Thermo-responsive *In Situ* Gels Loaded with Prednisolone Niosomal Nanoparticles for the Treatment of Skin Inflammation

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Abstract

Prednisolone (PRD) is known for its anti-inflammatory effects on the skin. PRD was loaded into non-PEGylated and PEGylated niosomes to develop a dermal delivery system while maintaining vesicles' integrity and avoiding their aggregation. All niosomes were then entrapped in thermo-responsive *in situ* gels to enhance dermal application. The thin-film technique was used to prepare niosomes with diameters of 354.3 ± 1.9nm, polydispersity index (PDI) of 0.3 ± 0.0, and ζ-potential of -19.4 ± 1.0mV. The physical characteristics (particle diameter, PDI, and ζ-potential) of niosomes were enhanced by PEGylation to 314.9 ± 4.2 nm, 0.1 ± 0.0, and -34.6 ± 2.2mV, respectively. PEGylated niosomes exhibited higher entrapment efficiency (EE%) of 93.4 ± 2.2% and drug loading (DL%) of 15.8 ± 0.4% compared to non-PEGylated niosomes (EE%: 85.2 ± 1.3%, DL%: 12.2 ± 1.5%). In addition, PEGylated niosomes demonstrated a sustained drug release profile for 6 h, while the non-PEGylated niosomes attained a complete drug release after

4 h. The rheological analysis exhibited a pseudoplastic flow behavior. Biological assessment for safety and efficacy proved the biocompatibility and suitability of PRD niosomes and their corresponding gels against human gingival fibroblasts. Moreover, a significant qualitative and quantitative reduction in rat paw inflammation was induced by formalin induction ($p < 0.0001$). Stability assessments and physicochemical and rheological characterization were carried out to assess the effect of PEGylation on niosomes. Compared to the non-PEGylated formulation, the stability investigations showed that PEGylated niosomes loaded *in situ* gel had a superior behavior regarding dynamic light scattering. The rheological characteristics of the gel did not significantly change during the three-month stability study. With high loading capacity, sustained release, and stable vesicles, the gel containing PEGylated niosomes has intriguing potential for dermal delivery.

Keywords: Dermal delivery, *In situ* gel, Stability, PEGylated niosomes, Prednisolone