RESEARCH SUMMARY STATEMENT

Dry eye disease (DED) is highly prevalent worldwide affecting ~50% population (including children and adults). In India, DES is highly emergent and estimated to affect more than 45% (275 million people) of the population that accounts for 50% of the urban community by 2030. Furthermore, the impact of increased screen-time during the COVID-19 pandemic is bound to aggravate this estimate. Cyclosporine A (CsA) is a drug of choice for the treatment of DED. CsA is a highly lipophilic and poorly water-soluble peptide and an immunosuppressant. The marketed CsA eye drops are emulsion-based and are suffer from vehicle-associated ocular irritation and poor bioavailability of (< 5%) attributed to poor precorneal drug retention. Therefore, the present study was undertaken to develop an aqueous-based CsA eyedrop by improving its aqueous solubility. In this context, supramolecular cyclodextrins (SCDs) based binary and ternary complexes were developed using *in silico* techniques, wet-lab experiments, and relevant *in vitro*, and *ex vivo* studies. Further, the binary and ternary complex loaded eye drops were formulated in polyvinyl alcohol (PVA) as a vehicle to improve the drug precorneal retention time. The optimized eye drops were evaluated against the DED mouse model to assess the efficacy and compared against the marketed formulation.

Although eye drops are associated with poor drug bioavailability, it is most preferred for topical application, and 90% of the marketed formulations are available as eye drops. The principal advantages of the newer aqueous-based eye drops are non-irritancy and improved precorneal retention. The supramolecular binary and ternary complex (developed using molecular modeling) improved the CsA solubility from ~20 µg/ml to ~120 µg/ml and ~400 µg/ml, respectively. The complexes showed improved release kinetics and sustained drug release. The formation of inclusion complex and conversion into completely amorphous form was confirmed by Fourier transform infra-red (FTIR), nuclear magnetic resonance (NMR) spectroscopy, X-ray photoelectron spectroscopy (XPS), differential scanning calorimetry (DSC), and X-ray diffraction (XRD) studies. The non-irritancy and non-toxicity of the optimized formulation were confirmed by Hen's Egg Test – Chorioallantoic Membrane (HET-CAM) assay and cytotoxicity assay on human corneal cells, respectively. The *in vivo* efficacy of the developed eye drops evaluated in mouse models of DED prompted improved performance of the ternary complex eye drops over other

tested formulations based on the tear volume measurements, corneal fluorescein-stained imaging, and histopathology.

The finding of the study clearly suggested that the SCDs based supramolecular complex formulated as aqueous eye drops can be used as a viable alternative to the emulsion based CsA eye drops for the management of the DED.

Impact of the Research work

- **Effective local-drug delivery, self-application, and increased comfort**
  Local drug delivery at the ocular surface is the most preferred mode of treatment during DED. CsA-SCDs based eyedrops are convenient and advantageous over conventional treatment modalities (emulsion-based eye drops) by offering direct access to the site of requirement, the possibility of self-application, reduction in the dose and dosing frequency, and high levels of compliance.

- **Solution for an unmet need in the ocular healthcare segment**
  With an estimate of ~50% of the worldwide population and ~45% of the Indian population experiencing DED by 2030, the exploration of newer delivery systems is warranted. An aqueous particle-free eye drop formulation paves a way to address the long-standing need for an effective, increased precorneal retention, and biodegradable delivery system for CsA during the incidents of DED.
- **The SCDs eye drops as a platform for technological innovation**
  The present study is a first-of-its-kind technological innovation in India utilizing a completely particle-free aqueous ocular formulation for CsA. The SCDs-based eye drops developed in the project paves the path as a platform technology for the management of other ocular surface complications such as bacterial and fungal infections, and inflammation.

- **Adaptable for large scale production**
  The SCDs-based eye drops are made entirely from biodegradable polymers, making them eco-friendly, cost-effective, easily scalable, and sustainable in the long run.

Key Publications

- **Chaudhari P**, Ghate VM, Lewis SA. Next generation contact lens: Towards Bioresponsive drug delivery and smart technologies in ocular therapeutics. *Eur J Pharm Biopharm*. 2021; 161; 80-99.
- **Chaudhari P,** Ghate VM, Lewis SA. Supramolecular Cyclodextrin Complex: Diversity, Safety, and Applications in Ocular Therapeutics. *Exp Eye Res*. 2019; 189; 107829.

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26/10/21