A CONTROLLED-RELEASE CAPSULE DEVICE FOR TRANSSCLERAL DRUG DELIVERY TO THE RETINA

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ABSTRACT

We report the design and testing of a transscleral drug delivery system that is implantable in the episclera and allows for controlled release of brain-derived neurotrophic factor (BDNF) or other protein-type drugs with zero-order kinetics. The microfabricated capsule consists of a drug reservoir sealed with a controlled-release membrane that contains interconnected collagen microparticles (COLs), which are the routes for drug permeation. The drug kinetics can be controlled by changing the drug formulation and/or the membrane COL density so that the size of the bursts is reduced, which extends the release period. When capsules were sutured onto sclerae of rabbit eyes, a drug mimic was found to spread to the retinal pigment epithelium. Implantation of the device was easy, and it did not damage the eye tissues.

KEYWORDS

Controlled release, drug delivery system, retinal neuroprotection, transscleral delivery

INTRODUCTION

The design of drug-delivery systems targeting the retina is a most challenging ophthalmological task. The principle delivery route currently in use is topical eye drop administration, but it delivers only low drug levels to the retina. Although intravitreal delivery allows for high concentrations of a drug to be delivered directly to the retina, the necessary surgical procedure often requires repeated injections, and/or vitreous hemorrhage [1]. Therefore, transscleral delivery has emerged as a more attractive method for treating retinal disorders because it can deliver a drug locally and is less invasive. Because of its large surface area and high degree of hydration, the sclera is permeable to drugs of different sizes (up to w70 kDa) [2]. Transscleral drugdelivery systems that range in size from microparticles to polymeric implants have been tested [3]. However, most of these systems are made of biodegradable polymers. Drug release profiles for biodegradable devices generally have a tri-phasic release profile, i.e., an initial burst, a diffusional release phase, and a final burst. This complex profile occurs because the polymers erode with time and, by doing so, affect drug dissolution. Thus, a nonbiodegradable device that contains a drug reservoir sealed with a semipermeable membrane allows for sustained release and reduces the sizes of the bursts.

Neuroprotection from retinal degenerative diseases by neurotrophic factor delivery to the retina remains a challenge for ophthalmology [4]. Intraocular administrations of brain-derived neurotrophic factor (BDNF) have been shown to rescue degenerating photoreceptor cells in animals [5]. However, suitable devices that specifically deliver neurotrophic factors continuously to the retina and with minimal invasiveness have yet to be developed. Therefore, we aimed to develop a membrane-based capsule that is implantable on the sclera (Fig. 1A) and would prolong the controlled delivery of BDNF or other protein-type drugs to the retina with zero-order kinetics.

EXPERIMENT

A schematic of the capsule fabrication is shown in Fig. 1B. A polydimethylsiloxane master mold for the reservoir was first fabricated via a microfabrication technique that used an AutoCAD design and a micro-processing machine (Micro MC-2, PMT Co.). Triethylene glycol dimethacrylate (TEGDM) prepolymer (Mw, 286.3; Aldrich) was UV cured in the mold for 3 min and peeled off to obtain a TEGDM reservoir. After loading a drug, the controlled-release membrane, which was made of polyethylene glycol dimethacrylate (PEGDM) (Mn 750, Aldrich) that contains interconnected

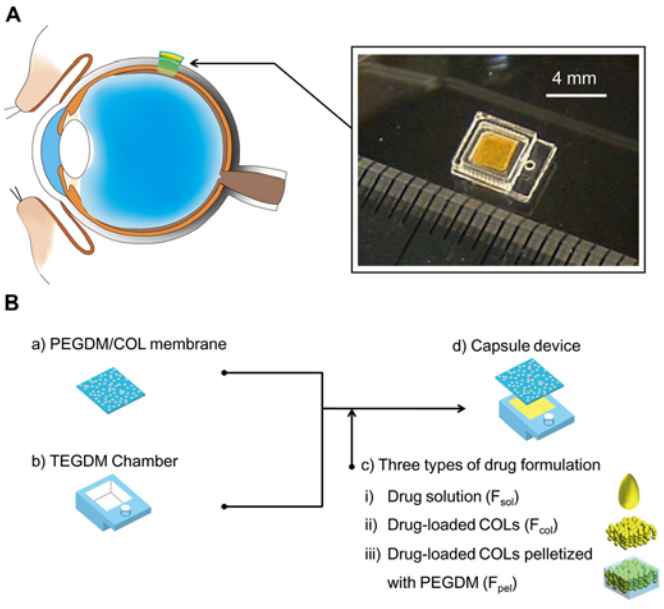

Figure 1. (A) A transscleral drug-delivery device, designed for the administration of protein-type drugs. (B) The capsule consists of a drug reservoir made of TEGDM and a controlled-release membrane made of photopolymerized PEGDM that contains COLs (PEGDM/COL membrane), which are the route for drug permeation. The capsule was designed so that various drug formulations could be contained in the reservoir.

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collagen microparticles (COLs), was sealed to the reservoir by UV curing TEGDM prepolymer, which in polymerized form served as the adhesive, for 3 min.

RESULTS AND DISCUSSION

Figure 1B shows the designed capsule consisting of two parts, a molded triethylene glycol dimethacrylate (TEGDM) reservoir to contain the drug and a new type of controlled-release membrane sealed around the top of the reservoir. The controlled-release membrane was produced by photopolymerizing a mixture of polyethylene glycol methacrylate (PEGDM) and COLs. The COLs are hydrogels containing a chemically crosslinked 0.8 (w/v) collagen network [6], which is permeable to molecules with molecular weights of <200 kDa.

Figure 2 demonstrates that drug release can be controlled by both the membrane and the drug formulation contained in the reservoir. The release of a drug mimic, 40-kDa FITC-dextran (FD40) was always dependent on the COL concentration (Fig. 2A-C), which indicated that FD40 travelled through the membrane-embedded COLs. Additionally, the sustained-release drug formulations, FD40-loaded COLs and FD40-loaded COLs pelletized with PEGDM, fine-tuned the release of FD40. To evaluate the release of the BDNF, capsules were filled with COLs that contained the protein and were sealed with a membrane with a different COL concentration. Figure 2D presents the zero-order kinetic profiles found for BDNF release during a 6-week assay period. Apparently, the release kinetics of BDNF can be fine-tuned by varying the concentration of the COLs in a membrane in much the same manner as was found for FD40.

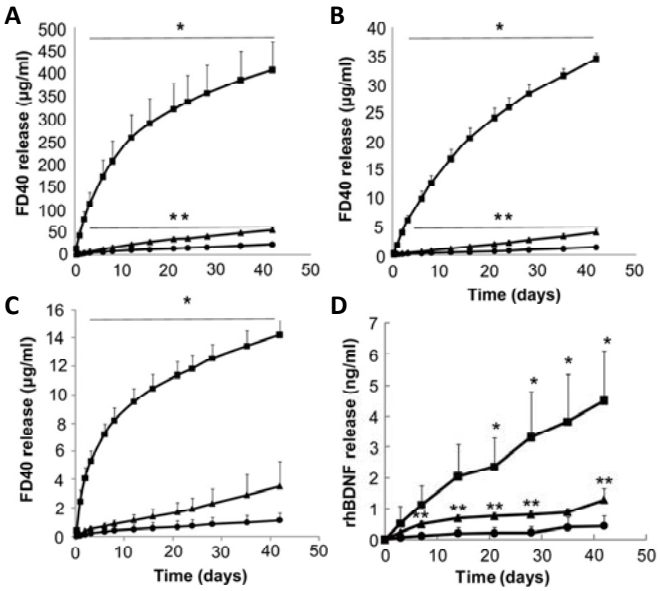

Figure 2. (A-C) Release of FD40 in vitro. The dependence of the release kinetics on the initial COL concentration for (A) FD40 in PBS (Fsol), (B) FD40-loaded COLs in PBS (Fcol), and (C) FD40-loaded COLs pelletized with PEGDM in PBS (Fpel). The concentrations of the COLs were 100 mg/ml (circles), 300 mg/ml (triangles), and 500 mg/ml (squares). The release rate for FD40 through a membrane that did not contain COLs was almost the same as one that contained COLs at a concentration of 100 mg/ml. Error bars represent the standard deviations of three samples (error bars that are not visible are smaller than the symbols). The Means±SDs are shown. *P < 0.05 for 300 mg/ml vs. 500 mg/ml **P < 0.05 for 100 mg/ml vs. 300 mg/ml. (D) Release of BDNF in vitro. BDNF-loaded COLs in PBS were added to capsule reservoirs that sealed with a membrane with a COL concentration of 100 mg/ml (circles), 300 mg/ml (triangles), or 500 mg/ml (squares). The release rate of rhBDNF through a PEGDM/COL membrane that contained 100 mg COL/ml was almost the same as one that contained no COLs. Means±SDs are shown. *P < 0.05 for 300 mg/ml vs. 500 mg/ml **P < 0.05 for 100 mg/ml vs. 300 mg/ml.

Our next challenge was to evaluate the capsule's ability to deliver a protein-type drug to the retina via the sclera. Capsules were sutured to the sclerae of three rabbits' left eyes with 10-0 nylon (Fig. 3A). The capsules abutted the sclerae but did not penetrate the conjunctivae or adjacent areas. Figure 3B shows a fluorescent image of FD40 within a capsule, and Figure 3C shows the release of FD40 locally at the sclera but not at the conjunctiva. This unidirectional release should reduce drug elimination by conjunctival lymphatic/blood clearance, thereby resulting in more effective delivery to the retina. One month after implantation, the capsules remained sutured and neither the PEGDM of the membranes (Fig. 3D) nor the reservoirs had eroded. The COLs in the membranes also survived with little biodegradation (Fig. 3D), most likely because the collagen molecules were stabilized by chemical crosslinking. Although the capsules were loosely covered with connective tissue by the end of the trial, they were easily removed from the implant site. Routine ophthalmological examinations showed no eye-related toxic effects. Intense FD40 fluorescence in the sclerae adjacent to the implantation sites was observed (Fig. 3E). Furthermore, FD40 had migrated to the retinal pigment epithelium (RPE) and adjacent regions (Fig. 3F), which indicated that transscleral delivery of FD40 to the retina had been achieved. To the best of our knowledge, this is the first report that a macromolecule can be delivered to the retina via a reservoir-based transscleral drug-delivery system, although quantification of the drug distribution still needs to be done. Proteins, as large as 50e75 kDa, penetrate into the choroid/RPE upon periocular injection [7]. Therefore, it may be possible to also deliver BDNF by the transscleral route. Given that the distribution of FD40 was somewhat concentrated at the RPE and adjacent regions, our device may be effective especially for lesions that surround the RPE. The capsule could also be used to deliver antiangiogenic drugs, e.g., Lucentis and Macugen (for the treatment of age-related macular diseases) [8], to a lesion, e.g., the choroidal neovascular membrane, because delivery by this route will be less invasive and safer than are conventional intravitreal injections. Our non-biodegradable capsule should therefore be

suitable for the transscleral delivery of protein-type drugs that require chronic suppressive-maintenance therapy over several weeks or months.

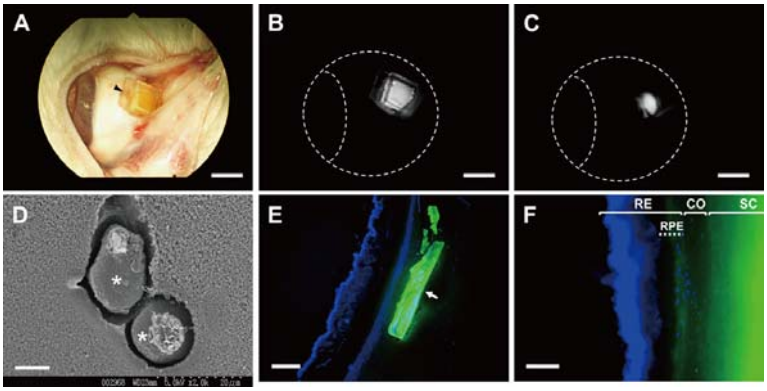

Figure 3. Episcleral implantation of a capsule. (A) Image of a capsule sutured to the sclera of a rabbit eye 3 days after implantation. Fluorescent images around the sclera (B) immediately before and (C) after removal of the capsule 3 days after implantation. (D) SEM image of a COL (asterisks) in the membrane of a used capsule that was removed 1 month after implantation. (E, F) The distribution of FD40 (green) in the retina and sclera around the implantation site 3 days after implantation (arrow: capsule). Cell nuclei were stained with 4,6-diamidino-2-phenylindole (blue). FD40 reached the retinal pigment epithelium. Abbreviations: sclera (SC), retinal pigment epithelium (RPE), choroid (CO), and retina (RE). Bars: 4 mm (A, B, and C), 10 μm (D), 400 μm (E), and 100 μm (F).

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