is used in the treatment of Coronary Artery Disease. Over the past decade, extensive research has been performed addressing the design of stents, which are commonly used for PTCA. Endoluminal metallic endoprostheses (stents) have reduced procedural complications in PTCA like elastic recoil of the vessel wall, balloon-induced dissection, and reoccurrence of restenosis [1]. Despite these improvements, bare metal stents may cause injury to the blood vessel resulting in neointimal proliferation [2]. This restenosis occurs in >20% of cases, leading to ischemic coronary syndromes requiring revascularization in >10% of cases as described recently [3]. To overcome the restenosis issue, stents for local delivery of several drugs were established. The antineoplastic agent Paclitaxel is often used, which inhibits mitosis and the assembly of microtubules. Similarly, the immunosuppressive drug Sirolimus and derivatives were employed, inhibiting cell division and proliferation [1]. First generation drug eluting stents (1G-DES) consist of a backbone stent (316 L stainless steel or Nitinol), a polymer (biodegradable or non-degradable), and drugs such as Paclitaxel or Sirolimus. These 1G-DES were designed to reduce in-stent neointimal formation and to minimize the appearance of restenosis [4]. Nevertheless, stent thrombosis events occur in 1G-DES patients beyond 1 month (late stent thrombosis) and up to 2 or 3 years (very late stent thrombosis) after implantation [1,5]. Suboptimal polymer biocompatibility and delayed vascular healing lead to late and very late thrombosis [4,6]. This Hypersensitivity reaction of vascular tissue

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is attributed to the drug load, the elution profile, and the polymer coating of the device [7]. Durable thick polymer coatings as used in commercially available Cypher™ and Taxus™ stents cause inflammatory responses and lead to local toxicity as shown by Silva et al. [8] and Lüscher et al. [9]. As these durable thick polymer coatings appear to support inflammatory reactions and potentially promote the occurrence of late and very late stent thrombosis, new polymers for DES need to be investigated [4].

Also, bioabsorbable stents show several drawbacks. The strength to inhibit the elastic recoil of the vessel wall is lower as compared to BMS, showing a significant degree of local irritation [2]. Another disadvantage is the inflammatory response in connection with the degradation process of the stent material [10]. The rate of biodegradation needs to be high enough to release effective doses of the drug, but the polymer has to be stable during the whole period of treatment. Therefore, new biodegradable and enhanced biocompatible polymers for stent production are required.

Here, we present a novel polymer for stent coating, consisting of Poly(ethylene carbonate) (PEC). PEC offers a unique degradation mechanism, and its degradation products are biocompatible, as shown *in vivo* by Dadsetan et al. [11]. The surface degradation of PEC is triggered by superoxide anions produced by polymorphonuclear leukocytes and macrophages [11–13]. Since inflammatory mechanisms are involved in the reaction of the vessel to the injury caused by stent placement [14], an increased drug release on demand could hypothetically be possible. The PEC/Paclitaxel stent exhibits a sustained drug release, which can favorably influence the vascular biological response to the implant [15]. During inflammatory processes in the vessel wall, increased Paclitaxel rates will be released to treat the inflammation by reason of the degradation mechanism. The postulated on demand release might lead to better arterial healing, reendothelialization, and therefore might avoid late stent thrombosis.

The aim of this study was a reproducible manufacture of a coated stent delivery system on a laboratory scale, consisting of PEC, Paclitaxel, and 316 L stainless steel stents, which can be used for *in vivo* experiments to examine the behavior of the stents in White New Zealand Rabbits in a subsequent study.

2. Materials and methods

2.1. Materials

Poly(ethylene carbonate) with a number average molecular weight of 272 kDa and a polydispersity of 2.0 was synthesized by Novartis Pharma AG (Switzerland) according to the procedure previously described [16]. Briefly, PEC was synthesized by copolymerization of ethylene oxide and carbon dioxide using a catalyst system. Stainless steel stents (ProX SV and ProX) and balloon catheters (euca V, diameter of 2.5 mm) were manufactured by Eucatech AG (Rheinfelden, Germany). Paclitaxel was obtained from Sigma (Sigma Aldrich Chemie GmBH, Steinheim, Germany) and ^{14}C-Paclitaxel [radio-labeled paclitaxel (paclitaxel-[2-benzoyl ring-UL-^{14}C])] was purchased from Hartmann (Hartmann Analytik GmbH, Germany). The liquid scintillation cocktail (Ultima Gold™ LS Cocktail) was obtained from Perkin Elmer (Rodgau, Germany). All other materials used were of analytical grade.

2.2. Stent coating

2.2.1. Basecoat and topcoat layer

Two balloon expandable stent systems consisting of stainless steel (316 LVM) were used. The ProX stents (Eucatech AG, Germany) with a length of 18 mm and a diameter of 1.8 mm were used for morphology and composition examinations. ProX SV stents (Eucatech AG, Germany) with a length of 18 mm and a diameter of 1.6 mm were used for loading and release experiments, because they will be used in the following animal study. The stents were coated with paracyclophane (SCS, Indianapolis, USA) in a Lab coater (Model PDS 2010, SCS, Indianapolis, USA) using chemical vapor deposition (CVD) as previously described [17]. The pyrolysis temperature was adjusted to 690 °C. After a reaction time of 3 h, a uniform pinhole-free poly(*p*-xylylene) (Parylene) layer was generated. In the second step, the Parylene coating was swollen in dichloromethane to allow good adherence of the topcoat. A PEC solution of 0.8% (w/w) in dichloromethane with or without Paclitaxel was sprayed onto the rotating stent at a distance of 0.5 cm using a self-constructed airbrush apparatus (Fig. 1). The residual dichloromethane was removed by drying under vacuum for 48 h.

2.2.2. Spray-coating technique

The spray-coating technique is based on an airbrush system (Fig. 1). After swelling in dichloromethane, the Parylene precoated stent was mounted horizontally on two Teflon™ needles connected to a rotating system. The polymer solution consisting of 0.8% Poly(ethylene carbonate) (w/w) in dichloromethane mixed with Coumarin-6, Paclitaxel, or radio-labeled Paclitaxel was pipetted into a 15 mL glass vial, which was connected to the airbrush pistol (Evolution Silverline, Harder & Steenbeck, Norderstedt, Germany). The pressurized air produced by a compressor (aero-pro HTC 10 A, Harder & Steenbeck, Norderstedt, Germany) flew through the nozzle (0.2 mm) by aspirating the polymer solution.

The airbrush apparatus was controlled by a chip based program, which rotates the stent, starts the ventilator and the spraying process, and moves the airbrush pistol four times back and forth.

An optimum flow rate (2.2 mL/min) and optimum spray pressure (1.4 b) were kept constant.

2.2.3. Dip-coating technique

After swelling in dichloromethane, the Parylene precoated stent was fixed onto a glass stirrer and dipped vertically into a solution of 0.8% PEC (w/w) in dichloromethane. The glass stirrer was connected to a drill machine to remove the excess of PEC solution from the stent by fast rotation.

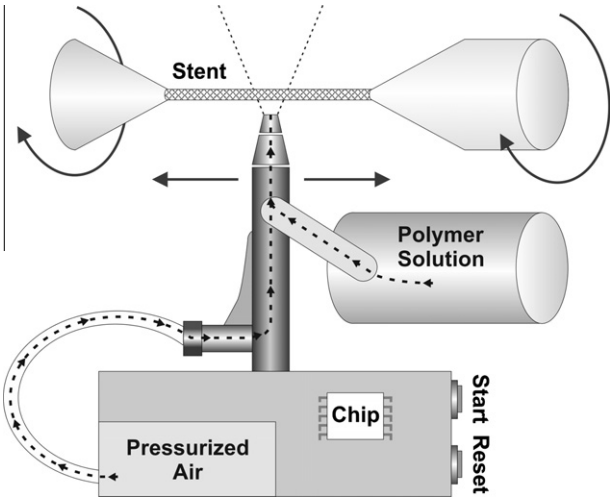

Fig. 1. Spray Coating Apparatus. Scheme of the Spray Coating Apparatus. A horizontally rotating coronary stent is spray-coated with polymer solution consisting of 0.8% Poly(ethylene carbonate) in dichloromethane loaded with Paclitaxel, radiolabelled Paclitaxel, or Coumarin-6.

2.2.4. Sterilization process

The sterilization was carried out at Eucatech AG, Rheinfelden, Germany. The coated stents were mounted onto the balloon catheter (balloon diameter 2.5 mm) using a standard production process. These balloon expandable coronary stent systems were packaged in Tyvek®-backed polyethylene bags that were heat-sealed. The stents were ethylene oxide sterilized using 6% EO gas. The sterilization cycle started with initial chamber evacuation following a preheating (50–60 °C) and humidification. Afterward, the chamber was filled with EO/CO_2. The exposure time with EO gas was 4 h. Afterward, in-chamber purge cycles began to decrease the amount of residual EO to tolerable levels prior to product release. Each load was accompanied by chemical indicators, which were used to verify the sterilization process.

2.3. Gel permeation chromatography

Gel permeation chromatography of sterilized and not sterilized Poly(ethylene carbonate) was performed to examine the effect of the sterilization process on PEC. An Eppendorf cup containing PEC was ethylene oxide sterilized according to a validated process by Eucatech AG, Rheinfelden Germany (2.2.4). The average molecular weights and weight distributions of sterilized and non-sterilized PEC were determined to figure out potential polymer degradation. Therefore, a Merck-Hitachi L-6000 pump (Merck Hitachi, Germany), a Merck T-6300 Column Thermostat (Merck Hitachi, Germany), a Rheodyne 7125 manual injector (Rheodyne, USA), and a Perkin Elmer Series 200 refractive index detector (Perkin Elmer, USA) were used. As mobile phase, $CHCl_3$ was used at a flow rate of 1 mL/min. The separation was performed at 25 °C using a PSS SDV linear M (8 mm × 300 mm, 5 μm) column with a pre-column of the same type (8 mm × 50 mm, 5 μm), both from PSS (Polymer Standard Service GmbH, Germany). Polystyrene standards of narrow polydispersity (Polymer Standard Service GmbH, Germany) were used for calibration. The polymer samples were dissolved at a concentration of 3 mg/ml and 100 μL of the solution were injected. Measurements were performed in triplicates.

2.4. Optimizing the spraying distance

To optimize the distance between nozzle and stent, four different gaps (3 cm, 2 cm, 1 cm, and 0.5 cm) were used. The optimal flow rate (2.2 mL/min) and the optimal pressure (1,4 b) were kept constant. The stent was spray coated by using the airbrush apparatus. Thereafter, the stents were dried under vacuum and examined with an optical microscope (Hertel & Reuss, Kassel, Germany) (magnification 48×) combined to camera equipment (Moticam 2000, Motic). Each distance was examined five times.

2.5. Scanning electron microscopy (SEM)

SEM was used to investigate the morphology of the coated and expanded stents. To examine the suitability of the coated stents as balloon expandable systems, the spray-coated and dip-coated stents were mounted onto balloon catheters and were ethylene oxide sterilized (Section 2.2.4).

To monitor the behavior of the coating after expansion, the stent-catheter systems were warmed-up to 37 °C for one hour. Afterward, the stents were expanded with an Encore™ Inflator (Boston Scientific, USA) for 30 s with 8 b. The stents were withdrawn, and the coating was examined by a JSM-7500F SEM (JEOL, Tokyo, Japan) instrument.

2.6. Confocal laser scanning microscopy (CLSM)

To investigate the homogeneity of the Poly(ethylene carbonate) layer on stents, the stents were spray coated with a 0.8% PEC solution containing 0.05% (w/w) Coumarin-6 related to PEC. Afterward, the stents were dried in vacuum for 48 h and examined by confocal laser scanning microscopy via a Zeiss Axiovert 100 M microscope coupled to a Zeiss LSM 510 scan module. The distribution of the PEC layer with the fluorescent marker Coumarin-6 was detected using an argon laser with an excitation wavelength of 488 nm. The green Coumarin-6 was identified with a 505–550 nm broad pass filter and a plan-neofluar (10×/0.3) objective. The overlay of the fluorescence and the transmission light was recorded.

2.7. TOF-SIMS

Time of flight secondary mass spectrometry (TOF-SIMS) was used to obtain the depth distribution of coating components on the spray coated stents in the different layers (The 25:75 (w/w) Paclitaxel/PEC coating, the Parylene basecoat, and the stent itself). Measurements were performed using a TOF.SIMS 5 instrument (Iontof GmbH, Münster, Germany). The TOF-SIMS is equipped with a bismuth liquid metal ion gun (LMIG) for secondary ion generation and three ion guns (Cesium, Oxygen, and C_{60}) for sputtering of samples. In this experiments, an oxygen ion gun with an 1 keV O^+ beam (O^+ ion current $I_0 = 271$ nA) was used for sputtering, which was performed on a large square area of 500 μm times 500 μm. Measurement of depth profiles is a standard application for dynamic TOF-SIMS. The TOF-SIMS 5 instrument is equipped with an electron flood gun for charge compensation of samples.

For measurement, the stent was sliced longitudinally and attached with a copper tape to the sample holder. To avoid high charging of the stent, it was flatly aligned by pressing it on the copper tape on the sample holder with a silicon wafer. All measurements were performed with negative polarity (analysis of negative ions). Depth profile analysis was used to obtain three-dimensional elemental distributions of the different layers. Software analysis of the measurement data can be assigned to smaller areas than the whole 500 μm times 500 μm. Such a selected area is called region of interest (ROI). Fig. 6 shows the selected ROI of the depth profile that is shown in Fig. 7.

2.8. Determination of drug loading

To study the drug loading of the spray-coated stents, the Parylene pre-coated stents were coated with a PEC layer containing the drug Paclitaxel at a weight ratio of 75:25 (w/w). One part radio-labeled ^{14}C-Paclitaxel was pipetted to 300 or 400 parts Paclitaxel to detect the drug loading via liquid scintillation counting (LSC). The higher the activity of the ^{14}C-paclitaxel solution, the less radio-labeled Paclitaxel was needed for equal counts. The airbrush apparatus was used to obtain a reproducible loading of the stents. The stents (ProX SV, 18 mm length, 1.6 mm diameter, 107 mm^2 surface) were coated once, twice, or three times to create different loadings. After each stent was dried, the PEC/Paclitaxel topcoat was dispersed in 1 mL dichloromethane for 12 h. The stent was removed and washed with one additional milliliter of dichloromethane. The activity of radio-labeled Paclitaxel in dichloromethane was quantified by LSC using a Tri-Carb 2100 TR counter, Packard BioScience, Germany. Therefore, 10 mL of scintillation cocktail was pipetted to the solution. The Paclitaxel loading was calculated based on the ^{14}C-Paclitaxel/Paclitaxel ratio of 1:300 or 1:400. Each amount was examined five times on different stents, and the Paclitaxel loading was calculated.

2.9. Drug release in vitro

To uncover a potential burst release of Paclitaxel, an *in vitro* drug release study was implemented. Therefore, Parylene pre-coated stents (ProX SV, 18 mm length, 1.6 mm diameter, 107 mm^2 surface) were spray-coated with a Paclitaxel/PEC (25:75) (w/w) layer using the airbrush apparatus. A ratio of 1:300 of radio-labeled Paclitaxel to Paclitaxel was used. Phosphate-buffered saline (PBS) pH 7.4 was chosen as release medium. To generate sink conditions and to enhance the solubility of Paclitaxel, 10% ethanol was added. Coated stents were incubated at 37 °C in 2 mL buffer solution in scintillation vials. At predetermined time intervals, the stent was placed in 2 mL of fresh buffer. Finally, the stents were removed and dried in vacuum for 24 h. The residual stent coating was dissolved for 12 h in 1.5 mL dichloromethane. Additional 0.5 mL dichloromethane was used to wash the withdrawn stent.

To determine the amount of released Paclitaxel, 0.5 mL of the release samples (PBS) was mixed with 5 mL of scintillation cocktail. The activity of the remaining coating was determined by mixing 2 mL of the washing liquid (DCM samples) with 10 mL of scintillation cocktail.

The activity of ^{14}C-Paclitaxel was quantified by LSC at a counting time of 15 min for each. The measurements were carried out in triplicate.

2.10. Statistics

Results are expressed as mean ± SEM (standard error of mean).

3. Results and discussion

The feasibility of Poly(ethylene carbonate) as stent-coating material was examined by Unger et al. [12]. The factors which were particularly advantageous as stent coating material could be identified as superior mechanical and specific degradation properties. After swelling in aqueous media, the PEC surface becomes hydrophilic [12], and therefore reduces protein adsorption. A further advantage of the polymer is the property to elongate more than 600% [12], so the topcoat of a PEC coronary stent will withstand the balloon expansion process without ruptures. In direct contact to superoxide anions, which are produced by macrophages during an inflammation process [14], the degradation of PEC can trigger an increased Paclitaxel release.

3.1. Optimizing the coating technique

The reproducible coating of small balloon expandable coronary stents with Poly(ethylene carbonate) is a challenging task. PEC is water-insoluble and only a few organic solvents can be used such as dichloromethane. During spray-coating, the solvent evaporates immediately, due to its low boiling point and the solid polymer layer adheres to the stent.

The stents were spray coated once, twice, or three times with a 0.8% (w/w) PEC solution using the spray-coating apparatus (Fig. 1). The optimum spray-coating parameters were obtained by varying the flow rate and the spraying pressure. Afterward, the results were analyzed using an optical microscope. The best results were achieved with maximum flow rate (2.2 mL/min) and minimum spraying pressure (1.4 b). With these parameters, a high amount of polymer solution was sprayed on the rotating stent.

The distance between airbrush nozzle and stent was a key parameter for optimal coating. The stents were spray-coated and the distance was altered. Fig. 2 demonstrates formation of PEC fibers at distances of 3 cm, 2 cm, and 1 cm. At longer distances, more dichloromethane evaporated during the spraying process resulting in more fiber formation. This effect is well-known by airbrush painters, and it can occur during the application of clear vanish. At longer distances between pistol and stent, the drying duration of dichloromethane is longer, and therefore fibers were built. The problem can be solved by diluting the spraying solution or by reducing the spraying distance. Since the PEC solution had a concentration of 0.8%, the distance was reduced. A high amount of spraying solution was useful to reduce the immediate evaporation of the solvent. So, optimal conditions for the spray coating of small balloon expandable stents with Poly(ethylene carbonate) were identified as: (1) a spraying distance of 0.5 cm, (2) a maximum flow rate of 2.2 mL/min, and (3) a minimum spraying pressure of 1.4 b. The distance is small enough to reach the stent struts while dichloromethane evaporates.

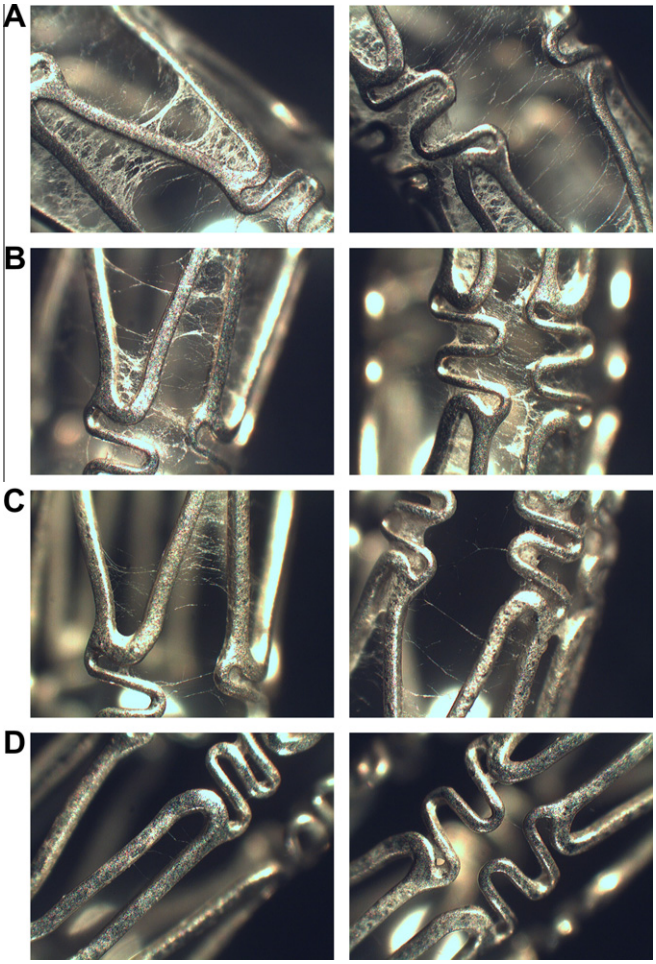

Fig. 2. Optimizing the spraying distance. Optical micrographs of stents spray-coated with 0.8% Poly(ethylene carbonate) in dichloromethane. The distance between airbrush nozzle and stents was altered: (A) 3 cm, (B) 2 cm, (C) 1 cm, (D) 0.5 cm. Magnification 48×. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3.2. Ethylene oxide sterilization

Since the Paclitaxel/PEC stent will be used in animal experiments, they have to be sterilized prior to use. PEC degrades during gamma-sterilization [16], and therefore, ethylene oxide is the only possibility for sterilization. The effect of ethylene oxide sterilization on PEC was examined by GPC. The average molecular weights and weight distributions of sterilized and not sterilized PEC were determined to figure out potential polymer degradation. In Fig. 3, the graphs of gel permeation chromatography (GPC) of sterilized

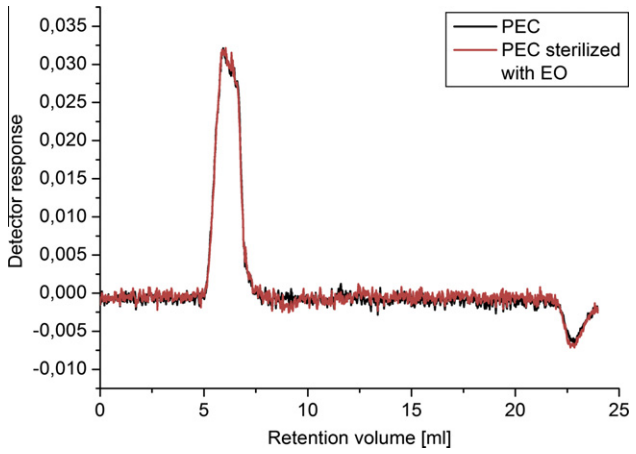

Fig. 3. Sterilization process. Gel permeation chromatography of sterilized (red) and not sterilized (black) PEC ($n = 3$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

and not sterilized PEC are shown. No degradation or alteration of Poly(ethylene carbonate) was found by GPC. So, ethylene oxide sterilization is an appropriate method for sterilization of Paclitaxel/PEC stent systems for *in vivo* experiments.

3.3. Morphology

Two different Paclitaxel concentrations were used to spray-coat the stents using the airbrush apparatus (Fig. 1). The coating consisted of 8% or 25% (w/w) Paclitaxel/PEC. The layer composed of 25 parts Paclitaxel and 75 parts PEC, which is comparable to the moderate release TAXUS™ stent [18,19].

Additionally, spraying times were varied to enhance the drug loading on the stents. The stents were coated either once or three times. Also, dip-coated stents with 25% (w/w) loading were produced to examine the morphological differences of the coating methods. After mounting of stents onto the catheter systems, they were sterilized by ethylene oxide, to investigate the effects of the sterilization process to the polymer coating. An excellent adherence of the stent coating could be observed during the crimping process.

To mimic the expansion of the coronary stents in the artery, the stents were expanded for 30 s with 8 b.

Fig. 4 reveals the morphology of the coated and expanded stents, which were examined by scanning electron microscopy (SEM). The structure of the spray-coated Paclitaxel/PEC film (Fig. 4A–D) was homogenous, demonstrating uniform roughness of the coating on each stent strut. Both Paclitaxel/PEC systems, the 8% loaded (Fig. 4A and B) as well as the 25% loaded (Fig. 4C and D; 25%), showed the same continuous yet slightly rugged surface structure. The three-times spray-coated stents (Fig. 4B and D) are more rough than the once coated ones (Fig. 4A and C), because the unevenness increases with additional spraying procedures.

In Fig. 4E, the morphology of the dip-coated stents is shown. The coating with 25% PEC/Paclitaxel was less homogeneous. The polymer accumulated in the stent bendings and formed lamellae. This phenomenon revealed the disadvantage of dip-coating techniques as described by Hirlekar et al. The review points out that the dip coating may result in bridging of the stent bendings. The bridged polymer may break off and enter the blood stream, which can lead to a medical emergency [2]. Therefore, the dip-coating was found to be inferior to the spray-coating technique and was used for several stent systems [20–24].

The stents were expanded to examine the behavior of the PEC coating during placement in the artery. Therefore, the bends of the stents were examined particularly. No cracks, ruptures, or delamination were observed. As shown by Unger et al. [12], elongation ratios of PEC of more than 600% are possible. The scanning electron micrographs (Fig. 4) confirm this conclusion.

3.4. Homogeneity of the polymer coating

To investigate the homogeneity of the Poly(ethylene carbonate) layer on stents the fluorescent dye, Coumarin-6 was incorporated into PEC. Coumarin-6 acts as lipophilic model drug instead of paclitaxel. This fluorescent dye can be detected via confocal scanning microscopy. Therefore, information concerning homogeneity of the drug in the PEC matrix and of the PEC matrix on the stents was achieved. The confocal scanning micrographs show the dispersion of PEC at the luminal (Fig. 5C and D) and abluminal (Fig. 5A and B) stent side. As expected, the amount of the polymer coating is homogenous on the outside (abluminal) of the stents. The green fluorescence is distributed uniformly, which revealed that the drug was evenly spread in the polymer matrix. The intensity of the fluorescence on the outside is higher than on the inside. Consequently, the PEC layer is thicker abluminal than luminal. This fact is advantageous for an *in vivo* application, because the site of action is the endothelium of the artery and not the blood. Also, in the JACTAX Liberté™ Paclitaxel eluting stent (Boston Scientific) was this approach put into practice [25]. The polymer in the JACTAX™ stent is arranged abluminal to the vessel side. So, it is applied to the outer surface of the stent. Therefore, less drug and polymer are needed and fewer interactions with the blood side are expected.

3.5. Analysis of stent coating with TOF-SIMS

Best depth profile results are obtained for perfectly plane samples with optimal orientation of the samples in the primary ion beam. From this point of view, the investigated stents were not optimal. They have a rough surface structure as can be seen in Fig. 4 and were not totally plane aligned on the sample holder. Thus, the data analysis of SIMS measurements has to be considered with care. Not optimal conditions lead to worse mass resolution of signals, a less sharp lateral image resolution, and a worse depth resolution in profile measurements. A possibility to gain better experimental results was the use of a smaller analysis area. The chosen ROI for the depth profile measurement is demonstrated in Fig. 6.

The signal intensities of PEC/Paclitaxel (Layer I, CNO^-), Parylene (Layer II, Cl_2^-), and the stent material (Layer III, FeO_2^-) are plotted against sputter time in Fig. 7. A schematic for an optimal sample is shown in the upper left corner. The overlap of plotted signals occurs because of the worse depth resolution. A clear layer structure could not be detected, but the layer system itself was investigated by TOF-SIMS. It was examined that the CNO^- signal is present at the surface and is characteristic for Paclitaxel, the topcoat layer. After 500 s of sputtering, a significant Cl_2^- signal was detected which indicates the begin of the Parylene layer. The FeO_2^- signal occurs at about 1500 s of sputtering duration the first time, which displays the stent material. The point of sputtering where 50% of the Paclitaxel layer (left dashed line) and the point where almost 100% of Paclitaxel layer and 50% of Parylene layer (right dashed line) were removed is also shown in Fig. 7.

The whole coating inside the ROI was removed when the FeO_2^- signal stays constant at about 5000 s of sputtering. The results clearly show that TOF-SIMS analysis is a useful method to confirm the order of the coating layers and might be well established to examine stent coatings with a chemically sensitive technique.

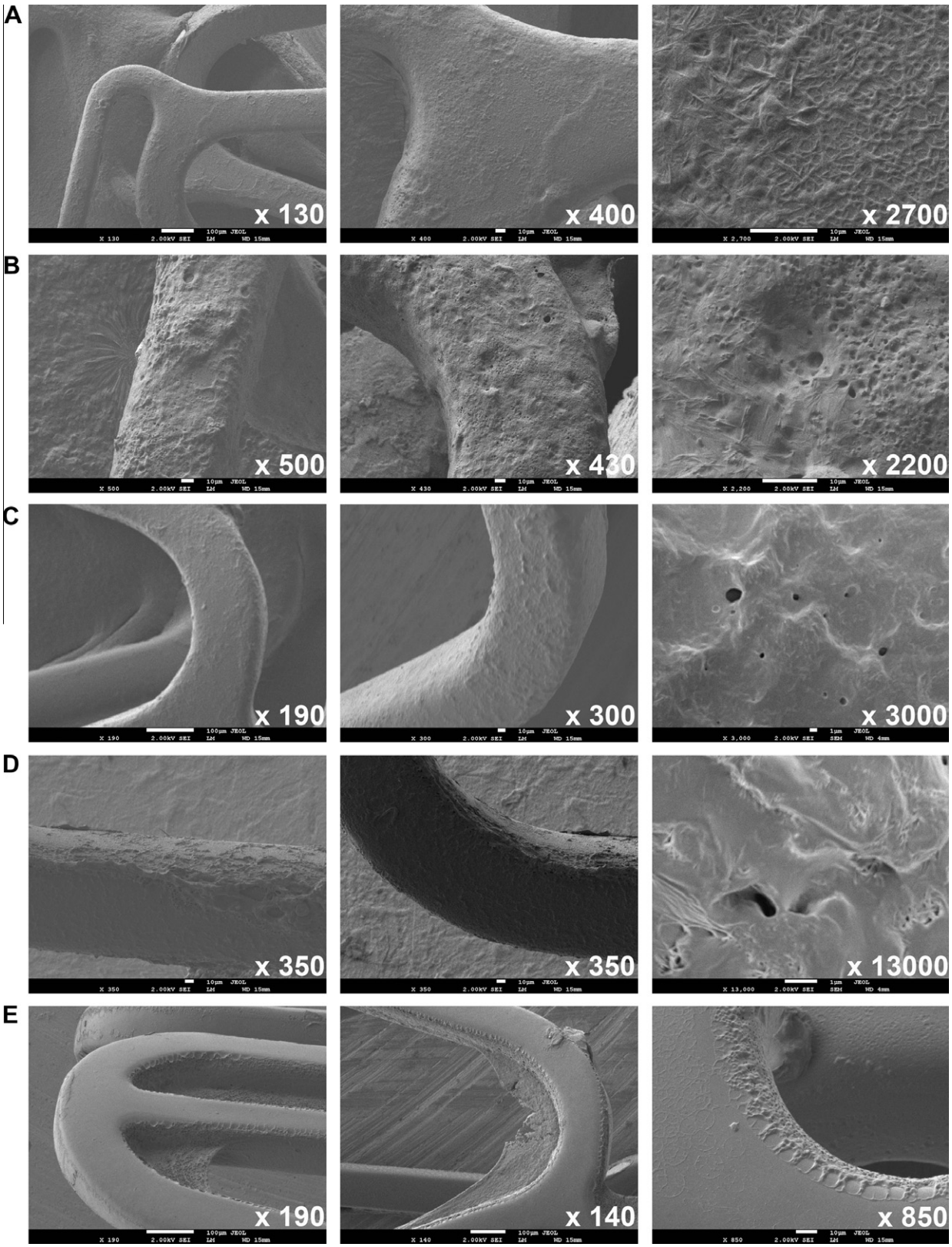

Fig. 4. Morphology of coated stents, Scanning electron microscopy. Scanning electron micrographs of spray- (A–D) and dip-coated (E) Paclitaxel eluting Poly(ethylene carbonate) stents. (A) Stents spray-coated once with 8% Paclitaxel loaded PEC solution; (B) stents spray-coated three times with 8% Paclitaxel loaded PEC solution; (C) stents spray-coated once with 25% Paclitaxel loaded PEC solution; (D) stents spray-coated three times with 25% Paclitaxel loaded PEC solution; (E) stents dip-coated once with 25% Paclitaxel loaded PEC solution.

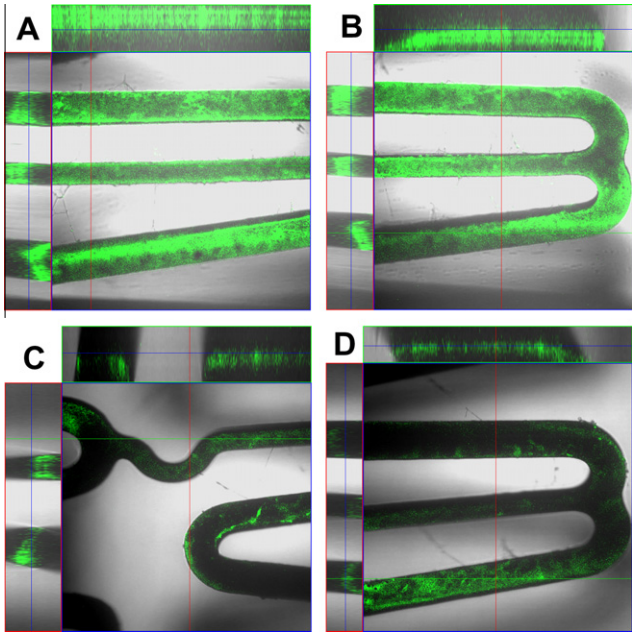

Fig. 5. Homogeneity of the Polymer Film on Stents – CLSM. Confocal laser scanning images of spray-coated Poly(ethylene carbonate) (PEC) stents with incorporated Coumarin-6 as fluorescent marker (magnification 10×). Z-stacks of the coated stents were performed. (A and B) abluminal (outside) and (C and D) luminal (inside) stent side. Green: Coumarin-6 in the Poly(ethylene carbonate) layer. Channel overlay of Coumarin-6 fluorescence and transmitted light are shown. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

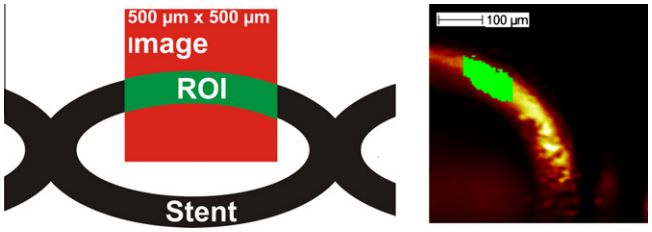

Fig. 6. Selection of analysis area and region of interest (ROI) in the performed depth profile measurement. Scheme of analysis area of TOF-SIMS measurement. The 500 µm times 500 µm imaging and sputtering area (red) in the left image was sketched in correlation to the stent. The analysis area (green) called region of interest (ROI) is shown in the schematics and in the two dimensional total ion image on the right side. The right image illustrates the ROI of the SIMS depth profile that was used for the preparation of the depth profile of Fig. 7. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3.6. Drug loading

To optimize the stent loading with Paclitaxel, times of spraying were varied. The stents were coated once, twice, or three times to create different loaded stents. Fig. 8A shows the drug loading of the 25% Paclitaxel/PEC coated stents. The loading increased from once coated stents of 36.68 µg (±4.85) Paclitaxel per stent to twice coated stents of 56.41 µg (±12.1) up to three times coated ones with a drug loading of 77.73 µg (±6.57) per stent. The surface area of the used stents was 107 mm^2. Referring to the stent surface, the drug loading was 0.32 µg (±0.05) (once coated), 0.53 µg (±0.11) (twice coated), or 0.73 µg (±0.06) (three times coated) Paclitaxel per mm^2 stent surface. In comparison to the commercially available Taxus™ stent with a loading of 1 µg/mm^2 [18], these loading

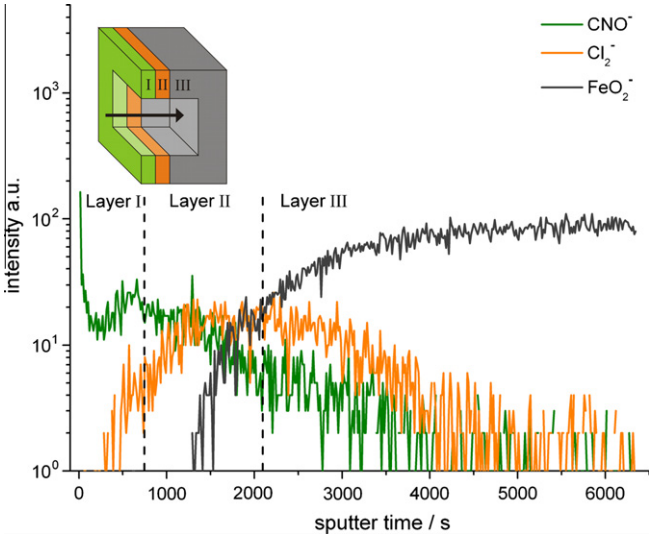

Fig. 7. SIMS depth profile of stent with coating layers. TOF-SIMS depth profile of a stent coating with data from ROI as marked in Fig. 6. The signal intensities of PEC/Paclitaxel (Layer I, CNO^-), Parylene (Layer II, Cl_2^-), and the stent material (Layer III, FeO_2^-) are plotted against sputter time. Dashed lines indicate estimated change of layers (more than 50% of upper layer is removed) from PEC/Paclitaxel to Parylene and from Parylene to the stent. A scheme of the measurement is shown in the upper left corner. The stent was analyzed with the FeO_2^- signal. In negative polarity measurements (oxygen as sputtering gun), oxide species of metal ions are commonly investigated. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

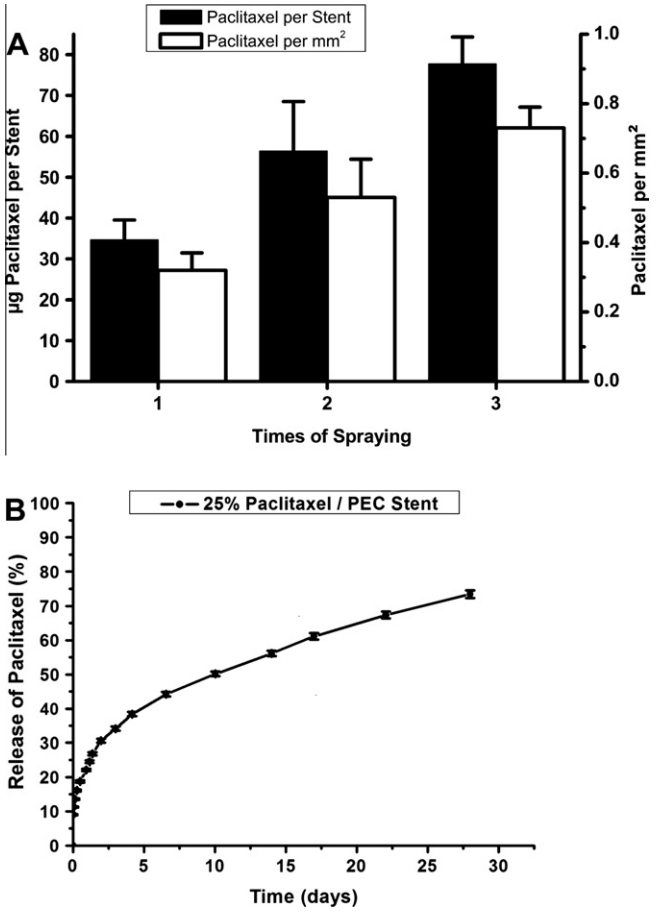

Fig. 8. Drug loading and release. (A) Drug loading of 25% Paclitaxel/PEC coated stents in µg per stent (left axis) and µg per mm^2 of stent surface (right axis) ($n = 5$). (B) Release in% of radioactive labeled Paclitaxel from 25% Paclitaxel/PEC coated stents ($n = 3$, mean ± STD). ($n = 3$).

levels were lower. Recent studies have shown that the effect of Paclitaxel on smooth muscle cell proliferation was sufficient at lower doses [26]. The high-dose JACTAX™ stent contains just 1/10 of the Paclitaxel dose in the TAXUS Liberté™ stent and performs equally successful [27,28]. In the Optical Coherence Tomography Drug Eluting Stent Investigation (OCTESI) study, the effects of different loaded Paclitaxel eluting stents (PES) were compared, revealing that a lower dose of Paclitaxel had no significant unfavorable effects [27,28], whereas endothelial cell migration was suppressed at high Paclitaxel concentrations. This could cause impaired endothelialization, which is needed for vascular healing and for the prevention of late stent thrombosis [26].

3.7. Drug release in vitro

In a first feasibility study, done by our group, of PEC/Paclitaxel coatings, different buffer solutions were used to simulate *in vivo* situations under non-degrading and degrading conditions. It was shown that the release profile under non-degrading conditions by using PBS or PBS/EtOH as release medium is analogical in appearance, just the PBS/EtOH curve showed slight increased Paclitaxel release. Buffer containing 10% ethanol was run to exclude poor solubility and to assure sink condition [12]. The mentioned study was carried out with stainless steel plates (2×2 cm).

The relevance of this *in vitro* drug release study of PEC/Paclitaxel stents was to uncover a potential burst release of the stent coating and to ensure prolonged drug release under non-degrading conditions. Since stents in comparison to steel plates offer a much bigger surface, burst release was one possibility of release. A burst release would not have been beneficial for a further *in vivo* application.

The used lipophilic drug Paclitaxel is practically insoluble in water [29]. The solubility has been reported to be in the range of 0.3–30 μg/mL [18]. To generate sink conditions, the solubility of Paclitaxel needs to be enhanced in the release medium. Usually, for release studies of Paclitaxel in aqueous media, surfactants are added. In literature, the use of PBS at pH 7.4 with addition of 0.05% sodium dodecyl sulfate [30], 0.05% Tween™ 20 [31,32], 30% isopropyl alcohol [33], 10% ethanol [12,34], or 10% dimethyl sulfoxide [35] was reported. Because alcohol is an accepted medium for the examination of drug release of the TAXUS stent, we used 10% ethanol in PBS for the release study [33].

Five individual stents were examined during 28 days. The *in vitro* release kinetics of the 25% Paclitaxel/PEC stents are shown in Fig. 8B. The release study revealed that *in vitro*, without inflammation more precisely without superoxide radicals, about 75% Paclitaxel was released within the first 28 days. The graphic (Fig. 8B) demonstrates also that the paclitaxel release in the first 2 days was faster than afterward, which is favorable *in vivo*. After stent placement accompanied with vascular injury, the inflammation process starts with proliferation and migration of macrophages [14]. To inhibit the restenosis formation in this early stage, sufficient amounts of Paclitaxel are needed. In this study, non-degrading conditions were chosen to expose a potential burst release from coated stents. As shown in Fig. 8B, the release mechanism during non-degradation conditions can be explained by diffusion-controlled drug release slightly influenced by swelling of PEC. PEC is slightly hydrophilic at first water contact, becoming very hydrophilic toward prolonged contact with water, which suggests water uptake and therefore swelling of PEC [12]. The swelling of the polymer promotes diffusion-controlled drug release, additionally.

Extrapolation of the release curve results in a maximum release of about 2 months, in case of *in vitro* conditions without inflammatory processes. Paclitaxel causes a delayed arterial healing, so that the re-growth of a functional endothelium with its antithrombotic factors is defective [36]. Also, Paclitaxel might be responsible for excessive fibrin deposition, which is a factor for late stent thrombosis [7,37]. So, the concept of a polymer that controls the drug release during a short time of about 2 months seems to be very attractive [4]. A maximum release of the cytostatic drug of 2 months can be ensured, and superoxide radicals for the drug release would not be imperative. For example, the JACTAX Liberté™ stent (Boston Scientific) shows a 100% drug release within 60 days [25,28]. The JACTAX™ stent acts as advancement for the TAXUS™ stent, which releases just 10% of Paclitaxel during 90 days [19,38].

Diffusion-controlled drug release is one of the commonly used mechanisms for the currently marketed drug eluting stents. The Cypher stent (Cordis Corp.) consists of Poly(ethylene-co-vinyl acetate) and Poly(n-butyl methacrylate). The combination of these polymers is mixed with Sirolimus and serves as base coat. This base coat is covered with a layer of Poly(-n-butyl methacrylate), which controls the drug diffusion.

Also the TAXUS stent (Boston Scientific), whose polymer matrix consists of Poly(styrene-b-isobutylene-b styrene) and paclitaxel, is a diffusion-controlled matrix system. Like the PEC/Paclitaxel stent the TAXUS stent does not exhibit a rate-controlling membrane. Both systems show a non-zero-order release [2,19].

As proven by Unger et al. [12], Paclitaxel incorporated in a PEC layer was completely released in superoxide containing media within less than 12 h. Superoxide anions are produced *in vivo* by macrophages during the inflammatory vascular response after stent placement, which will increase the Paclitaxel release by triggering the PEC degradation and leading to an increase of drug release.

In summary, the *in vivo* release kinetic is a combination of diffusion-controlled drug release and degradation-controlled drug release depending on the presence or absence of superoxide anions and accordingly depending on the presence or absence of macrophages and polymorphonuclear leukocytes [12]. So, an increased on-demand release of Paclitaxel accompanied with a diffusion-controlled release might take place *in vivo*. The drug release will increase during inflammatory processes, when Paclitaxel for inhibition of restenosis is desperately needed. Optimal Paclitaxel amounts can be released and a maximum release of about 2 months even under non-degrading conditions can be ensured. At the latest after 2 months, no drug elutes, and a new endothelium with its antithrombotic factors can be built which can avoid late stent thrombosis. Furthermore, PEC is a new polymer material that offers good biocompatibility *in vivo* [11]. It should not cause any hypersensitivity reactions of the vascular tissue.

We hypothesize that this specific release kinetics of PEC will be ideal for a drug eluting stent. At the time, the Paclitaxel/PEC stent system is under investigation in animal studies with white New Zealand Rabbits to test the postulated behavior *in vivo*.

4. Conclusions

This work presents a novel Paclitaxel eluting stent system that is based upon Poly(ethylene carbonate). The reproducible fabrication of different loaded PEC stents via a homemade spray-coating apparatus on a laboratory scale was possible. Ethylene oxide sterilization was found to be a feasible method for sterilization of PEC. SEM revealed the homogeneous coating with the polymer/drug layer. The homogeneity of the coating was uniform at the abluminal stent site, whereas the luminal site offers lesser coating, which is favorable for DES. The deposition of PEC/Paclitaxel and Parylene was confirmed by TOF-SIMS investigations, which at all has proven that it is a useful tool for the examination of stent coatings. A drug loading from 0.32 μg to 0.73 μg Paclitaxel per mm^2 stent surface could be achieved. Release studies during non-degradation

conditions in PBS supplemented with 10% ethanol showed diffusion-controlled drug release slightly influenced by swelling of PEC, revealing that 100% of the loaded Paclitaxel will be released via diffusion within 2 months. The *in vivo* release mechanism is a combination of diffusion-controlled drug release and degradation controlled drug release. We hypothesize that the specific release kinetics of PEC, the biocompatibility, and its favorable mechanical properties will be ideal for a next generation drug eluting stent. Object of further studies are animal experiments with white New Zealand Rabbits to test the postulated behavior *in vivo*.

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References

[1] N.D. Lambert, R.J. Applegate, The comparative safety of bare-metal and drug-eluting intracoronary stents, Expert Rev. Med. Dev. 7 (5) (2010) 611–624.
[2] R. Hirlekar, M. Patel, S. Jain, V. Kadam, Drug eluting coronary artery stents, Curr. Drug. Deliv. 7 (2010) 421–427.
[3] J.V. Llau, R. Ferrandis, P. Sierra, A. Gomez-Luque, Prevention of the renarrowing of coronary arteries using drug-eluting stents in the perioperative period: an update, Vasc. Health Risk Manage. 6 (2010) 855–867.
[4] A. Abizaid, J.R. Costa Jr., New drug-eluting stents: an overview on biodegradable and polymer-free next-generation stent systems, Circ. Cardiovasc. Interv 3 (4) (2010) 384–393.
[5] D.E. Cutlip, S. Windecker, R. Mehran, A. Boam, D.J. Cohen, G.A. van Es, P.G. Steg, M.A. Morel, L. Mauri, P. Vranckx, E. McFadden, A. Lansky, M. Hamon, M.W. Krucoff, P.W. Serruys, Clinical end points in coronary stent trials: a case for standardized definitions, Circulation 115 (17) (2007) 2344–2351.
[6] A. Farb, A.P. Burke, F.D. Kolodgie, R. Virmani, Pathological mechanisms of fatal late coronary stent thrombosis in humans, Circulation 108 (14) (2003) 1701–1706.
[7] G. Nakazawa, A.V. Finn, M. Vorpahl, E.R. Ladich, F.D. Kolodgie, R. Virmani, Coronary responses and differential mechanisms of late stent thrombosis attributed to first-generation sirolimus- and paclitaxel-eluting stents, J. Am. Coll. Cardiol. 57 (4) (2011) 390–398.
[8] G.V. Silva, M.R. Fernandes, R. Madonna, F. Clubb, E. Oliveira, P. Jimenez-Quevedo, R. Branco, J. Lopez, F.S. Angeli, R. Sanz-Ruiz, W.K. Vaughn, Y. Zheng, F. Baimbridge, J. Canales, C.O. Cardoso, J.A. Assad, R. Falotico, E.C. Perin, Comparative healing response after sirolimus- and paclitaxel-eluting stent implantation in a pig model of restenosis, Catheter Cardiovasc. Interv. 73 (6) (2009) 801–808.
[9] T.F. Luscher, J. Steffel, F.R. Eberli, M. Joner, G. Nakazawa, F.C. Tanner, R. Virmani, Drug-eluting stent and coronary thrombosis: biological mechanisms and clinical implications, Circulation 115 (8) (2007) 1051–1058.
[10] R. Wessely, New drug-eluting stent concepts, Nat. Rev. Cardiol. 7 (4) (2010) 194–203.
[11] M. Dadsetan, E.M. Christenson, F. Unger, M. Ausborn, T. Kissel, A. Hiltner, J.M. Anderson, In vivo biocompatibility and biodegradation of poly(ethylene carbonate), J. Control. Release 93 (3) (2003) 259–270.
[12] F. Unger, U. Westedt, P. Hanefeld, R. Wombacher, S. Zimmermann, A. Greiner, M. Ausborn, T. Kissel, Poly(ethylene carbonate): a thermoelastic and biodegradable biomaterial for drug eluting stent coatings?, J Control. Release 117 (3) (2007) 312–321.
[13] G.H. Stoll, F. Nimmerfall, M. Acemoglu, D. Bodmer, S. Bantle, I. Muller, A. Mahl, M. Kolopp, K. Tullberg, Poly(ethylene carbonate)s, part II: degradation mechanisms and parenteral delivery of bioactive agents, J. Control. Release 76 (3) (2001) 209–225.
[14] N.A. Scott, Restenosis following implantation of bare metal coronary stents: pathophysiology and pathways involved in the vascular response to injury, Adv. Drug Delivery Rev. 58 (3) (2006) 358–376.
[15] R. Jabara, N. Chronos, D. Conway, W. Molema, K. Robinson, Evaluation of a novel slow-release paclitaxel-eluting stent with a bioabsorbable polymeric surface coating, JACC Cardiovasc. Interv. 1 (1) (2008) 81–87.
[16] M. Acemoglu, F. Nimmerfall, S. Bantle, G.H. Stoll, Poly(ethylene carbonate)s, part I: syntheses and structural effects on biodegradation, J. Control. Release 49 (2,3) (1997) 263–275.
[17] C. Schmidt, V. Stuempflen, J.H. Wendorff, A. Hasenhindl, W. Gronski, M. Ishaque, A. Greiner, Structural analysis of poly(p-xylylene) (PPX) prepared by vapor phase pyrolysis of [2.2]paracyclophane, Acta Polym. 49 (5) (1998) 232–235.
[18] K.R. Kamath, J.J. Barry, K.M. Miller, The Taxus drug-eluting stent: a new paradigm in controlled drug delivery, Adv. Drug Delivery Rev. 58 (3) (2006) 412–436.
[19] G. Acharya, K. Park, Mechanisms of controlled drug release from drug-eluting stents, Adv. Drug Delivery Rev. 58 (3) (2006) 387–401.
[20] U. Westedt, M. Wittmar, M. Hellwig, P. Hanefeld, A. Greiner, A.K. Schaper, T. Kissel, Paclitaxel releasing films consisting of poly(vinyl alcohol)-graft-poly(lactide-co-glycolide) and their potential as biodegradable stent coatings, J. Control. Release 111 (1–2) (2006) 235–246.
[21] J. Pan Ch, J.J. Tang, Y.J. Weng, J. Wang, N. Huang, Preparation, characterization and anticoagulation of curcumin-eluting controlled biodegradable coating stents, J. Control. Release 116 (1) (2006) 42–49.
[22] L. Indolfi, F. Causa, P.A. Netti, Coating process and early stage adhesion evaluation of poly(2-hydroxy-ethyl-methacrylate) hydrogel coating of 316L steel surface for stent applications, J. Mater. Sci.: Mater. Med. 20 (7) (2009) 1541–1551.
[23] E. Kang, K. Vedantham, X. Long, M. Dadara, I.K. Kwon, M. Sturek, K. Park, Drug-eluting stent for delivery of signal pathway-specific 1, 3-dipropyl-8-cyclopentyl xanthine, Mol. Pharm. 6 (4) (2009) 1110–1117.
[24] Y. Levy, D. Mandler, J. Weinberger, A.J. Domb, Evaluation of drug-eluting stents' coating durability–clinical and regulatory implications, J. Biomed. Mater. Res. B Appl. Biomater. 91 (1) (2009) 441–451.
[25] E. Grube, J. Schofer, K.E. Hauptmann, G. Nickenig, N. Curzen, D.J. Allocco, K.D. Dawkins, A novel paclitaxel-eluting stent with an ultrathin abluminal biodegradable polymer 9-month outcomes with the JACTAX HD stent, JACC Cardiovasc. Interv. 3 (4) (2010) 431–438.
[26] R. Wessely, B. Blaich, R.S. Belaiba, S. Merl, A. Gorlach, A. Kastrati, A. Schomig, Comparative characterization of cellular and molecular anti-restenotic profiles of paclitaxel and sirolimus. Implications for local drug delivery, Thromb. Haemost. 97 (6) (2007) 1003–1012.
[27] G. Guagliumi, V. Sirbu, G. Musumeci, H.G. Bezerra, A. Aprile, H. Kyono, L. Fiocca, A. Matiashvili, N. Lortkipanidze, A. Vassileva, J.J. Popma, D.J. Allocco, K.D. Dawkins, O. Valsecchi, M.A. Costa, Strut coverage and vessel wall response to a new-generation paclitaxel-eluting stent with an ultrathin biodegradable abluminal polymer: Optical Coherence Tomography Drug-Eluting Stent Investigation (OCTDESI), Circ. Cardiovasc. Interv. 3 (4) (2010) 367–375.
[28] S. Garg, P.W. Serruys, Coronary stents: looking forward, J. Am. Coll. Cardiol. 56 (10) (2010) S43–78. Suppl.
[29] Monographs: Paclitaxel, European Pharmacopoiea Edition 7.2, 2011.
[30] M. Gagliardi, D. Silvestri, C. Cristallini, M. Guadagni, G. Crifaci, P. Giusti, Combined drug release from biodegradable bilayer coating for endovascular stents, J. Biomed. Mater. Res. B Appl. Biomater. 93 (2) (2010) 375–385.
[31] M. Boden, R. Richard, M.C. Schwarz, S. Kangas, B. Huibregtse, J.J. Barry, In vitro and in vivo evaluation of the safety and stability of the TAXUS Paclitaxel-Eluting Coronary Stent, J. Mater. Sci. Mater. Med. 20 (7) (2009) 1553–1562.
[32] S.V. Ranade, K.M. Miller, R.E. Richard, A.K. Chan, M.J. Allen, M.N. Helmus, Physical characterization of controlled release of paclitaxel from the TAXUS Express2 drug-eluting stent, J. Biomed. Mater. Res. A 71 (4) (2004) 625–634.
[33] E. Kang, H. Wang, I.K. Kwon, Y.H. Song, K. Kamath, K.M. Miller, J. Barry, J.X. Cheng, K. Park, Application of coherent anti-Stokes Raman scattering microscopy to image the changes in a paclitaxel-poly(styrene-b-isobutylene-b-styrene) matrix pre- and post-drug elution, J. Biomed. Mater. Res. A 87 (4) (2008) 913–920.
[34] N. Bege, T. Renette, M. Jansch, R. Reul, O. Merkel, H. Petersen, C. Curdy, R.H. Muller, T. Kissel, Biodegradable Poly(ethylene carbonate) nanoparticles as a promising drug delivery system with "stealth" potential, Macromol. Biosci. 11 (7) (2011) 897–904.
[35] L.L. Lao, S.S. Venkatraman, Paclitaxel release from single and double-layered poly(DL-lactide-co-glycolide)/poly(L-lactide) film for biodegradable coronary stent application, J. Biomed. Mater. Res. A 87 (1) (2008) 1–7.
[36] A.V. Finn, G. Nakazawa, M. Joner, F.D. Kolodgie, E.K. Mont, H.K. Gold, R. Virmani, Vascular responses to drug eluting stents: importance of delayed healing, Arterioscler. Thromb. Vasc. Biol. 27 (7) (2007) 1500–1510.
[37] E. Camenzind, P.G. Steg, W. Wijns, Stent thrombosis late after implantation of first-generation drug-eluting stents: a cause for concern, Circulation 115 (11) (2007) 1440–1455. discussion 1455.
[38] D.J. Kereiakes, L.A. Cannon, R.L. Feldman, J.J. Popma, R. Magorien, R. Whitbourn, I.M. Dauber, A.C. Rabinowitz, M.W. Ball, B. Bertolet, A. Kabour, M.C. Foster, J.C. Wang, P. Underwood, K.D. Dawkins, Clinical and angiographic outcomes after treatment of de novo coronary stenoses with a novel platinum chromium thin-strut stent: primary results of the PERSEUS (Prospective Evaluation in a Randomized Trial of the Safety and Efficacy of the Use of the TAXUS Element Paclitaxel-Eluting Coronary Stent System) trial, J. Am. Coll. Cardiol. 56 (4) (2010) 264–271.