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Development of a drug-eluting microstent for micro-invasive glaucoma surgery

Abstract: Glaucoma represents the leading cause of irreversible blindness worldwide. Therapeutic approaches are based on the lowering of intraocular pressure (IOP). Micro-invasive glaucoma surgery (MIGS) offers perspectives for implant based IOP-reduction with reduced complication rates compared to conventional surgical approaches. Nevertheless, available devices suffer from complications like hypotony and fibrotic encapsulation. The current work focuses on the development of a minimally invasive implantable drug-eluting microstent for the drainage of aqueous humour into suprachoroidal or subconjunctival space. Technical feasibility of a micro-scale resorbable nonwoven for the prevention of hypotony and of a drug-eluting coating for the prevention of fibrosis is assessed. Microstent base bodies with a length of 10 mm and an inner/outer diameter of 0.20 mm / 0.35 mm were manufactured. For the prevention of hypotony, resorbable nonwovens with an adequate flow resistance of 1.543 mmHg/µl min⁻¹ were manufactured in the inflow area of microstents. A drug-eluting coating in the outflow area of microstents was developed based on the model drug fluorescein diacetate. Micro-invasive ab interno implantation of a microstent prototype into suprachoroidal space of a porcine eye post mortem was successfully performed, using an injector device. Future studies will focus on the development of an antifibrotic drug-eluting coating and further in vitro, ex vivo and in vivo testing of the devices.

Keywords: glaucoma drainage device, drug-eluting microstent, micro-invasive glaucoma surgery.

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1 Introduction

Glaucoma represents the leading cause of irreversible blindness worldwide [1]. Therapeutic approaches are based on the lowering of intraocular pressure (IOP). A reduction of baseline-IOP by at least 30% usually prevents progressive damage of retinal ganglion cells [2]. First line treatment of an increased IOP is based on topically applied drugs. Consecutive treatment options include laser trabeculoplasty, incisional glaucoma surgery, particularly trabeculectomy, and glaucoma drainage devices (GDD). Currently emerging implants for micro-invasive glaucoma surgery (MIGS) show decreased complication rates but also device dependent limitations in IOP-reduction compared with trabeculectomy or conventional GDD [2,3].

Implants for MIGS like iStent (Glaukos Inc., Laguna Hills, CA, USA), CyPass micro-stent (Alcon Inc., Fort Worth, TX, USA) or XEN gel stent (Allergan plc, Dublin, Ireland) drain aqueous humour into Schlemm’s canal, suprachoroidal or subconjunctival space, respectively. Devices for suprachoroidal or subconjunctival drainage allow for more IOP-reduction compared with devices implanted into Schlemm’s canal but are also associated with a higher risk for hypotony [3]. Furthermore, scar formation and fibrotic encapsulation processes represent a major limitation of all available devices.

The current work focuses on the development of a minimally invasive implantable drug-eluting microstent for the drainage of aqueous humour into suprachoroidal or subconjunctival space. Technical feasibility of a micro-scale resorbable nonwoven for the prevention of hypotony and of a drug-eluting coating for the prevention of fibrosis is assessed.
2 Materials and methods

2.1 Microstent development

The microstent-concept and the concept of an injector device for minimally invasive implantation are shown in Figure 1. The 10 mm base body of the microstent is equipped with a resorbable nonwoven in the inflow area and with a drug-eluting coating in the outflow area.

![Figure 1: Schematic representation of the microstent (a) and the microstent loaded into the injector device based on a cannula that is withdrawn (arrow) from the implant (b).](image)

2.1.1 Base body

Manufacturing of the base body was conducted, using a semiautomatic dip-coating process (KSV NIMA Dip Coater, Biolin Scientific Holding AB, Stockholm, Sweden) and dipping mandrels with a diameter of 0.2 mm. A polymer solution based on 4% (w/v) Chronosil 80A (AdvanSource Biomaterials Corp., Wilmington, MA, USA) in chloroform (Sigma Aldrich Corp., St. Louis, MO, USA) was used. Tubing outer diameter was measured by means of a biaxial laser scanner (ODAC 32 XY, Zumbach Electronic AG, Orpund, Switzerland). After removal of dipping mandrels the base bodies were stored in a vacuum drying cabinet for four days at 40°C.

2.1.2 Resorbable nonwoven

Resorbable nonwovens were manufactured from Poly(4-hydroxybutyrate) (P(4HB); P4HB biopolymer, Tepha, Inc., Lexington, MA, USA) by means of electrospinning as described previously [5]. Process parameters of electrospinning are summarized in Table 1. The polymer was diluted in chloroform and methanol (J.T. Baker, Avantor Performance Materials Inc., Center Valley, PA, USA) 8.0/87.6/4.4% (w/w/w). Morphological analysis was performed using scanning electron microscopy (SEM; Quanta 250 FEG, FEI, Hillsboro, OR, USA). A test setup simulating in vivo pressure and flow conditions is used to analyze the volumetric flow rate as a function of the pressure difference for microstent prototypes [5].

![Table 1: Process parameters.](image)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Electrospinning</th>
<th>Electrospaying</th>
<th>Airbrush</th>
</tr>
</thead>
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<td>Volumetric flow rate</td>
<td>0.5 ml h⁻¹</td>
<td>1.0 ml h⁻¹</td>
<td>-</td>
</tr>
<tr>
<td>Reservoir pressure / discharge pressure</td>
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<td>-</td>
<td>0.2 / 0.2 bar</td>
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<tr>
<td>High voltage</td>
<td>8.1 kV</td>
<td>10.7 kV</td>
<td>-</td>
</tr>
<tr>
<td>Working distance</td>
<td>65 mm</td>
<td>30 mm</td>
<td>30 mm</td>
</tr>
<tr>
<td>Coating time</td>
<td>120 s</td>
<td>100 s</td>
<td>80 s</td>
</tr>
</tbody>
</table>

In vitro drug-release studies were performed in 500 µl of 0.9% saline solution (Fresenius Kabi AG, Bad Homburg vor der Höhe, Germany) at 37°C. After 1, 3, 24 and 50 h the saline solution was exchanged. 20 µl of the extracted fluid were mixed with sodium hydroxide (Merck KGaA, Darmstadt, Germany) and analyzed by means of a FLUOstar OPTIMA Microplate Reader (BMG LABTECH GmbH, Ortenberg, Germany).

2.1.3 Drug-eluting coating

A 1.827 g Chronosil 80A and 0.322 g fluorescein diacetate (FDA, Thermo Fischer Scientific Inc., Waltham, MA, USA) mixture 85/15% (w/w) in 40 ml chloroform, 5 ml dimethyl formamide and 5 ml tetrafluoroethylene (Carl Roth GmbH + Co. KG, Karlsruhe, Germany) was used as a model drug-eluting coating. A length of 5 mm in the outflow area is coated with an aspired mass of 52.78 µg according to a drug mass of 7.92 µg or a drug loading of 1.4 µg mm⁻².

Drug-eluting coatings were manufactured by means of electrospaying and airbrush process. Parameters of electrospaying and airbrush process are summarized in Table 1.

2.2 Development of an injector device

An injector device is designed using Creo Parametric 3.0 (PTC Inc., Needham, MA, USA). The device is based on a 23G x 1¼" cannula (B. Braun Melsungen AG, Melsungen, Germany) in which the microstent is loaded. During
deployment, a mandrel (0.36 mm diameter) is used to retain the microstent while the cannula is withdrawn from the implant [4].

Manufacturing of injector devices was conducted using a 3D printer and various photoreactive polymers (Form 2, Formlabs Inc., Somerville, MA, USA).

2.3 Implantation testing

Micro-invasive microstent implantation into a porcine eye was performed post mortem using an operating microscope (OphthalMic 900, Möller-Wedel GmbH & Co. KG, Wedel, Germany) combined with a digital single-lens reflex camera (D100, Nikon, Tokio, Japan).

3 Results

3.1 Microstent development

Manufactured base bodies showed a smooth surface and reproducible inner and outer diameter ($ID = 0.2 ± 0.00 \text{ mm}$ and $OD = 0.35 ± 0.02 \text{ mm}; n = 20$). Resorbable nonwovens in the microstent inflow area were manufactured with a total length of approximately $800 \mu\text{m}$ (Figure 2).

Volumetric flow rate as a function of the pressure difference for microstent base bodies with and without resorbable nonwoven is shown in Figure 3. Measured flow resistance of the microstent base body ($0.031 \text{ mmHg/µl min}^{-1}$) corresponds well to theoretical considerations according to Hagen-Poiseuilles law for stationary laminar flow in circular pipes ($0.029 \text{ mmHg/µl min}^{-1}$). The resorbable nonwoven permits a considerable increase of microstent flow resistance by two orders of magnitude to $1.543 \text{ mmHg/µl min}^{-1}$.

Figure 2: SEM of resorbable nonwoven in microstent inflow area (a, b) and Chronosil 80A/FDA coatings manufactured by means of electrospraying (c) and airbrush process (d).

Figure 3: Volumetric flow rate as a function of the pressure difference for a microstent base body and a microstent base body with resorbable nonwoven in the inflow area.

Drug-eluting coatings manufactured by means of electrospraying and airbrush process are shown exemplarily in Figure 2. A coating mass of $106.14 ± 80.66 \mu\text{g} (n = 7)$ and $88.25 ± 8.54 \mu\text{g} (n = 4)$ was measured, respectively. In vitro FDA-release over a time period of two days is comparable for both manufacturing processes (Figure 4).

Figure 4: In vitro release of FDA from Chronosil 80A coatings manufactured by means of electrospraying ($n = 7$) and airbrush process ($n = 4$); mean ± standard deviation, respectively.
3.2 Development of an injector device

A 3D-model and a prototype of the injector device are shown in Figure 5. Microstent base bodies can be loaded inside and subsequently released from the cannula.

Figure 5: 3D-model (a) and prototype (b) of the injector device.

3.3 Implantation testing

A microstent was successfully implanted post mortem into the Suprachoroidal space of a porcine eye (Figure 6). Micro-invasive ab interno implantation into suprachoroidal space was performed based on a clear corneal incision.

Figure 6: Micro-invasive microstent implantation into a porcine eye post mortem: insertion of eyelid retractor (a, b), paracentesis (c), insertion of injector device (#) into the anterior chamber (d), microstent implantation into suprachoroidal space (e) and microstent (*) localization after completion of the procedure (f).

4 Discussion

The presented microstent system is suitable for micro-invasive glaucoma surgery. Using a 23 G cannula (OD = 0.6 mm) ocular trauma is minimized and comparable to the commercially available CyPass micro-stent (Alcon Inc., Fort Worth, TX, USA). Initial flow resistance of the resorbable nonwoven (1.543 mmHg/µl min⁻¹) conforms well with the target value of 1.850 mmHg/µl min⁻¹ corresponding to a physiological aqueous humour flow rate of 2 µl min⁻¹ and a physiological pressure difference between the anterior chamber of the eye and the suprachoroidal space of 3.7 mmHg [6]. Therefore, the risk of postoperative hypotony is minimized [5]. Chronosil 80A as base material of the drug-eluting coating allows for a well-controlled drug release. Airbrush processing shows advantages over electro spraying, especially regarding reproducibility of coating mass and achieved surface quality. Future studies will focus on the development of antifibrotic drug-eluting coating.

Author Statement

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References