

Ocular Biodistribution of Cysteamine Delivered by a Sustained Release Microsphere/ Thermoresponsive Gel Eye Drop

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In patients with cystinosis, cystine accumulates in all the ocular tissues but is most easily evident as crystal deposits in the cornea can lead to photophobia, corneal erosion, and blindness. Corneal cystine crystals are treated by hourly administration of topical cysteamine eye drops. The eye drop formulation requires a high concentration of cysteamine per drop to account for its instability as it is easily oxidized to inactive cystamine. The strict dosing regimen and high concentration of drug per drop make this treatment inconvenient and painful for patients.

To decrease the number of eye drops and prolong the effect of treatment, a controlled release formulation is desired, our group has developed a thermoresponsive gel-based eye drop that contains cysteamine-loaded microspheres. The thermoresponsive hydrogel matrix is administered as a liquid drop and is retained within the conjunctival cul de sac. To achieve clinically relevant therapeutic levels, the drug delivery system is being optimized for zero order release for a targeted duration of one day. The controlled release formulation has the potential to provide patients with an alternative treatment for corneal cystinosis. Our most recent results, presented herein, describe ocular distribution of cysteamine from the gel drop in a rabbit model compared to hourly aqueous drops.

Following topical administration of cysteamine eyedrop formulations, cysteamine was detected in the cornea, aqueous humor and vitreous humor. Plasma concentrations of cysteamine from all treatment groups were below the limit of detection. As expected, multiple doses of 0.44% cysteamine eyedrops, when administered hourly, maintained drug concentrations within the cornea at a magnitude 5 times higher than a single dose of the sustained release formulation over 12 hours. Despite the difference in drug uptake, the sustained release formulation maintained drug release across 12 hours from a single drop, potentially reducing the need to readminister by 8-11 drops. Instillation tolerability studies resulted in transient effects that were reduced within 30 min to 60 mins.

These studies demonstrate distribution of cysteamine to the eye following topical administration, including high drug uptake to the cornea and low systemic uptake in plasma. We are currently performing studies in the CTNS^{-/-} mouse to confirm the efficacy of the gel drop in reducing crystal density over time.