Mucoadhesive Micelles for the Treatment of Dry Eye Disease

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Statement of Purpose:

Despite topical drops being ubiquitously used for the treatment of ocular diseases, it is estimated that only ~5% of topically administered drug reaches the anterior structures of the eye. This requires frequent dosing, which can lead to patient issues including drop out and delayed clinical efficacy. This is particularly true in dry eye disease, where patients have limited treatment options that require multiple drops daily that can be painful to administer and can take months to show clinical efficacy. We previously proposed the use of mucoadhesive self-assembling micelles as a solution to these problems [1]. Phenylboronic acid (PBA) is a synthetic molecule with a strong affinity for mucin due to its ability to complex with 1,2-cis-diols and has been used previously in biomedical applications. Thus, a series of block copolymer micelles incorporating mucoadhesive PBA into their outer shells was developed capable of targeted drug delivery to ocular tissues. Here we demonstrate the efficacy of these micelles in a diseased animal model.

Methods:

Copolymers were synthesized by RAFT polymerization and contained various PBA mole percentages. Copolymer composition and molecular weight were determined using proton nuclear magnetic resonance. Micelles were formed by precipitation into purified water from acetone. Cyclosporine A (CycA) entrapment efficiency and subsequent release from micelles was determined using high performance liquid chromatography (HPLC). A scopolamine-induced dry eye disease (DED) model was created in Norway Brown rats through the secretion of 25mg/day from a microosmotic pump in desiccating conditions. This model was used to compare the effectiveness of copolymer micelles with the current DED industry leader Restasis through tear film osmolarity measured by the TearLab device, tear volume measured with phenol red threads, and fluorescein staining of the corneal epithelium measured on the Phoenix Micron IV System slit lamp and scored using a modified Oxford Schema.

Results:

In-vitro release of CycA exceeded 7 days, which is the maximum anticipated longevity of the micelles on the ocular surface owing to the turnover rate of ocular mucin. Studies using the rat dry eye model show that 0.075% Similar to Restasis® dosed as prescribed, CycA-loaded micelles administered twice a day resolved dry eye symptoms by all three metrics. When dosing was extended to once every three days, Restasis® drops did not resolve symptoms by any of the three metrics. The micelles, though, were able to resolve the condition by all three metrics when dosed every three days, indicating the prolonged action of the micelle formulation. The micelles were also dosed once every five days, and resolution was seen when measured by tear osmolarity and tear volume. While there was a statistically significant difference seen between the control and the micelles dosed every 5 days in the fluorescein staining, it did not return to baseline levels.

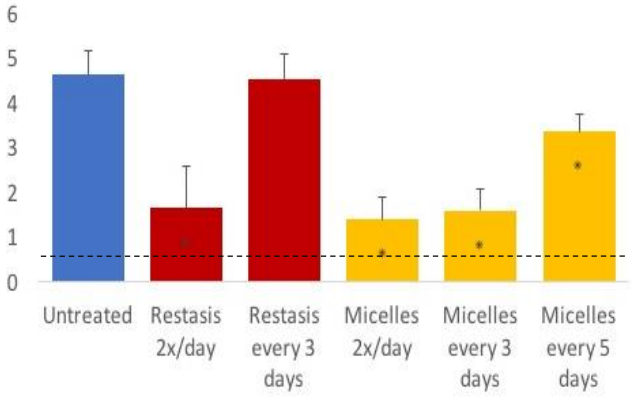

Figure 1. Oxford fluorescein staining results from dry eye induced rats. The dotted line represents baseline values.

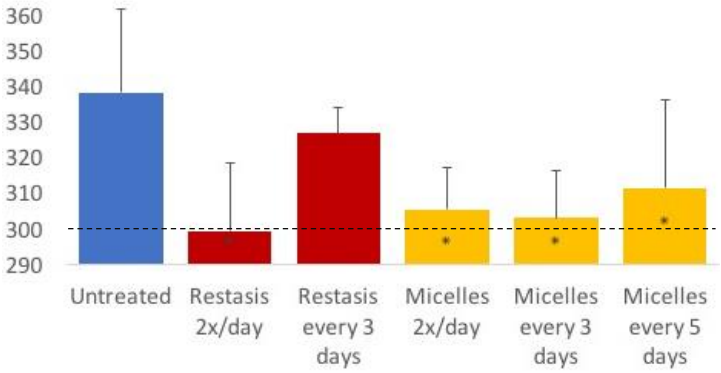

Figure 2. Tear osmolarity results from dry eye induced rats. The dotted line represents baseline values.

Conclusions:

Mucoadhesive micelles offer significant potential to increase the efficacy of topically applied ophthalmic drugs by decrease the dosage, frequency of dose, and off-target systemic toxicity. We have synthesized a series of poly(L-lactide)-b-poly(methacrylic acid-co-phenylboronic acid) copolymer micelles which show excellent mucoadhesivity, drug release characteristics, and biocompatibility. We have demonstrated in a diseased rat model that the micelles prolong the effect of the active pharmaceutical agent and allow us to decrease the dosing.

References:

[1] Prosperi-Porta, G.. Biomacromolecules. 2016; 17: 1449-1457.