Summary: Release and bioavailability

published in Kosmetik & Pflege 2013 (1), 36-37 and 2013 (2), 38-39

A key issue considering the efficacy of skin care products is the release of the active agents contained. In this respect, not only the concentrations but also the base formulations of creams, dispersions and solutions play an important part. The subsequent penetration into the horny layer depot, the passage into deeper skin layers and, where applicable, also the metabolization determine the dermal bioavailability of active agents in order to carry out their intended functions.

In Kosmetik & Pflege 2012 (1), 25-27, we discussed carrier systems such as liposomes and nanoparticles. Carrier systems improve the dermal bioavailability of active agents since they

- enhance the penetration and
- protect the therein encapsulated active agents against oxidative, hydrolytic or other external influences.

The term bioavailability actually originates from pharmacology and indicates the fraction of an active agent that is systemically available for the body in comparison to the dosage applied. From the cosmetic and dermatological point of view, only the dermal bioavailability is important, i.e. the portion of active agent that is locally available for the metabolization in the skin after the dermal application. Nevertheless, this particular factor is difficult to measure as also the individual skin layer would have to be determined in which the active agent is supposed to arrive in order to trigger the desired effects. Hence it is less complicated to compare dosage and effects of different cosmetic formulations and then draw relative conclusions. Just to mention an example: the availability of vitamin A and its derivatives is considerably higher in biodegradable nanoparticles based on phosphatidylcholine (PC) than in conventional preparations containing emulsifiers – which can be recognized by the relatively low threshold dose for irritations that in this specific case can be related to the transformation of vitamin A into vitamin A acid.

That vitamin A nanoparticles obviously involve a specifically high dermal bioavailability also is due to the fact that emulsifier free, PC-containing cosmetic and pharmaceutical preparations are characterized by a rather moderate release of active agents. Although they penetrate very quickly into the stratum corneum depot, they also leave it again in a quite steady manner. In this context we rather speak of a plateau release, i.e. short and distinct concentration peaks are missing. Similar to vitamin A preparations, the dosages of active agents can frequently be reduced.

Yet, release and dermal bioavailability are determined by various additional factors and substances. A few of them are summarized in the following overview: this basic information should not go unmentioned since it is relevant to the results of cosmetic treatments.

Amides (acid amides) belong to a substance group that on the one hand influences the penetration of other substances but also their own availability on the other hand. Amides consist of acids that are neutralized through a chemical bonding with amines.

- A very simple compound in this context is urea whose base components are carbonic acid and ammoniac. Urea is a so-called physical door opener. In higher concentrations, it blasts the hydrogen bridge bonds between the corneocytes, has keratolytic effects and binds water. Already in moderate concentrations up to 3 percent it serves to enhance the penetration of substances. It also has anti-itching effects.
- Allantoin (5-Ureidohydantoin) is structurally related to urea and has similar properties, however, due to its poor water solubility it cannot be used in higher concentrations.
- Long-chained fatty acid amides have inverse effects, they are barrier active. And to mention an example: Palmitic acid monoethanolamide has anti-itching effects and is applied in the case of atopic skin. Ceramides with their excellent affinity to the skin react analogously. Their availability also is supposed to stop at the stratum corneum, otherwise the apoptosis of skin cells would be stimulated.

- D-Panthenol is the pre-stage of pantothenic acid (vitamin B_5). As a component of facial tonics it makes the skin more permeable and hence receptive for the active agents of masks.
- Tertiary amides are formed by a secondary amine and a fatty acid. Similar to esters, they are rather nonpolar in comparison to their base components. That is the reason for their excellent penetrating properties which can be easily identified on the basis of pungent substances such as capsaicin (chilli) and spilanthol (para cress; wrinkle-reducing effects).

Antioxidants stabilize the availability of oxygen-sensitive substances such as vitamin A by impeding the breakdown during the passage through the horny layer. Encapsulations with a protecting outer layer serve the same purpose in the case of extended storage.

With a **barrier disturbed and dry skin,** the undesired availability of many environmental substances will increase. The sensitivity against germs, preservatives and perfumes is significantly augmented.

Derma Roller: During the microneedling treatment, the skin will be perforated. Particularly in case of skin scars, the skin recovery can thus be reactivated. An improved penetration of active agents in comparison with the application of liposomes and nanodispersions cannot be observed though.

Perfumes: Many of the terpenes contained in perfumes have allergenic characteristics due to the impact of atmospheric oxygen and UV light. Their dermal bioavailability is very high because of the increased lipophilicity and the small-sized molecules. The best solution for sensitive skin is to avoid them at all or alternatively utilize them separately. The same applies for a multitude of synthetic odorants.

Emulsifiers disturb the skin barrier and intensify the penetration due to their surface activity. In addition, the availability of lipid substances is drastically reduced based on the subsequent wash out effects. Sodium lauryl sulfate is used as a generic irritant in test procedures to analyze cosmetic products regarding their irritative effects.

Esters can be interpreted as chemical Trojan horses for acids. The polar acid function is neutralized due to the chemical bond with alcohols. The acids then become liposoluble and their availability increases. The acids are again released in the skin by enzyme activity (esterases).

Enzyme defects can reduce the availability of active agents. Thus, an insufficient activity of the enzyme delta-6-desaturase will impede the transformation of linoleic acid into gamma-linolenic acid. Many of the neurodermatitis patients suffer from this specific problem. The topical application of gamma-linolenic acid (evening primrose oil) can be beneficial in this context.

Lipid tissue such as for example in the case of cellulite impedes the passage of polar substances. Although nonpolar, liposoluble substances are stored they only feature a rather poor release rate. In the case of cellulite, caffeine containing products in combination with mechanical energy will show lipolytic (fat-splitting) activity. Caffeine is particularly available in liposomal dispersions and is used in concentrations of up to 2%.

Infrared radiation has the same effect as hot packs. The availability of active agents is improved.

Iontophoresis accelerates the penetration of charged particles into the skin. This technique is based on low-voltage direct current and mainly applicable to acids and salts.

Preservatives: Although a high availability is desired in preparations that have to be stabilized in antimicrobial aspect, it is no longer desired on the skin. Lipophilic preservatives such as parabens and halogenated phenols as well as their derivatives can be detected in the whole body. Combinations with carrier substances such as nanodispersions and liposomes are particularly unfavourable; hence it is suggested to avoid the use of preservatives in the manufacturing process.

Massages improve the availability of oils and dissolved active agents through mechanical energy.

Metabolization: The dermal availability of orally ingested essential fatty acids by way of nutrition is considerably reduced due to the metabolization during the passage through the liver. And vice versa, in the case of a topical application, it is the metabolization which causes anti-inflammatory effects.

Microdermabrasion: A previous dermabrasion leads to concentration peaks after the topical application of active agents since the balancing depot of the stratum corneum is

missing. The consequence is a high rate of side effects as e.g. through acids (pH), vitamin A (vitamin A acid) or hypertonic solutions (osmotic pressure). Erythema and irritations can be observed quite often.

Micronization: Micronized active agents (particle size in the µm range) are only interesting if we deal with insoluble solids. They are easier to disperse and their availability is improved due to their increased surface. Topical hormone preparations of pharmacies often are based on this principle.

Occlusivity: We speak of occlusive conditions when the TEWL level falls to zero after the application of cosmetic preparations – this can be triggered by products with high petrolatum content (vaseline). The skin then swells and the active agents can easily pass through the skin barrier. Both fleece and modeling masks are based on this principle. It should be mentioned though that occlusive creams also reduce the skin's recovery properties.

Oleic acid is a classic penetration enhancer.

Vegetable oils: The availability of vegetable oils is considerably improved if they are administered in a fine aqueous nanodispersion combined with phosphatidylcholine. In that case, they will not remain on the skin surface in the form of oil, but immediately penetrate into the skin.

Phase transition temperature: In the case of barrier affine active agents, the phase transition temperature during the transition from the crystalline into the liquid-crystalline phase plays an important part. The phase transition temperature of PC is around < 0 °C for instance. The integration of PC into the barrier lowers its phase transition temperature. The barrier is fluidized and becomes permeable. By combining PC with hydrogenated PC (PC-H) all the different states from permeable to non-permeable (100% PC-H; skin protection) can be fine-tuned.

Product matrix: The fact, whether the active agents are integrated into an aqueous gel, a fatty cream, a low-viscosity lotion, dispersion, a solution or into carrier bodies has a significant impact on the release characteristics of the agents.

Provitamins frequently are low-polar substances and therefore can easily pass the horny layer in comparison to the vitamins that form through metabolization. Examples here are D-panthenol and beta-carotene.

Radio waves generate heat in the skin. Hence they have the same effects as infrared radiation or hot packs. The only difference here is their tissue penetration.

Spreading substances improve the horizontal availability of active agents. Typical spreading substances are isopropyl myristate, adipic acid esters, volatile short-chained silicones and squalene exuded by the sebaceous glands.

Ultrasound accelerates the penetration of active agents due to its mechanical energy.

Growth factors: A very elegant way of release consists of stimulating the human growth factors by externally applied substances. Practically all the substances that are able to stimulate the skin recovery belong to this category. The intensifying effect of growth factors is utilized in this context.

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