Optimisation of multifunctional nanostructured lipid carriers: influence of a range of solid to liquid lipid ratios, preparation methods, and process parameters

Dorsa Golestaneh[1], Muhammad Sarfraz[1], Marcos Mariano[1], Tess Ames[1], Evan Matthews[2], Martina Gooney[3], Laurence Fitzhenry[1]

[1] Ocular Therapeutics Research Group, Pharmaceutical and Molecular Biotechnology Research Centre, Department of Science, South East Technological University, Waterford, Ireland; [2] School of Health Sciences, Department of Sport and Exercise Science, South East Technological University, Waterford, Ireland; [3] School of Health Sciences, Department of Nursing and Health Care, South East Technological University, Waterford, Ireland

Background: Dry eye disease is a chronic and multifactorial disorder characterised by tear film instability, hyperosmolarity, ocular surface inflammation, neurosensory abnormalities, and a loss of tear film homeostasis. Despite available treatments, current therapies are often insufficient and leave patients with unmet needs. The current study explores the fabrication of nanostructured lipid carriers (NLCs) that embed anti-inflammatory and antibacterial ingredients to address the multifactorial nature of dry eye while replenishing tear film layers. This study aims to optimise the solid to liquid lipid (S:L) ratio, preparation method, and processing parameters to develop a multifunctional NLC-based artificial tear formulation.

Methods: Nanostructured lipid carriers were prepared using various S:L ratios. The aqueous phase, including polysorbate 80 (1%) and water, was stirred at 65 °C. Simultaneously, the lipid phase, containing cholesterol: castor oil (S:L) in ratios ranging from 1:10 to 10:1, was dissolved in a 1:1 mixture of ethanol and acetone and stirred at 65 °C until the solvents evaporated. The lipid phase was then added dropwise to the aqueous phase while stirring at 65°C for 30 minutes to make pre-NLC formulations. The probe sonication method (4 minutes, 40% amplitude) was used for the preliminary screening of S:L ratios in the fabrication of NLCs because of its time efficiency. Dynamic light scattering (DLS) was used to identify the most suitable S:L ratio range. This range was further processed using probe sonication and high-pressure homogenization (HPH) at 500–1000 bar, the minimum pressure required for NLCs fabrication. Finally, the optimal method was selected based on DLS results, and processing parameters were optimised accordingly.

Results: Initial screening of S:L ratios revealed the following results: At 10:1 and 5:1 S:L ratios, precipitation occurred immediately and within 2 hours, respectively, due to high solid lipid content. At 1:5 and 1:10 S:L ratios, particle sizes ranged from 500-2000 nm. These four ratios were excluded from further testing. Ratios of 1:3, 3:1, and 1:1 were prepared using both probe sonication and HPH. Switching from probe sonication to HPH reduced particle sizes (from 500–700 nm to 350–450 nm) and polydispersity index (PDI) (from 0.65–0.8 to 0.45–0.55) in the 1:3 and 3:1 S:L ratios. At a 1:1 ratio, particle size remained similar (~300 nm), but HPH improved the PDI by 0.1. Next, the 1:1 ratio as optimal formulation was tested further by using four HPH cycle numbers (3, 6, 9, and 12) at 500–1000 bar. The 3 and 12-cycle samples showed the largest particle sizes and highest PDIs (~400 nm, PDI: 0.56 and ~330 nm, PDI: 0.46, respectively). The 6 and 9-cycle formulations produced the most desirable results (~300 nm, PDI ~0.40). Considering industrial time efficiency, the 6-cycle condition was selected as optimal. This formulation was also tested at higher pressure (1000–1500 bar), which resulted in a larger particle size and higher PDI (370 nm, PDI: 0.52). Zeta potential remained constant across all S:L ratios and methods (−16 to −18 mV).

Conclusions: Among the various formulations, the 1:1 ratio was identified as the optimal S:L ratio. The HPH method was selected over the probe sonication technique for its ability to produce smaller particle sizes with lower PDIs. Ultimately, the 6-cycle and lower pressure (500–1000 bar) were chosen as the optimal process parameters for the HPH method.