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Development of an antifibrotic drug-eluting coating for a minimally invasive implantable glaucoma microstent

Abstract: Primary open angle glaucoma represents an eye disease that usually is associated with an increased intraocular pressure (IOP). Implants for micro-invasive glaucoma surgery (MIGS) are gaining importance as a promising option for IOP lowering. Currently available devices are implanted into the eye *ab interno* based on a clear corneal incision and drain aqueous humour into the schlemm's canal, suprachoroidal or subconjunctival space. Fibrosis is known as a major limitation for long term success and often leads to the necessity of an additional medication or a surgical re-intervention. The current work focusses on the development of an antifibrotic drug-eluting coating for a minimally invasive implantable glaucoma microstent. Tubular microstent base bodies manufactured from a polycarbonate based silicone elastomer were spray-coated with a chloroform based mixture of the same polymer and the antifibrotic drug pirfenidone (PFD, P2116, Merck KGaA, Germany) in a polymer/drug ratio of 85/15% (w/w). Coating mass of 89 µg according to a drug loading of 1.96 µg mm⁻² was aspired. Coating mass was measured using an ultramicrobalance (XP6U, Mettler-Toledo International, Inc., Switzerland). Glaucoma microstent prototypes with a drug-eluting coating mass of (84 ± 19) µg (*n* = 12) were manufactured. Characterization by means of scanning electron microscopy (Quattro S, Thermo Fisher Scientific, FEI Deutschland GmbH, Germany) yielded a reproducible smooth surface of the coating. High performance liquid chromatography (KNAUER Wissenschaftliche Geräte

GmbH, Germany) was used for analysis of drug release behaviour in 0.9% NaCl solution at 37°C. The *in vitro* PFD-release is characterized by an initial burst phase of approximately 6 h followed by a more retarded release phase. The entire drug was released within 36 h (*n* = 3). Sterilization processing has a minor impact on drug release kinetics. Appropriate drug stability after sterilization could be proven. Future studies will focus on the antifibrotic properties of drug-eluting glaucoma microstents in animal studies.

Keywords: Glaucoma drainage device, GDD, Minimally invasive glaucoma surgery, Micro-invasive glaucoma surgery, MIGS.

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1 Introduction

Glaucoma represents a major cause for vision impairment and blindness worldwide [1]. Primary open angle glaucoma as the most prevalent type of the eye disease is usually associated with an increased intraocular pressure (IOP) [2].

Implants for micro-invasive glaucoma surgery (MIGS) are gaining importance as a promising treatment option with a decreased risk for serious complications compared to conventional glaucoma drainage devices (GDD) or surgical approaches for IOP-lowering, particularly trabeculectomy. Currently available devices for MIGS are implanted into the eye *ab interno* based on a clear corneal incision and drain aqueous humour into the schlemm's canal, suprachoroidal or subconjunctival space [3].

Fibrosis is known as a major limitation for long term success and often leads to the necessity of an additional medication or a surgical re-intervention. The aqueous humour drained from the anterior chamber of the eye and the incorporated growth factors, particularly the transforming growth factor-β (TGF-β), contribute to the proliferation of fibroblasts. Furthermore, wound healing after the implantation of a conventional GDD and also after the

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implantation of a MIGS-device is different to trabeculectomy, due to the inserted foreign body [4].

Pirfenidone (PFD) as a treatment option of idiopathic pulmonary fibrosis has been identified as a promising drug for the inhibition of fibrosis in animal models, such as New Zealand White rabbits or rats [4,5]. Therefore, the current work focusses on the development of an antifibrotic drug-eluting coating for a minimally invasive implantable glaucoma microstent.

2 Materials and methods

2.1 Microstent concept

Our microstent concept was described previously. A valve mechanism is used for controlled drainage of aqueous humour, a drug eluting-coating focusses on the prevention of fibrosis and an injector device is used for minimally invasive *ab interno* implantation into suprachoroidal or alternatively subconjunctival space (Fig. 1) [5-7].

Figure 1: Schematic representation of the microstent including global dimensions of the device (top) and the injector device for minimally invasive implantation of the microstent (bottom).

PFD loading of the drug eluting coating was chosen according to Jung et al. who implanted conventional Ahmed FP8 GDD (New World Medical Inc., USA) into New Zealand White rabbits adjunctive with an intraoperative injection of 200 μg PFD in a 200 μl solution incorporated with 1 mg ml^{-1} PFD [4]. Considering a surface area of the

drainage plate of the Ahmed FP8 GDD of 102 mm^2 a PFD loading of 1.96 $\mu\text{g mm}^{-2}$ was provided.

Transferred to the outflow surface area of our glaucoma microstent of 6.79 mm^2 a PFD mass of 13 μg according to a drug loading of 1.96 $\mu\text{g mm}^{-2}$ was aspired. Therefore, a mass of 89 μg was calculated for the drug eluting coating, assuming a polymer/drug ratio of 85/15% (w/w).

2.2 Microstent development

2.2.1 Base body

Tubular microstent base bodies were manufactured from a polycarbonate based silicone elastomer. The semiautomatic dip-coating process and the methods for diameter measurement of tubing were described previously [7].

2.2.2 Drug-eluting coating

Microstent base bodies were spray-coated with a chloroform based mixture of the polycarbonate based silicone elastomer and the antifibrotic drug PFD (P2116, Merck KGaA, Germany) in a polymer/drug ratio of 85/15% (w/w) (Fig. 2). Parameters of spray-coating processing were summarized in Tab. 1.

Figure 2: Setup for spray-coating of glaucoma microstents.

Coated specimens were dried for 7 days in vacuum at ambient temperature. Coating mass of 89 μg according to a drug loading of 1.96 $\mu\text{g mm}^{-2}$ was aspired. The coating mass was measured using an ultramicrobalance (XP6U, Mettler-Toledo International, Inc., Switzerland).

Table 1: Parameters of spray-coating processing of microstent base bodies.

parameter	value	unit
distance nozzle / microstent	30	mm
pressure (fluid reservoir)	0.2	bar
pressure (nozzle)	0.3	bar
nozzle orifice	1.7	-
mounting (vertical traversing)	20	mm
mounting (rotation)	60	min ⁻¹
coating duration	180	s

2.2.3 Sterilization

Sterilization of coated specimens was conducted by means of 10 MeV E-beam radiation using a dose of 30 kGy (Herotron E-Beam Service GmbH a STERIS Company, Bitterfeld-Wolfen, Germany).

2.2.4 Drug release *in vitro*

High performance liquid chromatography (KNAUER Wissenschaftliche Geräte GmbH, Germany) was used for analysis of drug recovery and drug release behaviour in 0.9% NaCl solution at 37°C. The test specimens were stored on a rotating platform-shaking device (Unimax 1010, Heidolph Instruments GmbH&Co. KG, Schwabach, Germany) at 100 rpm during the *in vitro* drug release studies.

2.2.5 Scanning electron microscopy

Scanning electron microscopy (SEM, Quattro S, Thermo Fisher Scientific, FEI Deutschland GmbH, Germany) was conducted at a vacuum pressure of 50 Pa and an accelerating voltage of 5 kV.

3 Results

Microstent base bodies yield a smooth surface and a reproducible inner and outer diameter of $ID = (0.20 \pm 0.00)$ mm and $OD = (0.36 \pm 0.02)$ mm ($n = 33$).

Glaucoma microstent prototypes with a drug-eluting coating mass of (84 ± 19) µg ($n = 12$) were manufactured. SEM characterization yielded a reproducible smooth surface

of the coated and uncoated areas and a smooth transition zone between these areas (Fig. 3).

Figure 3: Scanning electron micrograph of a microstent base body: uncoated area, transition zone and coated area.

Prior to sterilization and after sterilization ($79.73 \pm 5.59\%$ and $(61.77 \pm 0.83)\%$ PFD recovery was found within the drug eluting coating ($n = 3$, respectively). Drug release behaviour of unsterilized and sterilized test specimens ($n = 3$, respectively) is shown in Fig. 4.

Figure 4: Absolute (A) and percentage (B, normalized to recovered drug mass) cumulative *in vitro* release of pifrenidone of unsterilized and sterilized test specimens ($n = 3$); mean $\pm$ standard deviation, respectively.

The *in vitro* PFD-release of unsterilized and sterilized test specimens is characterized by an initial burst phase of approximately 6 h followed by a more retarded release phase. Drug release of sterilized test specimens is slightly retarded compared to unsterilized test specimens. Release of the entire drug was found within 36 h ($n = 3$, respectively).

4 Discussion

The presented drug-eluting coating for minimally invasive implantable glaucoma microstents permits local and controlled release of the antifibrotic drug PFD. The processing described within the current work is suitable for the manufacturing of drug-eluting microstents with a reproducible quality with regard to coating mass and coating morphology. Sterilization processing has a minor impact on drug release kinetics. Appropriate drug stability after sterilization could be proven. The diameter change of coated compared to uncoated microstents is negligible and therefore does not affect the cannula-based minimally invasive implantation procedure.

Jung et al. implanted conventional Ahmed FP8 GDD microsurgically into New Zealand White rabbits with an adjunctive intraoperative injection of 200 μg PFD and found reduced fibrosis compared to a control group without the use of an adjunctive drug therapy [4]. Within the current study, we aspired a comparatively small drug loading of 13 μg PFD. With regard to the implantation procedure as well as the global dimensions of the Ahmed FP8 GDD and our microstent device, drug loading was adapted considering the surface area in the outflow region of the devices.

In preliminary studies we could show reduced fibrosis using PFD-coated glaucoma microstents compared to an uncoated control group in a rat model. A total of 16.12 μg PFD was released within a time frame of 10 h *in vitro*. Disregardless of the relatively fast drug release the PFD coating effectively reduces capsule thickness and the growth

of the capsule throughout the 6 months observation period [5].

Future studies will focus on further characterization of drug eluting coatings, for example with regard to shelf life, and on the assessment of antifibrotic effects *in vivo*.

Author Statement

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