The Monthly Eye Drop: Development of a Long-term, Noninvasive Glaucoma Treatment System

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Statement of Purpose: Glaucoma is the second leading cause of blindness worldwide, expected to affect up to 3 million Americans by 2020 (Quigley HA. Lancet. 2011;377[9774]:1367-77). One of the main risk factors in glaucoma is an unsafe increase in intraocular pressure (IOP). IOP reduction in patients with glaucoma is typically accomplished through the administration of medicated eye drops several times daily, the difficult and frequent nature of which contributes to patient compliance rates estimated to be as low as 50% (Hermann MM. Int Ophthalmol. 2010;30[4]:385-90). Newer drug delivery methods for glaucoma aimed at improving patient compliance require clinician administration of invasive injections or implants. The purpose of this study was to develop and test a hydrogel/microparticle formulation that provides one month of therapeutic levels of glaucoma medication from a noninvasive, patient-administered drop. We hypothesize that this novel treatment method will address the issues of both compliance and poor bioavailability inherent to traditional eye drop medication while avoiding the need for clinician involvement or more invasive techniques.

Methods: Poly(lactic-co-glycolic) acid (PLGA) microparticles containing BT were fabricated using a standard double emulsion procedure. Poly-(N-isopropylacrylamide) (pNIPAAm)-based hydrogels containing poly(ethylene glycol) (PEG) were prepared by polymerization in the presence of ammonium persulfate overnight and washing with PBS. The microparticles and gels were combined by mixing following polymerization of the gel. The properties of the microparticles and hydrogels were individually characterized as well as the properties of the combined gel/microparticle system. In vitro release of BT from the gel/microparticle system was quantified by incubating a known mass of microparticles in buffer and measuring the absorption using a spectrophotometer. The feasibility of this new gel/microparticle system was determined by administering a single drop to the inferior fornix of New Zealand white rabbits. IOP was measured periodically using tonometry and histology was used to assess whether the gel/microparticle system resulted in any inflammation of the surrounding tissues.

Results: Microparticles were confirmed to have a diameter of 7.5±2.9 μm with a primarily poreless morphology. The pNIPAAm gel demonstrated a lower critical solution temperature (LCST) of approximately 34°C, which was unaffected by the addition of drug-loaded microparticles. Degradation of the gel at 37°C for over one month was negligible with or without microparticles. Drug release was similarly unaffected by the presence of the pNIPAAm-PEG hydrogel, with an average daily release within the calculated therapeutic range of topical BT drops (Figure 1) for both the microparticles alone and in the gel. In vitro cytotoxicity testing also demonstrated that the gel/microparticle system had no significant effect on conjunctival cell viability. Our in vivo study of the long term eye drop system demonstrated that the gel/microparticle drop could be easily administered in the same way as a traditional eye drop and form a stable, opaque gel. The gel eye drop was easily removed with tweezers or cold saline, leaving no evidence of gel or microparticles remaining in the conjunctival cul-de-sac. In vivo studies to quantify IOP decrease and assess the biocompatibility for one month or more are ongoing.

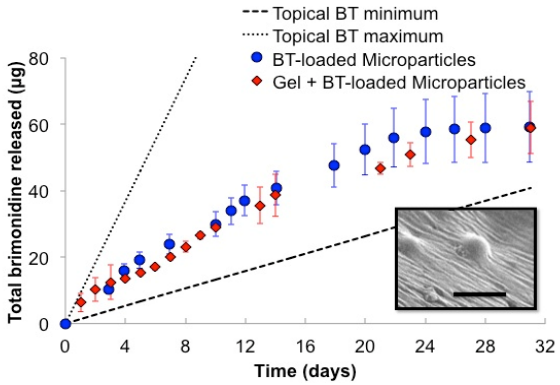

Figure 1. In vitro release of brimonidine tartrate from PLGA microparticles alone and combined with pNIPAAm gels (n=3). Also shown are the theoretical maximum and minimum amounts of BT absorbed from traditional eye drops, based on 2 drops per day of 0.15% BT solution and 1-7% absorption (Ghate D. J Glaucoma. 2008;17[2]:147-56).

Conclusions: The BT-loaded microparticles presented in this study are capable of releasing a therapeutically relevant amount of a common glaucoma medication for over 30 days. We have developed a cytocompatible, thermoresponsive hydrogel matrix for the microparticles that does not affect release. The gel/microparticle system has been shown to form a stable, solid drop in vivo in the inferior fornix and does not significantly degrade for one month while the drug is released. This controlled-release BT delivery system represents a simple and novel patient-administered formulation that we believe will provide adequate IOP reduction and biocompatibility without the need for intraocular injections or frequent drop administration.