Posterabstracts 2018

How to improve dermal penetration of poorly soluble actives?

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Introduction: Human skin is an important drug target, but not every drug is able to overcome the intact skin barrier. Various factors can hamper the successful topically application of pharmaceutical and cosmeceutical actives, for example their poor solubility due to the lipophilic character and associated poor bioavailability. Formulating poorly soluble drugs as nanocrystals (smartCrystals®) is an established strategy to increase their dermal availability [1]. A reduction in size leads to an increase in solubility and increased bioavailability [2]. To further promote the penetration efficacy of dermally applied drugs, penetration enhancers can be used. However, to date no systematic study has been conducted to demonstrate the influence of the size of nanocrystals and of penetration enhancers on the penetration efficacy of poorly soluble actives.

Material and Methods: The plant active hesperetin was used as model drug. Nanocrystals of different sizes (200 nm, 400 nm, 600 nm, 800 nm) were produced by high pressure homogenization, bead milling and combinations of these methods [3]. Skin penetration was studied by tape stripping: the formulation was applied on the skin of fresh porcine ears and after 30 min penetration time the tape stripping procedure was performed. Stratum corneum was removed layer by layer using 30 tape strips. The concentration of hesperetin on each tape was determined by using HPLC analysis. In the next step of this study the influence of penetration enhancers on the penetration efficacy was determined. Different actives were used to increase the penetration of hesperetin – urea (5%, 10% and 15% solution) as a moisturizer and hydrophilic active and olive oil as lipophilic excipient. The penetration enhancer was applied to the skin prior to the hesperetin nanosuspension. Skin bio-physical parameters, e.g. transepidermal water loss (TEWL), pH and skin hydration were also determined.

Results and Discussion: Results proved that both, the size of nanocrystals and the type of the penetration enhancer, have a tremendous influence on the penetration efficacy of the active. Penetration studies showed an increase in the penetration efficacy with decreasing size of nanocrystals, i.e. the highest amount of hesperetin penetrated into the stratum corneum by using nanocrystals with a size of about 200 nm. Results for the penetration enhancers were unexpected. In general urea is used as moisturizer and is known to enhance the penetration of many actives due to the improved hydration of the stratum corneum. However, in this study, instead of promoting the penetration of hesperetin, data show that urea even impairs the penetration efficacy of hesperetin. Results can be explained by the lipophilic nature of the model drug and by the theory of Neubert et al. [4], who suggested that urea can only enhance skin penetration for polar actives via improving the polar route of penetration. In contrast, olive oil – a lipophilic excipient - promoted the penetration of hesperetin, however only to a limited extent, when compared to the smartCrystals® in pure water. TEWL and skin hydration measurements confirmed

this theory.

Conclusion: Nanocrystals improve passive dermal penetration of poorly soluble actives in a size dependent manner - for effective dermal drug delivery small sized nanocrystals, i.e. sizes of about 200 nm should be preferred. Urea did not enhance the penetration efficacy of the lipophilic active hesperetin from nanocrystals. To further improve the dermal penetration of nanocrystals consisting of lipophilic actives, excipients and vehicles that improve the nonpolar penetration pathway, e.g. oils, should be used.

References:

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