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Solid lipid nanoparticles: a study of passive and iontophoretic permeation mechanisms through skin.

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Introduction: Solid lipid nanoparticles (SLN) are drug delivery systems developed in the nineties to be an alternative to other colloidal systems like liposomes, emulsions and polymeric nanoparticles. Its use as a drug carrier for topical drug application has been vastly studied for the last years. SLN showed some promising characteristics for this use as the possibility of drug control release, small size, good stability and capacity of protection of the drug encapsulated, besides being less toxic than other drug delivery systems. Meanwhile, despite the large number of studies, there are almost no researches showing how SLN could act to improve drug penetration through the skin. In general, improved drug skin penetration is usually associated with increased hydration of stratum corneum (SC) caused by an adhesive layer (formed by SLN) occluding the skin surface. Furthermore, although intact particles are not normally considered to permeate the horny layer, some studies showed that the follicular pathway may be relevant to drug skin penetration. It is known that the follicular route is the main via of drug penetration when iontophoresis, a physical method that uses a weak electric current to increase skin drugs penetration, is applied. Therefore, iontophoresis of SLN may increase the penetration of intact SLN, increasing the encapsulated drug release inside the skin. SLN marked with hydrophilic and hydrophobic dyes at once may help to elucidate SLN skin penetration in the presence and absence of iontophoresis. **Objective:** To study the influence of iontophoresis in the skin penetration pathway of fluorescent SLN. **Methods:** Fluorescent SLN were prepared and characterized using doxorubicin (DOX), as a hydrophilic fluorescent drug model, and BODIPY FSE-8 (BOD), as a SLN lipophilic fluorescent marker. Thereafter, passive and iontophoretic permeation studies were performed using modified "Franz" diffusion cells and pig skin as model membrane. Fluorescent SLN and a solution containing free DOX, BOD and non-fluorescent surfactants, at the same concentration and pH of the SLN dispersion, were applied at the donor compartment of the diffusion cells for 1 h passively and under influence of iontophoresis (0.5 mA/cm^2). After, the skin was removed, washed and used to prepare longitudinal and transversal slices to be analyzed by confocal laser scanning microscopy (CLSM). **Results:** Both passive and iontophoretic permeation of DOX and BOD solution and SLN induced an elevated fluorescence into the skin furrows. This fluorescence could be noted around corneocytes as well but in a minor degree. Besides that, it was observed that SLN permeation lead to a more heterogeneous fluorescence at the SC than DOX and BOD solution did, especially in regions near hair follicles. Iontophoresis increased the fluorescence of all skin samples, leading yet to the formation of some fluorescent aggregates right below the hair follicles, in the viable epidermis. Moreover, skin samples exposed to the iontophoresis of SLN presented some regions of punctual and strong fluorescence, indicating regions of localized transport. **Conclusion:** Our studies indicated that SLN changed the distribution of DOX and BOD fluorescence over and into the skin. Iontophoresis increased the model dyes permeation heterogeneously for both solution and SLN. Furthermore, iontophoresis of SLN seems to have improved dyes permeation in deep skin layers, especially in regions near hair follicles.

Keywords: SLN, Doxorubicin, BODIPY

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