Ocular bioavailability and efficacy study of dexamethaosone loaded dual nano-particulate system

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Background: The anatomical (ocular tissues), physiological (blinking and tear production), and innate microenvironmental factors (osmolarity, pH, tear enzymes, etc.) are common challenges for ocular bioavailability of ophthalmic drugs. Progress in pharmaceutical nanotechnology has opened new avenues for ophthalmic formulations aimed at enhancing corneal permeation and residence time. Dexamethasone is a first-line drug of choice for treating inflammation-associated eye diseases; however, its poor bioavailability remains a significant challenge.

Methods: In this study, we developed a microemulsion/liposome based dual nanoparticulate system, combining the advantages of both carriers to improve the bioavailability of dexamethasone in the eye. A high-pressure homogenization technique was employed for the development and scale-up of the dexamethasone (0.1%) loaded dual nanoparticulate system. Ocular bioavailability and product efficacy studies were conducted using a benzalkonium chloride (BAK)-induced dry eye disease (DED) rabbit model (5 animals per group), and compared with a vehicle (water for injection) and non-drug-loaded formulations. The treatment course lasted 28 days, with the instillation of 2 drops (50 µL) per day (1st at 8:00 am and 2nd at 8:00 pm) in both diseased eyes.

Results: A uniform dispersion of nanoparticles in the formulation was achieved (average particle size of 60 nm and polydispersity index < 0.2), with the high pressure homogenization techiques. Drug release was sustained for up to 12 hours, following a non-Fickian diffusion pattern. An in-house stability study confirmed the maintenance of sterility for up to one month after opening the eye dropper bottle (low-density polyethylene, LDPE). No drug leakage was observed from the developed system over a six-month period under predefined conditions (2–8°C and 25°C with 60% relative humidity). Relief from the disease was observed within 4 days of treatment. Tear break-up time (TBUT) and tear volume were restored to normal levels, while scores for all disease indicators including hyperemia, opacity, neovascularization, and tissue staining dropped to zero or baseline, confirming the high efficacy of the developed formulation. No signs of ocular toxicity were observed with continuous treatment for up to 28 days. Intraocular pressure (IOP) remained within the normal range (below 20 mmHg) throughout the study period (28 days). The drug concentration in the tears gradually increased with continuous administration of eye drops, reaching an average of 1.3 µg/mL in the right eye and 3.4 µg/mL in the left eye by Day 14. No significant differences were observed between Day 7, Day 14, Day 21, and Day 28, indicating that an equilibrium had been established between drug absorption and drug elemination within the eye. At the end of the study period (Day 28), a significant amount of the drug was detected in all major ocular tissues, while drug levels in both plasma and vitreous humour were below the detection limit. This indicates that the drug remained localized within the eye, with no/limited systemic distribution through the conjunctival route.

Conclusions: The developed system was considered an effective treatment option for ocular diseases, with minimal risk of steroid-associated intraocular pressure elevation.