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Short communication

Loteprednol etabonate-loaded nanoemulsions for the treatment of dry eye disease: quality by design approach

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Introduction

Oil-in-water nanoemulsion (NE) is an effective drug delivery system for treating the signs and symptoms of dry eye disease (DED). It enables the delivery of poorly soluble drugs and simultaneous replenishment of the compromised tear film (Singh et al., 2020). The most recent drug approved for the treatment of DED is EYSUVIS®, a nanosuspension with 0.25% loteprednol etabonate (LE). LE is a novel soft corticosteroid that has certain advantages over other corticosteroids for ophthalmic use because it has a lower risk of increasing intraocular pressure (Kersey and Broadway, 2005). However, due to its poor oil solubility, it is difficult to incorporate LE into a nanoemulsion in sufficient quantity, so there is no approved NE with LE on the market yet. Considering the advantages of NE as a vehicle and the advantages of LE as a drug, the aim of this work was to develop a functional nanoemulsion with LE for the treatment of DED. Therefore, the quality-by-design (QbD) concept was applied to optimize the formulation and process parameters in terms of physicochemical properties of the nanoemulsions, including drug content, nanodroplet size, polydispersity index, and zeta potential.

Materials and methods

LE was kindly provided by JGL Ltd. Experimental design was performed using JMP® 14.0 statistical software (SAS Institute Inc ©, 1989–2007).

The oil phase was prepared by mixing LE, castor oil (Fagron), Capryol™ 90 (Gattefossé) and Kolliphor® EL (BASF). The water phase consisted of double distilled water (DDW) and Soluplus® (BASF). Both phases were heated (if necessary) and then mixed at 15000 rpm with Ultra-Turrax® (IKA-Werke GmbH & Company). For the preparation of nanoemulsions, the coarse emulsions were subjected to a microfluidizer LM20 with Y-type interaction chamber (Microfluidics). The average nanodroplet size and polydispersity index were determined at 25 °C by dynamic light scattering using a Zetasizer Ultra (Malvern Panalytical Ltd). The zeta potential of the nanodroplets was determined at 25 °C by electrophoretic light scattering using a Zetasizer Ultra. Quantitative determination of LE was performed by high-performance liquid chromatography using an Agilent Infinity II 1260 (Agilent Technologies) with the XBridge C8 column (3.5 µm, 4.6 mm×100 mm, Waters Corporation). Drug loading was determined after filtration of NEs with a 0.45 µm polyethersulfone filter to ensure that any precipitated LE was removed.

Results and discussion

The nanoemulsions were prepared according to the chosen design of experiments. Table 1. shows the upper and lower limits of the formulation and process parameters, i.e., the design space from which the parameter values were selected. Fig. 1 shows that the nanodroplet size was appropriate for ophthalmic delivery (with the exception of formulation 11) and remained unchanged during storage at 25 °C for 30 days, which is a prerequisite for a stable nanoemulsion. Although in some formulations the drug

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content reached 0.20% immediately after NE preparation, the maximal drug content retained during 30-day storage was found to be that of 0.15% (Fig. 2).

Table 1. Formulation and process parameters set by experimental design. (A – LE (%), B - castor oil (%), C - Capryol™ 90 (%), D - Kolliphor® EL (%), E - Soluplus® (%), F - mixing temperature of the oil and water phases (°C), G - cycles passed through the interaction chamber, H - pump pressure of the microfluidizer (bar)

	Formulation parameters					Process parameters		
	A	**B**	**C**	**D**	**E**	**F**	**G**	**H**
1	0.1	20	3	5	0	25	10	2000
2	0.1	20	1	1	0.5	80	10	1000
3	0.15	10	1	1	0	25	5	1000
4	0.15	15	3	3	0.5	52.5	7.5	1500
5	0.2	20	1	5	1	25	5	1500
6	0.2	20	5	1	1	25	10	1000
7	0.1	10	1	5	0	80	5	2000
8	0.2	10	3	1	1	80	5	1000
9	0.2	10	5	5	0.5	25	5	2000
10	0.2	10	5	5	0	52.5	10	1000
11	0.2	20	5	1	0	80	5	2000
12	0.1	10	1	5	1	25	10	1000
13	0.2	10	1	3	1	80	10	2000
14	0.1	15	5	5	1	80	5	1000
15	0.2	15	1	1	0	25	10	2000
16	0.2	20	1	5	0	80	7.5	1000
17	0.1	10	5	1	1	25	7.5	2000
18	0.1	20	5	3	0	25	5	1000
19	0.1	20	1	1	1	52.5	5	2000
20	0.1	10	5	1	0	80	10	1500
21	0.15	20	5	5	1	80	10	2000

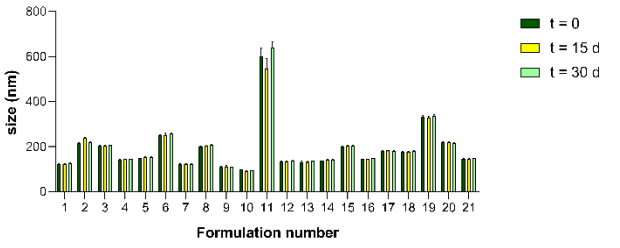

Fig. 1. Average nanodroplet size (n=3), measured at three time points (immediately after preparation, after 15 and 30 days of storage at 25 °C).

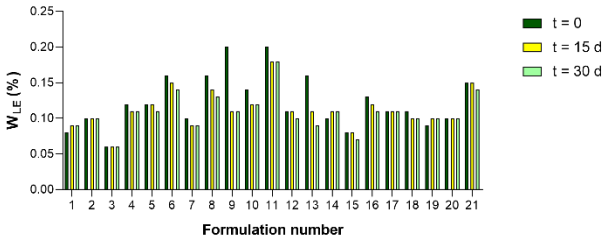

Fig. 2. LE content (%) (n=1), measured at three time points (immediately after preparation, after 15 and 30 days of storage at 25 °C).

Conclusion

The QbD approach enabled rational design of LE-loaded nanoemulsions. Consistent drug loading and droplet size were observed in most formulations, which may be a good indicator of stable NE. In-depth biopharmaceutical characterization will enable the selection of LE-loaded NE with fine-tuned physicochemical and biopharmaceutical properties, a promising candidate for the further development of medicinal product for improved treatment of DED.

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References

Kersey J.P., Broadway D.C., 2005. Corticosteroid-induced glaucoma: a review of the literature. Eye 20:407–416. doi: 10.1038/sj.eye.6701895.

Singh, M., Bharadwaj, S., Lee, K.E., Kang, S.G., 2020. Therapeutic nanoemulsions in ophthalmic drug administration: Concept in formulations and characterization techniques for ocular drug delivery. J. Control. Release 328. doi: 10.1016/j.jconrel.2020.10.025.