THE NATURAL WAY INTO THE SKIN

Ingredients | Natipide Eco, a COSMOS-approved carrier system for hydrophilic actives, has been proven to enhance the penetration of active ingredients into the skin.



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Encapsulation of active ingredients has become an important tool in both the dermato-cosmetic and personal care industries. This is due to the increasing requirements for safer, high-performing and more sophisticated consumer products. These trends have resulted in the development of a more efficient and controlled transport system for biological actives into the skin. **Natipide Eco** is a **Cosmos**-approved innovative carrier system for hydrophilic cosmetic actives. It is an ethanol-free liposomal concentrate based on natural unsaturated phospholipids from non-GMO soybean lecithin. Phospholipids are omnipresent in human skin and in all mammalian cell membranes, a fact which underlines the natural origin of these excipients. Arranged in bilayers, phospholipids are responsible for the fluid nature of biological membranes, hence their functionality (fig. 1, A). Due to their unique physicochemical proper-

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"ENCAPSULATION OF ACTIVE INGREDIENTS IS AN INCREASINGLY IMPORTANT TOOL IN PERSONAL CARE."

Dorothea Gutekunst, Research Scientist, Lipoid GmbH

ties, phospholipids spontaneously form, after hydration, submicron vesicles with one or more bilayers. These so-called liposomes entrap an aqueous volume in which a hydrophilic active can be dissolved (fig. 1, B).

Fig. 1 demonstrates the similarities between liposomal structures and mammalian cell membranes. This structural parallelism simplifies the fusion of liposomes with skin lipids which makes liposomes effective dermal penetration enhancers[1, 2].

Ready-to-use

To enable a simple, quick and large-scale production of liposomal cosmetic products, we developed **Natipide Eco** as a ready-to-use encapsulation system. Lipid composition and particle size have been carefully chosen to gain a maximum of interaction with the skin. This encapsulation system is composed of densely packed, stable liposomes facilitating an efficient encapsulation of hydrophilic cosmetic actives, as seen in fig. 2. Fig. 2, A shows the liposomal concentrate with a uniform size distribution around 200 nm.

Furthermore, the use of unsaturated soybean phospholipids in our new encapsulation system leads to liposomes with a flexible membrane. Due to their low phase transition temperature below 0 °C unsaturated phospholipids are in a fluid state at a skin temperature of 32 °C. The fluid-state liposomes interact with the rigid bilayer structure of skin lipids, thus increasing the penetration of an active through the lipid phase of the stratum corneum[2]. Particle size and composition of the encapsulation system meet the requirements for an effective dermal delivery system[3].

Easy to use

Natipide Eco comprises a yellowish-brown gel-like liposome concentrate and forms loaded liposomes upon mixing with an aqueous solution of a cosmetic active (see fig. 3). Even after dilution, liposomes are stable and in the same particle size range (see fig. 2, B). In contrast to conventional liposomal encapsulation procedures, no special equipment (for example, high-shear mixing) is needed to form liposomes with a sufficiently small size.

The encapsulation system is easy to handle due to its high process stability. These properties were analysed in several stability experiments with changing temperature profiles (20 – 80 °C) or shear rates (3.000 and 10.000 rpm).

A similar ease of use was demonstrated when incorporating the encapsulation system in a realis-

PHOSPHOLIPIDS are **omnipresent** in human skin and in all mammalian cell membranes

The requirements for safer, **high-performing** and more sophisticated consumer products are increasing

The penetration enhancing effect of the **liposomal system** increases with increasing skin depth

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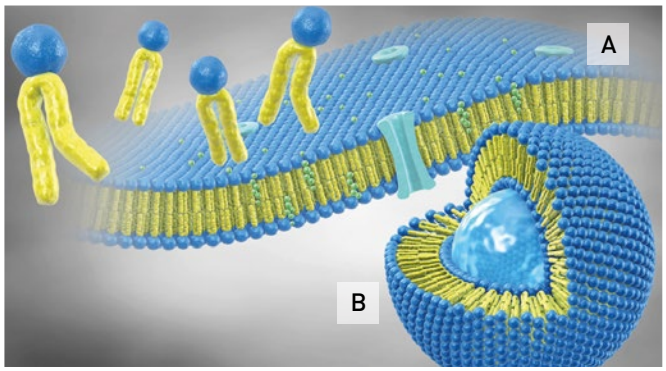

fig.1: Models of phospholipid arrangements: A shows a cell membrane focusing on its characteristic phospholipid bilayer with integral membrane proteins (light blue) and cholesterol molecules (green). (B) Liposomes are composed of a phospholipid bilayer surrounding an aqueous core. Their similarity to a mammalian cell membrane makes them effective delivery systems.

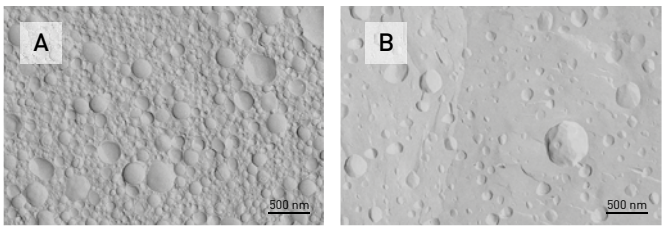

fig. 2: Freeze fracture electron microscopy images of Natipide Eco. (A) Densely packed unloaded liposomes of pure Natipide Eco with a characteristic particle size around 200 nm. (B) After preparing a 20 % aqueous solution of Natipide Eco, liposomes are still stable and in the same particle size range. Scale bars = 500 nm.

"LIPOSOMES WITH A FLEXIBLE SHELL LEAD TO AN INCREASE CONCENTRATION OF ACTIVES IN DEEPER SKIN LAYERS"

Christoph Heidecke, Head of Development, Lipoid GmbH

tic formulation system (see table 1). The **Advanced Effect Hydrogel** includes liposomally encapsulated niacinamide, which is prepared as an aqueous dispersion in the first step. For the final incorporation into the gel phase only a stirrer is necessary to obtain a homogeneous and stable liposomal gel.

The encapsulation system is compatible with a broad range of hydrophilic cosmetic actives such as allantoin, biotin and ectoine as well as botanical extracts such as green tea, aloe, and arnica montana.

To evaluate their compatibility, encapsulation experiments were performed with the liposomal concentrate in a ratio of 4:1. After one week no incompatibilities were observed, although incompatibilities can never be completely excluded. Therefore, we recommend careful testing in each case in the intended formulation system.

Improved bioavailability

A double-blind, randomised in-vivo pilot study was conducted as a proof of concept of this ready-to-use penetration enhancing system. To demonstrate its benefits, the commercially well-known cosmetic active niacinamide was chosen as model active.

To evaluate its penetration enhancing effect, a simple system was chosen as test formulation* to exclude the influence of other components as far as possible. To this end, niacinamide was dissolved in water, mixed with the liposomal concentrate and stabilised with citric acid. For comparison, a placebo formulation was used containing the same components, except for the liposome forming phospholipids.

Both formulations were applied on the inside forearm of four healthy female volunteers. Treated skin areas were analysed in comparison to untreated skin areas, before and four hours after application of test formulations. The penetration properties of

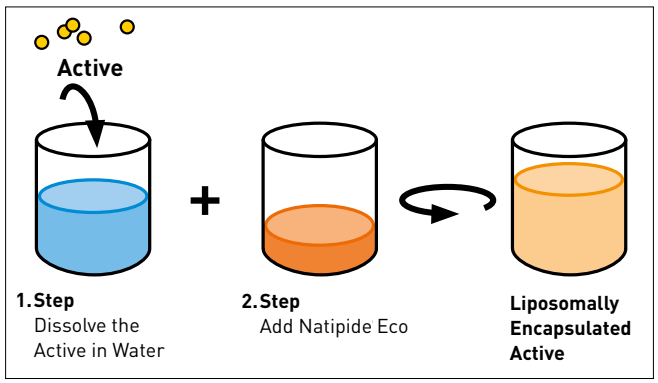

fig. 3: Two steps to loaded liposomes. No additional high-shear mixing is necessary to obtain a defined and reproducible liposomally encapsulated active.

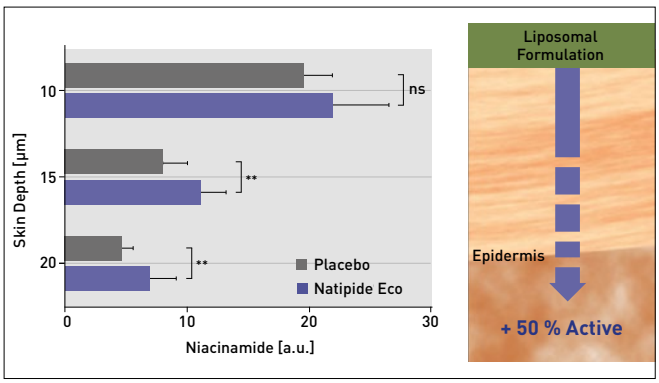

fig. 4: Comparison between the penetration properties of liposomally encapsulated (Natipide Eco – blue) and non-encapsulated (placebo – grey) niacinamide

The carrier system is based on natural unsaturated phospholipids from non-GMO soybean lecithin

Natipide Eco and placebo formulation were evaluated by using confocal Raman spectroscopy. With this technique it was possible to measure the amount of penetrated niacinamide in up to four depths below the skin surface (5, 10, 15, 20 µm). At each time point, an intensity profile, which is equivalent to the concentration of niacinamide, was detected. Niacinamide concentration profiles were summarised to a mean concentration over the repeated measurements (n = 7) on treated test area and in each depth.

Fig. 4 shows the changes in intensity profiles of scattered light induced by different niacinamide concentrations (niacinamide, a.u.) plotted against an increasing skin depth (µm). The liposomally encapsulated niacinamide penetrates deeper into the skin. The difference in penetrated active is especially high in 15 µm and 20 µm skin depth. Represented by one subject as an example, n = 7, mean ± SEM, student's t-test, ns = $p > 0.05$,** = $p \leq 0.01$. The change of niacinamide in % calculated between non-encapsulated and encapsulated active was 50 % at 20 µm.

While the difference in niacinamide concentration between the two test formulations was not significant at 10 µm skin depth, the niacinamide concentration at 20 µm skin depth was significantly increased when liposomally encapsulated niacinamide was applied to the skin. The penetration enhancing effect of the liposomal system increases with increasing skin depth.

Penetration enhancing effect with two benefits

In summary, **Natipide Eco** elevates the concentration of penetrated niacinamide up to 50 % in comparison to the aqueous formulation without liposomes.

Our results confirmed the beneficial influence of unsaturated phospholipid vesicles with a particle size around 200 nm to obtain a deep penetration into skin as reported in literature[2–5]. Our in-vivo study demonstrated that the use of liposomes with a flexible shell led to an increased concentration of a model active in deeper skin layers. Liposomal encapsulation offers two benefits: its penetration enhancing effect can increase the effect of active ingredients in skin; it can also reduce the required concentration of the active in the formulation while retaining its physiological effect. □

* The frame formulation, the references and additional information can be found on the Internet – see Internet panel