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Review Article

Cosmetic features and applications of lipid nanoparticles (SLN®, NLC®)

E. B. Souto* and R. H. Müller†

*Department of Pharmaceutical Technology, Faculty of Health Sciences, Fernando Pessoa University, Rua Carlos da Maia, 296, 4200-150 Porto, Portugal and †Department of Pharmacy, Pharmaceutical Technology, Biopharmaceutics and NutriCosmetics, Free University of Berlin, Kelchstr. 31, D-12169 Berlin, Germany

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Synopsis

A detailed review of the literature is presented in attempts to emphasize several advantages of solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) for cosmetic applications. Examples of several actives are given and the main features of the solid core of SLN and NLC for topical delivery of cosmetics are discussed. Lipid nanoparticles have been more and more explored in pharmaceutical technology, showing superior advantages for topical purposes over conventional colloidal carriers.

Résumé

Un examen détaillé de la littérature est présenté dans les tentatives de souligner les plusieurs avantages des nanoparticule lipidique solide (SLN) et lipidique nanostructurés (NLC) pour applications cosmétiques. Exemples de plusieurs substances actives sont données et les caractéristiques principales du noyau plein de SLN et de NLC pour la libération topique des produits de beauté sont discutées. Les nanoparticles lipides ont été de plus en plus explorées en technologie pharmaceutique, montrant des avantages supérieurs pour les porteurs colloïdaux conventionnels pour administration topique de buts.

Correspondence: Eliana B. Souto, Department of Pharmaceutical Technology, Faculty of Health Sciences, Fernando Pessoa University, Rua Carlos da Maia, 296, 4200-150 Porto, Portugal. Tel.: +351 225 074630; fax: +351 225 074637; e-mail: eliana@ufp.pt

Introduction

To understand the features and actions of cosmetic formulations and their ingredients, knowledge of the skin's functions is required. One of its most important features is related to the protection of human organism, and the control of dissipation of the heat generated by the metabolism [1]. Although the skin has an important endocrine activity and may have an excretion of sweat exceeding in volume the output of the kidney, this excretory activity is minor in the elimination of solid residues. The protective and impermeable qualities of the skin protect the organism from losing water, minerals and dissolved proteins, as would occur rapidly if the unprotected subcutaneous tissues were exposed to the environment.

Being a vital organ, the skin must be nourished as the other organs of the body. Such nourishment is usually – in addition to the supply by the body – supported by the use of well-known cosmetic formulations. However, one must take into account that the skin's functions can be disturbed by some systemic diseases, by vitamin deficiencies and by disturbances of endocrine glands. In these cases, active ingredients with a particular pharmacological activity are required. Thus, the barrier between cosmetics and topical pharmaceuticals is sometimes hard to establish because of several borderlines. In general, cosmetic formulations have

usually aesthetic and personal hygiene functions. With the modern tendency of the customer to request a cosmetic with some kind of therapeutic nature, more difficulty is to clarify the role of such topical preparations. Here, as well as in the vast majority of circumstances, cosmetics will be concerned only with the common range of biological variation of normal skin. Keeping in mind the fact that skin is composed of a matrix of connective tissue (epidermis) that rests upon the dermis (confining the nerves, blood and lymphatic vessels), it is most likely that lipid-based formulations will be the most appropriate for topical application of actives. Containing physiological and biodegradable lipid ingredients, these formulations resemble the skin' structure and therefore no or little disturbances will occur when applied topically.

During the recent decades, an unmeasured number of research papers have been published describing the use of lipid-based carriers for topical applications. These include liposomes [2], oil-in-water (o/w) emulsions [3], multiple (w/o/w) emulsions [4] and microemulsions [5, 6]. With the purpose of increasing physicochemical stability of both incorporated actives and the system itself, solid lipid nanoparticles (SLN) [7] and nanostructured lipid carriers (NLC) [8] have been developed.

The aim of this paper was to review the scientific literature regarding the several properties of lipid nanoparticles (SLN and NLC) for cosmetic purposes. In addition, several examples of practical applications of these carriers in the cosmetic/pharmaceutical industry are discussed.

Cosmetic features of SLN and NLC

It is a common sense that fine appearance of the skin usually reflects good health and human vigour. Therefore, cosmetic industry is concerned about not only the elegance of the product (prime requirement to be purchased), but also the appearance of the formulation itself, in addition to the protective and pharmaceutical functions about which the cosmetic might be advertized. Here, SLN and NLC play an important role because of their submicron-size and pearl-like nature.

Protective aspects

Many cosmetics appeared in the market having trade-names that suggest some activity, but such activity could never be demonstrated scientifically. Nevertheless, if a claim is made for the activity of a product, it should certainly be capable of scientific evidence. The protective action of SLN and NLC on the skin is well documented in the literature and is mainly related to their small size and lipid composition.

Adhesiveness, occlusion and skin hydration

Submicron-sized particles show adhesiveness when in contact with surfaces. This property has been demonstrated for polymeric nanoparticles and for liposomes. Regarding lipid nanoparticles, it has been published that approximately 4% of lipid nanoparticles with a diameter of approximately 200 nm should form theoretically a monolayer film when *c.* 4 mg of formulation is applied per cm^2 [9]. Being hydrophobic in character, this mono-layered film has an occlusive action on the skin retarding the loss of moisture caused by evaporation. Experimental verification of moisture barrier properties has demonstrated the different degree of occlusion, depending on the size of the applied particles [10]. The occlusion factor can be determined *in vitro* using the test by de Vringer [11]. Briefly, the evaporation of water from a beaker covered with a cellulose acetate filter to which the formulation is applied is determined as a function of time. A beaker covered with the filter paper only is used as reference. An occlusion factor can be calculated, being 0 if no occlusion occurs and water evaporation of sample and reference are identical, being 100 when maximum occlusive effect occurs. It was experimentally observed that the occlusion factor of lipid microparticles (>1 μm diameter) was only 10%, compared to a factor of 50% when using lipid nanoparticles of approximately 200 nm [12]. Although studies of this kind do not fully mimic the natural conditions of moisture loss, the lower the size of the particles, the greater is the barrier for evaporation, whereas the higher the size is, the more the amount of water that will be evaporated. Figure 1 compares this effect based on the different structure of the adhesive microparticle/nanoparticle layer on the skin.

When applying lipid particles onto the skin, a film layer will be formed, having a surface area which is dependent on the particle size. The space filled with air in a layer of optimal packing density is independent on the particle size, which is considered to be 24% if assuming a three-dimensional hexagonal packing of ideal spherical-like particles. However, comparing a layer of nanoparticles

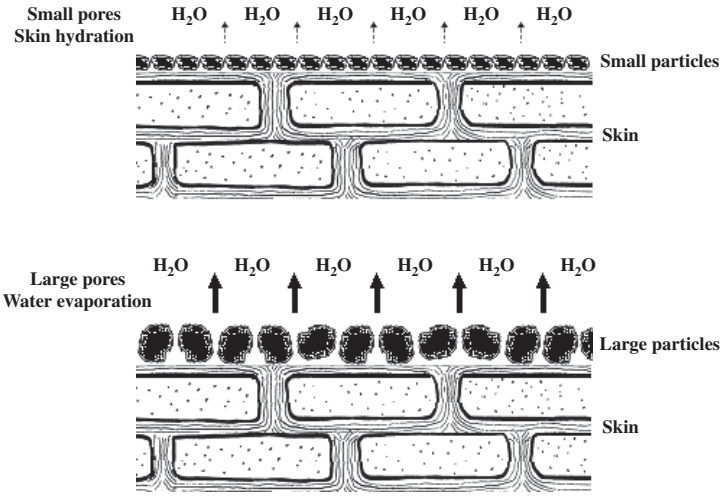

Figure 1 Occlusion effect of lipid particles depending on their size. An aqueous solid lipid nanoparticles or nanostructured lipid carriers dispersion (diameter 500 nm, upper) in comparison with a solid lipid microparticle dispersion (diameter 1 μm, lower).

(Fig. 1, upper) with a layer of microparticles (Fig. 1, lower), the dimensions of the air channels will be much smaller in the former; thus, the hydrodynamic evaporation of water will decrease. On the contrary, larger pores will facilitate the water loss from the surface of the skin and enhance the moisture loss. In certain conditions, e.g. when the horny layer of the skin has become macerated, an increased rate of moisture loss may be desired. By manipulating the particle size of lipid nanoparticles, different effects can be obtained.

The occlusion produced by the typical ointment formulations does not ensure rapid hydration, particularly if the horny layer is excessively dry. It is then desirable to use a preparation capable of supplying water. Lipid nanoparticle suspensions are suitable for the purpose because when applied onto the skin, the pressure leads to fusion of the particles forming a dense film. This fusion is promoted by capillary forces involved during water evaporation. The formation of this nanoparticle film has been proven by scanning electron microscopy [13].

Under ageing the dermis loses much of its elasticity. The skin stretched by muscular movement then fails to shrink back to its normal smoothness and wrinkles are formed. Because of their hydration properties, it can be assumed that lipid nanoparticles may enhance skin elasticity [14], and these particles can further be used to formulate anti-ageing products. It has also been shown the photo-protection properties of carnauba wax-decyl oleate NLC (320–400 nm) both active-free and when used as vehicles for inorganic sunscreens [15].

A consequence of the occlusive properties, SLN and NLC may also be the increase in skin penetration of active ingredients. The total amount of coenzyme Q10 and α-tocopherol penetrated was measured by the Tape™-stripping test (BSN Medical GmbH & Co., Hamburg, Germany) (five strips), after administering the actives both in lipid nanoparticles and in lipid microparticles. When applying the nanoparticle system (200 nm diameter), an increase of 40% occurred in the penetration of actives in comparison with the administration of microparticles (4.5 μm diameter) [12].

Lubrication, smoothness and emolliency

If a cosmetic formulation is intended to be applied between adjacent skin areas or into areas that might rub against clothing, it is usually aimed that such cosmetic should have a lubricant effect. Having a spherical-like shape, lipid nanoparticles impair excellent lubricating action. The evaluation of such properties is usually performed by rheological analysis. Viscoelastic properties of sensitive systems such as colloidal dispersions can be evaluated applying oscillation tests, where the dispersion is subject to a sinusoidal stress, providing information on its intermolecular and inter-particle forces. Thus, viscous and elastic components can be distinguished.

It has been observed that viscoelastic properties of lipid nanoparticle dispersions are dependent on the concentration of lipid phase [16]. The storage modulus (G′), loss modulus (G″) and complex viscosity (Eta) of SLN and NLC of similar composition were evaluated as a function of the frequency at a constant stress amplitude of 5 Pa, applying a frequency sweep test (Fig. 2).

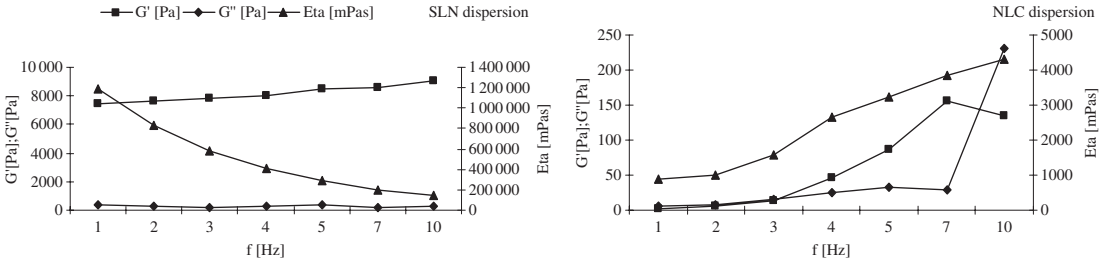

Figure 2 Comparison between oscillation test results of solid lipid nanoparticles and nanostructured lipid carriers (modified after [16]).

In both SLN and NLC, dispersions G′ was higher than the G″ values, which means that both systems are more elastic than viscous in the investigated frequency range. However, SLN were shown to be more pseudoplastic than NLC (decrease of viscosity on the applied frequency). For pure elastic materials, as soon as the force is lowered or released, the deformation recovers; on the contrary, pure viscous materials have a phase shift of 90° because when the applied force reaches its maximum, the material is pulled apart with its highest speed. In practice, these results show that lipid dispersions are sufficiently viscous (or fluid) to be easily applied, and sufficiently elastic to adhere and self-immobilize onto the skin.

One of the aims of the toiletry and cosmetic products was to reduce the desire to scratch that may increase the skin damage. The mechanical barrier and lubricating effect of lipid nanoparticles protect and support the skin, which is particularly useful in case of skin irritation and allergic reactions. The careful adjustment of the emolliency of cosmetic formulations based on lipid nanoparticles is accomplished by the degree of hydration obtained with such systems [17]. This is mainly controlled by the selection of the type of lipids and surfactants used for the production of lipid nanoparticles. These aspects will influence both the index of recrystallinity and the size of the particles [9, 18]. Highly crystalline particles can be produced using very pure lipids such as tripalmitin and tristearin, creating a high occlusiveness and therefore high emolliency. On the contrary, supercooled melts can be obtained when using lipids of low melting temperatures such as tricaprin and trilaurin, which do not show occlusive properties.

Control of pH and osmotic effects

As the surface of the skin normally exhibits a slightly acidic character but with a broad range (pH 4.0 to 7.0) [19], it shows a marked resilience if those values are changed. In most of the cases, it is unlikely that any dermatological preparation will have a deleterious effect by causing a lasting deviation from the physiological pH range. However, strong acidic or alkaline formulations will act as primary irritants and, in those circumstances, the pH obviously has to be adjusted. Another advantage of dispersions of lipid nanoparticles is the fact that these can be produced with optimum pH for topical application. In addition, if necessary, an optimized formulation suitably buffered can be developed.

Some attention should also be given to the osmotic effects of a topical application. Although marked deviation from isotonicity has an irritant effect, the intact horny layer is relatively tolerant to osmotic changes. However, some customers can be less tolerant and a broken surface is also susceptible. In these circumstances, SLN and NLC show suitable isotonicity with the appropriate body fluids. Although the need for an isotonic preparation has no profound therapeutic implications, a markedly hypertonic preparation causes an unpleasant sting and tends to discourage the customer for its use.

Formulation aspects

Whitening effects

The whitening effects of lipid dispersions are one of the most elegant properties of such formulations. This will allow weakening of the coloration of coloured actives such as coenzyme Q10 (yellow). Other examples are those actives that can turn into coloured intermediate products during the shelf life (vitamins) [20]. If incorporation of those actives into SLN or NLC is achieved, a whitening effect is obtained, which is considered more appealing to the customer from the marketing point of view.

Chemical stabilization of actives

One of the most important features of SLN and NLC is their solid matrix. In fact, lipid nanoparticles are derived from o/w emulsions replacing the liquid lipid (oil) by a lipid which is solid both at room temperature and at body temperature. The solid matrix has the advantage of being able to stabilize active ingredients which are chemically labile against degradation by other species, e.g. water or oxygen. The choice of the lipid plays an important role because active must be solubilized/retained within the lipid matrix during storage time. The enhancement of chemical stability of several cosmetic actives such as retinoids [21–26], ascorbyl palmitate [17, 27] and coenzyme Q10 [28, 29] by incorporation into lipid nanoparticles has been published.

Effects to the skin

The protective aspects of cosmetic applications are passive, rather than active. Cosmetic formulations can be used for simple toiletry and protective purposes or can have additionally some skin activity. Regarding the use of lipid nanoparticles, these show some advantages related to their solid core, and the main points to be considered are the release of the active ingredient and its penetration into the skin layers.

Release profile

The release of active ingredients incorporated into SLN and NLC is the prime necessity before an activity onto the skin can be achieved [30]. The release profile will be dependent on the method of production of lipid nanoparticles, the composition of the formulation (i.e. composition and concentration of surfactant), the solubilizing properties of the surfactant for the incorporated active, in addition to the solubility (and concentration) of the active in the lipid matrix (oil/water partition coefficient). These factors influence the inner structure of the particle and therefore the rate of release of incorporated ingredient [26, 31, 32]. Depending on the matrix structure, the release profiles can vary from very fast release, medium release or extremely prolonged release [33].

Skin penetration

Although it is necessary to consider the function of topically applied cosmetic actives in some detail, a majority of those substances are not intended for deeper skin penetration and absorption, and will only have a superficial action. Percutaneous absorption includes both active penetration and absorption into the blood stream, possibly with pharmacological action at sites far from the application area. Cosmetic actives are intended to have a predominantly local effect, thus it is undesired to have an absorption into the blood. Lipid nanoparticle dispersions show the ability to control the rate of penetration of actives into the skin [34].

Penetration of actives when applying common topical base ingredients does not occur to any large extent, although such materials may become enmeshed or entrained in the outer regions of the horny layer when massage is applied. Modulation of release and active penetration into certain layers of the skin can be achieved as a consequence of e.g. the creation of supersaturated systems [33]. These systems can be created by incorporation of lipid nanoparticles into topical formulations (creams, ointments, emulsions, gels). The increase in saturation solubility will lead to an increased diffusion pressure of the active into the skin. During shelf life, the active remains entrapped into the lipid matrix because this latter preserves its polymorphic form. After application of supersaturated cream onto the skin, and because of an increase in temperature and water evaporation, increasing the thermoactivity, the lipid matrix transforms from a more unstable polymorph into a more ordered polymorph leading to the release of active into a system already saturated with the same active, and thus creating a supersaturation effect. Penetration studies using several interesting cosmetic ingredients have been performed, e.g. retinoids [26] and molecular sunscreens [35].

In some special circumstances, a prolonged release of the active but with little penetration may be desired. This is the case of particulate and molecular ultraviolet (UV) blockers, because of the side effects they show if penetration into the skin occurs [36].

Applications of SLN and NLC in cosmetics

A review of the recent literature has been made to collect several examples of cosmetic ingredients and other actives that have been used for incorporation into lipid particles (Table I).

Table I Examples of cosmetic ingredients incorporated into lipid particles

Incorporated cosmetic ingredients	References
Alpha lipoic acid	[37]
Ascorbyl palmitate	[17, 27]
Coenzyme Q10	[28, 29, 38–40]
N,N-diethyl-m-toluamide (DEET)	[41, 42]
Ferulic acid	[43]
Insect repellents	[44]
Isotretinoin	[25]
Juniper oil	[45]
Nicotinamide	[46]
Perfumes	[47, 48]
Podophyllotoxin (POD)	[49]
Retinoids	[21–26, 30, 50]
Sunscreens	[15, 51–56]
Tocopherol	[55, 57–59]
3,4,5-Trimethoxybenzoylchitin	[55]

SLN and NLC as topical vehicles for sunscreens, anti-acne and anti- ageing actives

Lipid nanoparticles proved to have a synergistic effect of the UV scattering when used as vehicles for molecular sunscreens [60]. Advantages taken from these observations are the possibility to reduce the concentration of the molecular sunscreen, consequently its potential side effects, as well as the costs of formulation of expensive sunscreens. In addition, lipid nanoparticles can be explored to formulate sunscreen products with lower and medium sun protection factor.

The loading capacity of lipid nanoparticles depends mainly on the miscibility of the active in the lipid selected for their production. It can range from about 4% (e.g. ferulic acid) [43], 25% (e.g. tocopherol) [59], or even up to 50% and more, in case of well lipid miscible lipophilic actives (e.g. tocopherol and coenzyme Q10). 'Super-loaded' NLC were developed having a sunscreen loading of 70% [56]. This was achieved by using the liquid sunscreen as oil component in the NLC formulation, and cetyl palmitate was added to create a solid matrix.

The first two cosmetic products based on NLC technology were introduced to the market by the company Dr Rimpler GmbH in Wedemark/Hannover, Germany. The products NanoRepair Q10 cream and NanoRepair Q10 Serum (Dr. Kurt Richter Laboratorien GmbH, Berlin, Germany) were introduced to the cosmetic market in October 2005 revealing the success of lipid nanoparticles in the anti- ageing field [61]. Also, in Barcelona in April 2006 the company Chemisches Laboratorium Dr Kurt Richter GmbH (CLR/Berlin, Germany) has reached the cosmetic market with NLC concentrate formulations [NanoLipid Q10 CLR™ and NanoLipid Restore CLR™ (Dr. Kurt Richter Laboratorien GmbH, Berlin, Germany)].

SLN and NLC as topical vehicles for perfumes, fragrances and repellents

Prolonged release of perfumes has the advantage of creating a once-a-day application with prolonged effect over several hours. This was demonstrated to be possible with the use of lipid nanoparticles in comparison with typical o/w emulsions. The release can be slowed down by incorporating perfumes/fragrances in a SLN instead of an oil droplet [47, 48]. In the first 3 h, similar release patterns were observed between lipid nanoparticles and oil droplets because of the release of perfume from the outer layers of the particles. During the remaining 10 h, the release from SLN was prolonged. After 6 h 100% of perfume was released from the emulsion, but only 75% was released from SLN [48]. This property can also be advantageous for the delivery of insect repellents to be applied onto the skin (Table I).

Summary and future trends of SLN and NLC

Solid lipid nanoparticles and NLC have remarkably wide range of properties and have shown greatly to control the skin penetration of several actives. In addition, they do not show toxic effects, and can therefore be safety used in dermatological and cosmetic preparations to achieve distinct features. However, to appreciate the implications of dermatological and cosmetic preparations, the dynamic character of the epidermal tissue needs to be kept in mind in the development of a preparation in accordance with the requirements. This means that natural defensive barrier needs to be respected and this can be accomplished with SLN and NLC because of their biocompatible chemical nature.

Submicron-sized particles exhibit particular properties; therefore, they must be considered a novel class of materials regarding toxicological issues. Nonetheless, SLN and NLC being composed

of lipid materials, and if these are for topical applications for sunscreen formulations, only two UV blockers (i.e. titanium dioxide and zinc oxide) have been considered as unsafe because of the risk of dermal absorption. For such particulate-loaded lipid nanoparticles, special toxicological studies should be performed.

To summarize the advantages of lipid nanoparticles in comparison with traditional cosmetic formulations, one can point the fact that occlusion is achieved without the use of greasy oils such as paraffins, hydration is enhanced because of water retention on the stratum corneum making the skin soft and supple, and a flexible film of lipid particles is formed instead of a hard film created by solid paraffins at the surface of the skin.

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