Development of a novel valved drug-eluting glaucoma implant for safe and durable reduction of intraocular pressure

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Abstract

For the reduction of intraocular pressure, implants are well accepted in therapy of refractory glaucoma. Encapsulation and the resulting long term failure are the major limitations of today's commercially available devices. This paper describes methods for the development and characterization of a novel drug-eluting microstent for glaucoma therapy. Microstents were coated with a polymer-drug compound of poly(4-hydroxybutyrate)/paclitaxel 85/15 % (w/w) and analyzed in vitro with regard to coating mass, morphology and release kinetic. Achieved coating mass was 485.7 ± 16.4 µg (n = 18). Release of therapeutic potent doses paclitaxel (5.8E-7 ± 2.5E-7 mol L⁻¹, n = 4) within 1 month was proven. The presented technology is suitable for the reproducible manufacturing of drug-eluting microstents. Inhibition of fibrosis in vivo will be investigated in future trials.

1 Introduction

Glaucoma as an optic neuropathy often is associated with an increased intraocular pressure (IOP). Therapy of glaucoma focuses on IOP-reduction by means of medical therapy, laser treatment and filtering surgery. In case of refractory glaucoma, drainage devices are more and more accepted as alternative to conventional filtering surgery [1]. Today's major limitation of commercial glaucoma implants alongside with ocular hypotension is implant encapsulation due to fibrosis and the resulting drainage failure [2]. In previous investigations we developed valved microstents for mechanical IOP regulation and in particular for the prevention of ocular hypotension [3]. Antiproliferative drugs like Mitomycin-C (MMC) or Paclitaxel (PTX) have been applied in glaucoma surgery which has been reviewed by Schmidt et al. [4]. To ensure long-term efficacy of our valved microstents, we established a technology for the manufacturing of drug-eluting surface coatings in this study. Fibrotic encapsulation of our microstent should be prevented by diffusion-controlled release of PTX. The concept of our microstent for the drainage of aqueous humour from the anterior chamber of the eye into the suprachoroidal space is shown in Image 1.

![Image 1 Microstent concept: valve in inflow area and drug-eluting surface coating (orange) in outflow area](image-url)

2 Methods

2.1 Manufacturing of coated microstents

The manufacturing process of coated microstents is shown in Image 2. Valved microstents (IDxODx 0.3x0.64x10 mm) were manufactured from silicone tubing (Silastic Rx-50 Medical Grade Tubing, Dow Corning Corporation, USA) cut by a femtosecond laser (Spectra-Physics, USA) [3]. For protection of valve and microstent lumen during further processing, the endings of the tubes were occluded by silicone (NuSil MED-4234, NuSil Technology LLC, USA).

To enable surface coating, chemical activation using ammonia plasma was carried out before a layer of poly(4-hydroxybutyrate) was coupled. Activation conducted, using a plasma system with a 300 W radio frequency generator (Diener electronic GmbH + Co. KG, Germany) at ammonia pressure of 0.3 mbar for 1 minute at 15 % generator power. For the coupling of a P(4HB) layer, microstents were treated for 8 h at 55°C in a P(4HB)/1,2-dichloroethane (EtCl₂, Carl Roth GmbH + Co. KG, Germany) solution (18.2 g L⁻¹ polymer concentration) including 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC, Merck KGaA, Germany) and N-hydroxysuccinimide (NHS, Merck KGaA, Germany) (1.8 g L⁻¹ each) [5]. The microstent inflow area that is not meant to be coated afterwards, including the valve mechanism, was protected by a brass cover.

Before coating, microstents were cut to final length of 10 mm attending that the lumen in the inflow area remains occluded. Then 5 mm in microstent outflow area were spray coated with 480 µg ± 10% (7.2 µg mm⁻²) P(4HB)/PTX, 85/15 % (w/w) (PTX, Cfm Oskar Tropitzsch e.K., Germany). After coating, microstents were stored for 12 h at 40°C in a vacuum drying cabinet (Memmert GmbH & Co KG, Germany) and then sterilized by ethylene oxide.
2.2 Characterization of coated microstents

The coating mass was determined gravimetrically by means of a microbalance (XP6U, Mettler Toledo, Switzerland). The coating morphology was investigated using biaxial laser scanning (ODAC 32 XY, Zumbach Electronic AG, Switzerland), optical microscopy (SZX10, Olympus, Japan) and scanning electron microscopy (SEM) (XL 30 ESEM, Philips, The Netherlands). The in vitro PTX release was analyzed in phosphate buffered saline by means of high performance liquid chromatography.

Image 2  Processing of microstents: a) silicone tubing with manufactured valve, b) closure of lumen by silicone, c) wet chemical activation, d) cutting to final length, e) preparation for coating process, f) coating, g) coated microstent

3 Results

The presented process was applied for manufacturing of \( n = 18 \) coated microstents. Coating conducted as two phase process because there was identified 5 % weight loss after primary drying. Finally achieved coating masses \( (485.7 \pm 16.4 \, \mu g, \, n = 18) \) were reproducible and inside the range of the aspired coating mass \( (480 \, \mu g \pm 10 \%) \).

A selective, stable coating of 5 mm in microstent outflow area was achieved. There is a soft transition from uncoated to coated area, the mean diameter in uncoated area \( (0.62 \, mm) \) and in coated area \( (0.70 \, mm) \) is almost constant (Image 3). Mean coating thickness is 0.04 mm. Activation process and coating had no negative effect like conglutination on valve mechanism (Image 4b). Outflow lumen was neither affected by processing. Morphological analyses revealed a smooth and homogeneous surface of the microstent in uncoated and coated regions (Image 4c-e).

In vitro PTX release studies \( (n = 4 \, \text{microstents}) \) demonstrated an initial burst release of \( 25.6 \pm 0.9 \% \) PTX within the first 4 days followed by a continuous slow release of \( 35.6 \pm 2.4 \% \) PTX within 1 month (Image 5). After terminal determination of residual PTX, there was found a recovery of \( 77.3 \pm 8.8 \% \) PTX.

4 Conclusion

Established manufacturing technology is suitable for a reproducible manufacturing of drug-eluting microstents. Analysis of dose-dependent effects of PTX on human sclera fibroblasts (hSF) and human choroidea fibroblasts (hCF) showed typical dose response curves with half maximal inhibitory concentration (IC_{50}) values between \( 1E^{-9} \) and...
Mean cumulative PTX release from $n = 4$ microstents over a time period of one month. Therefore, it can be stated that the in vitro PTX release studies prove release of therapeutic potent doses within 1 month ($5.8E^{-7} \pm 2.5E^{-7}$ mol L$^{-1}$, $n = 4$). This release is 2 orders of magnitude above the IC$_{50}$ values determined by Stahnke et al. [6]. Considering systemic distribution by vascular system and tissue diffusion the drug PTX might be locally diluted 100-fold without loss of biological activity. Future in vivo investigations of the PTX-eluting microstents will provide more information about their potential for fibrosis inhibition and thus for the durable reduction of IOP.

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### 6 References


