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Loteprednol etabonate-loaded nanoemulsions for the treatment of dry eye disease

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Dry eye disease is a complex disorder marked by disrupted tear film homeostasis and inflammation of the ocular surface. Oil-in-water nanoemulsions offer an effective strategy for incorporating drugs with low water solubility and show strong potential for managing dry eye disease. The main goal of this research was to develop biopharmaceutically optimized nanoemulsions for delivering loteprednol etabonate (LE) to the eye. Loteprednol etabonate (LE) is a corticosteroid well suited for the treatment of dry eye disease, as it is rapidly metabolized into an inactive form and has a favorable safety profile. Beyond formulating LE-loaded nanoemulsions, the research aimed to establish in vitro methods for their biopharmaceutical evaluation, guided by the key physiological and structural characteristics of the ocular surface. A method for assessing nanoemulsion stability on the ocular surface under biorelevant dilution with artificial tear fluid was successfully developed. The influence of medium complexity and shear stress mimicking blinking on nanoemulsion stability was examined. A quality-by-design approach enabled the optimization of LE nanoemulsions and identified the formulation and processing parameters most critical to achieving consistent drug content. This process identified a lead nanoemulsion with suitable physicochemical properties for ocular administration, robust long-term stability, and compatibility with membrane filtration as a sterilization method. A high-throughput *in vitro* corneal epithelial model was established to evaluate biocompatibility, and the lead LE nanoemulsion showed excellent biocompatibility. Additionally, a novel approach combining dilution and ultrafiltration was developed to study LE distribution between the oil and aqueous phases under biorelevant dilution. Results confirmed that LE dominantly remains in the oil phase even at high dilutions, suggesting that its likely partitions from the oil droplets into the corneal epithelium. The feasibility of transforming LE nanoemulsions into a dry form was also demonstrated. Using electrospinning, the nanoemulsions were converted into hydrophilic, biocompatible nanofibers that rapidly dissolve in aqueous medium and regenerate the original nanoemulsion upon reconstitution.