Nanostructured Lipid Carriers: a new approach for Psoriasis topical therapy

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Abstract

Psoriasis is a common chronic, autoimmune and systemic inflammatory disease of the skin and joints and occurs in 2–3% of the world population. It is affected by genetic and environmental factors and is associated with co-morbidities as loss of quality of life, cardiovascular disease, among others [1–3].
Current therapeutic strategies for the treatment of psoriasis generally employ oral and parenteral administration routes for methotrexate (MTX) as it inhibits epidermal cell proliferation and has anti-inflammatory action at low doses [4]. It should be noted that there is a large number of adverse effects (such as liver toxicity, gastrointestinal side-effects, including nausea, vomiting, diarrhea and stomatitis) associated to systemic administration of MTX.
In the scope of the psoriasis therapy, nano-dermatology and the development of nanoparticles for dermatological applications is without a doubt an area of increasing magnitude and interest. Drug carriers can provide a sustained drug release over a prolonged period of time, and shields it from degradation. Hence, therapeutic effect can be maximized and toxicological concerns related to drug overdose and clearance can be minimized. Additionally, patient compliance is higher, as these therapeutical strategies enable a reduction in the frequency of drug administration.
The aim of the present work was to develop and assess the potential of nanostructured lipid carriers (NLCs) loaded with MTX as a new approach for topical therapy of psoriasis. MTX-loaded NLCs were optimized using a factorial design approach. Preliminary screening drug/lipid solubility, allowed us to select Witepsol E85 as the solid lipid and Miglyol1 812 as liquid lipid for the NLC loaded with MTX. Then, a 3-level, 3-factor Box-Behnken design was conducted and validated by ANOVA analysis; the correspondence between the predicted values and those measured experimentally confirmed the robustness of the design. Properties of optimized MTX-loaded NLCs such as morphology, size, zeta potential, entrapment efficiency, storage stability, *in vitro* drug release and cytotoxicity were investigated. NLCs loaded with MTX exhibited spherical shape (mean diameter of 252 nm), a polydispersity of 0.06, zeta potential of -14 mV and an entrapment efficiency of 87%. *In vitro* release studies revealed a fast initial release followed by a prolonged release of MTX from the NLC up to 24 h. The release kinetics of the optimized NLC best fitted the Peppas–Korsmeyer model for physiological and inflammatory environments and the Hixson–Crowell model for skin simulated conditions.
No toxicity was observed in fibroblasts and human keratinocytes cell lines. Cellular uptake of NLCs by keratinocytes was time and energy dependent. Endocytosis' process was mediated by clathrin and macropinocytosis. Upon internalization, 10% of the NLCs are discharge by exocytosis and/or trancytosis mechanisms, which demonstrate the good viability of the carrier for skin drug delivery (major percentage of the drug remains within the cell). *In vitro* skin penetration study demonstrated that MTX-loaded NLCs had higher skin penetration when compared to free MTX, suggesting a significant role of drug-nanocarriers on topical administration. MTX-loaded NLC provided drug fluxes of 1.8 mg/cm^2/h, higher ($P < 0.001$) than with the free drug (control, 0.7 mg/cm^2/h).
The results reveal the potential of NLCs for the delivery of MTX to topical therapy of psoriasis.

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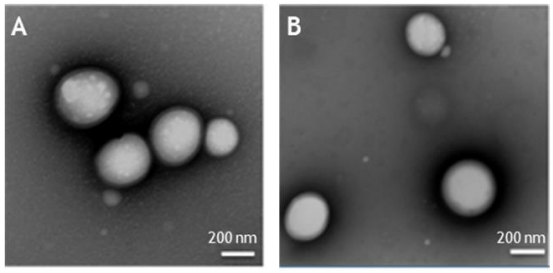
Figures



Transmission electron microscopy images of NLCs (A) and MTX-loaded NLCs (B). Amplification of 80,000 x.