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A multifunctional bilayered microstent as glaucoma drainage device

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ABSTRACT

Commercial non-degradable glaucoma implants are often associated with undesired hypotony, fibrosis, long term failure, and damage of adjacent tissues, which may be overcome by a multifunctional polymeric microstent for suprachoroidal drainage. This study reports the design and fabrication of such devices with tailorable internal diameters (50–300 μm) by solvent-free, continuous hot melt extrusion from blends of poly[(ε-caprolactone)-*co*-glycolide] and poly(ε-caprolactone) [PCL]. A spatially directed release was supported by bilayered microstents with an internal drug-free PCL layer, and a quantitative description of release kinetics with diclofenac sodium as model drug was provided. Furthermore, the slow degradation pattern (>1 year) was analyzed and potential effects of 1–5 wt.% drug loading on material properties were excluded. Translational aspects including sterilization by γ-irradiation on dry ice, *in vitro* biocompatibility, and *in vivo* implantation were addressed. The promising results support further functional analysis of long-term *in vivo* performance and suppression of disadvantageous capsule formation.

1. Introduction

Effective and safe drug delivery remains a major challenge in the treatment of eye diseases [1,2]. For many types of pathologies, surgical intervention is required, which inherently creates a need for a local drug therapy to modulate cellular response on surgical traumata [3]. Accordingly, regenerative medicine requires multifunctional implants, which can be translated into a therapy and address simultaneously the diverse clinical needs, which is not given for existing systems.

An example of eye diseases with high incidences throughout the world and a strong impact in health economics are glaucomas. Glaucomas are typically associated with increased intraocular pressure (IOP) and a disturbed outflow of steadily produced aqueous liquid due to morphological changes (open-angle glaucoma) or obstruction (closed-angle glaucoma) of tissues. The resulting pressure-induced structural and functional defects of the retinal ganglion cells and the optical nerve head can lead to blindness [4]. Surgical intervention may be required, *e.g.* if topical medication fails [5] and laser trabeculoblasty [6] will not provide a suitable IOP reduction in open-angle glaucoma. In such cases, penetrating glaucoma surgery is recommended to create new functional outflow pathways, aiming to establish a status where patients do not need additional medication [7]. Besides trabeculectomy with decreasing case numbers and clinical success [8,9], glaucoma drainage devices (aqueous shunts) as a biomaterial based approach can be used [10,11]. Such devices enable percolation of aqueous liquid through a tube to a filtering plate in the subconjunctival space (*e.g.*, Molteno®; Baerveldt®), to the Schlemm's canal (*e.g.*, Eyepass™), or to the suprachoroidal space (*e.g.*, Solx®). However, while the indications for aqueous shunts have broadened, there are a number of unsolved clinical drawbacks of existing systems [12]. To better fulfill distinct requirements as described below, a number of scientific, conceptual, technological, and surgical challenges need to be addressed by an aqueous shunt device that exhibits multifunctionality.

A first requirement is a suitable regulation of aqueous outflow that does not cause hypotony after implantation as is the case for the available devices, mostly due to their large internal tube lumina (*e.g.*, 300 μm) [13]. The occlusion of the device tube with a degradable suture as presently performed intraoperatively by ocular surgeons [11,14] is a difficult to standardize process. It also bears the risk of increasing IOP if the suture is not removed in time. Depending on the IOP of the patient and the aimed site of drainage (subconjunctival, suprachoroidal), inner diameters of 40–70 μm are required [13], which is a challenge for polymer processing.

Second, fibrous capsule formation in response to surgical trauma needs to be avoided. Otherwise the outflow may be ruled by the fibrous

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capsules with interindividual, time-, and product-specific differences in thickness rather than by the device [15,16]. Capsule formation can presently not be prevented and is addressed by additional medication, needling of the capsule, capsule excision [17], or placement of an additional implant. All these actions contradict the desired regenerative approach. Therefore, a modulation of cellular responses needs to be achieved by bioactive molecules, which should i) be delivered locally rather than orally [18], ii) be available directly at the implant surface rather than in a separate ocular depot [19], and iii) be released in a sustained rather than rapid fashion [20,21]. Additionally, we propose that the drug release should be spatially directed to the site of cellular responses, *i.e.*, to the outside of the tube rather than to the lumen. Drug embedment, however, may adversely affect the properties of the implant's matrix materials, which is a scientific challenge to be addressed by proper selection of the matrix polymers.

Third, the long-term presence of drainage implants with mechanical properties that cannot match all surrounding tissues, particularly when having to fulfill a supportive role, is known to result in tissue damage. Therefore, the device should be degradable rather than biostable, ideally leaving back a functional flow pathway as aimed for in a regenerative approach. Importantly, hydrolytic matrix degradation needs to be well controlled and slow. Considering possible interference of different levels of embedded drugs with diffusion processes of water and polymer degradation products, the selection of a suitable polymer again is an essential prerequisite to establish multifunctionality.

Fourth, a device designed for intrascleral implantation with a drainage of aqueous to a suprachoroidal rather than a subconjunctival location should allow the minimization of device-induced damage to the conjunctiva, particularly their erosion and eventual penetration as in the case of tubes of existing commercial subconjunctival drainage devices [12].

Finally, as a fifth point, the implants should be biocompatible, suitable for handling during implantation, sterilizable, and compatible with industrial production processes (*e.g.*, hot-melt extrusion rather than dip coating), which are all essential preconditions for a translation in regenerative therapies.

Based on these scientific requirements and compared to previous approaches [22,23], multifunctionality of a polymeric suprachoroidal glaucoma implant might be achieved by establishing i) a tubular structure, herein called microstent, with small orifice sizes as required for an optimal drainage functionality, ii) an integrated drug release functionality without impeding material properties desired for structural function, iii) a spatially oriented direction of drug release to the implant surface, which should be realized by a microstructuring of the microstent with a challenging bilayered design, iv) hydrolytic degradation functionality for slow implant removal to enable tissue regeneration, and v) biocompatibility and feasibility for implantation as sterilized devices (Fig. 1).

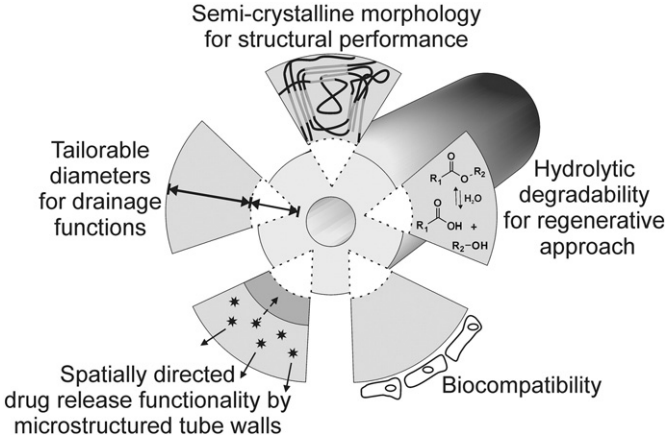

Fig. 1. Scheme of multifunctional microstent as glaucoma drainage device.

This concept was evaluated using poly(ε-caprolactone) [PCL] and its blend with poly[(ε-caprolactone)-*co*-glycolide][PCG]. This selection was based on the recently observed interesting mechanical properties [24], the improved PCG degradability due to glycolide diads acting as weak links [25,26], and its proposed semi-crystallinity that should allow reducing possible interference of drug payload and material properties and degradation. This study covers the microstent design and fabrication with tailorable orifices, the analysis of spatially directed release and quantitative description of release kinetics with diclofenac sodium as model drug, the analysis of degradation pattern, potential drug loading effects on material properties, and translational aspects including sterilization, *in vitro* biocompatibility, and *in vivo* implantation.

2. Material and methods

2.1. Materials

Diglycolide (≥99%), ε-caprolactone (>99%), $(Bu)_2SnO$ (98%, all Aldrich), 1,8-octanediol (>99%, Fluka), and ethyl acetate (>99%, Acros) were used in polymer synthesis. The employed poly(ε-caprolactone) was Capa® brand material from Solvay (now Perstorp, Warrington, UK). Diclofenac sodium (99.3%) was purchased from Fagron (Barsbuettel, Germany). For high performance liquid chromatography (HPLC), solvents of isocratic grade were used (Merck). All other chemicals were of analytical grade.

2.2. Polymer synthesis and coextrusion for blending and drug incorporation

Copolymerization of purified diglycolide (recrystallization from ethyl acetate) was conducted in the melt with ε-caprolactone as comonomer, 1,8-octanediol as starter molecule, and $(Bu)_2SnO$ as catalyst to yield PCG with a weight average molecular weight M_w of ~23 kDa, a polydispersity of 1.4, and a glycolide content of 8 wt.%. PCG was blended with commercial PCL powder with a M_w of ~80 kDa (Capa® 6808, Perstorp, Cheshire, UK) at a 50:50 weight ratio and subjected to coextrusion at 100 °C with a co-rotating twin screw extruder (Prism Eurolab 16, L/D 25, Thermo Electron, Karlsruhe). A rod die was used with a die temperature of ~55 °C and an extruder speed of 50 rpm. The product was cooled in a water bath at ambient conditions. For drug loading, the required quantity of diclofenac sodium (wt.%) was premixed with the polymer powder and homogenized in the extruder.

2.3. Processing by hot melt extrusion and melt compression

Single layer stents were obtained by extrusion of the blend through a vertical catheter die with a width of 1.8 mm and a 1.0 mm core at a die temperature of ~60 °C using a single screw extruder (Gimac TR 14, L/D 24, Castronno, Italy). The extruded stents were stabilized by filling their core with water at room temperature and by immersion in a water bath for cooling. For double layer stents, two single screw extruders were connected to a custom made double layer catheter die (width 1.4 mm, core 0.7 mm, Erocarb, Giez, Switzerland). PCL (Capa® 6800 granules) was fed to the inner stent layer by a Polylab system at 130 °C (Haake Rheocord with Rheomex 19, L/D 25, Thermo Electron, Karlsruhe), while the Gimac TR 14 extruder (80 °C) was used for forming the outer layer consisting of the blend material. In order to stabilize the extruded double layer stents, support air with an excess pressure of 30 mbar was applied to the stent core. In both cases, single and double layer stents, the diameter of stents was controlled by adjusting the extrusion and the haul-off speeds.

Polymer films were prepared between hot metal plates in a Collin P200E platen press (Collin, Ebersberg, Germany) at 100 °C. Samples were pressed to thin films at 50 bar with ~100 μm spacers (3 min) and subsequently cooled down to 20 °C with persisting exposure to a pressure of 50 bar.