Cyclosporine-A Topical Drops for Dry Eye Syndrome
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Purpose
The objectives of this study are to (i) prepare, optimize and characterize cyclosporine-A (Cys-A) loaded mixed nanomicellar (MMF) aqueous drops and determine the in vivo ocular toxicity and tolerability, Ocular tissue distribution of Cys-A after single and multiple Cys-A MMF topical drop administration and compare with Restasis®.

Methods
Cys-A MMF were prepared following solvent evaporation technique. MMF Size, polydispersity index, surface potential, shape, qualitative proton nuclear magnetic resonance (1H NMR), critical micellar concentration (CMC), MMF entrapment and loading studies were studied to characterize the MMF. In vitro cytotoxicity studies were conducted in rPCEC and D407 cells with single and multiple dosing of Cys-A MMF. Similarly, tolerability and toxicity studies were studied in rabbits with topical drop instillation. In vivo ocular Cys-A tissue distribution were studied in rabbits with single and multi drop instillation. Cys-A in the individual ocular tissue was quantified with sensitive LC-MS/MS analysis.

Results
Cys-A was loaded into MNF to generate an overall loading of 1 mg/mL. CMC for the MMF was found to be 7.07 x 10-3 wt%. Optimized MMF demonstrated high drug loading and entrapment efficiency. Average MMF size was found to be ~20 nm with narrow polydispersity index (0.147). TEM studies showed MMF to be spherical with smooth surface morphology. Absence of free or unentrapped Cys-A in MMF was confirmed by 1H NMR spectroscopy. Similarly, ocular tolerability and toxicity studies in rabbits demonstrated the formulation to be safe and well tolerated. There was observed no difference in IOP. Histological studies demonstrated no toxicologic changes in the anterior (conjunctiva / cornea / iris) or posterior segments (vitreous/retina) of the eye indicating the formulation to be safe. In vivo Cys-A ocular tissue distribution studies with topical drops showed higher Cys-A concentrations (~53.7 ng/g tissue) in retina-choroid relative to Restasis (~3.76 ng/g tissue).

Conclusion
A clear aqueous safe and well-tolerated Cys-A loaded MMF is prepared and evaluated in preclinical studies. High levels of Cys-A was quantified in retina/choroid with topical drop instillation.