Abstract of Dissertation

The eye is a complex organ with a unique anatomy and physiology. Topical formulations are still the most widely preferred non-invasive route of drug administration used to treat ocular diseases. This is owing to their ease of administration and high patient compliance. Nonetheless, the use of these conventional ocular formulations present bioavailability drawbacks as a result of the numerous anatomical constraints such as tear turnover, and static ocular barriers (sclera, different layers of the cornea, blood-aqueous and blood-retinal barriers) and dynamic ocular barriers (tear dilution, conjunctival blood flow, choroidal blood flow, and lymphatic clearance). These barriers pose a challenge and impede deeper ocular drug permeation. As a result, only around 5% of the topically administered dose penetrates deeper eye tissues. To overcome these ocular drug delivery barriers and improve ocular bioavailability, tremendous effort has gone into ocular research to develop safe and patient-friendly novel drug delivery systems/devices/biomaterials, such as emulsions, ointments, suspensions, nanomicelles, nanoparticles, liposomes, dendrimers, implants, microneedles, contact lenses, nanosuspensions, and *in situ* thermosensitive gels. The design of these drug delivery systems ranges from employing natural/synthetic polymers, peptides/proteins and ocular bioactives for treatment and management of ocular diseases.

There have been great advancements in the area of ocular drug delivery. However, there is still no system that meets all the requirements of an ideal ocular drug delivery system. The goal of this research was to develop a stimuli-responsive intracamerally-injected thermo-ocugel system for post-cataract surgery infection and inflammation treatment or prophylaxis. A dual drug-loaded *in situ*-forming injectable thermoresponsive chitosan-gelatin hydrogel was developed employing naturally-derived polymers and crosslinkers that would aid cytocompatibility and biocompatibility in terms of presenting optimal mechanical properties, in combination with the anti-inflammatory agents such as dexamethasone sodium phosphate (DSP), and anti-bacterial agents such as moxifloxacin hydrochloride (MOX) The properties of the ocular drug delivery system were explored by employing double crosslinking approach to fabricate an ocular system capable of forming an *in-situ* hydrogel at ocular physiological conditions. The double crosslinking approach enabled the dual incorporation of MOX and DSP, in addition to forming the *in situ* thermoresponsive hydrogel. This drug delivery system acted as a reservoir for both MOX and DSP to prolong their residence time and control their release. thus to decreasing the need for frequent administration.

The drug delivery system exhibited thermoresponsive behaviour with gel formation occurring within a temperature range of 25 to 38 °C with the highest gelling point at 32 °C. Rigidity (G') of this system started increasing from 5 hours of genipin crosslinking and reached 3.5 kPa in 12 hours. The system allowed for dual drug encapsulation efficiencies of 91.48% and 75.27%, and drug loading of 1.87% and 6.14% for DSP and MOX, respectively. The system showed a burst release of 52.75 ± 3.12%, and 60.94 ± 8.31% in 12 hours, which increased to 76.61 ± 5.91% and 81.71± 4.85% in 3 days, followed by a steady release of 0.53 ± 0.15 % and 0.81 ± 0.26% per week for DSP and MOX, respectively. The system showed a rapid fluid uptake of 126.02% in the first 3 days followed by a gradual increase up to 198.72% in 28 days. The system exhibited a low level of erosion (1.5%) on the first 3 days whereas a slightly higher degree of erosion rate (16.58%) was observed between 3 and 14 days and the overall surface erosion was 18.20% in 28 days. The dual drug incorporation, fluid uptake and surface erosion properties of the fabricated novel thermo-ocugel system were suitable for the application as potential treatment of post-cataract surgery infection and inflammation.

The thermo-ocugel's *in vivo* performance and safety was evaluated in order to provide more evidence of its ocular compatibility and drug levels achieved in normal ocular conditions. Significant inflammatory alterations, as well as any differences in the ocular tissues as a result of the thermo-ocugel injection or the injection technique, were assessed via histological analysis. The thermo-ocugel introduction to ocular tissues following intracameral injection resulted in notable cases of inflammation. However, the inflammation cases showed great resolution within a period of 21 days for the dual drug-loaded thermo-ocugel. The high therapeutic concentrations (>0.2 µg/mL) attained in the first 7 days for MOX highlight that the drug level attained would be sufficient to induce a therapeutic antibiotic effect while still remaining under the reported non-toxic concentrations of 150 µg/mL for the required antibiotic treatment period of 7 days. The release profile for DSP indicated concentrations which were above the MEC (0.5164 µg/mL) for the 28-day period of investigation. The thermo-ocugel thus achieved therapeutic levels of both the antibiotic and anti-inflammatory agent over the required treatment periods, while significantly reducing administration frequency, which is one of the drawbacks associated with antibiotic and anti-inflammatory eyedrop formulations on the market for post-cataract surgery infection and inflammation. Furthermore, the prolonged maintenance of effective ocular anti-inflammatory drug concentrations is a good indication of the thermo-ocugel's efficacy in counteracting the pathological tissue changes that occur when inflammation is prompted following ocular surgical procedures.