Synthesis and Evaluation of Hybrid Tri-block Copolymer Nanomicelles for Sustained Corneal Drug Delivery of Curcumin

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Background: Dry eye syndrome (DES) is perpetuated by a vicious cycle of ocular surface inflammation, tear film instability and hyperosmolarity, independent of the particular triggering event (Shimazaki, 2018). Developing a new delivery system to treat DES with minimal toxicity and improved efficacy over clinically used eye drops is considered a major necessity, due to the limited drug-delivering capabilities of current traditional delivery systems (Bachu *et al.*, 2018). The first challenge for ocular drug distribution is the precorneal lacrimal fluid inside the anterior section of the eye, which due to turnover and removal through the nasolacrimal duct, results in a high proportion of the delivered drug being removed within minutes (Urtti, 2006). Furthermore, the lacrimal fluid abundant in peptides and proteins that can attach to the drug molecules and reduce their release. The next barrier, is the cornea, which limits permeation of both hydrophilic and hydrophobic drugs after topical application (Bachu *et al.*, 2018). In this study, we investigated sustain of curcumin via self-assembled nanomicelles fabricated from a positively charged hybrid triblock copolymers. The micelles were designed to enhance both ocular surface retention and improve permeation, thereby improving the overall bioavailability of curcumin in DES treatment.

Methods: Triblock copolymers were chemically synthesised. NMR, FTIR spectroscopy, and GPC were used to characterize the block polymers. A nanoprecipitation technique was used to prepare nanomicelles from the characterized triblock copolymers. The physicochemical properties of the self-assembled nanomicelles were investigated, including hydrodynamic size, zeta potential, morphology, drug-loading content, and loading efficiency using DLS, TEM and UV spectroscopy. The physicochemical properties of the developed nanomicelles were optimised using different factors including polymer content, drug content, stirring speed, organic: aqueous ratio and surfactant concentration. *In vitro* drug release of curcumin-loaded nanomicelles was investigated.Ex vivo penetration of nanomicelles across porcine cornea was monitored in a setup using multi-photon microscopy after topical application.

Results: NMR and FTIR were used to characterize the polymers' synthesised and demonstrated the correct triblock configurations have been achieved. The polymeric micelles fabricated were spherical in shape with an average particle size of 180 nm and zeta-potential of around +24 mV. Drug-loading efficiency and content were 75.37 and 3.47%, respectively. Nanomicelles demonstrated sustained-release for over a 9 days. The positively charged polymeric micelles penetrated the cornea significantly better compared to the control solution.

Conclusions: The triblock polymers were successfully synthesized and characterized. The hybrid tri-block nanomicelles loaded with curcumin showed sustained-release. The nanomicelles, being positively charged, also showed high corneal penetration, which will help to overcome the retention and permeation issues commonly seen with traditional topical formulations applied to the eye. This research could therefore ultimately lead to a product capable of effectively treating DES with fewer treatment applications and potentially improved patient compliance when compared to current treatments.