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IN VITRO RELEASE AND *EX VIVO* SKIN PERMEATION OF A NANOSTRUCTURED FORMULATION FOR TOPICAL DELIVERY OF CAPSAICINOIDS

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Introduction: Formulations based on the association of nanocarriers and hydrogels have been deeply studied in the past years[1,2,3]. Such systems can provide a controlled release of the active substances, due to both the hydrogel network and the reservoir property of the nanocarriers[4], besides being capable of an appropriate delivery of the substances to the active sites, such as the skin. In this work it is proposed the use of chitosan as the hydrogel-forming biopolymer[5] and Eudragit RS 100® as the biocompatible polymeric wall of capsaicinoids-loaded nanocapsules for developing an innovative formulation for topical delivery. The capsaicinoids (capsaicin and dihydrocapsaicin) are the substances responsible for the hot and pungent taste of chilly peppers and have been applied as analgesic for the treatment of chronic pain in several diseases[6].
Objective: The aim of this work was to characterize a chitosan hydrogel containing capsaicinoids-loaded nanocaspules by means of the determination of the *in vitro* release and *ex vivo* skin permeation, as well as to relate the results obtained in both studies.
Materials and Methods: The hydrogel containing nanocapsules (n=3) was obtained by the incorporation of a nanocapsule aqueous suspension prepared by the interfacial deposition of preformed polymer method[7] in a chitosan hydrogel (chitosan 3.5% and lactic acid 1.5%). The formulation was characterized in terms of capsaicinoids content (HPLC-UV), particle size analysis (laser diffraction), morphology [transmission electron microscopy (TEM)], pH (potentiometry), *in vitro* release (dialyses bags method, quantification by HPLC-UV) and *ex vivo* skin permeation (pig skin in Franz diffusion cells, quantification by HPLC-UV). For the *in vitro* release and skin permeation studies, the control, representing the free drug, was a chitosan hydrogel containing a hydroalcoholic solution (30% ethanol) of capsaicinoids.
Results and Discussion: The hydrogels containing capsaicinoids-loaded nanocapsules presented capsaicin and dihydrocapsaicin content close to 95%, considering 0,161 mg/g and 0,183 mg/g as 100%, and pH of 4.42 ± 0.21, which is acid, due to the presence of lactic acid, but suitable for topical application. It was possible to detect the nanoparticles in the hydrogel network by TEM and by laser diffraction, after dilution of the hydrogel. Considering the *in vitro* release, it was observed a more prolonged release of the capsaicinoids due to the nanoencapsulation. The skin permeation study showed that, for the nanostructured formulation, after 8h of permeation, the capsaicinoids amount that was retained on the skin surface, without permeation through the skin layers, remained the same, probably due to the fact that capsaicin and dihydrocapsaicin were not yet significantly released from the nanocapsules. For the chitosan hydrogel containing free capsaicinoids (control), it was observed that, after 8h, the amount retained on the skin surface was lower than after 4 and 2h, probably because the drugs were not encapsulated and they could diffuse through the hydrogel and permeate through the skin layers.
Conclusions: The proposed formulation presented suitable properties for topical delivery. The nanoencapsulation of capsaicinoids promoted a controlled release from the vehicle, which was verified by the *in vitro* experiment and confirmed by the skin permeation test. So, it was possible to relate the data observed on the *in vitro* release and the *ex vivo* skin permeation.

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