Enhanced Coated Hydrogel Device for Controlled Release of Drugs for Cataract Surgery

Floyd Karp[a, b], Neil Geislerb[c], Shai Garty[b, c], Tueng Shen[c], Buddy D. Ratner[b]
[a]Inson Medical Systems, Inc, Bellevue, WA 98005 U.S.A.,
[b]Bioengineering and [c]Ophthalmology Departments, University of Washington, Seattle, WA 98195 U.S.A

Introduction: Cataract is the leading cause of treatable blindness worldwide, and the population afflicted with cataract is increasing globally. The primary treatment for cataract is the surgical removal of the clouded, opacified natural lens followed by implantation of a polymeric intraocular lens (IOL). One of the principal complications from the surgery can be intraocular infection. Post-operative infection is a painful potential complication and can lead to permanent blindness. Infection often results from bacterial colonization of the new lens implant and subsequent antibiotic resistant biofilm formation. Acute inflammation may follow IOL implantation due to tissue disturbances which activate edema and trigger immune system responses. Avoiding infection is addressed in modern surgical practice by extreme attention to cleanliness and the use of antibiotic eye-drops several times a day for up to two weeks following lens implantation. Steroid drugs are usually also externally applied postoperatively for two weeks to control inflammation. To combat the risk of infection while also reducing any inflammation, and to alleviate the challenges of poor patient compliance of frequent application of eye drops, we have developed a surface-coated polymeric hydrogel drug release device that delivers effective levels of antibiotic over an extended period of time within the lens capsule of the eye.

Materials and Methods:

The hydrogel, 70:30 poly(hydroxyethyl methacrylate) (pHEMA), - poly(hydroxypropyl methacrylate) (pPHMA) was synthesized as 60% w/w dissolved in 1:1 water and ethylene glycol. Tetraethylene glycol dimethacrylate (TEGDMA) was used as a crosslinker. The monomer mixture was polymerized using ammonium persulfate as the free radical initiator and sodium metabisulfite as the accelerator.

We have performed drug model release studies with several fluoroquinolone antibiotics including Norfloxacin, Erythromycin, and Levofloxacin, because they are effective as wide range antibiotics when introduced into the ocular environment. In addition, we have investigated release of the anti-inflammatory drug Dexamethasone.

The polymeric hydrogels were formed into small beads (1.5 x 1.3mm) via molding in a glass tube with a suspended polyvinylidene fluoride (PVDF) strand, and then demolded, dried and then CO_2 laser cut to length.

By design, in order to prolong the release duration, a hydrophobic barrier coating was added to the surface of the drug loaded bead. The surface hydroxyl groups of pHEMA and pHPMA were reacted with octadecyl isocyanate under an inert atmosphere to yield a contiguous coating. The coating density was determined by the reaction time, from 6 min and up to 60min. After coating, the beads were dried again, and then placed at 37°C in a solvent reservoir with the drug of choice in solution. The drug loading into the hydrogel is made possible by swelling the material in this solvent which stretches the coating to permit the drug molecules to rapidly pass through the otherwise rate-controlling barrier.

For *in vitro* determination of the drug release rate the beads were held in gently agitated reservoirs of 37°C buffered saline to determine the release profiles of different coating densities. The drug release was quantified spectrophotometrically using a UV/Vis microplate reader. The pharmaceutical efficacy of the released antibiotic was further examined *in vitro* by exposing cultured bacterial bio-films to the released antibiotics. The efficacy of the IOL assembly in preventing infections and reducing inflammation was investigated with a rabbit model. Our *in vivo* model was performed using New Zealand white rabbits. Three in vivo trials were performed: the first a controlled comparator trial where subjects (n=6) were challenged with bacterial infection. Rabbits underwent IOL implantation with the drug-loaded hydrogels attached, enabling *in situ* drug delivery without the need for topical eye drops. The remaining rabbits forming the control group (n=6) had similar IOLs implanted without the hydrogels, and were treated with standard topical antibiotic eye-drops instead. A second phase of this *in vivo* study used a bacterial challenge of induced endophthalmitis model (n=9) and control subjects (n=3). The control subjects were treated conventionally with eyedrops of identical drugs. The third was an *ex vivo* model for posterior capsule opacification (PCO) in canine ocular tissues (n=12) and control subjects (n=12). A fourth pre-clinical trial is planned which evaluates the combined use of an antibiotic bead along with an anti-inflammatory bead

Results and Discussion:

The hydrogel pHEMA-pHPMA is well tolerated upon implantation and related polymers are used in biomedical applications. The drug release profiles demonstrated that the coated hydrogel devices are capable of delivering a clinically relevant dosage of drug *in vitro* over the critical 14 days post-operative time period.

The *in vitro* bacterial culture model showed that the device delivers drug in quantities capable of lethal effect on the study bacteria. The initial of the three *in vivo* studies showed both groups of subjects recovered from surgery without evidence of infection. In the subsequent bacterial challenge study the control subjects (eye drops) all developed fulminate infections and were euthanized after only 3 days. All subjects receiving the therapy beads initially developed infections, and all subjects recovered (using only 1/3000 the antibiotic as found in drops). In the *ex vivo* model of PCO, 100% of treated subjects had no cell migration (n=12) and all control subjects showed model PCO (n=12).

Conclusions:

The drug delivery device provides sufficient drug to prevent/treat infections. The device is simple to use during IOL implantation surgery. Other drugs could be delivered using this method. These results from the coated hydrogel drug delivery device demonstrate the feasibility of delivering sufficient antibiotic into the eye, as performed in standard cataract surgery.

References:

1.Anderson E.M, Noble M, Garty S, Bryers J.D, Shen T.T, Ratner B.D (2009) Sustained release of antibiotic from poly(2-hydroxyethyl methacrylate) to prevent blinding infections after cataract surgery. *Biomaterials*, 30(29):5675-81. **2**. Garty, S., Shirakawa, R., Warsen, A., Anderson, E.M., Noble, M.L., Bryers, J.D., Ratner, B.D., Shen, T.T., (2011) Sustained antibiotic release from an intraocular lens-hydrogel assembly for cataract surgery. IOVS V52(9):6109-6116

A**cknowledgement:** NIH grant 1R43EB011281-01

©2013 Society For Biomaterials