Coated Hydrogel Device for Controlled Release of Drugs for Cataract Surgery

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Introduction:

Cataract is the leading cause of treatable blindness worldwide [1], and the population afflicted with cataract is increasing. The primary treatment for cataracts is the surgical removal of the 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. Avoiding infection is addressed in modern surgical practice by extreme attention to cleanliness and the use of antibiotic eyedrops several times a day for up to two weeks following lens implantation.

To combat the risk of infection, and to alleviate the challenges of poor patient compliance to 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), is 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 during a thermal cure.

Researchers at the University of Washington used Norfloxacin in an initial series of experiments. In addition, Inson Medical Systems, Inc., has performed *in vitro* release studies with other commonly used antibiotics including Erythromycin and Ciprofloxacin. In the initial University studies the drug was introduced into the monomers prior to polymerization. For the Inson beads an immersion of the dried hydrogel in a concentrated aqueous/methanol solution is used for drug loading.

Initially, the polymeric hydrogels were formed into small beads via molding in a glass tube with a suspended wire and cutting to length. For production efficiencies, a precision stainless steel multicavity mold is now used. Following hydrogel bead fabrication the beads are dried.

By design, in order to prolong the release duration, a hydrophobic barrier coating was added to the surface of the drug loaded bead. . . The hydroxyl groups of pHEMA and pHPMA were reacted with octadecyl isocyanate (C18-NCO) under an inert atmosphere to yield a contiguous coating of assembled methylene chains [2]. The coating density was determined by the reaction time, from 5 min and up to 60 min. The antibiotic release rates were determined by placing the bead in gently agitated saline reservoirs at 37°C. The drug release was quantified spectrophotometrically. The pharmaceutical efficiency of the released antibiotic was examined by exposing cultured bacterial biofilms to the released drugs.

The efficacy of the IOL assembly in preventing infections was investigated with a rabbit model. Our *in vivo* model was conducted using New Zealand white rabbits. Three Pre-Clinical Trials Completed: 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).

Results and Discussion

The hydrogel pHEMA-pHPMA has been found to be biocompatible and is used in other 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 having a 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 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

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