Nanovectors to enhance the accumulation of vitamin K1 into the skin.

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Purpose: Vitamin K1 (VK1), a very lipophilic and photosensitive molecule contained in some vegetables, have been successfully used to prevent acneiform reactions affecting the skin in patients receiving cetuximab for the treatment of metastatic colorectal cancer. However, VK1 is present on the market in fat semisolid formulations (es. Rencoval®, VigorSkinK1® and VigorSkinK1 Plus®). The purpose of this study was therefore to evaluate the possibility to use an alternative formulation for the administration of vitamin K1 on the skin, overcoming the drawbacks associated with the use, for more administration in a day, of fatty formulations.

Methods: Liposomes (Lipo) were obtained according to the ethanol injection method (Batzri *et al*. 2003) in order to use a preparation method cheaper and easy to perform. Transfersomes (Trans) were prepared by the thin lipid film hydration method as previously reported in our study (Scognamiglio et al., 2012) instead Ethosomes formulations, were prepared according to the method described by Touitou *et al*. (2000), with modifications. All the formulations were characterized in terms of size, VK1 encapsulation, physical stability during storage. Moreover, the deformability properties of the vesicles and the suitability to be administered on the skin by nebulization were also tested. The possible effects of the treatment with the lipidic vesicles on the organization of the major constituents of the stratum corneum was assessed by attenuated total reflection Fourier transform infrared (ATR-FTIR) spectroscopy. Finally, the ability of different vesicles to allow VK1 accumulation and permeation of VK1 into and through the skin was investigated in Franz diffusion cells and confocal laser scanner microscopy (CLSM) experiments.

Results: All these carriers were very stable for at least 6 months and any significant alteration of vesicles size, as well as of VK1 encapsulation, was observed following vesicles aerosolization, suggesting the possibility to administer these formulations on the skin by nebulization. Transfersomes showed the highest deformability (DI) and also on the case of ethosomes DI was higher than liposomes one. The ATR-FTIR spectra seemed in agreement with the penetration of intact vesicles within the stratum corneum, which enrich the lipidic components and increase the order of the structure. CLSM studies, confirmed that lipid components of the vesicles remain mainly located in the outer layers of the skin, although, in the case of ethosomes and transfersomes a more deep penetration was observed. Finally, in ex-vivo experiments, the use of transfersomes and ethosomes, especially in the nebulized form, enhanced the accumulation of VK1 into the skin.

Conclusions: In conclusion, transfersomes probably represented the formulation that, if administered in form of aerosol, could offer a good compromise between a high penetration into the skin and a limited permeation through it. This transfersomes-based formulation could be proposed to administer VK1 on the skin, by nebulization, as approach alternative to the use of a fat ointment.

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