Abstracts

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Novel delivery system smartPearls – efficient delivery system for antioxidants in anti-pollution

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Since a few years, the hot topic in cosmetics and dermal delivery is anti-pollution formulations to protect skin against pollution in the environment. Anti-pollution products are the new mega trend in cosmetics, promising billions of annual sales [1]. The anti-pollution strategy consists of 2 approaches, a mechanical one (= restoration of the protective lipid barrier on the skin) and a molecular one (delivery of protective molecules, mainly antioxidants). The mechanical barrier can protect e.g. against fine dust but not against damaging radiation (e.g. IR, blue light – photo aging [2]). Radiation penetrates undistorted into skin. Thus, skin damaging can only be neutralized on molecular level. Broadly used therefore are antioxidants [3] like rutin.

However, most of the antioxidants being effective on the molecular level are very poorly soluble in both water and lipophilic media (e.g. oils). A simple but very effective strategy is the increase in their saturation solubility cs. This increases the concentration gradient between the dermal formulation and the skin (cs-cskin), thus, increasing the passive diffusive flux of the antioxidant molecules into the skin. One successful approach was the use of nanocrystals, possessing an increased cs due to their nano-dimensional size.

However, the consumer is getting more and more reluctant towards nano, very pronounced in food products, but the same trend is predicted in cosmetics. Companies do not want to have the addendum <nano> in the INCI list of their products any more. A smart solution is the use of amorphous antioxidants. The cs in the amorphous state is even higher than in the nanocrystalline state. Thus, amorphous is superior to nano. However, the problem by now was the instability of the amorphous state, i.e. re-crystallization in the dermal products – excluding their use. However, the stability problem was elegantly solved by the development of the delivery system smartPearls [4].

The smartPearls are porous silica micrometer particles, no nanoparticles. The active is loaded in the amorphous state inside the pores (2-50 nm pore size). Both large surface area and small diameters of the pores hinders the active to re-crystallize [5]. Rutin smartPearls were already developed with amorphous stability over 1.5 years. However, rutin was loaded in several steps, repeating the addition of rutin DMSO solution and evaporation of DMSO multiply. This process is not favorable for industrial large-scale production. Aim was to optimize the production of rutin

smartPearls, make it industrially friendly – the prerequisite for final market products.

For loading the pores of smartPearls, a novel “immersion evaporation” method was successfully employed. Briefly, the empty silica particles were immersed in ethanolic rutin solution, and subsequently the ethanol was evaporated. Via light microscopy and differential scanning calorimetry (DSC) amorphous state and its long-term preservation were investigated.

Extent of increase in saturation solubility cs was determined compared to standard raw drug powder. Saturation solubility was determined in situ by UV/VIS measurement using Sirius® inform in water (pH 5-6). Tyndall-Rayleigh scattering from silica is automatically corrected by this device, and thus not interfere with the signal from dissolved rutin. By rutin smartPearls, saturation solubility of 129 µg/ml was reached, being almost 3-times higher than the raw drug powder (46 µg/ml). Important is also the enormous increase of the dissolution rate. Dissolved rutin that have penetrated skin will be immediately replaced in the formulation by new rutin molecules dissolving fast from the smartPearls. Thus, a continuous flow into the skin can be maintained.

In summary: smartPearls are a superior delivery system to nanocrystals. With the development of the more industry-friendly production process, the pre-requisite for introduction into market products has been fulfilled – shown exemplarily for rutin. The smartPearls can be used to deliver generally antioxidants within an anti-pollution strategy.

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What to consider when performing the follicular closure technique?

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For overcoming the skin barrier, there are three potential pathways: (1) the intercellular, (2) the transcellular and (3) the follicular penetration pathway. For many substances it is assumed that two or even all penetration routes are used in parallel.

When investigating the follicular penetration it is necessary to have two areas, which are optimally comparable to each other and do only differ that for one of the areas the follicular penetration pathway is excluded. For this purpose, the method of selective follicle closure was developed where a closure material is placed on each follicle [1]. Studies show that skin areas with available follicular pathway are able to deliver the model drug caffeine faster and in higher amount than a comparable area where this pathway is blocked [2].

Since further investigation of this pathway is desired, this study is concerned to verify that by performing the selective follicular closing technique no side effects like penetration enhancing are induced in the treated skin area. It also indicates which parameters in the protocol, like used closure material and application protocol, have an influence on the success or the failure of the follicular closure.

Two different closure materials (standard nail vanish, solvent free nail vanish) and four application protocols (spreading with pipette, careful finger massage, 5 Hz finger massage, 5 Hz automatic massage) were investigated. For all experiments ex vivo porcine ear skin was used. Penetration experiments were performed by covering the whole area of interest with the closure material and applying a caffeine gel. Also areas which were next to the covered area were investigated. Skin layers were separated using tape stripping and the heating technique for dermis and epidermis separation. Samples were homogenized and extracted with PBS by using a standardized extraction protocol. For analyzing the concentration of the extracted caffeine HPLC was used. To investigate the influence of the different application protocols the follicular closing was performed and a fluorescein gel was applied. Cryosections of the follicles were investigated using the confocal laser scanning microscopy. It could be determent whether the follicle got contaminated with the fluorescein gel.

It could be shown that using the standard nail varnish is leading to a secure follicular closure. The

solvent free nail varnish did not prevent substances from penetration. Not only the closure material but also the application protocol has an influence on the follicular closure. Only spreading the formulation with the tip of the pipette or applying a carful finger massage keeps the follicular closure intact. No penetration-enhancing effect attributable to the nail varnish could be observed.

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Stability studies and rheological behavior of liquid poloxamer 407-based formulations containing sertaconazole nitrate

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Introduction

Fungal infections of skin and nails are common, with a lifetime prevalence of 70% for tinea pedis[1] and a prevalence of 10% for onychomycosis[2], increasing with age.
Simultaneous treatment of tinea pedis and onychomycosis is desirable as both often occur at the same time. However, due to the different physicochemical behavior of stratum corneum and human nail plate, no such treatment currently exists.

Semisolid poloxamer 407-based formulations have shown to allow drug permeation into and through both human nail and stratum corneum[3]. Formulations with the model API ciclopirox-olamine could effectively inhibit growth of T. rubrum in an infected nail plate model as well as in an infected stratum corneum model[4] [5].

Based on these results, liquid formulations containing sertaconazole nitrate are being developed as an option for simultaneous treatment of tinea pedis and onychomycosis.
In this study, the physical and chemical stability of the formulations as well as their rheological behavior was examined.

Methods

Various poloxamer 407-based formulations containing 0.3% up to 1% (w/w) sertaconazole nitrate were manufactured and stored for 24 weeks at 30°C. The ingredients were varied within a pseudoternary phase diagram, with a fixed ratio of poloxamer 407 and medium chain triglycerides on one side, a fixed ratio of isopropylic alcohol and propylene glycol on the second side, and water on the third side. Chemical stability of sertaconazole nitrate was determined using an HPLC method. Physical stability was assessed by the following criteria: Macroscopic appearance (consistency, occurrence of creaming), microscopic appearance (crystal formation, size of emulsion droplets). The size of emulsion droplets was determined with a microscope camera and the image processing software ImageJ. Rheological behavior was measured with a rheometer using a cone-plate 60mm 1° geometry in rotational mode. The apparent viscosity was determined at 4°C, 20°C and 32°C.

Results
The API content of all formulations remained above 95% of the declared content after 24 weeks. The formulations showed creaming within one day or up to one week, depending on their viscosities. The homogeneity was restored by manually shaking the vial. No crystallization of API was observed under the microscope. The size of the emulsion droplets increased over time, depending on the specific composition. A high amount of poloxamer 407 + medium chain triglycerides and a low amount of isopropylic alcohol + propylene glycol resulted in smaller droplets after 24 weeks. Most formulations behaved like Newtonian fluids, only those with a high amount of poloxamer 407 showed a yield point at low shear stress. The viscosity ranged between 20mPa*s and 1010mPa*s at 20°C.

Conclusion
Six liquid Poloxamer 407-based formulations with up to 1% sertaconazole nitrate were developed. All six formulations were physically and chemically stable over 24 weeks at 30°C.
A broad range of viscosities was found, with medium to high viscosities offering a compromise between ease of application and adherence at the site of action. Creaming occurred within one week after manufacture and was reversible by shaking the vial. No coalescence of the emulsion droplets was observed, however the droplet size increased to various extent depending on the composition.

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Response of the endogenous antioxidant system after administration with anti-oxidants and moderate stress induction in keratinocytes

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The skin is exposed to many stress factors which, in turn, can promote a shift of the antioxidant (AO) network towards the prooxidative side, supporting the development of various skin disorders. A lot of studies have demonstrated that AOs can counteract the development of oxidative stress, although several studies revealed that the AOs do not always yield positive effects but weakened the metabolism, instead.

The AO status of skin cells (secondary keratinocytes, HaCaT cells) after UV exposure at different wavelengths has been successfully investigated by electron paramagnetic resonance (EPR) spectroscopy. An increased radical formation could be counteracted by a targeted supplementation with the endogenous AO coenzyme Q10, which was loaded into nanocarriers. A physiological concentration of Q10 provides an effective protection against radical formation for the UVA and UVB spectral region, respectively. But the process of supplementation was limited; the cell viability was negatively affected after the AO concentration exceeded a specific threshold.

These initial investigations raise the questions, how the endogenous AO system can counteract an excess of exogenously supplied AOs and to what extent such an over- supplementation can influence the efficiency of the endogenous AO system.

To answer these questions HaCaT cells were treated with various ß-carotene concentrations with subsequent stress treatment by moderate irradiation (700-2000nm). To facilitate the uptake of ß-carotene, an innovative nanocrystal formulation was used. By resonant Raman spectroscopy a concentration-dependent uptake of ß-carotene was demonstrated. The redox status was determined before and after supplementation with two selected ß-carotene concentrations (0.02

and 0.1 µg/ml) and moderate irradiation. Significant redox changes were shown by EPR spectroscopy. By a fluorescent-based assay, the endogenous redox status for the AO glutathione was evaluated in parallel. An increased formation of reactive oxygen species (ROS) after irradiation was shown, which could be reduced after supplementation with both ß-carotene concentrations. An active interdependence between the applied ß-carotene concentrations (exogenous AOs), the endogenous AO system glutathione and the radical formation was shown. Nevertheless, a more effective protection against moderate stress could be observed for the lower dose. The high dose turned pro-oxidative.

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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.

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How does the emulsifier concentration affect API stability in emulsion gels and skin penetration?

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Introduction: The partitioning of APIs and functional excipients (e.g. the preservative phenoxyethanol) in emulsion systems is affected by various factors such as emulsifier type and concentration. As polysorbate 80 is an often-used emulsifier and good solubilizer, this emulsifier was chosen in varying concentrations (0.15%, 1.5% and 5.0%) to determine the influence on chemical stability and skin penetration in correlation to the micellar solubilization of betamethasone dipropionate (BDP) in emulsion gels. In addition, polyethylene glycol 400 (PEG 400) was added to increase BDP partitioning into the aqueous phase.

Methods: In order to determine solubility, BDP was added to various solutions (0.15%, 1.5%, 3.0% and 5.0% polysorbate 80 or 20%, 40%, 60% PEG 400 in citric buffer, w/w) to form suspensions. After 24 h, the clear filtrates were analyzed.

Emulsion gels were prepared with 30% medium chain triglycerides, 0.5% xanthan gum, polysorbate 80 (0.15%, 1.5%, 5.0%), 0.5% phenoxyethanol and 0.064% BDP. Either citric buffer pH 5 or phosphate buffer pH 8 were used as aqueous phase. Another emulsion gel with 1.5% emulsifier and 13.5% PEG 400 was prepared (all w/w).

For API stability measurements, 0.5 g of every emulsion gel was mixed with 10 mL of an aqueous 10% calcium chloride solution. BDP and degradation products were extracted with methanol acidified with 0.1% trifluoric acid. The formulations were tested at the start and after 3, 6, 9 and 12 weeks of storage at 25 °C or 40 °C.

Emulsion gel and acceptor medium (citric buffer) were filled into separate dialysis chambers (membrane cut-off of 5 or 300 kDa) and equilibrated at 25 °C for 24 h (n=5). The concentrations of BDP, phenoxyethanol and polysorbate 80 were recalculated assuming a dilution of the aqueous phase of the emulsion gel with the acceptor.

BDP penetration into the epidermis was determined using viable pig ear skin as described by Herbig et al. [1]. All samples were analyzed by a UHPLC coupled to a photodiode array detector or

a mass detector (polysorbate 80, skin samples).

Results: A good correlation between the solubility of BDP and the polysorbate 80 concentration was seen (R^2>0.999). Upon addition of PEG 400, significantly more BDP was dissolved in citric buffer.

With increasing emulsifier concentration in the emulsion gels, significantly higher BDP degradation was seen at 40 °C and pH 8 ($p<0.05$). Upon addition of the cosolvent PEG 400, the stability of BDP decreased regardless of the buffer system used compared to the cosolvent-free formulation.

Varying emulsifier concentrations showed no impact on the free BDP and phenoxyethanol concentration in the emulsion gels. Upon addition of PEG 400 more BDP was distributed into the aqueous phase due to increased solubility. BDP solubilization was demonstrated with increasing emulsifier concentrations (micellar molecular weight 127 kDa [2]), when using a membrane allowing micellar transport.

The emulsifier concentration had no significant impact on the ex vivo skin penetration. The formulation with PEG 400 showed significantly lower values due to decreased thermodynamic activity.

Conclusion: Due to an increased solubilization of BDP in the aqueous phase with increasing emulsifier concentration, more BDP was degraded at accelerated conditions. Rational formulation design is necessary for ensuring the ideal emulsifier concentration for minimized degradation and sufficient formulation stabilization.

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GPI salt, a powerful active ingredient fighting against inflammageing

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GPI salt is a semi-synthetic molecule derived from sunflower seed lecithin and acts against inflammageing to prevent the appearance of signs of ageing.

The transcription factor NF-kB (nuclear factor kappa-B) plays a central role in inflammatory processes of the skin. Multiple factors including reactive oxygen species, glycation, the production of Advanced Glycation End products (AGEs) and stress contribute to the translocation of NF-kB into the nucleus leading to inflammatory reactions.

The mechanism of action of GPI salt is based on the inhibition of the translocation of NF-kB into the nucleus, suppressing the production of pro-inflammatory mediators. Furthermore, the formation of AGEs is reduced, which normally support the translocation of NF-kB into the nucleus.

In vitro, it was shown that GPI salt significantly reduces the release of pro-inflammatory mediators and counteracts the signs of premature ageing, including skin redness, swelling and collagen degradation.

In vivo, the soothing effect of GPI salt was demonstrated on normal and reactive skin. After 24 hours, GPI salt visibly reduces skin redness and the inflammatory reaction. GPI salt allows to quickly alleviate skin reactions before long-term skin damages and signs of ageing are caused. With respect to sensitive skin, GPI salt helps to reduce skin irritation in only 4 hours and allows to immediately relieve a cutaneous reaction providing comfort to the skin.

To summarize, GPI salt acts upstream the pro-inflammatory cascade and leads to the deactivation of the NF-kB signalling pathway by reducing the production of AGEs and by inhibiting the translocation of NF-kB into the nucleus. The reduced translocation leads to a diminished release of pro-inflammatory mediators. GPI salt prevents inflammageing and provides a fast soothing effect to alleviate discomfort related to cutaneous reactions.