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Short communication

Ophthalmic nanoemulsion with loteprednol etabonate – preformulation parameters for a highly loaded formulation

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Introduction

Oil-in-water nanoemulsions (NE) have proven to be a highly effective drug delivery system for alleviating the signs and symptoms associated with dry eye disease (DED). This innovative approach allows for the administration of poorly soluble drugs while simultaneously replenishing the tear film (Singh et al., 2020). 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 (Mohamed et al., 2022). LE is a poorly water-soluble, but also a poorly oil-soluble drug. Therefore, it is challenging to incorporate LE into a NE. Excipient selection must be carefully considered to maximize LE loading.

To perform initial excipient screening for the development of LE-loaded NE, the solubility of LE was tested in various oils and surfactants.

Materials and methods

LE was kindly provided by JGL Ltd. The solubility of LE was determined in medium chain triglycerides (Fagron), castor oil (Fagron), soybean oil (Sigma Aldrich), sesame oil (Sigma Aldrich), squalane (Sigma Aldrich), Capryol™ 90 (Gattefossé), Kolliphor® EL (BASF), Tween 80 (Fagron) and Tyloxapol (Sigma Aldrich). Soluplus® was acquired from BASF. Quantitative determination of LE was performed by high-performance liquid chromatography (HPLC) using an Agilent Infinity II 1260 (Agilent Technologies) with the XBridge C8 column (3.5 µm, 4.6 mm×100 mm, Waters Corporation). The solubility of LE in oils and surfactants was determined by adding an excess amount of the drug to 5 g of oil or surfactant. Samples were stirred on a magnetic stirrer at 25 °C for 48 h to reach equilibrium. The samples were then centrifuged for 30 min. The supernatants were diluted with 2-propanol (VWR International). The mobile phase consisted of double distilled water (DDW) and acetonitrile (ACN; Merck-Millipore) in a 58:42 (*V*/*V*) ratio. The following HPLC conditions were used: column temperature 45 °C, flow rate 1 ml min^{-1}, injection volume 5 µL, detection wavelength 255 nm. System suitability was evaluated according to the following criteria: the relative standard deviation (RSD) of the detector response factor for standard solution injections in the sequence is not greater than 2.0%. The HPLC method was validated in terms of linearity, accuracy, and repeatability. The method was found to be linear ($R^2 \geq 0.999$), accurate (recovery 98–102%) and repeatable (RSD of peak area ≤ 3.0%).

Based on the solubility results of LE, the oil and surfactants were selected for the preparation of NE. The oil phase was prepared by mixing LE (0.1-0.3%, *w*/*w*), castor oil (10- 20%, *w*/*w*), Capryol™ 90 (1-5%, *w*/*w*) and Kolliphor® EL (1-5%, *w*/*w*). The water phase consisted of DDW and Soluplus® (0-1%, *w*/*w*). The oil and water phase were mixed with Ultra-Turrax® (IKA-Werke GmbH & Company) and the obtained coarse emulsions were then subjected to a microfluidizer LM20 with a Y-type interaction chamber (Microfluidics). Drug loading was determined by HPLC method after filtration of NEs with a

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0.45 µm polyethersulfone filter to ensure that any precipitated LE was removed.

The droplet size and polydispersity index (PDI) of the NEs were determined at 25 °C by dynamic light scattering (DLS) using a Zetasizer Ultra (Malvern Panalytical). Morphological evaluation of NE was performed using TEM Morgagni 268 (FEI, USA) operating at 70 kV. NE sample was pipetted onto a flat surface, a Formvar®/Carbon copper grid with a mesh size of 100 (Em-tec GmbH, Germany) was immersed in the droplet and dried under ambient conditions.

Results and discussion

The solubility of LE in the tested oils was very low (Fig. 1), indicating inefficient drug loading in NE with an oil phase content of less than 10% (*w*/*w*). The highest LE solubility among the tested oils was in castor oil (2.43 ± 0.12 mg/ml), while among the tested surfactants, the highest LE solubility was in Capryol™ 90 and Kolliphor® EL. In addition to castor oil, Capryol™ 90 and Kolliphor® 90, Soluplus® was selected for LE-loaded NE development due to its excellent solubilization properties, especially for poorly soluble drugs.

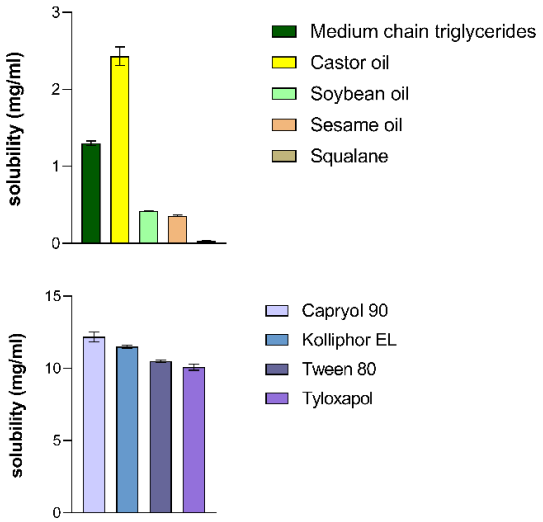

Fig. 1. Solubility of LE in different oils and surfactants (values are mean ± SD, n=3).

The prepared NEs had a milky-white appearance and were stable at 25 °C for at least 30 days. The average size of the nanodroplets measured by DLS was in the range of 150-250 nm, depending on the content of the oil phase and surfactants. TEM analysis confirmed the spherical shape of oil droplets and the size measured by DLS (Fig. 2). Depending on the content of the oil phase and surfactant, LE content of 0.25% was achieved immediately after the preparation of NE, but it decreased significantly 7 days after the preparation.

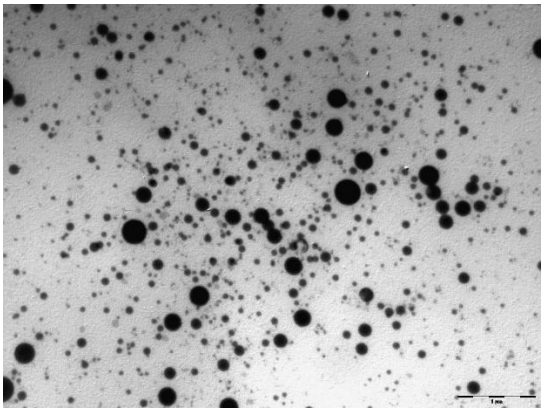

Fig. 2. TEM image of LE-loaded NE (NE composition (*w*/*w*): LE 0.2%, castor oil 20%, Capryol™ 90 2.5%, Kolliphor® EL 5%, glycerol 2.5%, Soluplus® 1%, DDW ad 100%).

Conclusion

LE, a poorly water- and oil-soluble drug, was successfully incorporated into NE composed of castor oil, Capryol™ 90, Kolliphor® 90 and Soluplus®. An approach using systematic design of experiments is needed to bring to light a formulation with suitable physicochemical properties, appropriate LE content and stability during storage.

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