TFC034

In vitro skin penetration studies of Doxorubicin from solid lipid nanoparticles dispersed in a nanogel

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Introduction: Doxorubicin (DOX) is an antineoplastic agent widely used in solid tumors treatment. However, when topically applied, DOX cannot reach deep layers of the epidermis, where skin tumors are commonly located. It is because DOX strongly interacts with negatively charged lipids of the stratum corneum (SC) (Taveira et al., 2011), the outside skin layer. DOX physicochemical characteristics can be cloaked by encapsulating it in a nanoparticulate delivery system, likely decreasing this SC interaction and favoring DOX penetration through the SC until the tumor site. Solid lipid nanoparticles (SLN) are a new generation of nanoparticles formed by lipids that are solid at room and body temperature. They can protect the drug against degradation and may favor its delivery to deep skin layers. However, SLN dispersions have a low viscosity, making difficult its topical administration. Their incorporation in hydrophilic polymers can facilitate SLN administration as well as increase the retention time of the formulation on the skin. **Objective:** to evaluate skin penetration of DOX encapsulated in SLN dispersed in a gel (SLN-DOX nanogel). **Methods:** SLN, consisting of stearic acid/CTAB:monoolein (1:2)/water (40/20/40), were prepared by the microemulsion method. DOX was added to the oil phase (8.0 wt% of the stearic acid concentration) during the microemulsification step. SLN dispersion (DOX-SLN) obtained was incorporated into a poloxamer 407 gel, forming the SLN-DOX nanogel. Particle size, polydispersity index (PdI) and zeta potential of SLN incorporated in the gel were determined using a zetasizer Nano ZS 90. Penetration studies were performed using "Franz" diffusion cells and dermatomed pig skin (700 □m) as the membrane. The donor compartment was filled with 300 µL of DOX-SLN nanogel or DOX free dispersed in the gel (DOX-gel), both of them containing 200 µg of DOX. The receiver compartment was composed of isotonic Hepes buffer pH 7.4 at 25 °C, stirred at 300 rpm for 24 h. After this period, the amount of DOX present in the SC, viable epidermis (skin without the SC) and receptor solution was analyzed by HPLC after DOX extraction with methanol:water (1:1) solution. **Results:** Mean particle size, PdI and zeta potential of SLN-DOX incorporated in the gel was 196.75 (± 40.37) nm, 0.20 (± 0.04) and +15.1 (± 3.8) mV, respectively. Skin penetration studies showed that, after administration of DOX-gel, a large amount of DOX was retained in the SC. In this case, the drug was not detected in the viable epidermis and in the receiver compartment. On the other hand, the administration of the DOX-SLN nanogel decreased the amount of DOX found in the SC but significantly increased the amount of DOX found in the viable epidermis and dermis. **Conclusion:** The obtained semi-solid DOX-SLN nanogel showed to be composed of nanoparticles with mean particle size, PdI and zeta potential suitable for topical application. The encapsulation of DOX in SLN increased DOX penetration to deep skin layers probably due to a decrease in drug interaction with the SC.

Keywords: solid lipid nanoparticles, penetration studies, doxorubicin, nano gel.
Financial support: FAPESP and CNPq.