Nanoparticulate Delivery to the Skin by exploiting Passive Physical Principles

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ABSTRACT SUMMARY
Increasing dermal penetration/permeation is still a challenge for many cosmetic actives and drugs. An overview is presented to exploit physical principles for delivery improvement, e.g. ranging from simple occlusion to generated supersaturation effects. The principles are exploited in combination with dermal nanocarriers. In contrast to chemical enhancers, these principles have no/little regulatory hurdles.

INTRODUCTION
Nanoparticulate delivery to the skin is very limited when it is based on penetration/permeation of the intact carrier itself into/through the skin. Some exceptions are transfersomes by G. Cevc or ultrasmall nanoparticles << 50 nm. More successful is the exploitation of physical conditions generated passively by the application of nanoparticles to the skin. Creating a certain physical condition, e.g. occlusion, supersaturation increased concentration gradients, leads to penetration due to physical principles, and physics is reproducible (= reliable). Different approaches are reviewed, mainly focusing on the newly developed delivery systems solid lipid nanoparticles (SLN), nano lipid carriers (NLC) and nanocrystals (trade names: NanoCrystal, smartCrystal, ARTCrystal). However, many of the principles can also be applied to other nanocarriers, e.g. liposomes.

RESULTS AND DISCUSSION
The main passive mechanisms to enhance penetration are:

Occlusion: Occlusion e.g. generated by covering the skin with plastic foils/use of patches is a very old principle. However, the plastic foils are uncomfortable. Therefore the elegant approach is to generate an “invisible patch” by adsorbing a dense occlusive (mono)layer of nanoparticles such as SLN or NLC (1). The extend of occlusion can be quantified by measuring an occlusion factor.

Controlled interaction with skin lipids: The structure of the lipids of the stratum corneum affects penetration, thus modulating it can enhance penetration. Most molecular penetration enhances are not regulatorily accepted, therefore they cannot be used in dermal products. A much smarter approach is affecting the skin lipid structure by application of drug-loaded lipid nanoparticles (SLN, NLC). Their excipients are well tolerated and accepted. For the corticoid prednicarbate different skin penetrations and targeting to certain layers could be shown by changing the lipid particle matrix composition of SLN (2). However, the detailed mechanisms are not yet fully understood, i.e. empirical development is required.

Penetration into the stratum corneum: The basic idea is that nanoparticles penetrate into the outer stratum corneum layers, from which they can release their drug load which then can penetrate more efficiently into the skin layers below. Such penetration requires small sizes, it was shown for dendrimer nanoparticles (3).

Elimination of penetration determining API dissolution: Molecules might have a high affinity to the skin, penetrate well but the penetration is limited to a very slow dissolution of the poorly water soluble API in the water phase of a cream. Dissolution can be accelerated by surface enlargement, i.e. using micronized API. Maximum acceleration of dissolution ve-
Locality can be achieved by using nanocrystalline API (4).

**Increased concentration gradient by supersaturation:** This can be generated by increasing the solubility of cosmetic actives or drugs. However, solubilizers (e.g. micelles) are not necessarily effective when the solubilized molecule likes more its micellar environment than the skin environment, thus not penetrating into the skin but staying in the micelle. An approach overlooked for many years is the dermal use of nanocrystals. Nanocrystals possess not only an increased dissolution velocity, but also an increased saturation solubility $Cs$ (4). Increases in $Cs$ are up to 100 fold and more. The lipophilic molecules are dissolved in the unliked hydrophilic water phase which they try to leave, thus accumulating in the more lipophilic skin.

**Generated supersaturation by solubility change:** The principle of dermally applied microemulsions is that they absorb water from the skin, which reduces the solubility of the drug in the microemulsion. A supersaturated system is forming, with increased diffusion pressure into the skin. The same can be generated with a suspension of drug-loaded lipid nanoparticles (= lotion), e.g. as shown for cyclosporine. Application to the skin induces polymorphic transition in the lipid nanoparticles, the drug is expelled from the particle matrix leading to a supersaturated system in the surrounding water phase (5).

**Hair follicle accumulation:** In recent years increasing attention focused on the accumulation of drug-loaded nanocarriers in hair follicles (6). Localisation of nanocarriers in the follicle can be exploited as drug depot in the skin from which the drug diffuses into the surrounding skin cells. Hair follicle targeting is ideal to treat special skin conditions like acne. The drug is delivered exactly where it is needed. The accumulation is size-dependent, nanoparticles in the range of roughly 700-800 nm accumulate more efficiently. To deliver sufficient drug to the follicle, the drug loading of the nanocarrier should be high, because the number of particles actually localizing is limited. Ideal are nanocrystals which consist of pure drug, i.e. have practically a drug loading of 100 %.

**CONCLUSION**

The outlined physical principles are well described in the literature, but some of them are little exploited by now in dermal products. For example, dermal nanocrystals appeared for the first time in cosmetic products in 2007 (JUVENA Switzerland), but not yet in dermal pharma products. More consequent exploitation could lead to many improved dermal products.

The nanocarriers used should be preferentially from class I, at least from classes II and III of the nanotoxicological classification system (NCS) (7) to ensure optimal tolerability.

**REFERENCES**