FORMULATION AND CHARACTERIZATION OF TRANSFEROSOMES FOR OCULAR DRUG DELIVERY

Santosh Bhujbal, Ilva D. Rupenthal , Priyanka Agarwal

Buchanan Ocular Therapeutics Unit, Department of Ophthalmology, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand

Santosh.bhujbal@auckland.ac.nz

BACKGROUND

Inflammasome activation is critical in the manifestation of numerous ocular inflammatory diseases. Recent research has confirmed a significant upregulation of the NLRP3 inflammasome complex in tears and ocular surface of dry eye disease (DED) patients. While inflammasome inhibitors have shown promise in various inflammatory conditions, their application in DED remains unexplored. Tonabersat effectively inhibits inflammasome activation by blocking ATP release through connexin43 hemichannels. However, its poor solubility and bioavailability limit its clinical translation.

This study aimed to develop and characterise transfersomes (TFS) for ocular drug delivery of tonabersat. The prepared TFS were characterised for vesicle size, shape, polydispersity index, zeta potential and entrapment efficiency. Conjunctival and corneal tolerability, corneal spreading dynamics and ocular penetration were determined ex vivo using an oily solution in medium chain triglycerides (MCT) as the control.

METHODS

FORMULATION AND CHARACTERIZATION OF TONABERSAT-LOADED TFS AND MCT SOLUTION

TFS were prepared using Phospholipon 90G, Tween 80 (edge-activator), and tonabersat at a ratio of 9:1:0.5 by the thin-film hydration technique (Figure 1). The phospholipid film was hydrated using phosphate buffered saline containing 0.003% w/v benzalkonium chloride. The final concentration of tonabersat in the TFS formulation was 0.1% w/v. A 0.1% w/v oily solution of tonabersat in MCT was used as a control.

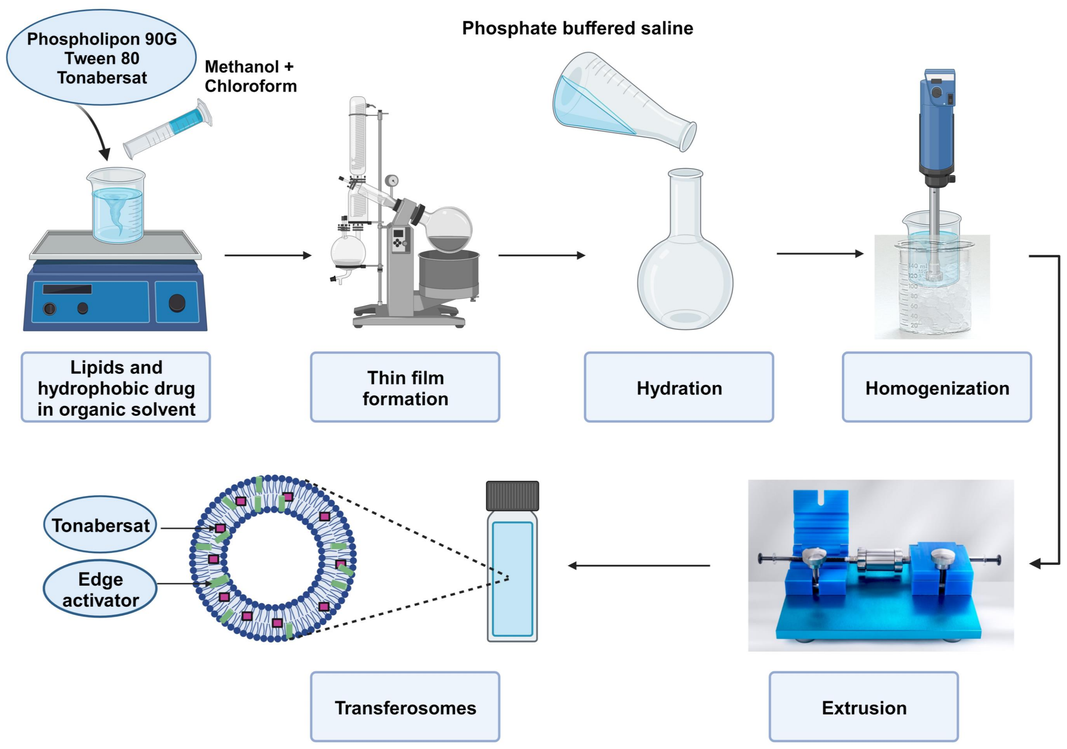

Figure 1: Schematic representation of the TFS preparation.

The vesicle size, polydispersity index (PDI), and zeta potential (ZP) of TFS were measured using a Zetasizer Nano ZS (Malvern Instruments, UK) at 25 ± 1 °C. The morphology of the optimised TFS was evaluated by transmission electron microscopy (TEM; ThermoFisher, Netherlands). The tonabersat content was measured by HPLC (Agilent, Germany). The entrapment efficiency (EE) was calculated as: EE (%) = [(total amount of drug in the vesicles – amount of drug detected only in the supernatant) / total amount of drug in the vesicles] x 100. Conjunctival and corneal tolerability was tested using HET-CAM and BCOP tests. The contact angle and spreading dynamics were observed ex vivo using a goniometer (Ossila, UK). Ocular penetration was evaluated using an ex vivo porcine whole-eye model with simulated lacrimal flow.

RESULTS AND DISCUSSION

CHARACTERIZATION OF TONABERSAT FORMULATIONS

Test method	TFS	MCT
Description	Translucent, white liposomal dispersion	Clear colourless oily solution
Assay (%)	99.94 ± 4.27	104.17 ± 1.47
Vesicle size (nm)	125.50 ± 0.66	Not applicable
PDI	0.261 ± 0.013	Not applicable
ZP (mV)	0.012 ± 0.023	Not applicable
EE (%)	81.57 ± 8.34	Not applicable

SAFETY AND TOLERABILITY OF TONABERSAT FORMULATIONS

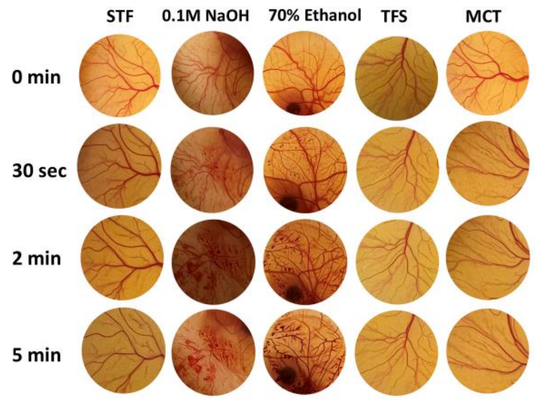

Figure 3: Conjunctival irritation using the HET-CAM test.

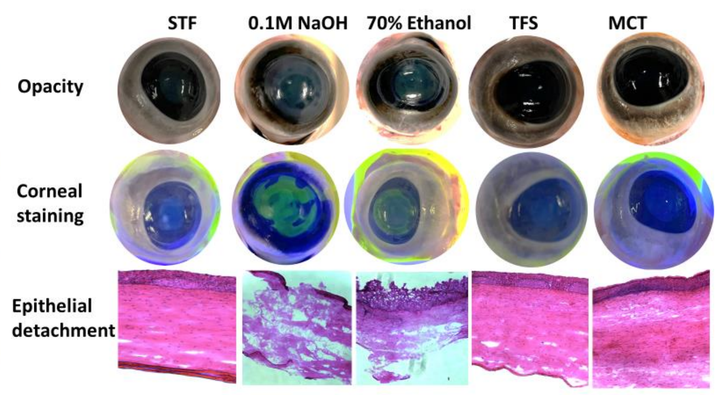

Figure 4: Corneal irritation using the BCOP assay.

CORNEAL SPREADING DYNAMICS (CONTACT ANGLE) AND TRANSMISSION ELECTRON MICROSCOPY (TEM)

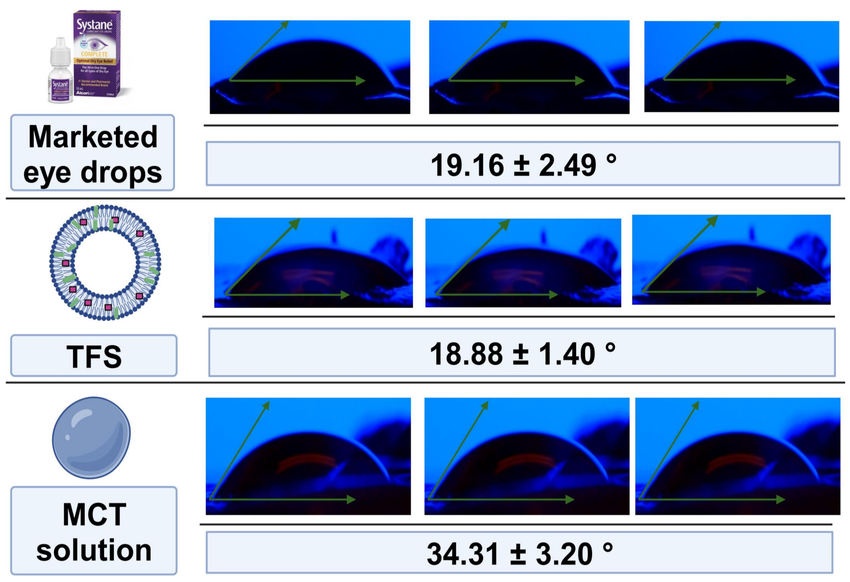

Figure 5: Contact angle measurement in triplicate using a goniometer.

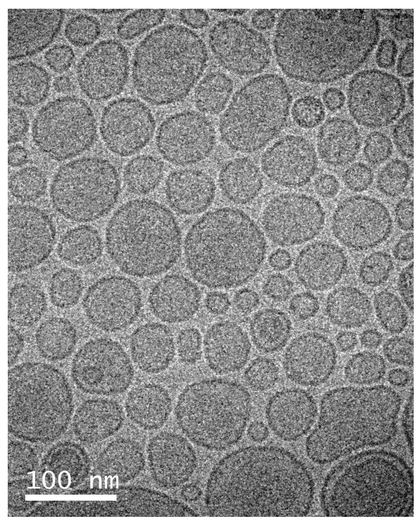

Figure 6: TEM image showing spherical and unilamellar TFS.

4. EX VIVO OCULAR PENETRATION OF TONABERSAT

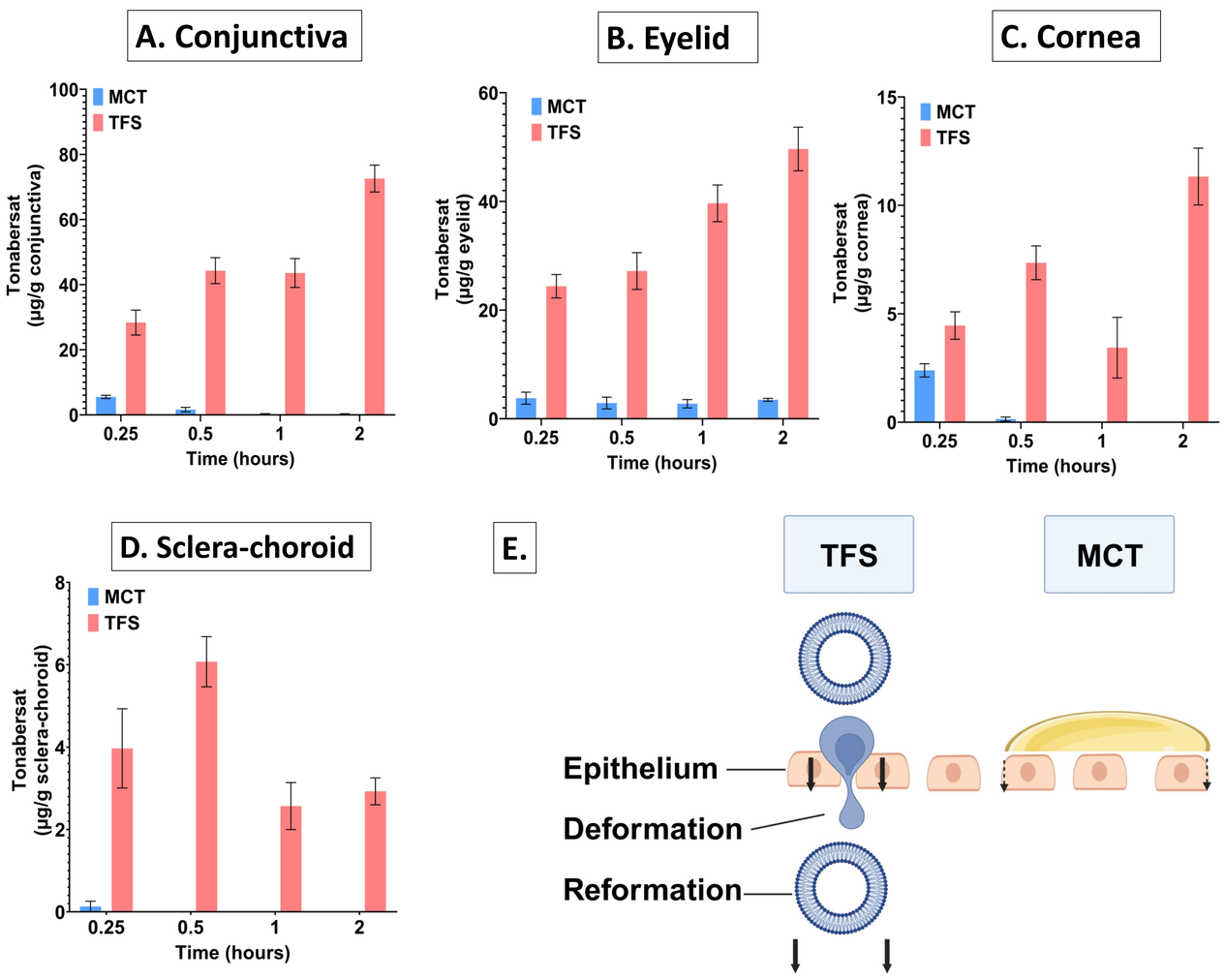

Figure 7: Graphical representation of MCT and TFS in A. Conjunctiva, B. Eyelid, C. Cornea and D. Sclera-choroid. E. Schematic representation of corneal penetration of tonabersat from TFS and MCT formulations.

CONCLUSION

TFS present a promising approach for improving ocular bioavailability, permeability and therapeutic potential of poorly soluble tonabersat for the treatment of DED.