Lipid Nanoparticles (SLN, NLC) for innovative consumer care & household products

KEYWORDS: SLN, NLC, lipid nanoparticles, occlusion, penetration enhancement, dermal delivery, antioxidants, UV protection, IR protection, anti-aging

Abstract Solid lipid nanoparticles (SLN) and nano(structured) lipid carriers (NLC) are nanoparticles with a particle matrix composed of solid lipid or solid lipid blend, resp., introduced to the cosmetic market a little bit more than 5 years ago. They combine advantages of various traditional nanocarriers, e.g. chemical stabilization of labile actives and good skin compatibility. Dermal effects are adherence leading to film formation (“invisible patch”), repair/re-inforcement of natural protective lipid film, occlusion and related effects of increased skin hydration and enhanced penetration of actives. Further they can be used for protection against UV and IR radiation in anti-aging. As cosmeceutical formulation the silver-nanolipid (sNLC) complex is effective against irritated, inflamed skin conditions and supportive in therapy of atopic dermatitis and psoriasis.

INTRODUCTION
In the last twenty years lipid nanoparticles (SLN, NLC) were developed which are characterized by the solid state of the lipid particle matrix, which nowadays are contained in many dermal cosmetic products since 2005. Meanwhile they are on their way into clinical phases for pharmaceutical products. They are derived from the nanoemulsions by replacing the liquid lipid (oil) by a solid lipid or a solid lipid blend. This article describes the rational behind the development of these delivery systems in the light of other nanoparticles, the basic technical features and highlights the differences between the 1st (SLN) and 2nd generation (NLC). The action and performance of the lipid nanoparticles on the skin are described, and from this derived their use in consumer care but also high level exclusive facial cosmetic products. Special emphasis is given to their protective effect on the skin by film formation (e.g. against environmental hazards, UV, IR), repair and re-enforcement of natural skin barrier which makes them ideal for cosmeceuticals products against irritated, itching skin and atopic dermatitis. The first NLC product is presented being supportive in the treatment of atopic dermatitis (enabling earlier termination of glucocorticoid treatment, prolongation of symptom-free intervals).

THE IDEA BEHIND THE LIPID NANOPARTICLE STORY
During the last half century various nanocarrier systems originally developed for pharmaceutical use where employed to innovate cosmetic and in general consumer care products with superior performance. Figure 1 gives an overview of the key systems. Looking back, it started with nanoemulsions in the 1950ies. The liquid oil droplets stabilized with lecithin or a surfactant/polymer with a size below 1,000 nm (Figure 1, upper left) were developed pharmacologically for e.g. infusion for parenteral nutrition (1, 2) and i.v. delivery of lipophilic drugs. The liposomes followed in the mid of the 1960ies by Bangham (3, 4), a phospholipid bilayer with aqueous core allowing incorporation of both hydrophilic and lipophilic actives. They entered the cosmetic market in 1986 (Capture by Dior) (5, 6). The polymeric nanoparticles developed by Speiser (7) as carriers for drugs did not yet enter the pharmaceutical market, cosmetic use is limited. The dermal microemulsions developed in the 1980ies appeared very promising. They are no real emulsions (no dispersed system with definite droplets), but are considered as “critical solutions” with pulsing forming and dissolving water and oil droplets (Figure 1, middle) (8). Microemulsions are in some pharmaceutical dermal products because they are highly effective in delivering actives into the skin. However, due to their high surfactants concentrations, being potentially irritating to the skin, they had no breakthrough in cosmetics. From this it can be summarized, that the cosmetic market was waiting for a new efficient cosmetic carrier system since the middle of the 1980ies.

To meet this urgent need, the lipid nanoparticles were developed. The idea behind was to develop a carrier system which combines advantages of existing carrier systems, but at the same time avoiding or minimizing their disadvantages, and it should be industrially friendly.

BASIC APPROACH & TECHNICAL FEATURES OF SLN AND NLC
Lipid nanoparticles are composed of a lipid matrix being solid at room temperature. In case of solid lipid nanoparticles (SLN) this matrix is a solid lipid only, in case of nano(structured) lipid carriers (NLC) it is a solid blend of an oil with a solid lipid.
particle matrix, leaving only a limited space to incorporate cosmetic actives or drugs (e.g. 1% vitamin A). Due to formation of a perfect crystalline matrix, drugs could even expell from the particle matrix forming drug crystals in the water phase. A classical example is the use of “highly purified” lipids such as tristearin (10). To overcome this problem, particles were created having on purpose a disordered structure with a lot of imperfections, i.e. using chemically not well defined, polydispere industrial lipids (“dirty lipids”). This leaves a lot of space for actives. This was achieved in NLC by mixing structurally very different lipid molecules, i.e. long chain solid glycerides with shorter chain glycerides of oils. The particle matrix was nanostructured, incorporation was increased, e.g. for vitamin A 5 fold (9). In addition, cosmetically interesting oils are contained in the NLC. In general, apart from higher loading with actives, the physical long-term stability of the drug inclusion is basically higher for NLC than for SLN. However, it should be made clear that there is still a meaningful use of SLN as the first generation of lipid nanoparticles. In case of low loadings with actives, the SLN loading capacity is still sufficient. They have comparable film forming properties and occlusive effects as NLC. They showed reduction in side effects when incorporating skin-initiating drugs. In general the crystallinity of SLN is higher than of NLC, which is even favorable to act as UV scatterer. Due to their longer existence, of course there is a very broad data base to which one can draw on when developing a product. NLC have some add-ons which are not necessarily needed for each type of product but often are desirable. In articles this is often compared to different models in car industry. The first generation model “VW beetle” is a solid and reliable car doing the job of transporting you (= SLN delivering the active), the “New Beetle” is just smarter in performance, from speed to the fancy look (= NLC). Very important, the NLC are still patent protected and provide an exclusive product.

CONSUMER CARE: LIPID NANOPARTICLE ACTION ON THE SKIN

Lipid nanoparticles are dispersed in the water phase of gels and o/w creams/lotions. In general, adhesiveness increases with decreasing particle size. Classical example from daily life is the increase in adhesion to bakery when moving from crystalline coarse sugar to iced sugar. Therefore, identical to all nano-sized materials, the lipid nanoparticles adhere strongly to surfaces. They form a dense film on the skin, which can be compared in efficiency with a pharmaceutical dermal patch, but being invisible due to the small particle size (Figure 2, upper) (11). The film formation reinforces a too thin natural lipid film on the stratum corneum, and repairs damages. This was the marketing concept when introducing the NLC on the cosmetic market in South Korea and China. From this, the lipid nanoparticles are sensible to use in skin care products for all skin conditions which are associated with distorted skin barrier, ranging from irritated red skin to atopic dermatitis and psoriasis.

The enforced lipid film on the skin provides an effective protective barrier against any hazards from the environment, reflecting UV radiation are being a barrier against air pollutants. The film has occlusive properties, increasing skin hydration, thus due to the volume increase a skin lift occurs reducing wrinkle depth (Figure 2, lower left).

Cosmetic actives incorporated into the solid particle matrix are chemically stabilized, important to guarantee lasting dermal effects during the product shelf life. From the formed particle film on the skin, the actives diffuse via solid phase diffusion into the...

NLC – WHAT IS DIFFERENT IN THE IMPROVED SECOND GENERATION?

The SLN were developed at the beginning of the 1990ies. Use of a solid lipid only created a relatively well ordered crystalline...
“acceptor medium” skin, driven by the concentration gradient. Penetration is enhanced due to the occlusive effect of the lipid nanoparticle film (Figure 2, lower right).

**NLC FOR FACIAL COSMETIC PRODUCTS**

High-level anti-aging products for the face are the preferential application for NLC. The first products were Cutanova Cream Nanovital Q10 (clay cream), Cream Nanorepair Q10 (night cream) and the Serum Nanorepair Q10 for the eye region (by Dr. Rimpler GmbH, Germany). In a human study the product Nanorepair Q10 was compared to a formulation of identical composition having the NLC replaced by oil. With the NLC formulation, after 6 weeks wrinkle reduction was stronger and increase in hydration higher, these effects were even found lasting when measured 1 week after termination of product application (12).

Other examples of facial cosmetics are some products in the line IOPE by the company AmorePacific (e.g. Super Vital Extra Moist Cream), or Swiss Cellular White, a whitening product from la prairie. Meanwhile NLC technology is used by major companies worldwide (13). In general, identical to unloaded liposomes, NLC themselves being unloaded have already cosmetic effects (Figure 1, upper & lower left). In addition the NLC can be employed to make cosmetic actives (already used in the market) more active. Re-formulation of established actives such as Q10, vitamin A etc. using NLC technology can lead to superior performing market products. This can be explained by the combination of the effects of the NLC themselves and the improved dermal delivery. Apart from new products, NLC are therefore of interest for companies to make a strategically necessary relaunch of already marketed products. The well established formulation is used in the new product, and NLC are simply admixed (c.f. section “How to incorporate lipid nanoparticles into products”).

The face is exposed to radiation all day long. Therefore of increasing importance in anti-aging is the protection of the facial skin against UV radiation, but also infrared (IR) radiation. The scientific and cosmetic community is getting aware of the potential damaging effects of IR light, leading e.g. to the formation of free radicals, the induction of metalloproteinases and alteration of dermal structural proteins (14, 15). More and more products appear on the market being especially designed to minimize IR damaging, highlighting this in the product advertising. NLC are also an interesting formulation technology for such products (c.f. section “NLC for protection against environmental UV & IR radiation”).

**NLC FOR PROTECTION AGAINST ENVIRONMENTAL UV & IR RADIATION**

Penetration of molecular sunscreens into the skin can cause side effects. Penetration into the skin and related side effects can be reduced, when the sunscreens are incorporated firmly into the matrix of NLC (design of particle matrix as delayed (!) release formulation) (16). In addition, it was found that the sunscreens have a higher UV absorption effect when incorporated into the solid lipid particles (17). The higher absorption leads to less penetration of UV radiation into the skin, in addition the NLC act themselves as particulate UV scatterers (Figure 3, upper). Consequently the amount of molecular sunscreen in the product can be reduced, leading to a better tolerated, more skin-friendly product. There are also concerns about skin penetration of particulate scatterers such as ultrasmall titanium dioxide, causing side effects such as irritation of immune system (18). This can be avoided by incorporation of the 10-120 nm TiO<sub>2</sub> nanoparticles into NLC of e.g. diameter 400 nm. Due to their size, the TiO<sub>2</sub> cannot diffuse out of the NLC, in addition a stronger scattering effect was found from TiO<sub>2</sub> when incorporated into the NLC matrix (Figure 3, lower).

IR radiation causes in the skin production of reactive oxygen species (ROS, Figure 4, left). IR as long wave radiation cannot be effectively scattered by particles, the current approach is to block the oxidative stress cascade by antioxidants. Antioxidants are therefore incorporated into creams. However incorporating them into NLC increases their penetration and makes them more effective in blocking the cascade (Figure 4, right). Alternatively, unloaded occlusive film forming NLC can be combined with antioxidant nanocrystals (19). The occlusion by the NLC film could promote antioxidant penetration. NLC are therefore highly suited in anti-aging products to complement the action of traditional anti-aging compounds with an effective protection against UV & IR radiation at simultaneously better tolerability (reduced potential side effects). Molecular sunscreens can be used at lower concentration but maintaining the same SPF, in addition TiO<sub>2</sub> is firmly enclosed. The superior tolerability can be highlighted in the product information.

![Figure 2. Effects of lipid nanoparticles (LN) on the skin: LN adhere, form a film on the skin (upper), which protects against hazards from the environment and increases dermal penetration of actives (lower, details c.f. text).](image-url)
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COSMECEUTICAL NLC AGAINST IRRITATED, ITCHING SKIN AND ATOPIC DERMATITIS

A good consumer care product can be very beneficial in skin conditions characterized by irritation & redness, itching and inflammation. Good skin care can also be supportive in the treatment of skin diseases like atopic dermatitis and psoriasis. Therapy can be accelerated, or drug therapy can be terminated earlier and being replaced by application of top level skin care products only (= natural approach).

To differentiate such products, they are classified as cosmeceuticals. According to Wikipedia: “Cosmeceuticals are cosmetic products with biologically active ingredients purporting to have medical or drug-like benefits.” (20). The effects can be pronounced, but not to the extent that they can be classified as drug-effects, especially when the cosmeceuticals are only exploiting natural effects targeting towards normalization of skin condition. This is the case in cosmeceutical use of NLC leading to restoration of normal skin barrier and bacterial colonization of skin.

Irritated, damaged skin is characterized by a distorted protective skin barrier/lipid film, and microscratches, both promoting colonization of undesired bacteria, especially in the scratches, causing in summary inflammation and redness. (Figure 5, upper). Creams with microsilver particles (about 10 µm) are on the market, the silver particles release silver ions Ag⁺ having an antibacterial effect (= oligodynamic effect after Nägli, Figure 5, middle).
HOUSEHOLD PRODUCTS – STIMULATIONS FOR INNOVATIVE PRODUCTS

The NLC can be used in very different household products, exploiting the various properties described above. Important for the use in different products is the release kinetics of the incorporated active. It should be fast for promotion of skin penetration of the active (e.g. Q10). Release should be slow (= very delayed) in case of sunscreen products, where the molecular sunscreen should be firmly incorporated in the particle and not penetrate into the skin. Release is determined by the localization of the active in the lipid nanoparticle (Figure 7) [24].

NLC can be used in fragrance products to prolong the release of the fragrance [25, 26]. Fragrance evaporates fast from ethanolic solutions, delayed from the more viscous liquid lipid (oil) of o/w emulsions, and more delayed from the solid lipid of NLC due to reduced diffusion. Other delayed release products are e.g. insect repellents [27]. Prolonged release is also desired for mouth wash. The NLC can be made mucoadhesive, they adhere to the mouth mucosa and release the active over a longer time (e.g. mint flavor, sage extract etc.). Another application is antiperspirants. Active loaded NLC can also be adsorbed to natural and synthetic fibres. Positively charged NLC can be used for hair conditioning, to replace the physically unstable liposomes. NLC loaded with skin-care actives can be adsorbed to the fibres on the surface of nappies. Interesting is also the loading of fibers in textiles. Textiles loaded with actives (e.g. antimicrobial, skincare) are getting more and more popular, but the problem is the removal of the active after multiple washing. Reloading of the textiles could be performed by NLC dispersed in the fabric conditioner. They adsorb to the fibers, reloading textiles such as T-shirts. To summarize: It is just a question of your fantasy where to exploit NLC in different household products.

HOW TO INCORPORATE LIPID NANOPARTICLES INTO PRODUCTS

NLC suspensions are on the market as concentrates, typically 20-40% particle content. They are admixed to gels, creams and lotions by replacing a part of the water by NLC concentrate. The concentrates are prepared by high pressure homogenization. The active is dissolved in the melted lipid/lipid blend, which is then dispersed in a hot surfactant solution leading to a coarse o/w emulsion. This emulsion is homogenized, the obtained hot nanoemulsion cooled to room temperature leading to the crystallization of SLN/NLC. Typically the cosmetic formulation is prepared first, and at the
end of the production process after cooling to room temperature the NLC concentration is admixed by gentle stirring. In general an NLC particle concentration of about 1-2 % is recommended, that means an NLC concentrate with 40% particles need to be diluted by a factor 20 to 40 (i.e. 5.0 kg to 2.5 kg concentrate for 100 kg final product).

Interesting is the re-launch of products being already on the market. The good properties of the existing product appreciated by the consumer, they can be combined with additional benefits of the NLC. The product is produced as usual, but with a reduced water content (e.g. taking out 5% water), and after production 5% of NLC concentrate are admixed. The consumer experiences still the valued features of the precedent product, it contains additionally the new NLC technology for further improved performance.

Producers of NLC concentrates are Dr. Rimpler GmbH (www.rimpler.de) nearby Hannover and Chemisches Laboratorium Dr. Richter GmbH (www.clr-berlin.com) in Berlin, Germany. Development of custom-specific NLC formulations is offered by PharmasoL GmbH Berlin (www.pharmasol-berlin.de), also this company owns the present patents in Europe and the US.

REGULATORY & TOXICOLOGICAL / TOLERABILITY ASPECTS

The size of NLC is typically well above 200 nm, that means they are no nano products according to the legislation in Europe and the US. This is important. Despite that nano is still selling very well in cosmetics (at least in Europe and Asia), the consumer is getting more concerned about nano. This is primarily in food but begins also in household products. Looking at this in an objective manner, scientifically unsound and non-differentiating articles in the popular press contributed to this perception. However, as a company one has to deal with it, and from the marketing point it might be beneficial that one does not need to label a cosmetic product as nano product in the future. Despite this, the NLC still benefit from nano effects, because the change in physico-chemical properties occurs when moving in size into the nanodimension, i.e. below approx. 1,000 nm. That means the NLC have beneficial nanoproperties, without being legally classified as nano product!

Toxicologically they are very well tolerated. They are above the toxicologically critical size of 100 nm, and they are completely biodegradable. Based on this they are placed in the well tolerated class I (green class) of the nanotoxicological classification system (NCS) (28).

NLC PRODUCT PERSPECTIVE

The NLC were the first lipid nanoparticles appearing on the market in the cosmetics products. First products were Nanorepair and Nanovital by Dr. Rimpler GmbH in Germany in 2005, followed in 2006 by 3 products in the line IOPET by AmorePacific in South Korea. These were the “kick off products” which initiated a broad use in 2006 by 3 products in the line IOPE by AmorePacific in South Korea. Nanovital by Dr. Rimpler GmbH in Germany in 2005, followed in 2006 by 3 products in the line IOPE by AmorePacific in South Korea. These were the “kick off products” which initiated a broad use in 2006 by 3 products in the line IOPE by AmorePacific in South Korea. Nanovital by Dr. Rimpler GmbH in Germany in 2005, followed in 2006 by 3 products in the line IOPE by AmorePacific in South Korea.

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