Lipid Nanoparticles (SLNs and NLCs): Wide Range of Application from Cosmetics to Cancer Chemotherapy

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ABSTRACT: The present review compiles the applications of lipid nanoparticles mainly solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) for the delivery of pharmaceutical actives. The attempts to overcome the low solubility and bioavailability of some drugs by their incorporation into lipid nanocarriers have been summarized. A special focus of this review is on different routes of administration of SLNs and NLCs which begins from oral route especially for administration of anticancers, parenteral route for drug targeting, pulmonary and topical route for administration of antimicrobial, anti-proliferative and anti-inflammatory agents, ophthalmic application to finally cosmetic application of lipid nanocarriers.

Key words: SLNs, NLCs, drug targeting, pulmonary application, topical application.

INTRODUCTION:
Solid lipid nanoparticles (SLN), prepared from a lipid matrix that is solid at body and room temperature, stabilized by suitable surfactants and having size from 50 to 1000 nm (Ghalandarlaki et al., 2014), they were developed at the beginning of the 1990s as an alternative carrier system to emulsions, liposomes and polymeric nanoparticles and since then they have received great and still increasing attention in pharmaceutical technology research (Bhalekar et al., 2009). SLNs are valuable in many aspects such as (Kaur and Singh, 2014, Doktorovova et al., 2014): (i) use of organic solvents can be avoided to produce SLNs, (ii) have negligible toxicity, (iii) lipophilic compounds can be effortlessly encapsulated, (iv) bioavailability of highly lipophilic molecules can be increased via lymphatic uptake, (v) degradation of chemical/moisture/light/oxidation of sensitive molecules can be prevented by their incorporation in the nanoparticle matrix, (vi) sustained drug release from the nanoparticle matrix is possible due to solid nature of the matrix leading to prolonged drug release and minimization of the adverse side effects of the encapsulated drug molecule, (vii) penetration through skin or mucus barrier is possible due to nano size. (Das et al., 2012, Rostami et al., 2014). Nanostructured lipid carriers (NLC), i.e. nanoparticles composed of a mixture of a solid and a liquid lipid which lipid matrix is solid at room and body temperature, NLCs are the second generation of lipid nanoparticles. NLC show a higher loading capacity when compared to SLN by conceiving a less arranged solid lipid matrix, i.e. by mixing a fluid lipid with the solid lipid, a higher element drug stacking can be obtained. Thus, the NLC have an extended drug stacking capacity in evaluation to SLN and the probability of drug expulsion throughout storage is less. (Selvamuthukumar and Velmurugan, 2012).

Lipid nanoparticles (SLNs and NLCs) showed bioavailability enhancement, controlled drug delivery of entrapped drugs via modification of dissolution rate and improvement of tissue distribution and targeting of drugs. They have been reported in various application routes (Üner and Yener, 2007):
- Parenteral for drug targeting (intravenously, intramuscularly or subcutaneously),
- Oral,
- Pulmonary application,
- Ophthalmic,
- Topical (in cosmetics and dermatological preparations).

Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLCs) in various administration routes
- Oral administration of SLNs and NLCs
Drugs owing poor solubility and bioavailability after oral administration can be formulated as SLN and NLC.
to overcome these problems. After intake the lipid matrices composed of triglycerides are normally digested by pancreatic lipases into monoglycerides and diglycerides. The monoglycerides could form micelles and mixed micelles (with bile salts) that still contain the drug. Then these lipids may perform absorption along with the drug by means of chylomicron formation mainly into the lymphatic system. This transportation surrounds the liver and minimizes the first pass effect. Lymphatic uptake can be affected by particle size as smaller size results in higher uptake (Svilnov and Tzachev, 2014).

Several drugs (hydrophobic and hydrophilic) such as Apomorphine, α-Asarone, Carvedilol, Clozapine, Digoxin, Insulin and Praziquantel have been incorporated in the SLN and/or NLC formulations for oral administration. In most cases, the aim was to improve oral bioavailability either by increasing GI absorption or by bypassing the first-pass metabolism. (Das and Chaudhury, 2011).

Oral administration of anticancer agents is preferred by patients for its convenience and potential for outpatient treatment. In addition, oral administration facilitates prolonged exposure to a cytotoxic agent. (Calixto et al., 2014)

Holpuch et al (Holpuch et al., 2010) tested a SLN formulation as a local oral cancer chemoprevention strategy and found that the penetration and subsequent internalization of nanoparticles within proliferating basal layer cells demonstrates the feasibility of nanoparticle formulations for local delivery and the stabilization of oral chemopreventive compounds. Aditya et al (Aditya et al., 2013) made curcumin and genistein co-loaded NLCs based on oleic acid, lecitin, Tween®80 and glycerol monostearate. These NLCs were found to be promising vehicles for the oral delivery of poorly bioaccessible molecules such as curcumin and genistin. Chinsriwongkul et al (Chinsriwongkul et al., 2012) and Liu et al (Liu et al., 2011) researched NLCs loaded with the anticancer drugs all-trans retinoic acid (ATRA) and DTX respectively. NLCs based on oleic acid enhanced the entrapment efficiency of the drug in the NLCs; however, all drug-loaded NLCs had prolonged release in addition to being more cytotoxic than the free drug. (Calixto et al., 2014)

- **Drug targeting using SLNs and NLCs via parenteral administration**

Targeting drug delivery is one of the most important fields of nanomedicine. The absence of selective targeting to the tumor usually results in low antitumor activity and severe side effects. Therefore, an active tumor-targeting delivery system of chemotherapeutic drugs is urgently needed (Yang et al., 2013). One of the most important strategies is the use of biodegradable nanoparticles in drug delivery, such as SLNs and NLCs as drug carriers. Due to their potential to encapsulate drugs, they are able to transport drugs to different parts of the body. Targeting may be achieved by one of the following ways (Rostami et al., 2014):

**- Antibody mediated targeted drug delivery**

The drug may be incorporated into the core or located on the surface of lipidic nanoparticle and directs it via a targeting antibody to the desired site of action for various diagnostic and therapeutic applications (Rostami et al., 2014)

**- Nanoparticle -magnetic targeting drug delivery**

Magnetic drug targeting is the main application of iron oxide nanoparticles. In an external magnetic field they are able to deliver particles to the desired target area (Alexiou et al., 2005) and fix them there while the drug is released to make a local effect (Liu et al., 2011). By integrating magnetic heating elements into solid lipid nanoparticles, release control and treatment enhancement has been achieved. The heating is performed around 45–55°C (Jordan et al., 1999) which cause melting of the solid lipid matrices and the encapsulated drug molecules released out of the nanoparticles. Meanwhile, the temperature rising, also described as hyperthermia (Jordan et al., 1999), could potentially stimulate the immune response for non-specific immunotherapy of certain diseases. By precisely controlling the concentration and distribution of a drug inside the body, potential side effects and required drug dosage could be significantly reduced. (Rostami et al., 2014)

**- pH sensitive nanoparticles**

pH sensitive carriers are another option for targeted drug delivery which were used by Kashanian and coworkers. They prepared aqueous dispersions of lipid nanoparticles using a modified, pH-sensitive derivative of phosphatidyl ethanolamine for pH-sensitive nanoparticles preparation. SLNs were prepared using polysorbate 80 as the surfactant and tripalmitin glyceride and N-glutarylphosphatidyl ethanolamine as the lipid components. The SLNs prepared in this study were able to control the release of triamcinolone acetonide under acidic condition (Kashanian et al., 2011).

**- Cationic solid lipid nanoparticles in drug delivery**

It was firstly reported by Olbrich et al. (Olbrich et al 2001) that the cationic SLNs could efficiently bind and transflect plasmid DNA. Also, Liu et al. (Liu et al. 2010) prepared N3-O-toluyl-fluorouracil loaded cationic solid lipid nanoparticles (N3-O-toluyl-fluorouracil-SLNs) which enhance the GI absorption of N3-O-toluyl-fluorouracil by oral administration.
- **Pulmonary application**

For the pulmonary application, lipid nanoparticles have several advantages (Fig. 3). SLN and NLC have good tolerability in the airways, their biodegradable lipid content resulting in non-toxic, often even endogenous degradation products [Pilcer and Amighi, 2010]. In addition, nanoparticles can be easily entrapped into particles or aerosolized into droplets with aerodynamically suitable properties due to their size, which lead to sufficient deep lung deposition of the drug. Moreover, SLNs and NLCs adhere to the mucosal surface of the lung for longer time compared to larger particles [Ponchel et al., 1997, Jacobs and Muller, 2002, Lenaerts et al., 1990]. All these advantages lead to sustained and enhanced therapeutic effects and therefore result in a longer dosing interval and better patient compliance [Patlolla, et al., 2010]. This can play an important role in treatment for chronic diseases since many of the existing inhalation formulations have to be applied at least twice a day due to the relatively short duration of the drug in the lung [Pilcer and Amighi, 2010].

![Advantages of lipid nanoparticles for pulmonary application](image)

**Fig. 3.** A) Advantages of lipid nanoparticles for pulmonary application and B) formulation challenges for lipid nanoparticles and other aqueous formulations for pulmonary application. (Weber et al., 2014)

Lipid nanoparticles must meet certain requirements to be suitable for pulmonary application. First of all, they could be sterilized by one of the following methods: autoclaving, gamma ray irradiation and sterile filtration, if the particle size is smaller than 200 nm [Mukherjee et al., 2009]. Secondly, controlling the pH value and the osmolarity of the formulation for inhalation. A lipid nanoparticle formulation can be isotonized by adding ionic and nonionic (glycerol or carbohydrates) isotonization agents. If necessary, the pH value of SLN or NLC formulations can be adjusted to neutrality using acids, bases, buffers with low ion concentrations or buffers composed of peptizers [Weber et al., 2014]. Good biocompatibility is also an important criteria. Tolerability of SLNs and NLCs can be achieved by using biodegradable and biocompatible lipids and surfactants/stabilizers. For example of solid lipids used: Cetyl palmitate [Rudolph et al., 2004] Compritol 888 ATO [Hu et al., 2010] and Glycerol monostearate [Zhang et al., 2011, Li et al., 2010]. Liquid lipids (Oils): Oleic acid [Pardeike et al., 2011], Miglyol 812 [Patlolla et al., 2010] and Castor oil [Weber, et al., 2012], and Surfactants: Poloxamer 188 [Li et al., 2010, Zhang et al., 2011], Polysorbate 20 [Pardeike et al., 2011, Weber, et al., 2012], Polysorbate 80 [Rudolph et al., 2004, Videira et al., 2012] and Polylvinyl alcohol [Pandey and Khuller, 2005]. Finally, it is necessary that the generated aerosols SLN or NLC formulation show good aerodynamic properties for sufficient deposition in the desired airway regions. The aerodynamic size distribution of an aerosol is recognized to be in the range of 0.5–10 µm. However, the optimal aerodynamic size is related to the desired site of deposition and therefore varies depending on the therapeutic approach [Capstick and Glifton, 2012].

Lipid nanoparticles are investigated as a possibility to improve therapy of these severe pulmonary diseases. Jafar-Maalej et al. [Jafar-Maalej et al., 2011] developed SLN and NLC loaded with beclomethasone dipropionate they observed a sustained release with a cumulative released amount of 20% beclomethasone from SLN and 77% from NLC, respectively, after 16 days was demonstrated in vitro. Another glucocorticoid i.e., dexamethasone was incorporated into NLC by Weber et al. [Weber, et al., 2012]. This formulation was successfully adjusted to isotoncity and then sterilized. The developed NLC showed good stability during jet stream nebulization.

- **Nanoparticles for topical administration**

SLN and NLC for the topical application to the skin are made of lipids such as glycerol palmito stearate, glycerol behenate, or the wax cetylpalmitate. For NLC, liquid lipids such as oleic acid or medium chain triglycerides (Miglyol® 812) are added. Nanodispersions formulated by 5 to 40% of lipid. The higher concentrated preparations are of semisolid appearance and are cosmetically adequate as they are. According to the mode and concentration of the lipid, 0.5 to 5% surfactant such as Poloxamer 188, lecithin, Polysorbate 80, TegoCare® 450, Tyloxapol, Miranol® Ultra C32 have to be added to stabilize the particles [Korting et al., 2007]. To facilitate dermal application, liquid dispersions which are obtained when the lipid content is low (10%) can be incorporated into a gel or cream base which does not induce aggregation or dissolution of nanoparticles [Wissing and Muller, 2001].

Lipid nanoparticles offer many advantages over suspended particles which are: increased drug chemical stability, high occlusion, film formation, improved skin hydration and controlled drug release (Fig. 3) [Pardeike et al., 2009].
Therefore drug classes as anti-inflammatory drugs, antimicrobial drugs and anti-proliferative agents could be successfully incorporated in lipid nanocarriers to be administered topically:

- Anti-inflammatory drugs

Anti-inflammatory drugs represent a broad range of molecules, many with potential for topical delivery. Reports on nanoparticle delivered drugs with anti-inflammatory properties for topical use. These drugs can be divided into steroids, e.g. corticosteron [Jensen et al., 2010], and nonsteroidal anti-inflammatory drugs (NSAIDs), e.g. naproxen [Puglia et al., 2008].

- Antimicrobial agents

The most prominent topical antimicrobial in consumer products is nanoparticle formulated imidazole and silver. Silver nanoparticles possesses antimicrobial properties and the mechanism by which silver functions as a disinfectant is not yet fully understood, but may be related to silver ion induced metabolic inhibition. (Prow et al., 2011)

- Anti-proliferative agents

Hyperproliferative skin disease is not limited to cancer, but also precancerous lesions. It can also be caused by inappropriate inflammatory responses. Several anti-cancer and anti-proliferation drugs have been delivered with nanoparticles, including 5-aminolevulinic acid (ALA), 5-fluouracil (5FU), paclitaxel, podophyllotoxin, and Realgar [Prow et al., 2011].

- Nanotechnology in cosmetics

The use of nanotechnology has found applications in the field of cosmetics by taking the name of nanocosmetics. Solid lipid nanoparticles have been found to improve the penetration of active compounds into the stratum corneum and could be used to control delivery of cosmetic agents over a prolonged period of time and in vivo studies have shown that an SLN-containing formulation is more efficient in skin hydration than a placebo. [Raj et al., 2012] It was also found by Sanad et al. (Sanad et al., 2010) that when SLNs was loaded with 0.5% oxybenzone (a molecular sunscreen), SPF values became about 6 fold higher when compared to that of 0.5% oxybenzone suspension. The amount of oxybenzone could be reduced while maintaining the protection level. Moreover, anti-photoageing drugs and antioxidants as tretinoin derivatives, isotretinoin, retinol, and vitamin A palmitate, have also been delivered to skin with SLN (Prow et al., 2011).

NLCs are interesting for formulations where higher concentrations of cosmetic actives are required. Compared to SLNs, the loading capacity can be improved when creating the imperfect matrix structure of NLCs, for example for retinol from 1.0% to 5.0% (Saupe et al., 2005). The loading capacity of NLCs depends also on the miscibility of the active in the lipid selected for their production. It can range from about 4% (e.g. ferulic acid), 25% (e.g. tocopherol), or even up to 50% and more, in case of well lipid miscible lipophilic actives (e.g. tocopherol and coenzyme Q10) (Müller et al., 2007). ‘Super-loaded’ NLCs were developed having a sunscreen loading of 70%. This was achieved by using the liquid sunscreen as oil component in the NLCs formulation (Souto and Muller, 2008). The first marketed NLCs products were cosmetics, employing these particles for coenzyme Q10 delivery to the skin for anti-ageing purposes. Topical application of aqueous NLCs dispersions is known to create a mono-layered lipid film onto the skin, which avoids water evaporation, and thus increases the skin’s moisture and hydration (Doktorova et al., 2009).

- Applications of nanoparticles in ophthalmology

SLNs and NLCs are the modern nanocarriers having the benefit of delivering ocular drugs to precise target sites and hold promise to modernize the therapy of many eye diseases. Existence of several barriers in the eye which consist of superficial barriers include the ocular surface epithelium and the tear film, and internal barriers consist of the blood-aqueous and blood-retina barriers may hindered direct and systemic drug access to the specific site of action. Topical application is the favored route for the majority of drugs, even when the goal tissues are at the posterior part of the eye where intraocular injections are now the most frequent route of administration. Many problems related to drug bioavailability, together with side effects and repeated painful treatments to reach therapeutic drug levels were achieved upon using direct administration by any of these two routes. Incidentally, the advantages of using nanoparticles include better topical route of large, poorly water-soluble molecules such as glucocorticoid drugs or cyclosporine for immune-related, vision-threatening diseases. Other massive and unstable molecules, for example nucleic acids, delivered using nanoparticles suggest better outcome for gene transfer therapy in harsh retinal diseases. Also, in the case of bromonidine (standard treatment for glaucoma) or corticosteroids (treatment for a severe intraocular inflammatory process), nanoparticle-mediated drug delivery increases the contact time of the administered drug with its target tissue. In addition, nanocarriers permit indomethacin (non-steroidal antiinflammatory drug) to reach inner eye structures using the transmucosal route. Finally, nanoparticles permit the opportunity of targeted delivery to reach exact types of...
cancer, for example melanoma, leaving normal cells unharmed. (Zou et al., 2013, Diebold and Calonge 2010).

**Conclusion:** In this review, NPs applications through different routes of administration were introduced. Nanoparticulate drug delivery was one of the most promising technologies to overcome poor stability in physiological medium and delivering them across biological barriers. Lipid nanoparticles, even applied as dispersion or as a dry powder formulation, can enhance the bioavailability of an encapsulated drug and improve and prolong therapeutic effects.

**REFERENCES:**


الدهون النانوية (SLNs و NLCs): مجموعات واسعة من التطبيقات من مستحضرات التجميل إلى العلاج الكيميائي للسرطان

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هذا الاستعراض يجمع تطبيقات الجسيمات ذات النانوية الدهون الصلبة (SLN) وحاملات الدهون ذات البنية النانومترية (NLC)، و.randLT، وحملات الدهون ذات البنية النانومترية (NLC)، وحملات الدهون ذات البنية النانومترية (NLC)، و成立于 في حاملات الدهون الصلبة (SLN) و SLNs الذي يبدأ من إدماجها في حاملات الدهون. وهناك تركيز خاص في هذا الاستعراض على طرق مختلفة لتعاطي الاف، لاستهداف مضادات السرطان، والطرق الوريدية للعوارض المستهدفة التوزيع والطريق الرئوي، والطريق الموضعي لتعاطي مضادات الميكروبات، ومضادات للالتهابات، والتطبيقات الرمدي و أخيرا التطبيقات في مستحضرات التجميل.