Mucoadhesive Polymeric Micelles for Enhanced Ocular Drug Delivery

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Introduction

- Dry eye disease (DED) occurs due to insufficient tear production or tear evaporation, resulting in sore red eyes. Affecting over six million Canadian adults, DED has more prevalence among women and the elderly.[1]
- Restasis® eye drops are 0.05% cyclosporine A (CycA)-loaded emulsion that are administered twice daily for DED-associated inflammation. However, ocular burning occurs in 17% of patients administering Restasis®.[2]
- In this work, we prepared CycA-loaded mucoadhesive eye drops using our proprietary mucoadhesive phenylboronic acid-modified polymeric micelles.
- This study aimed to enhance the loading capacity and prolong ocular delivery of CycA for improved effectiveness against DED.

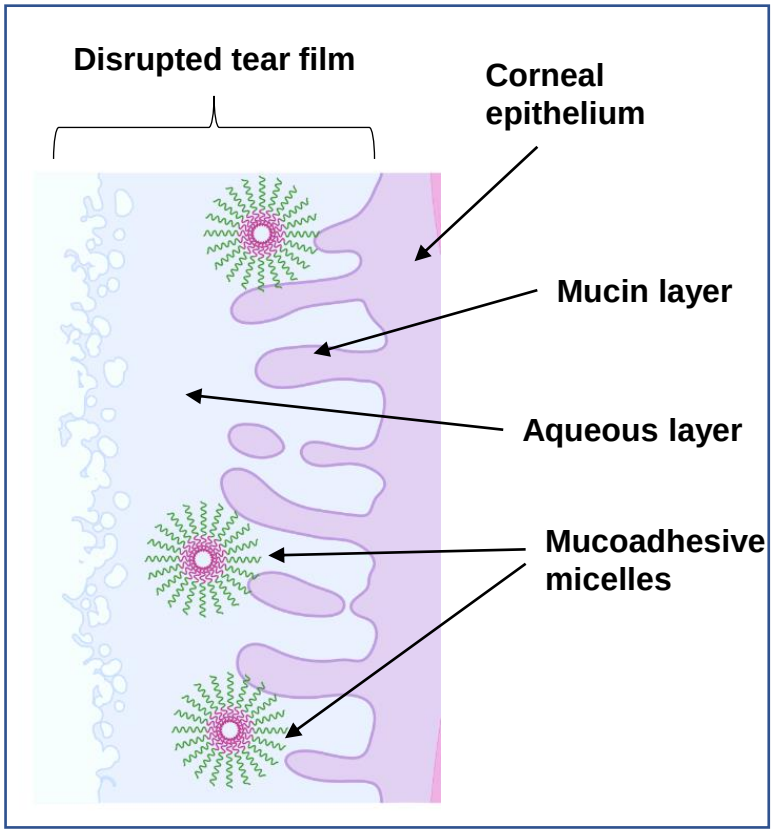

Fig. 1. Diagram of the mucoadhesive micelles on eye surface, created by BioRender.com

[1] Caffery, B.; Srinivasan, S.; Reaume, C.; Fischer, A.; Cappadocia, D.; Siffel, C.; et al. Prevalence of dry eye disease in Ontario, Canada: A population-based survey, *Ocul. Surf.***2019**, *17*, 526-531.
[2] FDA, Restasis (0.05%) package insert

Micelle Formulation and *in vitro* Characterization

Micelle formulation:

Dissolving CycA-polymer mixture in acetone → Addition of water (polymer conc. 10 mg/mL) → Evaporation of acetone → pH adjustment to physiological pH

Micelle shape and size: The micelles had an average size of ~ 150 nm as measured by DLS. TEM revealed the micelles' spherical shape with no detected aggregates.

Drug loading: The micelles encapsulated triple the amount of CycA as Restasis® with an encapsulation efficiency ~ 100%.

Micelle stability: Storage of the micelle formulations in the fridge over nine months resulted in a minimal change in the micelle size, a similar result was obtained with freeze drying.

***In vitro* release studies:** The micelle formulations showed sustained CycA release over 10 days studies in PBS (pH 7.4) at temperature 37°C and 100 rpm.

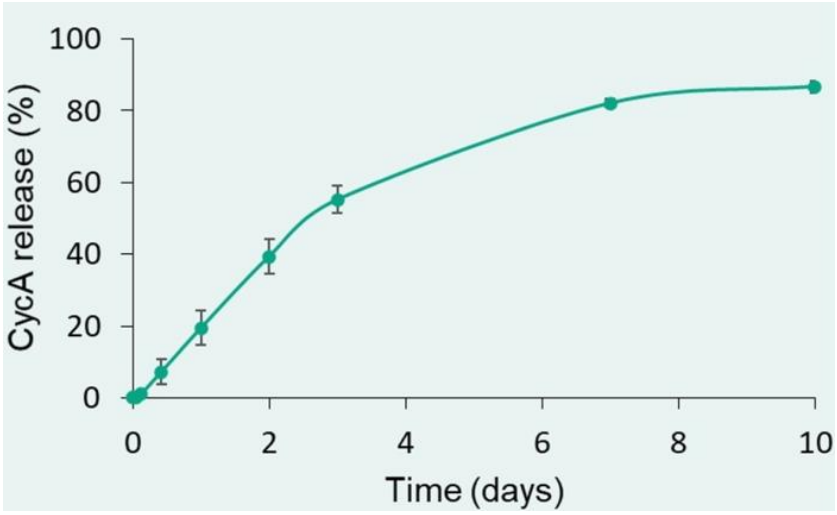

Fig. 2. *In vitro* release profile of CycA from a selected micelle formulation

CyA- cyclosporine A; DLS- dynamic light scattering; TEM- transmission electron microscopy; PBS- phosphate-buffered saline

Animal Studies*

Tolerability studies: Fluorescein staining and OCT revealed no signs of irritation upon instillation of the formulation in rabbit eye.

Efficacy studies: The efficacy of the CycA-loaded micelles was assessed in rats using scopolamine-induced DED model with tear volume measurement and fluorescein staining.

The micelle formulation restored the tear volume of rat eye to the baseline when administered once every three days. No significant differences were detected in tear volumes and fluorescein staining scores between micelle formulations instilled once every three days and Restasis® instilled twice daily ($p > 0.05$).

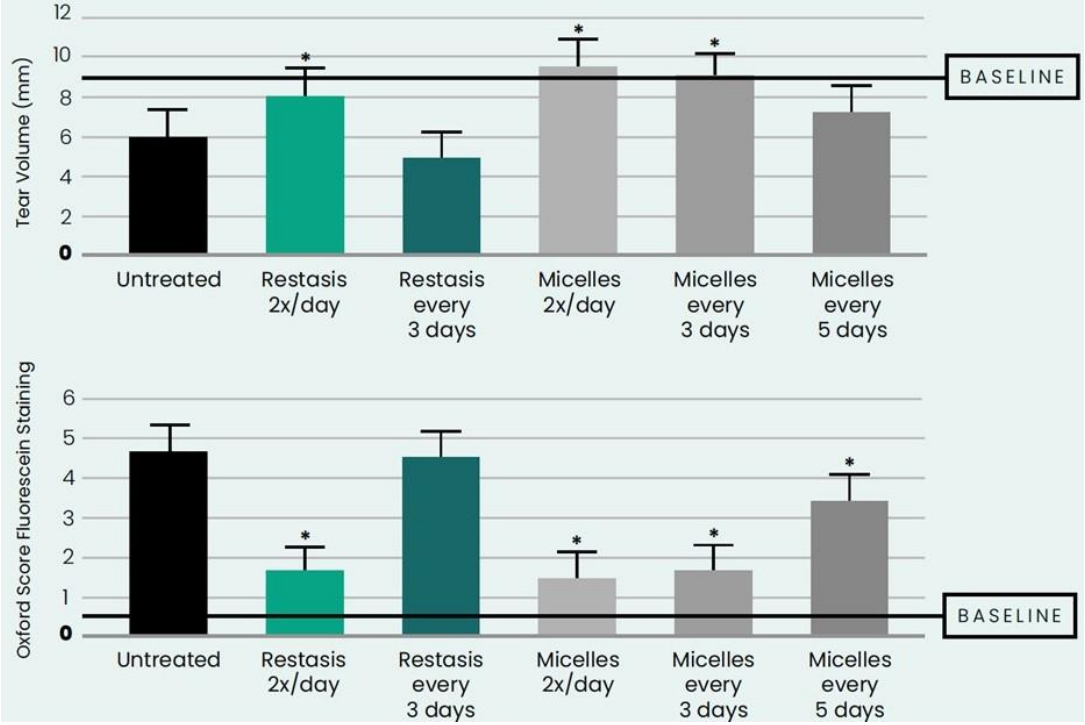

Fig. 3. Tear volume and fluorescein staining scores after instillation of CycA-loaded micelle formulations and Restasis® in rat eye with scopolamine-induced DED

* McMaster's Animal Research Ethics Board has approved the animal study protocol.
OCT- optical coherence tomography; CyA- cyclosporine A; DED- dry eye disease

Animal Studies* (Continued)

Pharmacokinetic studies: CycA micelle formulations and Restasis® were instilled in rabbit eye for 15 days, followed by CycA extraction from corneal tissues and LC-MS assay.

The micelle formulations resulted in an approximate four-fold increase in CycA penetration in corneal tissues of rabbit eye relative to Restasis® when both were instilled twice daily.

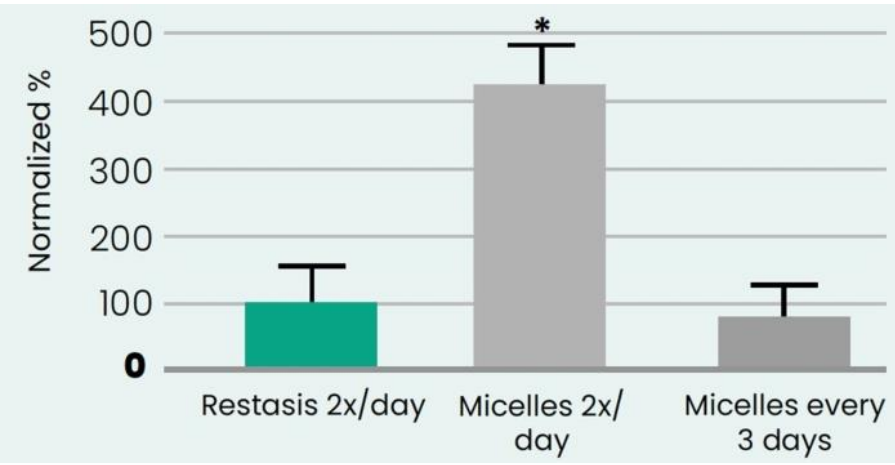

Fig. 4. Recovered CycA from rabbit corneal tissues after instillation of CycA-loaded micelle formulations relative to Restasis®

Conclusions

- The PBA-modified mucoadhesive micelles enhanced the loading capacity and ocular bioavailability of CycA relative to Restasis®.
- The CycA-loaded micelle formulation is effective against DED upon instillation once every three days.
- The micelle formulations could be freeze-dried for storage in powder form, which can be reconstituted before use.

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CyA- cyclosporine A; PBA-phenylboronic acid; DED- dry eye disease