The most common methods for intraocular drug administration are the use of topical drops, intravitreal injections, subconjunctival injections, and/or transscleral administration. Each of these forms of drug delivery must be administered frequently in order to maintain a therapeutic effect. Drops can be required several times a day; and injections can be required monthly. In each case, the frequency that these treatments are required often results in low compliance by patients. The implantable Capsule Drug Ring (CDR) is designed to be a sustained delivery device for use with ocular therapeutics. It is a refillable and versatile reservoir which is able to be inserted into the lens capsule during cataract surgery by ophthalmologists for the purpose of ocular drug delivery eliminating the need for specialists and frequent treatments.

Methods

The capsule drug ring (CDR) prototypes were manufactured by hot melt extrusion of Bionate® (DSM), a polycarbonate urethane. As the Bionate® tubing was extruded from the dye, it was wrapped around a 8mm pipe to incorporate the correct inner and outer diameters into the polymer before fully setting. A filter composed of polyether sulfone was fitted to one end of the devices for controlled drug release. The other end was sealed. In vitro biocompatibility was assessed with human lens epithelial cell (B-3), mouse macrophage (J774A.1), and mouse fibroblast (L-929) cell lines. Cell migration and proliferation were assessed after in vitro culture. Pro-inflammatory cytokines (i.e. MIP-1α, MIP-1β, MCP-1, IL-1β, TNF, TGF-81) were quantified using cytometric bead array (CBA). Preliminary in vivo biocompatibility and pharmacokinetics testing has been performed in rabbits.

Figure 1. Many major ocular diseases including glaucoma and AMD (left) are treated by drug delivery to the posterior portion of the eye. Many methods of drug delivery have been developed for treatment of these diseases (right). The CDR is the only drug delivery method which takes advantage of the unique properties of the capsular bag.

Figure 2. (Top) The CDR is formed by hot melt extrusion of Bionate®. As it is pulled off the extruder it is wrapped around a tube to induce the desired curvature. 

(Middle) Another prototype of the CDR which has the filter attached to one end of the reservoir while the other end is sealed. (Bottom) The major features of the CDR are shown. The device will fit in the capsular bag behind the iris. The circular design prevents vision obstruction by the device. By controlling the porosity of the PES filter we can control drug diffusion kinetics out of the device.

Figure 3. In vitro biocompatibility was assessed with human lens epithelial cell (B-3), mouse macrophage (J774A.1), and mouse fibroblast (L-929) cell lines. Cytometric bead array (CBA) analysis was performed on media harvested from J774A.1 and L-929 cell lines during incubation with components of the CDR device. 

(Lef) The MCP-1 and TGF-81 proinflammatory cytokines which were produced by L-929 fibroblasts were harvested and quantified by CBA. The production of these cytokines had a general increasing trend over incubation time. It is worth noting that each component showed a lower concentration of produced cytokines when compared with tissue culture polystyrene (TCP). IL-1β was also measured but was not produced in concentrations above the lower detection limit of the assay. 

(Right) J774A.1 macrophage production of MCP-1, TNF, MIP-1α, and MIP-1β cytokines were quantified by CBA. Macrophages incubated with VitroStealth® did not proliferate as quickly as those incubated without VitroStealth® and generally tended to express higher concentrations of TNF and MCP-1.

Figure 4. (Left) Efficacy of the CDR was, in part, quantified by measuring the amount of released Avastin® from the devices over time. This figure shows in vitro release of Avastin® over 40x days. An immediate burst effect is not seen with our devices. Increasing Avastin® release continues to occur to 30+ days. 

(Right) Rabbits were implanted with CDRs after cataract surgery and the in vivo release of Avastin® was quantified. Avastin® was detected in efficacious concentrations out to at least 12 weeks.

Conclusions

• The CDR was manufactured as a drug delivery device to be placed into the capsular bag during cataract surgery.
• Using Avastin® as a drug of choice for treatment of AMD, sustained release was measured in vitro out to 40 days.
• Avastin® was detected at concentrations >60 ng/mL in vivo out to 12 weeks.
• In vivo biocompatibility of the CDRs was promising showing the production of inflammatory cytokines at similar levels as tissue culture standards.