EXPERT OPINION

Lipid nanoparticles as novel delivery systems for cosmetics and dermal pharmaceuticals

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Introduction: Lipid nanoparticles are innovative carrier systems developed as an alternative to traditional vehicles such as emulsions, liposomes and polymeric nanoparticles. Solid lipid nanoparticles (SLN) and the newest nanostructured lipid carriers (NLC) show important advantages for dermal application of cosmetics and pharmaceuticals.
Area covered: This article focuses on the main features of lipid nanoparticles, in terms of their preparation and recent advancements. A detailed review of the literature is presented, introducing the importance of these systems in the topical delivery of drugs and active substances.
Expert opinion: Lipid nanoparticles are able to enhance drug penetration into the skin, allowing increased targeting to the epidermis and consequently increasing treatment efficiency and reducing the systemic absorption of drugs and cosmetic actives. The complete biodegradation of lipid nanoparticles and their biocompatible chemical nature have secured them the title of 'nanosafe carriers.' SLN and NLC represent a new technological era, which has been taken over by the cosmetic and pharmaceutical industry, which will open new channels for effective topical delivery of substances.

Keywords: lipids, nanostructured lipid carriers, nanotechnology, solid lipid nanoparticles, topical delivery

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1. Introduction

Recent years have been characterized by an increasing interest in nanotechnology that has made its imprint in many fields, including cosmetic and pharmaceutical products. The history of nanoparticle application in pharmaceutical research begins with polymeric nanoparticles that are submicrometer carriers made from non-biodegradable and biodegradable polymers [1]. These vehicles showed important features such as site-specific targeting and controlled release of the incorporated actives but, on the other hands, showed no irrelevant problems, such as cytotoxicity of the employed polymers and a complex industrial scaling up [2]. This is enough to understand why these carriers have a limited importance for the pharmaceutical market.

The nineties have been the cornerstone of nanotechnology applied to the pharmaceutical field. The research conducted by the groups of Prof. Rainer H. Muller and Prof. Maria Rosa Gasco have produced alternative nanoparticles made from solid lipids, also known as solid lipid nanoparticles or, more simply, SLN [3,4].

During the last years, the interest on lipid nanoparticles increased significantly as evidenced by the high number of published articles regarding this topic. Lipid nanoparticles show the capability to put together the advantages of other nanometric carriers (such as liposomes, nanoemulsions or the above-mentioned polymeric nanoparticles) minimizing the problems associated with these vehicles. From a certain point of view, they were a natural and logical evolution of these nanocarriers. In fact, the first

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Article highlights.

- Lipid nanoparticles possess important features useful for topical delivery of drugs and active substances.
- Both SLN and NLC are able to enhance drug penetration into the skin and to target the epidermis reducing drug systemic absorption.
- In the cosmetic field, lipid nanoparticles are able to enhance the chemical stability of actives sensitive to light oxidation and hydrolysis.
- Skin hydration and the occlusion effect depend on the small size of lipid nanoparticles and their ability to form a thin film on the skin surface.
- The complete biodegradation of lipid nanoparticles and their biocompatible chemical nature have secured them the title of 'nanosafe carriers.'

This box summarizes key points contained in the article.

generation of lipid nanoparticles (SLN) derives from the substitution of nanoemulsion oil phase (liquid) with a solid lipid.

Main advantages associated with SLN compared with other colloidal system are high biocompatibility, good physical stability, possibility of controlled release of drug and active substances, easy large scale production and cheap raw materials. Despite these important features, the SLN system shows some limitations such as drug expulsion phenomena, particle concentration in the aqueous dispersion ranging from about 1% to a maximum of only 30%, insufficient total drug payload due to the limited solubility of drugs in the solid lipid [5-8].

At the turn of the century, in order to overcome these limitations, a second generation of lipid nanoparticles was developed the so-called NLC or nanostructured lipid carriers. NLC innovation consists in the addition of a liquid lipid to form a blend of solid and liquid lipids. This addition distorts the formation of perfect lipid crystals minimizing drug expulsion phenomena [9]. NLC lipid matrix, obtained from a blend of a solid lipid with a liquid lipid, is characterized by imperfections providing space to locate a high amount of actives.

1.1 Main ingredients and techniques for the production of lipid nanoparticles

SLN are composed of solid lipid (0.1 – 30% w/w) dispersed in an aqueous medium, stabilized with 0.5 – 5% (w/w) of surfactant, while NLC are generally produced using blends of solid and liquid lipids mixed in a ratio of 70:30 up to a ratio of 99.9:0.1 [10]. The lipids used to prepare both SLN and NLC are triglycerides, fatty acids, waxes and partial glycerides. The surfactants are chosen depending on the administration route and are often used in association in order to prevent particle agglomeration more efficiently. The parenteral route of administration limits the number of surfactants to be used, while the topical application offers a wider choice of use. An overview of ingredients commonly used for the preparation of lipid nanoparticles for topical application is reported in **Table 1**.

The production of lipid nanoparticles can be realized by different techniques. Generally, all the techniques required a common step, that is, the formation of a precursor oil-in-water 'nanoemulsion' followed by subsequent solidification of the dispersed lipid phase. Nanoemulsion preparation became the critical step when the aim is to prepare lipid nanoparticles with a very small particle size and a narrow polydispersity index, for instance, SLN for parenteral administration.

To overcome the polydispersity and larger than desired droplet sizes, researchers often subject the precursor emulsions to large mechanical forces such as *high shear homogenization*, *high pressure homogenization* and *ultrasonication*.

High shear homogenization (HSH) and ultrasound (US) are 'cheap and fast' dispersing techniques even if both methods show some drawbacks. Very often, for instance, the dispersion quality obtained by HSH technique is compromised by the presence of microparticles, while US technique can be affected by metal contamination. Since these problems are often due to long processing times (for both HSH and US techniques), a possible way to minimize these drawbacks is the association of two short cycles of HSH and US during the preparation [11].

High pressure homogenization (HPH) represents the main and most known method to produce lipid nanoparticles and it is subdivided into hot and cold techniques. Hot homogenization is the most used approach between HPH methods. Notwithstanding it is a 'hot' method, it may be suitable for temperature-sensitive compounds since the time of exposure to an elevated temperature is relatively short. The main flaw is the difficulty to incorporate hydrophilic active/ingredients due to drug distribution into the aqueous phase during homogenization [12].

The cold homogenization is recommended for preparing lipid nanoparticles containing either highly temperature-sensitive compounds or hydrophilic compounds.

Other valid methods of preparation are the *microemulsion technique* and *the emulsification-solvent evaporation* or *solvent diffusion methods*.

The first method is based on the evidence that the addition of a microemulsion to water leads to precipitation of the lipid phase forming fine particles [4]. Instead the emulsification-solvent evaporation or solvent diffusion methods belong to the solvent-based approaches [13]. In these techniques, the lipophilic material is dissolved in a water-immiscible organic solvent that is emulsified in an aqueous phase. After the solvent evaporation, a nanoparticle dispersion is formed by precipitation of the lipid in the aqueous medium. The advantage of these methods is the avoidance of any thermal stress while the main problem is the complete removal of the solvent used during the preparation [14].

2. Application of lipid nanoparticles in cosmetics

There are really few differences between the application of lipid nanoparticles in pharmaceutical products for dermal delivery

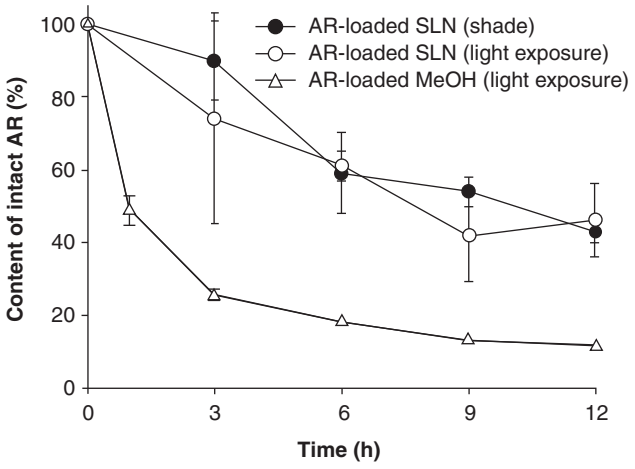

Figure 1. Effect of light on the chemical stability of all trans retinol (AR) in solid lipid nanoparticles (SLN). SLN were prepared with 3 mg/g of AR, 100 mg of surfactant mixture eggPC–Tween 80 (67:33, w/w). And one group of samples was exposed to light and the other group was shaded from light. Data represent means ± SD (n = 3).
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and in cosmetic field and these differences are mainly concerned to technological aspects. Notwithstanding this similitude, the time for production and market introduction of a cosmetic product is much shorter compared with a dermal pharmaceutical due to minor regulatory hurdles. In **Table 2** are reported some examples of lipid nanoparticle-based cosmetic products that are currently on the market.

One of the most important features of lipid nanoparticles is the ability to enhance the chemical stability of actives that are sensitive to light, oxidation and hydrolysis. Some examples reported in literature include vitamin E [15,16], ascorbyl palmitate [17-20], retinol and retinoids (**Figure 1**) [21-24], -carotene [16,25], lipoic acid [26,27], lutein [28] and some sunfilters [29-31].

This feature is due to the solid lipid matrix of lipid nanoparticles; therefore, the choice of the lipid plays a critical role because the active compounds must be solubilized and or retained within the lipid matrix during storage.

The occlusion effect is another important feature reported for SLN [32,33] and NLC [34,35]. Occlusion is responsible of a reduced skin water loss and of a consequent increase in skin hydration. Generally an increase in this effect is observed with a decrease in particle size, which consents a high adhesiveness and a fast film formation. Muller *et al.* assessed that with lipid nanoparticles (both SLN and NLC), the extent of the occlusion, and consequently the skin hydration, can be adjusted in a controlled way [36]. Particularly, occlusion can be increased by decreasing the particle size (at given lipid concentration) or alternatively at given particle size by increasing the number of particles (concentration of lipid).

In general, skin occlusion increases the stratum corneum hydration and consequently influences the percutaneous absorption of active ingredients contained in the cosmetic formulation. Numerous scientific evidences report lipid nanoparticle capability to control the rate of penetration of actives into the skin, so limiting the undesired active absorption into the systemic bloodstream [37,38]. Release profile from lipid nanoparticles is drastically influenced by several variables such as type of lipid (solid or oil) used to formulate the vehicle, concentration of surfactant (or surfactants), solubility and concentration of active in the lipid matrix and, least but not last, the method of production of lipid nanoparticles [39].

The prolonged release of actives with a scarce penetration through the skin is particularly required by cosmetic market. Molecular UV blockers, perfumes and repellents are typical examples of products for whom a prolonged release is required [40].

Some significant studies regarding this application of lipid nanoparticles are given below.

Wissing and Muller evaluated the efficacy of lipid nanoparticles and of a conventional o/w emulsion for the delivery of benzophenone 3, a well-known molecular sunfilter. Lipid nanoparticles showed to possess the characteristics of physical UV blockers on their own and so they improved the photoprotection level of benzophenone 3 in a synergistic way [41]. The same authors studied the influence of the inclusion in SLN on the release rate of the molecular sunscreen oxybenzone [42]. The results showed that the rate of release is strongly dependent on the formulation and could be decreased by 30/60% in SLN formulation (**Figure 2**). The highest loading capability of NLC with respect to SLN was investigated by Xia and coworkers, in an attempt to formulate a sunscreen with an elevated sun protection factor [43]. The results demonstrated that NLC was able to load an amount of molecular sunscreen up to 70%, which is appropriate to obtain a sunscreen endowed by a high sun protection factor. Similar evidences were obtained by Nikolic and coworkers [44]. The authors demonstrated that *in vitro* sun protection factor can be increased up to approximately 45% when the organic UV filters were incorporated into NLC, in comparison with a reference nanoemulsion. Puglia and coworkers evaluated the *in vitro* percutaneous absorption through excised human skin of octyl methoxy cinnamate (OMC) from SLN and NLC [31]. *In vitro* results showed that OMC, when incorporated in viscosized NLC dispersions (OMC-NLC), exhibited a lower flux with respect to viscosized SLN dispersions (OMC-SLN) and two reference formulations: a microemulsion (OMC-ME) and a hydroalcoholic gel (OMC-GEL). Photostability studies revealed that viscosized NLC dispersions were the most efficient at preserving OMC from UV-mediated photodegradation.

Diethyltoluamide (DEET) is widely used ingredient in insect repellent products. Unfortunately, its use is often compromised by a massive systemic absorption. Iscan and coworkers formulated DEET-loaded solid lipid nanoparticles in order to reduce the percutaneous permeation and to maintain

Table 1. Main ingredients used for the preparation of lipid nanoparticles for topical application.

Solid lipids	Literature
Beeswax	[44,52]
Carnauba wax	[28,43,44]
Cetyl alcohol (Lorol® C16)	[20]
Cetyl palmitate (Precifac® ATO 5, Cutina® CP)	[15,23,26,28,33,34,42,50,51]
Glyceryl behenate (Compritol® 888 ATO)	[11,17,19,21,23,26,30-32,38,43,44,47-49,50,54,55,57,58,67,68,71,75,84]
Glyceryl Cocoate (and) Hydrogenated Coconut Oil (and) Ceteareth-25 (Softisan® 601)	[26,49]
Glyceryl monostearate (Imwitor® 900, Geleol®)	[20,21,26,49,50,52,59,75]
Glyceryl palmitostearate (Precirol® ATO 5)	[47-51,62,63,66,74,75,77-79]
Glyceryl Trimyristate (Dynasan® 114)	[26,33,47,48,50,56,81]
Glyceryl Tripalmitate (Dynasan® 116)	[21,23,26,27,33,41,51,70,71,72]
Glyceryl Tristearate (Dynasan® 118)	[26,44,50,76]
Hard fat (Witepsol® E 85, Suppocire® NA 150)	[18,83]
Hydrogenated Coco-Glycerides (Softisan® 142)	[50]
Hydrogenated Palm Oil (Softisan® 154)	[44]
PEG-8 Beeswax (Apifil®)	[20,27,44]
Stearic acid	[16,37,45,46,57,82]
Stearyl alcohol	[26]
Oil	**Literature**
Caprylic/Capric Triglyceride (Miglyol® 812)	[11,18,27,28,31,32,34,41,43,44,49,54,55,57,58,63,70,71,84]
Castor oil	[57,59]
Squalene	[77,79]
Oleic acid	[63,78,82]
Surfactants	**Literature**
Poloxamer 188 (Lutrol® F68, Pluronic® F68)	[11,17,27,31,37,38,47-49,54,55,58,63,71,77,79,82,84]
Polysorbate 80 (Tween® 80)	[20,21,24,28,42,46,49,50,51,56,59,66,73,74-78,81]
Polysorbate 20 (Tween® 20)	[16,45,59]
Tyloxapol	[19,33,41,70-72]
Polyglyceryl-3 Methylglucose Distearate (TEGO® CARE 450)	[15,18,20,33,34,42]
Sodium cholate	[48,71]
Phosphatidylcholine (Epikuron® 200, Phospholipon® 80/H)	[17,19,21,77,83]
Soybean lecithin (Lipoid® S75)	[37,47,66]

the efficacy of the active on the skin surface for a long duration [45]. Results showed that incorporation of DEET into solid lipid particles reduced its release rate and skin permeation. In a more recent paper, Puglia and coworkers studied the effect of concurrent encapsulation of DEET and OMC in SLN on their *in vitro* permeation profiles through excised human skin [46]. Results from the *in vitro* study demonstrated that the particles were able to reduce the skin permeation of the two cosmetic ingredients in comparison with an oil-in-water emulsion.

3. Application of lipid nanoparticles in topical drug delivery

3.1 Lipid nanoparticles and cutaneous inflammations

3.1.1 Glucocorticoids

Topical corticosteroids are widely used for the treatment of different kind of dermatitis. Maia *et al.* investigated the effect of prednicarbate incorporation into SLN, obtaining an increase in drug penetration through human skin of about threefold compared with a conventional cream containing the same amount of the glucocorticoid [47]. In a more recent work, the same authors demonstrated the key role of SLN on prednicarbate epidermal targeting [48].

Different evidences on glucocorticoid-loaded SLN for epidermal targeting were obtained by Sivaramakrishnan *et al.* [49]. In *in vitro* experiments performed using excised human skin, the authors observed that SLN loaded with betamethasone valerate and prednicarbate did not guarantee a drug epidermal targeting and besides a low drug incorporation into lipid matrix was observed too.

In a more recent paper, Jensen and coworkers evaluated the influence of lipid composition and drug lipid solubility on the *in vitro* release profile of corticosteroids from SLN for topical administration [50]. The results emphasize that the corticosteroid solubility in the lipid phase greatly influences drug distribution in the lipid particles and release properties. Therefore, the knowledge of drug solubility and lipid polarity contributes to optimize SLN release properties.

Table 2. Examples of lipid nanoparticle-based cosmetic products that are currently on the market.

Product name	Main active ingredients	Producers
Cutanova Cream Nano Repair Q10 Intensive Serum NanoRepair Q10 Cutanova Cream NanoVital Q10	Q 10, polypeptide, Hibiscus extract, ginger extract, ketosugar Q 10, polypeptide, mafane extract Q 10, TiO_2, polypeptide, ursolic acid, oleanolic acid, sunflower seed extract	Dr. Rimpler GmbHWedemark - Germany
SURMER Crème Legère Nano-Protection SURMER Crème Riche Nano- Restructurante SURMER Elixir du Beauté Nano- Vitalisant SURMER Masque Crème Nano-Hydratant	kukuinut oil, Monoi Tiare Tahiti®, pseudopeptide, milk extract from coconut, wild indigo, noni extract	Lancray International S.A. Paris (France)
NanoLipid Restore CLR Nanolipid Q10 CLR Nanolipid Basic CLR NanoLipid Repair CLR	black currant seed oil containing ω-3 and ω-6 unsaturated fatty acids coenzyme Q10 and black currant seed oil caprylic/capric triglycerides black currant seed oil and manuka oil	Chemisches Laboratorium Dr. Kurt Richter, (CLR) Berlin (Germany)
IOPE SuperVital Cream Serum Eye cream Extra moist softener Extra moist emulsion	coenzyme Q10, ω-3 und ω-6 unsaturated fatty acids	Amore Pacific Corp. (SouthKorea)
NLC Deep Effect Eye Serum NLC Deep Effect Repair Cream NLC Deep Effect Reconstruction Cream NLC Deep Effect Reconstruction Serum	coenzyme Q10, highly active oligosaccharides Q10, TiO_2, highly active oligosaccharides Q10, Acetyl Hexapeptide-3, micronized plant collagen, high active oligosaccharides in polysaccharide matrix	Beate Johnen, Aschheim (Germany)
Regenerationscreme Intensiv	*Macadamia Ternifolia* seed oil, Avocado oil, Urea, Black currant seed oil	Scholl, Mannheim, Germany
Swiss Cellular White Illuminating Eye Essence Swiss Cellular White Intensive Ampoules	Glycoprotiens, Panax ginseng root extract, Equisetum Arvense extract, Camellia Sinensis leaf extract, Viola Tricolor Extract	Laboratoires La Prairie SA Zurich, Switzerland
SURMER Creme Contour Des Yeux Nano-Remodelante	kukuinut oil, Monoi Tiare Tahiti®, pseudopeptide, hydrolyzed wheat protien	Lancray International S.A. Paris (France)
Olivenöl Anti Falten Pflegekonzentrat Olivenöl Augenpflegebalsam	Olea Europaea Oil, Panthenol, Acacia Senegal, Tocopheryl Acetate Olea Europaea Oil, Prunus Amygdalus Dulcis Oil, Hydrolized Milk Protein, Tocopheryl Acetate, *Rhodiola rosea* Root Extract, Caffeine	Dr. Theiss Naturwaren GmbH, Homburg (Germany)

The effect of lipid nanoparticles on penetration profile of glucocorticoids was studied in intact and barrier-impaired skin as well [51]. The results of the *in vitro* percutaneous absorption studies evidenced that, when formulated in SLN, the permeation of the drug across the skin was significantly reduced compared with a reference ointment. Further analysis pointed out that a large proportion of drug remained in the upper layer of the skin. This result was most likely related to the large surface area and adhesive properties of SLN.

Similar results were obtained by Zhang and coworkers [52]. The researchers formulated betamethasone 17-valerate-loaded SLN for prolonged and localized delivery of active drugs into the skin. Monostearin SLN showed remarkable controlled-release properties and a significant epidermis drug reservoir, while beeswax SLN failed this aim. Again the diffusions of corticosteroids into the skin appeared to be dependent on the lipid composition of SLN.

The work of Schlupp and coworkers described the results of drug release and skin penetration from SLN of prednisolone, prednicarbate and betamethasone 17-valerate [53]. The results emphasize that SLN influence skin penetration by a mechanism of interaction between drug carrier and skin surface. This

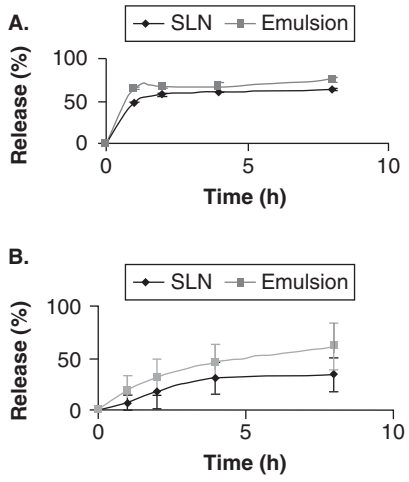

Figure 2. A. Franz diffusion cell: release of oxybenzone from solid lipid nanoparticles (SLN) and emulsion containing 5% oxybenzone with regard to the lipid mass. **B.** Franz diffusion cell: release of oxybenzone from SLN and emulsion containing 10% oxybenzone with regard to the lipid mass.
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interaction appears to be strongly influenced by the lipid nature and the nanosize of the carrier but not to be derived by testing drug release.

3.1.2 NSAIDs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used widely in the treatment of painful musculoskeletal conditions. Lipid nanoparticles have been studied as vehicles for NSAID topical administration in order to increase their local soft-tissue and joint concentration, while reducing their systemic distribution to avoid side effects.

Indomethacin is one of the most potent NSAIDs, used topically for the treatment of dermatitis and rheumatic diseases. Ricci *et al.* investigated indomethacin percutaneous absorption from NLC-based gels and a reference gel formulation [11]. The *in vitro* percutaneous absorption studies showed lower drug fluxes through excised human skin membranes from NLC-based formulations in comparison with gel control.

NLC-based formulation showed a more prolonged anti-inflammatory activity compared with control formulation. Furthermore, after the application of this formulation, higher amounts of indomethacin were found in the stratum corneum.

In order to study deeply inside the mechanism of indomethacin release from lipid nanoparticles, Castelli and coworkers characterized indomethacin-loaded SLN and NLC by differential scanning calorimetry (DSC) [54]. DSC static and dynamic measurements performed on indomethacin-loaded lipid nanoparticles showed that the oil nanocompartment incorporated into NLC solid matrix drastically influenced drug distribution inside the nanoparticle system. Therefore, the authors assessed that the controlled release of the drug from NLC could be explained considering both drug partition between oil nanocompartments and solid lipid and a successive partition between solid lipid and water.

The importance of lipid nanoparticle approach for NSAID topical administration was treated by Puglia and coworkers in another work regarding the *in vitro* evaluation of percutaneous absorption of ketorolac (a powerful NSAID endowed with analgesic activity) through excised human skin [55]. The authors, in particular, evaluated two alternative strategies to optimize the drug delivery: the synthesis of some polyoxyethylene glycol ester derivatives of ketorolac and the drug-loaded NLC. From the results obtained, skin permeation of ester prodrugs was significantly enhanced compared with ketorolac, while the results of drug release from NLC outlined that these carriers were ineffective in increasing ketorolac percutaneous absorption. The result of the present work is in line with the evidences previously described and again it seem that NLC are more appropriate for sustained release due to the possible formation of a drug reservoir into the skin.

Flurbiprofen is a well-known NSAID used for the treatment of different musculoskeletal disorders.

Jain and coworkers investigated the effect of flurbiprofen-loaded SLN on *in vitro* drug release [37]. Particularly the authors evaluated the effect of SLN inclusion in a topical formulation, comparing the flurbiprofen release profile from SLN dispersion with respect to SLN gel formulation. *In vitro* drug release, determined using cellophane membrane, showed that SLN dispersion exhibited higher drug release compared with SLN gel formulation. Both the SLN dispersion and SLN gel formulation possessed a sustained drug release over 24-h period, even though this sustained activity was more evident with the SLN containing gel formulation. *In vivo* results, regarding the evaluation of edema inhibition by flurbiprofen, corroborated the *in vitro* evidences.

Results of flurbiprofen sustained release from lipid nanoparticles have been found by Bhaskar and coworkers as well [56]. The authors formulated both SLN- and NLC-enriched hydrogels and evaluated, by *in vitro* and *in vivo* models, the transdermal delivery of flurbiprofen. The administration of flurbiprofen through gels resulted in sustained and continued drug release for 24 h. *In vivo* anti-inflammatory activity of both the formulations, SLN and NLC based, was maintained for longer period of time due to slow release of the drug.

Gonzalez-Mira and coworkers formulated NLC composed of stearic acid or glyceryl behenate as solid lipids and a mixture of medium-chain triglycerides and castor oil as liquid lipids, for skin administration of flurbiprofen [57]. The results obtained from permeation studies evidenced that the NLC dispersions showed higher fluxes and a higher penetration-enhancing ratio compared with reference vehicle. The authors postulated that skin permeation of drug released from lipid matrices is directly related to polymorphic transition undertaken by lipid molecules. These transitions are induced

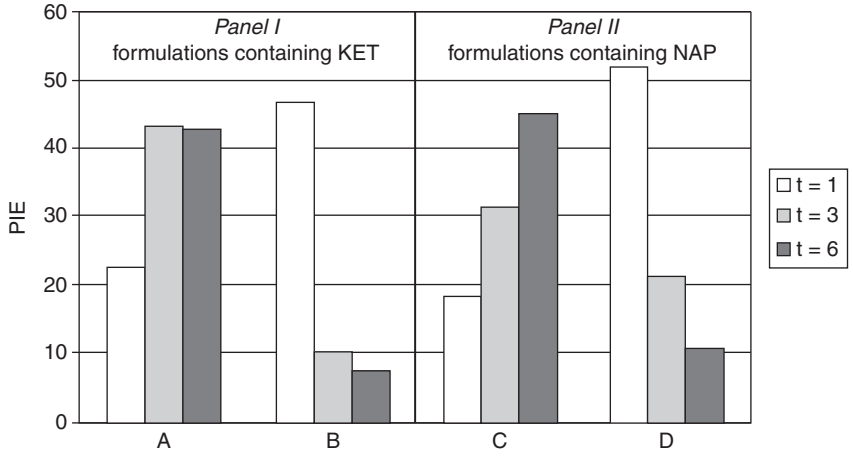

Figure 3. Percentage of inhibition of the erythema by the different topical formulations containing ketoprofen **(A: ketoprofen loaded NLC hydrogel and B: control hydrogel)** or naproxen **(C: naproxen loaded NLC hydrogel and D: control hydrogel)**. Data represent the mean for ten subjects.
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by water evaporation phenomena from the NLC dispersion after its application onto the skin.

Ketoprofen and naproxen are two NSAIDs used for the treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. Puglia *et al.*, formulated ketoprofen- and naproxen-loaded NLC formulations and determined the permeation profiles of the two drugs by *in vitro* and *in vivo* experiments [58]. The results showed that NLC were able, on one hand, to reduce drug penetration and, on the other, to increase the drug permeation and accumulation in the stratum corneum. Furthermore, an interesting anti-inflammatory prolonged effect was observed for drug-loaded NLC compared with the reference forms (**Figure 3**).

Joshi and Patravale investigated the *in vitro* release and the *in vivo* anti-inflammatory activity of valdecoxib and celecoxib, two well-known NSAIDs, when loaded in NLC-based gels [59,60]. The results evidenced that the NLC-based gels guaranteed a prolonged activity and a higher skin tolerability with respect to marketed formulations.

3.2 Lipid nanoparticles and acne

Acne is the most common cutaneous disorder of multifactorial origin with a prevalence of 70 – 80% in adolescence [61]. Although topical therapy has an important position in acne treatment, side effects associated with various topical antiacne agents affect their utility and patient compliance. Lipid nanoparticles, endowed with important features for skin administration, can play a pivotal role in improving the topical delivery of antiacne agents by enhancing their dermal localization with a concomitant reduction in their side effects.

Münster *et al.* have reported the use of SLN as carriers for follicular targeting of nonsteroidal antiandrogen prodrug RU 58841 myristate (RUM) [62]. RUM-loaded SLN were found to exhibit follicular uptake and were localized in the upper skin layers. SEM studies revealed the presence of intact SLN in hair follicles. Therefore, SLN can act as local depot at the target site and further sustain the release of the drug along with concomitant reduction in its systemic absorption resulting in improved acne treatment.

Cyproterone acetate is an antiandrogen used in therapy to reduce sebum secretion rate and acne lesions. Stecova and coworkers observed that cyproterone acetate-loaded SLN increased the drug skin penetration of about fourfold compared with a cream and a nanoemulsion used as reference vehicles. Instead the incorporation into the lipid matrix of NLC resulted in a two- to threefold increase in cyproterone acetate absorption [63].

Another strategy used to treat acne symptoms is the use of retinol and retinoids [64]. Shah and coworkers evaluated the effect of solid lipid nanoparticles on tretinoin topical delivery and the vehicle ability in improving the photostability of the drug [21]. The results pointed out a significant improvement in tretinoin photostability, while *in vitro* permeation studies through rat skin showed a similar permeation profile between tretinoin-loaded SLN and a marketed cream.

In another study, Mandawgade *et al.* prepared tretinoin-loaded SLN using highly purified grade stearine obtained from fruit kernel fats [65]. Tretinoin-loaded SLN-based gels showed lesser skin irritancy, greater skin tolerance, occlusive effect and slow drug release than a commercial product.

Liu and coworkers studied the SLN approach in an attempt to reduce skin irritation and systemic absorption of isotretinoin [66]. The results of *in vitro* permeation studies demonstrated that isotretinoin-loaded SLN consented a high cumulative amount of drug in the skin, showing, at same time, a skin targeting effect.

Castro *et al.* prepared different formulations of all-trans retinoic acid (ATRA)-loaded SLN using glyceryl behenate as

lipid matrix and obtaining nanoparticles characterized by high encapsulation efficiency and stability [67]. The same researchers evaluated, in *in vivo* experiments, both the effect of SLN on the reduction of skin irritation due to ATRA topical administration and the comedolytic effect of ATRA-loaded SLN formulations [68]. ATRA-loaded SLN, as compared with placebo, showed a significant comedolytic effect similar to that observed for commercial products, while produced, in *in vivo* experiments, a significant reduction of ATRA-induced skin irritation compared with marketed products.

3.3 Lipid nanoparticles and skin mycoses

Superficial fungal infections of skin are among the most widespread diseases known to man [69]. Topical therapy is the best choice for the treatment of these pathologies since it lends itself to self-administration, patient compliance and absence of systemic effects.

SLN and NLC have been investigated for topical delivery of different antifungal agents.

Clotrimazole and ketoconazole are two antifungal agents widely used for the treatment human mycoses. Souto and coworkers prepared clotrimazole-loaded lipid nanoparticles and evaluated the drug permeation profile from the nanoparticle system [70]. A significant difference between SLN and NLC carrier type was found in terms of clotrimazole release. In particular, NLC loaded with clotrimazole showed a faster drug release than SLN-loaded clotrimazole, even though the release rate was mainly influenced by drug concentration. A fast release was observed with low concentration while high concentrations were usually responsible for clotrimazole prolonged release.

In a recent work, Souto and Müller observed that lipid nanoparticles proved to preserve the amount of loaded clotrimazole and ketoconazole from a long storage time at different temperatures and in another *in vitro* study they observed an interesting prolonged effect of clotrimazole when vehiculated with SLN [71,72].

Econazole nitrate and miconazole are two antifungal used in therapy to treat various skin infections. Sanna and coworkers investigated the topical delivery of econazole nitrate from SLN [73]. At this aim, *ex vivo* drug permeation tests were carried out using porcine stratum corneum, while *in vivo* study of percutaneous absorption was carried out by tape stripping technique. The results showed that the controlled drug delivery properties of lipid nanoparticles are strictly influenced by their lipid content. *In vivo* studies demonstrated that SLN promoted a rapid skin penetration of econazole nitrate and improved the drug diffusion in the deeper skin layers after 3 h of application compared with a reference formulation. The same authors, in a more recent work, demonstrated that permeation profiles of econazole nitrate from lipid microparticles were influenced not only by lipid content but also by the particle size [74].

Bhalekar and coworkers studied through an *ex vivo* model whether the inclusion of miconazole nitrate in SLN could influence the permeation profile of the drug through the skin [75]. The results of experimentation have pointed out an increased uptake of miconazole in skin when enclosed in lipid nanoparticles with respect to a marketed gel. Instead, a miconazole nitrate-loaded SLN preparation, formulated by Jain and coworkers, showed a sustained drug release over 24-h period and in tape stripping experiments, a 10-fold greater retention of the drug compared with reference formulations [76].

3.4 Lipid nanoparticles and psoriasis

Psoriasis is a chronic inflammatory skin disorders that may drastically impair the patient quality of life. Topical therapy is the most commonly used in patients, even though the use of topical formulations based on conventional excipients shows some drawbacks that limit drastically their use in therapy. With the advent of newer drug delivery systems such as lipid nanoparticles (SLN and NLC), the possibility to improve the efficacy and safety of the topical products has increased manifold.

Psoralen is the parent compound of a family of natural products known as furocoumarins. It occurs naturally in the seeds of *Psoralea corylifolia* and is widely used in PUVA (= Psoralen + UVA) treatment for psoriasis. Fang and coworkers studied the percutaneous absorption of three psoralen derivatives (5-methoxypsoralen, 8-methoxypsoralen and 4,5,8-trimethylpsoralen) from SLN and NLC using mice skin as permeation membrane [77]. The permeation of psoralens increased in the order 8-methoxypsoralen> 5-methoxypsoralen> 4,5,8-trimethylpsoralen for all formulations tested. Enhanced permeation and controlled release of psoralen delivery were both achieved using NLC while SLN were not able to improve psoralen skin permeation over the aqueous suspension.

Acitretin, a retinoid widely used for the treatment of severe psoriasis in adults, was included by Agrawal and coworkers in NLC system to improve its topical delivery [78]. The NLC were incorporated in a gel base and *in vitro* skin studies in human cadaver skin and double-blind clinical studies in psoriatic patients were conducted. A higher deposition of acitretin was found in human cadaver skin from the acitretin-loaded NLC-based gel compared with a reference gel. Furthermore, clinical studies demonstrated significant improvement in therapeutic response and reduction in local side effects with acitretin-loaded NLC-based gel (**Figure 4**).

Lin *et al.* studied the combination of calcipotriol and methotrexate in NLC for topical therapy of psoriasis [79]. The permeation profile of each drug alone or in association was determined using hyperproliferative skin as permeation barrier. Calcipotriol-loaded NLC system provided drug fluxes slightly higher or comparable with the hydro-alcoholic gel used as reference formulation, while the methotrexate amount permeated through the skin was significantly higher than that with the control.

3.5 Lipid nanoparticles and atopic dermatitis

Atopic dermatitis is a chronic relapsing form of eczema characterized by scaling, itchy, inflamed skin that can be

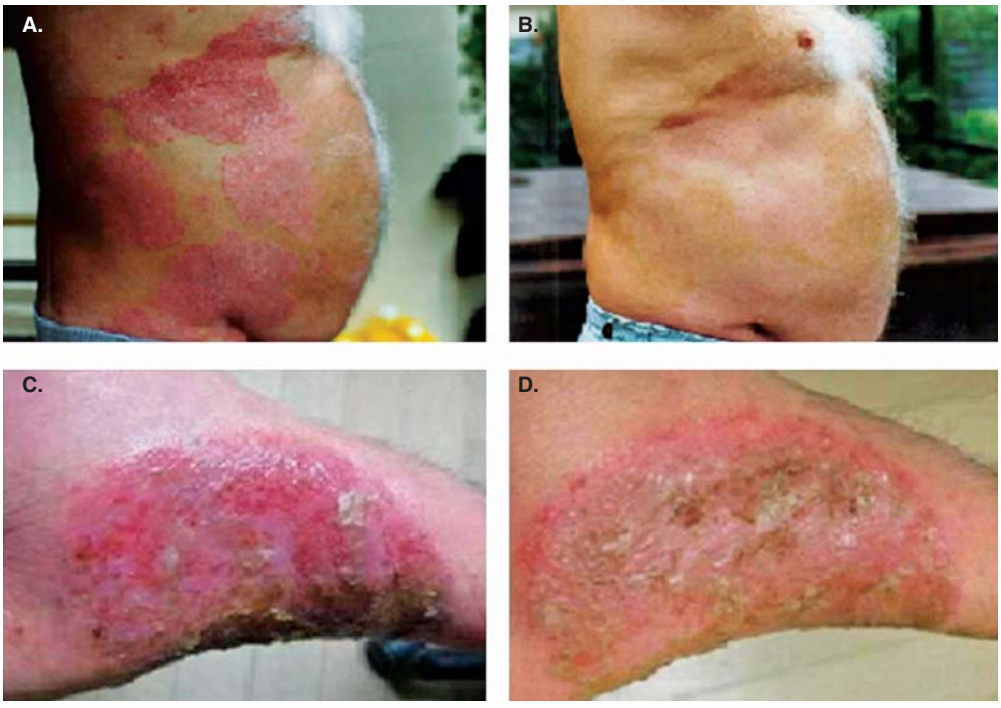

Figure 4. Photographs of psoriatic patient before (A) and after **(B)** treatment with acitretin-loaded nanostructured lipid carriers (NLC) gel. Photographs of psoriatic patient before **(C)** and after **(D)** treatment with a plain acitretin gel.
Reproduced with permission from Elsevier [78].

triggered by an interplay of genetic, immunologic and environmental factors [80].

Tacrolimus is the drug of choice that inhibits T-cell activation resulting in suppression of inflammation. Lipid nanoparticles have been studied as vehicles for topical administration of tacrolimus, with the attempt to target the drug to site of action limiting the production of adverse effects. Pople and coworkers formulated tacrolimus-loaded lipid nanoparticles and evaluated *in vitro* drug release using pig ear skin, while the targeting and localization of drug in various layers of the skin has been studied in an *in vivo* model [81]. *In vitro* studies revealed much higher drug release, skin penetration and enhanced skin accumulation as compared with a marketed product. Tacrolimus-loaded lipid nanoparticles showed significantly higher drug levels penetrating into deeper skin layers where dendritic cells responsible for immunopathogenesis of the atopic dermatitis mainly reside.

3.6 Other applications of lipid nanoparticles

The hair loss treatment is a topic that is currently the object of study by researchers for a potential application of the lipid nanoparticle approach.

Minoxidil is an antihypertensive showing an interesting side effect represented by hair growth. Common side effects of minoxidil include redness or irritation at the treated area. Furthermore, alcohol present in topical preparations may dry the scalp, resulting in dandruff. Silva and coworkers have developed minoxidil-loaded NLC as an alternative to conventional topical alcoholic solutions [82]. Minoxidil-loaded NLC were approximately 250 nm in size before the entrapment in a freshly prepared hydrogel and remained below 500 nm after the addition to the gel network. More recently, Padois *et al.* prepared minoxidil-loaded SLN and evaluated their effectiveness in terms of skin penetration and skin corrosion in comparison with marketed formulations [83]. SLN suspension has been shown as efficient as commercial solutions for skin penetration and was noncorrosive, while commercial solutions had a corrosive potential.

The use of local anesthetics is widely diffused to alleviate pain after surgery, trauma or medical procedures. Their action is characterized by a rapid but short effect, compared with the potential duration of pain, so the development of a topical drug delivery system, which is not only able to release the anesthetic in a prolonged fashion at the site of action but also able to reduce the risk of systemic toxicity, could be particularly useful.

Puglia and coworkers evaluated the potential use of NLC for the topical delivery of benzocaine and lidocaine, two popular local anesthetics [84]. The release pattern of the two anesthetics was evaluated *in vitro* determining their percutaneous absorption through excised human skin and *in vivo* by the radiant heat tail flick test effected in mice. *In vitro* evidences show that both anesthetics, when incorporated in lipid nanoparticles dispersions, exhibited a lower flux compared

with a reference formulation. *In vivo* studies demonstrated that benzocaine and lidocaine can be released in a prolonged fashion when incorporated in NLC.

4. Conclusions

SLN and NLC have produced a significant contribution to the development of a new and safe strategy for drug and cosmetic active delivery to the skin. These systems, in fact, can be formulated to reach the desired release profile and to control important factors that are referred to dermal preparations such as the occlusion effect, the skin hydration and, at least but not last, the percutaneous absorption of loaded drugs or active compounds. Additionally, these systems are nonirritating and nonsensitizing because they are formulated using nontoxic and high-biocompatible raw materials.

Lipids, in fact, are natural materials and are easily degraded by natural processes and even the degradation products (mainly fatty acids and glycerol) are known to be natural constituents of our body. The production of these carriers is feasible in laboratory and on large scale since the preparation methods are very simple and reproducible. Furthermore, some preparation methods do not involve the use of organic solvent and this point makes lipid nanoparticles particularly attractive for cosmetic industry, which is increasingly directed toward the use of natural products and reagents.

5. Expert opinion

Scientific literature reports, with different examples, the benefits associated to the application of lipid nanoparticle strategy to the formulation of products aimed to dermal administration. The main advantages recognized to these nanocarriers are the capability to enhance the drug penetration into the skin increasing treatment efficiency, to target the epidermis and to reduce the systemic absorption and consequently the side effects of many drugs and cosmetic actives that should limit their activity to the skin layers. Both pharmaceutical and cosmetic markets are very sensitive to all the new discoveries coming from technological research, which are characterized by proven efficacy and safety. Lipid nanoparticles, because of their biocompatible chemical nature, are able on one hand to respect the features of epidermis, which is a natural defensive barrier endowed with a dynamic character, and on the other can boast the overcoming of all major safety requirements. In the last years, in fact, the scarce experience about the interaction between nanosized material and body has unleashed a witch-hunt against everything that is nano. The complete biodegradation of lipid nanoparticles has secured them the title of 'nanosafe carriers' and besides has defined them the prototype of modern cosmeceuticals. Cosmeceuticals are, in fact, basically functional cosmetics, formulated using ingredients coming from a list of raw materials that are generally recognized as safe (GRAS). This class of products derives from the cosmetics industry's desire to go beyond simply adorning the skin. Future challenge of lipid nanoparticles could be to improve the wellness of the skin by tackling important functional issues to meet the demands of the consumers. Since these vehicles are widely investigated for dermal drug delivery, the authors hope that the same scientific method employed to study drugs could be applied to the clinical study of cosmeceuticals formulated with lipid nanoparticles. Another topic that should be addressed is represented by the search of new raw materials, to meet new and growing market needs. Given the high number of applications, the possibility of using new lipid matrices and more and more tolerated surfactants is strongly required. A wider choice of lipid raw materials could intensify technological research in this area, facilitating the setting up of important industrial processes such as the spray drying, whose use in this area is, till today, rather limited.

In conclusion, lipid nanoparticles represent a new technological era that has been taken over by cosmetic and pharmaceutical industry. Both SLN and NLC will open a new channel for an effective topical delivery of a vast variety of drug and cosmetic actives.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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