Preliminary *in-vitro* and *in-vivo* evaluation of Paclitaxel from glaucoma drainage device

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Introduction

Glaucoma drainage devices (GDDs) control intraocular pressure (IOP) of the eye by creating an alternate pathway from the anterior chamber channeling aqueous out of the eye through a tube to a subconjunctival bleb. Currently marketed designs are made of silicone rubber and polyethylene or polypropylene which creates extensive fibrosis within the eye leading to reduced filtration. InnFocus LLC has been developing a glaucoma drainage device called the MIDI-Ray made from a novel extremely soft biomaterial called poly(styrene-*b*-isobutylene-*b*-styrene) (SIBS).[1] The MIDI-Ray GDD is composed of a 350 um OD, 100 um ID tube and a 7 mm circular and concave microplate, where the tube is centrally attached (Figure 1). This study evaluated *in-vitro* drug release and determination of appropriate dosage of a drug required to prevent encapsulation of the implant in the rabbit eye. The drug tested was the antiproliferative drug Paclitaxel. Jampel *et al.* reported that 50 ug of Paclitaxel is the lower level of what was found to be effective in a non-primate eye model without being toxic.[2]

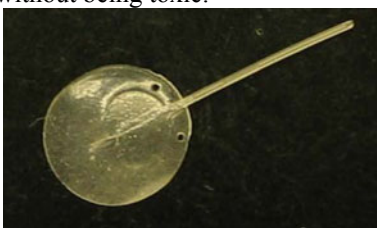

Figure 1. MIDI-Ray Glaucoma drainage Device

Material and Methods

SIBS composed of 20 mol% polyisobutylene rubbery segment was synthesized with molecular weight of 60,000 g/mol. Paclitaxel loaded MIDI-Rays were prepared by spotting solution of Paclitaxel and SIBS (2:1 wt) in THF on both sides of MIDI-Ray plate using a controlled fluid dispenser. Solvent was completely dried at reduced pressure. Paclitaxel release was studied *in-vitro* by incubating in 1 mL of phosphate buffered saline (PBS) solution containing 2 M of N,N-diethylnicotinamide (DENA). At selected time points, the elution medium was completely removed from MIDI-Ray and replaced with fresh medium. The concentration of Paclitaxel in medium was determined using HPLC (Spectra system). Each sample of 50 uL was injected into a C18 3.5 um (sunfire) column. A mixture of acetonitrile and water (52/48 v/v) was used as a mobile phase at a flow rate of 1.0 ml/min. UV detector was set at 227 nm.

A pilot rabbit study was conducted according to ACUC guidelines using a control, low, medium and high dose of Paclitaxel loaded on the MIDI-Ray. A fornix based incision was made and subconjunctival space dissected. The tube was placed into the anterior chamber via a 27G needle track made 2 mm below the limbus, the plate was sutured at 6 mm from the limbus and covered with conjunctiva. IOP measurements were obtained pre- and post-operatively with a Perkins tonometer and pneumatonometer. Slit lamp biomicroscopy follow-up, gonioscopy and funduscopy were done pre- and post-op and at POD 1, 7, 14, 21, 28, 35, and 42 followed by euthanasia.

Results and Discussion

Figure 2 shows the Paclitaxel *in-vitro* elution profile of Paclitaxel for 28 hrs. Fast releases of Paclitaxel were observed at the first hour followed by a slower release rate over time. The total Paclitaxel released after 28 hrs is around 50% of the Paclitaxel loaded on the MIDI-Rays.

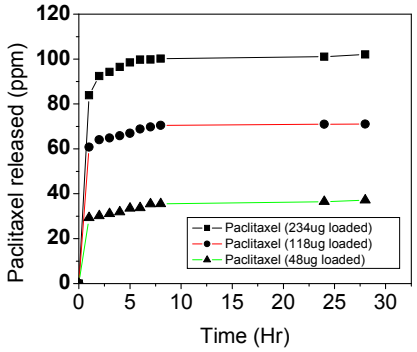

Figure 2. *In-vitro* Paclitaxel release profiles

All Paclitaxel loaded MIDI-Rays showed effects on tissue, most notable starting at POD 14 with a focal cystic bleb. The highest and medium dose presented some gelatinous tissue on the bleb at POD 14 and 28 indicating some conjunctival melt. The control MIDI-Ray with no drug showed typical response with a thin capsule as seen in previous MIDI-Ray rabbit studies. The lowest dose MIDI-Ray showed some white thin cystic bleb areas starting at POD 14. The affected areas were not generally on top of the plate but focused to one area near the limbus suggesting a dynamic healing conjunctiva.

Conclusions

In-vitro study demonstrated fast (1-2 hrs) release of Paclitaxel from MIDI-Ray in PBS/2M of DENA medium. *In-vivo,* the lowest dose (~30 ug) of Paclitaxel on MIDI-Ray still presented a clinically unacceptable bleb area, suggesting that a much lower concentration of Paclitaxel is required.

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References

1. Pinchuk L, Biomaterials, 2008;29:448-460.
2. Jampel HD, Ophthalmology & Visual Science, 1993;34:3076-3083.