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Applications and limitations of lipid nanoparticles in dermal and transdermal drug delivery via the follicular route

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ABSTRACT

Lipid nanoparticles (LN) such as solid lipid nanoparticles (SLN) and nanolipid carriers (NLC) feature several claimed benefits for topical drug therapy including biocompatible ingredients, drug release modification, adhesion to the skin, and film formation with subsequent hydration of the superficial skin layers. However, penetration and permeation into and across deeper skin layers are restricted due to the barrier function of the stratum corneum (SC). As different kinds of nanoparticles provide the potential for penetration into hair follicles (HF) LN are applicable drug delivery systems (DDS) for this route in order to enhance the dermal and transdermal bioavailability of active pharmaceutical ingredients (API). Therefore, this review addresses the HF as application site, published formulations of LN which showed follicular penetration (FP), and characterization methods in order to identify and quantify the accumulation of API delivered by the LN in the HF. Since LN are based on lipids that appear in human sebum which is the predominant medium in HF an increased localization of the colloidal carriers as well as a promoted drug release may be assumed. Therefore, sebum-like lipid material and a size of less or equal 640 nm are appropriate specifications for FP of particulate formulations.

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1. Introduction

Lipid nanoparticles (LN) are colloidal dispersions composed of a dispersed lipid phase which is stabilized by an emulsifier or a blend thereof. If solid lipids are utilized the LN are specified as solid lipid nanoparticles (SLN) [1], and if admixed liquid lipids are supplemented they are defined as nanolipid carriers (NLC) [2]. Both colloidal systems may increase the solubility and bioavailability of active pharmaceutical ingredients (API), protect these compounds from outer influences such as light or oxygen, and facilitate drug targeting [3]. Further advantages are the simple and scalable manufacturing processes such as high pressure homogenization, microemulsion technique, and ultrasonication, their non-toxicity and biocompatibility based on ingredients featuring GRAS (generally recognized as safe) status and potential drug release modifications at the site of action [4]. As many stable and well-characterized compositions have been described, they may serve as a platform for reformulations of known API in order to extend the life cycle of a drug product.

Since LN are subject of university research since the early 1990s [5–7], many applications and specific formulations have been proposed within the last decades. They were investigated as parenteral [8], oral [9], pulmonary [10], ophthalmologic [11], nasal [12], and dermal drug delivery systems (DDS) [13]. Due to a broadly established intellectual property protection based on EP 0605497 B1 [14], US 8663692 B1 [15], and EP 0526666 B1 [16], prospective novelty and non-obviousness can solely be achieved by innovative compositions providing a unique and surprising benefit in structural modifications and/or biopharmaceutical performance. Especially in dermal drug delivery, various concepts and rationales for LN as DDS have been described in the state of the art.

For instance, an adhesion of the dispersed lipid matrix to the stratum corneum (SC) was reported for [1,2,6,7-^{3}H(N)]-corticosterone-loaded tripalmitin SLN without any penetration into the SC [17]. Epidermal targeting of podophyllotoxin by SLN [18] and of ketoprofen and naproxen by NLC [19] was explained by the preferential localization of the LN on the skin surface. SLN formed a reservoir for betamethasone-17-valerate on the skin so that the drug penetrated across the SC [20]. This accumulation on the surface may contribute to a film formation due to water evaporation which subsequently promotes hydration and occlusion of the skin [21]. This effect is favored by the large specific surface area of LN compared to other dosage forms, e.g., patches,

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ointments, and lipid microparticles [13]. Scanning electron micrographs revealed the loss of the platelet morphology of glycerol dibehenate-based SLN after 2 h of accumulation on pig skin probably caused by the mixture of skin and formulation lipids [22]. Khurana et al. confirmed an interaction between cetyl palmitate-based and meloxicam-loaded SLN and SC lipids via differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy as shifts of phase transition temperatures and stretching bands were detected [23]. Micrographs of rat skin displayed a looser packing of corneocytes after application of penciclovir-loaded SLN based on glycerol monostearate compared to the application of a cream and the normal rat skin as control [24]. Küchler et al. identified the lipophilicity of the lipid matrix and the compound as the promoters for partition into skin lipids [25]. The two different mechanistic approaches – either surface localization or interactions with skin lipids – are also discussed for the liquid lipid component of NLC, e.g., the permeation of genistein from NLC was enhanced potentially due to lipid switches of the formulation and skin as the NLC allow for an elevated mobility of the oil [26], while the increased penetration of Q10 was explained by the superficial occlusion properties of the oil component [27].

An increased solubilization in NLC may also improve skin deposition as for tacrolimus [28], celecoxib [29], and psoralen [30] since dissolved compounds build up a higher concentration gradient enabling an improved penetration and/or permeation. Therefore, LN may ensure constant drug levels in the upper skin layers [31]. The encapsulation in LN provides the opportunity to decrease the local irritation of API such as tretinoin which was increased by the formation of ion pairing due to the introduction of lipophilic amines [32]. Besides, the association of compounds to LN can improve their deagglomeration and thereby the physical stability of the formulation [33]. Aside from that, a controlled release from LN was observed for various API such as betamethasone-17-valerate [34], indomethacin [35], and clotrimazole [36].

Additional advantages of SLN and NLC are simple modifications of formulation parameters such as increasing the lipid content in order to obtain formulations with a plastic flow behavior [37], the introduction of phospholipids in order to form gels [38], the gelation of the aqueous phase with common gelling agents, e.g., carbopols [39], or the incorporation of the LN into topical dosage forms such as creams [40]. Recent formulation advancements of LN include surface modifications with various compounds such as cationic phospholipids namely 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP) and dioleoylphosphatidylethanolamine (DOPE) for dermal delivery of plasmid DNA [41], dicetyl phosphate for negative charging and subsequent improved skin distribution of retinyl palmitate [42], cell penetrating peptides (CPP) such as polyarginine for permeation enhancement of spantide II and ketoprofen [43], adsorbed silver to NLC for reinforced antimicrobial effects in therapy of atopic dermatitis [44], and chitosan for coating of tretinoin-loaded NLC for increasing antibacterial properties [45]. Refinements of the dispersed lipid matrix are the introduction of two different solid lipids such as Compritol® and Precirol® with an observed sustained release of lidocaine [46] and the incorporation of fatty alcohols into a Precirol® matrix, where longer chains of C16 and C18 enhanced the permeation of econazole nitrate [47].

The effective application of LN in transdermal drug delivery is generally restricted. For instance, it was shown that tristearin LN provided a slight permeation enhancement just like an emulsion and diethylene glycol monoethyl ether, whereas colloidal silica was superior in this regard [48]. An ethyl oleate-based microemulsion of aconitine was more effective in transdermal drug delivery compared to glycerol dibehenate-based SLN which showed an improved skin deposition [49]. However, LN as transdermal drug carrier were described for tretinoin especially with the addition of oleic acid [50], buprenorphine and its esters [51], and nitrendipine [52]. The addition of permeation enhancers such as ethanol and limonene to NLC with a low viscosity increased the permeation rate of olanzapine and simvastatin [53]. The transdermal permeation of triamcinolone acetonide acetate from SLN could also be increased by iontophoresis [54].

Table 1
Occurring lipids of sebum and employed lipids for LN.

Lipid components of sebum	Common lipids of lipid particles
Glycerides	Glycerol distearate [121], glycerol dibehenate [121], glycerol tripalmitate [18], medium-chain triglycerides [122], olive oil [124], sesame oil [127], coconut oil [128], hydrogenated palm oil [69], hard fat [119]
Free fatty acids	Stearic acid [123], oleic acid [122]
Waxes	Cetyl palmitate [122]
Squalene	Squalene [129]
Cholesterol and derivatives	

In conclusion, it is generally assumed that LN remain on the surface of the skin or potentially increase the penetration or permeation of API due to lipid exchanges between the skin and dispersions. Recently, hair follicles (HF) are regarded as a versatile penetration route for dermal and transdermal drug delivery beside the SC. It is commonly stated in the literature that a penetration in HF may be realized by colloidal DDS such as polymeric nanoparticles [55,56], albumin nanoparticles [57], anorganic nanoparticles [58], liposomes [59,60], and nanoemulsions [61], whereas other authors describe microparticles for follicular penetration (FP) such as polymeric microparticles [62,63], anorganic microparticles [64], chitosan microparticles [65], and drug microcrystals [66]. It was also observed that the HF may function as a reservoir for nanoparticles for a longer time period compared to the SC [67]. Most interestingly, the predominant environment in HF is sebum that consists of lipids that are frequently used for SLN and NLC, whereas these differ significantly from the composition of the SC (Table 1). The only part of the human body where waxes and squalene can be found is sebum [68]. Thus, the HF represent a considerable penetration route for LN as well, while penetration into deep or across SC layers is limited due to a surface accumulation of LN as previously outlined. Due to the fact that a preferential interaction between the lipid matrix of a solid lipid particle dispersion and sebum was recently described [69], the utilization of LN as a carrier system through or into the HF due to the similarity of the lipids can be regarded as a strategy for dermal and transdermal drug delivery. The subsequent drug release due to the erosion or dissolution of the lipid matrix in sebum was observed [70] and may consequently contribute to FP of the API. Therefore, the present review deals with the recent descriptions and ideas of LN for dermal or transdermal drug delivery via the follicular route.

2. Hair follicles and associated diseases

2.1. Anatomical and physiological considerations

HF are skin appendages apart from eccrine sweat glands, apocrine sweat glands, and nails. These invaginations consist of an inner and outer root sheath and distinguish themselves by their typical structure starting with the orifice at the epidermis, which is followed by the infundibulum as the compartment around the upper hair shaft. The infundibulum is generally less densely cornified than the SC. In depths up to 500 µm sebaceous glands with their ducts may be directed to the infundibulum [71]. Subsequently, the isthmus follows as compartment between the sebaceous glands and the bulge. In deeper areas follicles reach

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