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Self-assembled mPEG-hexPLA polymeric nanocarriers for the targeted cutaneous delivery of imiquimod.

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Abstract

mPEG-hexPLA micelles have shown their ability to improve delivery and cutaneous bioavailability of a wide range of poorly water soluble and lipophilic molecules. Although poorly water soluble, imiquimod (IMQ) is only moderately lipophilic and it was decided to investigate whether mPEG-hexPLA polymeric micelles could be used as a drug delivery system for this "less than ideal" candidate for encapsulation. Nanosized IMQ micelles ($d_n = 27$ nm) were formulated and characterized. Moreover, the innovative use of size exclusion chromatography allowed the exact drug localization inside the formulation to be determined; it appeared that the use of acetic acid to solubilize IMQ led to a higher IMQ content outside the micelle than inside. IMQ micelles (0.05%) were formulated in a gel using carboxymethyl cellulose (CMC). In vitro application of this formulation to porcine and human skin led to promising delivery results. IMQ deposition in human skin was 1.4 ± 0.4 µg/cm^2 while transdermal permeation was only 79 ± 19 ng/cm^2: the formulation displayed >17-fold selectivity for cutaneous deposition over transdermal permeation. The optimized 0.05% gel significantly outperformed Aldara® cream (containing 5% IMQ) formulation in terms of delivery efficiency to human skin (2.85 ± 0.74% vs 0.04 ± 0.01%). Despite IMQ being only partially incorporated in the micelles, the biodistribution profile showed that the optimized 0.05% gel delivered as much as 518.2 ± 173.3 ng/cm^2 (1.04 ± 0.35% of the applied dose) to the viable epidermis and 236.4 ± 88.2 ng/cm^2 (0.47 ± 0.18% of the applied dose) to the upper dermis where the target antigen presenting cells reside. In contrast, for Aldara® cream, the delivery efficiencies in those layers were less than 0.02%. The optimal 0.05% gel thus allowed therapeutically relevant drug levels to be achieved in target tissues despite a 100-fold dose reduction.