Microemulsions Containing Naratriptan: Development, Characterization, and Permeation Study for Migraine Treatment.

Ana Claudia Sueiro[1,2], James C Birchall[2], Priscila Gava Mazzola[1].

[1]Faculty of Pharmaceutical Sciences, University of Campinas (UNICAMP), Campinas, São Paulo, Brazil.

[2]School of Pharmacy and Pharmaceutical Sciences, College of Biomedical and Life Sciences, Cardiff University, Cardiff, United Kingdom.

Background: Migraine, affecting approximately 15% of the global population, is recognized as a disabling condition. Conventional treatments, such as oral tablets, face limitations in efficacy, particularly in patients experiencing nausea and vomiting. Naratriptan, a selective serotonin agonist used in migraine treatment, is typically administered orally, but its effectiveness may be compromised in these cases. Therefore, transdermal administration via microemulsions emerges as a promising alternative to enhance treatment efficacy and improve patient adherence. This study aims to develop a transdermal microemulsions containing naratriptan and evaluate their physicochemical characteristics, including microstructure analysis using dynamic light scattering (DLS), encapsulation efficiency (EE), permeation studies and cytotoxicity assays.

Methods: The microemulsions (F2N and F4N) were prepared using the low-energy temperature inversion method, incorporating Naratriptan as the active ingredient, along with Capryol PGMC, Kolliphor RH 40, Transcutol P and water. Physicochemical properties of the formulation were assessed by the Hydrodynamic Size (DH), Polydispersity Index (PDI), and Zeta Potential (ZP) analysis of the prepared microstructures (Zetasizer Nano ZS). The ultrafiltration method was used to determine the encapsulation efficiency of prepared formulations. In vitro permeation assays were performed using vertical Franz diffusion cells. The antiproliferative activity of both loaded (F2N, F4N) and unloaded (F2, F4) formulations, Naratriptan in solution (N), and the Doxorubicin (positive control) was investigated using an immortalized keratinocyte cell line (HaCat).

Results: All microemulsions presented a translucent gel appearance without phase separation, indicating stability of the formulation. In relation to DH, the average size of the microstructures was approximately 18 nm, the polydispersity index (PDI) was less than 0.2 and the Zeta potential (ZP) was close to neutrality at approximately 0.32 mV. The encapsulation efficiency (EE) was 72.5% for F2N and 73.7% for F4N. The formulations showed a permeation of approximately 20% within 24h, throughout the variety of membranes tested. In cytotoxicity tests, the drug proved to be safe, and the formulations exhibited antiproliferative activity affecting the cell line (HaCat) investigated.

Conclusions: Microemulsions containing Naratriptan were developed, exhibiting physicochemical characteristics such as DH, PDI, and encapsulation efficiency suitable for transdermal delivery. However, the formulations encountered significant challenges, including low in vitro drug permeation and cytotoxicity observed in HaCat cell cultures. These findings underscore the necessity for formulation optimization to enhance drug permeation while ensuring safety and efficacy.