IMPROVED PERMEATION AND RETENTION OCULAR DELIVERY OF CEFAZOLINE USING THERMOSENSITIVE-MUCOADHESIVE *IN SITU* GELS

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Background: Keratitis bacteria, caused by *Pseudomonas aeruginosa*, is still becoming a significant health problem. Cefazoline (CFZ) is available as liquid eye drops and are used as a treatment for keratitis. However, conventional eye drop shows several limitations, mainly due to short retention time in the ocular tissue, resulting in low ocular bioavalibility of drugs applied ocularly. In an attempt to overcome these drawbacks, alternative drug delivery system should be developed. Here, we incorporated CFZ into thermosensitive-mucoadhesive *in situ* ocular gels.

Methods: Ocular *in situ* gels with thermosensitive and mucoadhesive properties were prepared using Pluronic F127 (P127) and Pluronic F68 (P68) as thermosensitive polymers, as well as hyaluronic acid (HA) as mucoadhesive polymer. The *in situ* gels were further evaluated their thermosensitive characteristics, mucoadhesive properties, rheological properties, hemocompatibility, *ex vivo* ocular permeation and retention ability.

Results: The optimized formulations were *in situ* gel containing P127, P68 and HA with the concentration of 15%, 5% and 0.2%, respectively. All formulations contained 0.35% CFZ. The optimized formulations showed gelation temperature around ocular temperature (35^{o}C), showing desired thermosensitive properties. Essentially, the mucoadhesive strength in ocular tissue was observed to be 9748.69 ± 1184 g with more than 4 hours mocoadhesion time. The rheological evaluation showed that the *in situ* gel possessed desired rheological properties for thermosenstitive preparations. Moreover, no hemolysis was observed in hemocompatibility study. Finally, the incorporation of CFX in this system could enhance permeation and retention of CFZ in porcine ocular tissue in *ex vivo* studies with 1.27 ± 0.13 mg and 1.53 ± 0.16 of CFZ permeated and localized in the ocular tissue following 24 h administration of thermosensitive-mucoadhesive *in situ* ocular gels

Conclusions: Thermosensitive-mucoadhesive *in situ* ocular gels containing CFZ was successfully formulated. The combination of P127, P68 and HA resulted in gels with desired characteristics. Importantly, this approach improved the permeation and localization of CFZ in the ocular tissue, which could potentially improve the treatment of bacterial keratitis.