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Nanocrystals: development of a ready-to-use formulation for dermal application

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Introduction: Many of the pharmaceutical actives possess poor water solubility, which impairs their dermal application. In this case, the use of nanocrystals is a viable approach for improved drug delivery. Previous studies suggest that the penetration efficacy depends on nanocrystal size in relation to the right penetration enhancers [1]. Based on the acquired knowledge, the aim of this study was to find a suitable vehicle for nanocrystals in order to develop a ready-to-use formulation with optimal penetration properties.

Materials and Methods: Hesperetin was used as a model drug. It is a natural flavonoid with high anti-oxidant activity, poor water solubility and lipophilic character. Nanocrystals were produced by using high pressure homogenization [2]. The bulk suspension and the nanosuspension contained 5% (w/w) active and 1% (w/w) surfactant, respectively. In the first step of the study the penetration efficacy of hesperetin from nanocrystals and the bulk material was investigated and compared. Then, nanocrystals and the bulk material were incorporated into various commercially available dermal vehicles with different properties (hydrogel, oleogel, cream, ointment with absorption base) to determine the impact of the composition of the vehicle on the penetration efficacy of hesperetin. The study was performed with pig´s ear skin, the method of classical tape stripping was used to determine the dermal penetration of the active.

Results and Discussion: Nanonization led to an enhanced dermal penetration of the poorly water soluble active hesperetin. A 2-fold increase in the penetration efficacy was achieved by using the nanocrystals instead of the bulk material. Additionally, active derived from nanocrystals was found in deeper skin layers. Thus, the nanonization is an excellent possibility to enhance the dermal penetration of poorly soluble actives.

However, liquid formulations might not be the most convenient product for a patient. Thus, in the next step, a screening for the optimal vehicle for nanocrystals was carried out. The nanosuspension was incorporated in vehicles commonly used in prescriptions and the dermal penetration of hesperetin was determined. Results revealed that each vehicle tested led to a reduction in the penetration efficacy. Data indicate that the average penetration rate of hesperetin from all the formulations is about 2%, i.e. the total amount of penetrated drug is 3-fold lower by formulating the nanocrystals in vehicles compared to the aqueous nanosuspension. Furthermore, no pronounced differences in the penetration efficacy were observed by comparison of the different vehicles. However, different explanations and theories can be considered. The penetration

of hesperetin into the skin is regarded to be a passive diffusion process governed by Fick's first law of diffusion [3]. It postulates that the diffusion coefficient depends i.e. on the viscosity of the medium - the higher the viscosity, the slower is the penetration. All the vehicles had a higher viscosity than the aqueous nanosuspension, which consequently led to a decrease in the penetration efficacy of hesperetin. In addition, another parameter should be considered: if nanocrystals are applied to the skin as aqueous suspension, much more nanocrystals get in direct contact with the skin surface, whereas less nanocrystals will reach the skin surface when formulated in a vehicle [3]. The dissolution of the active from nanocrystals occurs on the skin surface. Thus, the more nanocrystals come into contact with the skin surface, the more drug is dissolved and can penetrate into the skin. In parallel, the penetration efficacy of hesperetin bulk material from the different vehicles was compared. The amount of penetrated active was lower when bulk material was used instead of nanocrystals. And also, in this study it was found, that the theory from above is valid, i.e. the formulation of bulk material into semi-solid vehicles decreased the dermal penetration efficacy of hesperetin when compared to the liquid, aqueous bulk suspension.

Conclusion: Nanonization, when compared to the bulk material, led to a 2-fold increase of the amount of penetrated active. Incorporation of nanocrystals into different semi-solid vehicles led to a reduction of the penetration efficacy in comparison to the aqueous suspensions. Hence, to date, the ideal formulation for nanocrystals seems to be an aqueous suspension.

References:

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