P 29

Development of ophthalmic nanoemulsion for advanced delivery of poorly water- and oil-soluble loteprednol etabonate

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Oil-in-water nanoemulsions (NE) hold great potential for effective dry eye disease (DED) treatment by replenishing the deficient lipid layer of the tear film with appropriate lipid components and efficiently delivering poorly water-soluble drugs. Loteprednol etabonate (LE) is a soft corticosteroid approved by the Food and Drug Administration in 2020 for a short-term treatment of DED in the form of a nanosuspension (0.25% *w/w*). Incorporation of LE into ophthalmic NE would allow the corticosteroid to be delivered to the eye surface in a dissolved form, reducing the required dose of LE and providing an even better benefit-risk ratio. However, incorporating LE in sufficient quantity into a NE is challenging due to its poor oil solubility. This study aims to develop an ophthalmic NE of LE for the treatment of DED. The quality-by-design (QbD) approach is used to optimize the formulation and process parameters that affect the physicochemical properties of NE, which are critical for the performance of NE (i.e., drug content, nanodroplet size, size distribution and zeta potential, viscosity, and surface tension). NEs were prepared using the LM20 microfluidizer (Microfluidics). Using QbD principles, five formulation parameters (concentration of LE, castor oil, Capryol™ 90, Kolliphor® EL, and Soluplus) and three process parameters (mixing temperature of the oil and water phases, number of cycles passed through the interaction chamber, and pump pressure of the microfluidizer) were selected for the custom experimental design developed using JMP 14.0 statistical software (JMP®, version 14.0, SAS Institute Inc., Cary, NC, 1989–2007). Nanodroplet size, polydispersity index, and zeta potential were determined at 25 °C using a Zetasizer Ultra (Malvern Panalytical). The content of LE was quantified by high-performance liquid chromatography using an Agilent Infinity II 1260 and an XBridge C8 column. Viscosity (flow curve) was measured using a rheometer (MCR 102, Anton Paar) and surface tension was determined using the Du Noüy ring method and a Kruss K100 tensiometer.

QbD approach employed in this work facilitated rational design of LE-loaded NE, with the aim to optimise ophthalmic delivery of LE. Regression modelling approach uncovered parameters with the greatest impact on the responses, as well as their interactions. Further indepth biopharmaceutical characterization will enable selection of optimized LE-loaded NE - formulations which might become candidates for further development of a medicinal product for the treatment of DED.