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REVIEWS

SOLID LIPID NANOPARTICLES AND NANOSTRUCTURED LIPID CARRIERS: CURRENT PERSPECTIVES IN WOUND CARE

Yoana Sotirova

Department of Pharmaceutical Technologies, Faculty of Pharmacy, Medical University of Varna

ABSTRACT

INTRODUCTION: When the skin's integrity is compromised, one or more of its safeguarding mechanisms can be impaired. In this line of thought, wound healing often requires topical delivery of active pharmaceutical ingredients (APIs) to ensure proper skin regeneration. Unfortunately, the dermal route of administration has drawbacks in terms of insufficient drug penetration and low bioavailability. The employment of solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) in this field could be a promising approach due to their ability to increase drug permeation and provide sustained release and targeted delivery.

Aim: This review aims to provide an update on the use of SLNs and NLCs in wound management and contribute to the advancement of innovative and effective treatments.

MATERIALS AND METHODS: Systematic research was conducted in various databases to identify relevant scientific publications on the use of lipid nanoparticles (LNPs) as drug delivery systems for topical wound care.

RESULTS AND CONCLUSION: Lipid nanoparticles, including SLNs and NLCs, have been extensively investigated as delivery platforms for a wide range of compounds in wound healing. The encapsulation of synthetic, semi-synthetic, and natural molecules within these lipid-based nanosystems has demonstrated promising outcomes such as enhanced anti-inflammatory and antimicrobial effects, as well as improved wound healing, leading to faster regeneration and increased tear resistance. Overall, lipid nanoparticles offer a valuable strategy for wound management with the potential to revolutionize the field and offer improved therapeutic options for better patient outcomes.

Keywords: *lipid-based drug delivery systems, nanotechnology, wound management*

Address for correspondence:
Yoana Sotirova
Faculty of Pharmacy
Medical University of Varna
84 Tzar Osvoboditel Blvd
9002 Varna
e-mail: yoana.sotirova@mu-varna.bg

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INTRODUCTION

The skin is the largest organ in the human body, covering an area of more than 2 m^2 in an adult. In addition to contributing to body temperature and homeostasis maintenance (1), skin can be seen as one of the most effective first-line defenses of the organism. As an outermost barrier, the latter provides protection against various extrinsic factors at several levels: microbiological by means of commensal microbes

and antimicrobial peptides, chemical by its moderately acidic pH value of approximately 5.5, physical through the rigid structure of stratum corneum, and immunological due to the presence of myeloid and lymphoid cells (2–4).

One or more of the skin's safeguarding functions can be disturbed by damage or a breach of its integrity, defined as the term *wound*. Owing to the strictly orchestrated self-preservation system of the organism, wound healing begins immediately after the injury occurs. Despite its complexity, this process can be conditionally divided into four stages: hemostasis (activation of platelets, blood clot formation, and vasoconstriction); inflammation (vasodilation, an influx of immune cells, and facilitated physiological debridement); proliferation (neo-angiogenesis, formation of granulation tissue, and epidermal reconstruction); and maturation (collagen reorganization and wound contraction) (5–9).

Skin regeneration proceeds in this relatively simple pattern only in „normal" acute wounds. These injuries typically recover in less than eight weeks, vis-à-vis chronic wounds, when the healing time might be prolonged to 12 weeks or more (5,10). Factors such as the presence of pathogenic bacteria, oxidative stress, and impaired re-epithelialization can delay skin repair and lead to chronification (11). For this reason, the topical application of active pharmaceutical ingredients (APIs) with antimicrobial, antioxidant, anti-inflammatory, and/or epithelializing properties would benefit the proper wound-healing process.

Dermal drug delivery is commonly used for wound healing due to its localized and non-invasive nature. Unfortunately, this route of administration has some disadvantages, e.g., limited drug penetration and poor drug absorption, which, however, can be overcome by the utilization of nanosized delivery platforms. This nanotechnological approach has shown several benefits for topical wound care: increased bioavailability and facilitated drug penetration into the wound bed; sustained release and targeted delivery to the wound site; reduced frequency of application; and minimized risk of systemic side effects (12–14).

Among drug delivery systems, lipid nanoparticles (LNPs) possess numerous advantages in wound healing. Their high biocompatibility, biodegradability, and low toxicity (15,16) make them safe for topical administration. Their ability to improve drug stability, solubility, and bioavailability results in enhanced wound healing. Additionally, the small particle size and large surface area of LNPs can increase the drug-loading capacity and enable the co-delivery of multiple APIs (17–19).

AIM

This review aims to provide an update on the use of LNPs, including solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), for wound care. It focuses on recent progress by presenting the related studies published in the last five years. By highlighting the potential of LNPs in this field, this review would contribute to the advancement of innovative and effective treatments.

MATERIALS AND METHODS

For the 2018–2023 period, a systematic review of scientific publications addressing the use of LNPs as drug delivery systems for topical wound care was performed in the available databases (ScienceDirect, Scopus, PubMed, and Web of Science).

RESULTS

Brief Characterization of Solid Lipid Nanoparticles and Nanostructured Lipid Carriers

Solid lipid nanoparticles and NLCs are lipid-based nanoparticles that have gained significant attention as drug delivery systems. They generally comprise a lipid core and a surfactant shell (20,21) of non-ionic, cationic, anionic, or amphoteric stabilizers (22–25). Regarding the utilized lipids, SLNs contain only solid ones at room and body temperature, such as glycerides, waxes, and fatty acids (26–29). In contrast, liquid lipids (vegetable or mineral oils) are also included in NLCs (30). Hence the difference in the inner matrix of the two drug delivery systems (Fig. 1). The presence of liquid lipids in NLCs enhances their loading capacity, drug release, and stability while reducing the tendency of drug expulsion (31).

Despite the differences in their composition and structure, both SLNs and NLCs share standard preparation techniques: hot homogenization (melting of the lipid matrix and emulsification in a surfac-

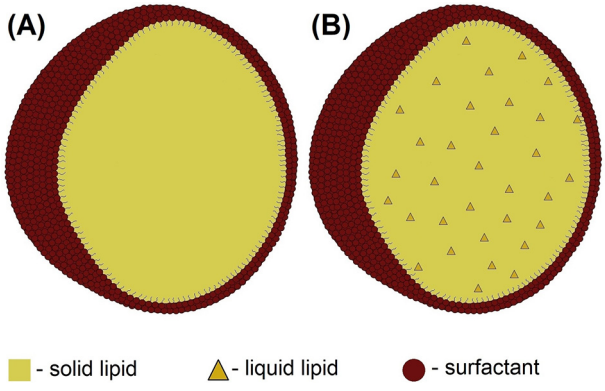

Fig. 1. Schematic representation of the matrix structure of solid lipid nanoparticles (A) and nanostructured lipid carriers (B).

tant solution under high shear conditions) (32), solvent emulsification-evaporation (includes pre-dissolution of the lipids in organic solvents) (33), microemulsion method (34), high-pressure homogenization (involves applying high pressure to the pre-emulsion) (35,36), and supercritical fluid technology (the supercritical fluid acts as a solvent for the lipids) (37). Several modifications have been made to these methods (e.g., using co-surfactants and sonication techniques) to improve the stability and reduce the mean particle size of SLNs and NLCs (38,39).

Solid lipid nanoparticles and NLCs have shown promise in various medical applications, including cancer therapy, gene delivery, skin care, and wound healing. In general, the composition and method of preparation are critical in determining the physicochemical properties of LNPs and must be carefully optimized for each specific application. The choice between SLNs and NLCs depends on the specific drug and its physicochemical properties, as well as on the desired release kinetics and stability of the formulation. For this reason, despite the advantages of NLCs, both lipid-based drug delivery systems are still being exploited (13,40–42).

Lipid Nanoparticles in Wound Management

As a favorable drug delivery system for wound healing, LNPs have been widely utilized as carriers for various APIs. To summarize the recent advances in this field, related studies from the past five years are presented in Table 1.

Lipid Nanoparticles as a Delivery Platform for Synthetic APIs

Several studies on the encapsulation of synthetic drug molecules in LNPs are included in this research; they concern antimicrobials (cefadroxil, a first-generation cephalosporin, and silver sulfadiazine, a topical sulfonamide), an antioxidant (allopurinol, a xanthine-oxidase inhibitor), and APIs with pleiotropic effects.

Moglad et al. prepared SLNs of cefadroxil and integrated them in a hydrogel that was found to be skin-compatible and easily spreadable. *In vivo* studies noted a remarkable wound contraction and complete epithelialization within a 17-day treatment with the formulation (43). Mastiholimath et al. developed a similar semisolid vehicle for SLNs loaded with silver sulfadiazine and proved its antimicrobial properties against *Escherichia coli* (44). Valsartan SLNs also demonstrated an antibacterial effect (against Gram-positive and Gram-negative bacteria). The nanodispersion was additionally incorporated into hypromellose gel and showed enhanced *in vivo* wound healing, as evidenced by histological examination revealing re-epithelialization after 12 days of application (45). After a similar research period, complete recovery of an excised wound was observed in rats after the application of a simvastatin-SLN-loaded self-gelling system. The novel semisolid also retained moisture with a slow release of simvastatin over 72 h (46).

One more statin representative, atorvastatin, was encapsulated in NLCs and incorporated into a composite dressing. The membrane was proven to be cytocompatible, with uniform nanoparticle distribution, and provided sustained release of the wound-healing API (47). Natarajan et al. also utilized scaffolds as a vehicle for their pioglitazone-in-NLCs system. The dressing was biocompatible, with optimal porosity, and led to significantly higher wound contraction rates than in control groups (48). In a randomized controlled trial involving patients with diabetic foot ulceration, phenytoin-loaded NLC hydrogel significantly reduced the wound area compared to a blank control and plain phenytoin semisolid (49). Another LNP system with an *in vivo* demonstrated wound-healing effect was elaborated by Varrica et al. The allopurinol-loaded NLC dispersion was also proven suitable for topical use in terms of

Table 1. Studies of lipid nanoparticles (LNPs) for wound treatment classified by the origin of the encapsulated active pharmaceutical ingredient (API), the type of colloidal carriers, and the final dosage form of application.

Active Ingredient	Type of LNPs	Dosage Form	Reference
Synthetic APIs			
Cefadroxil	SLNs	Carbopol hydrogel	(43)
Silver sulfadiazine	SLNs	Carbopol hydrogel	(44)
Valsartan	SLNs	Hydroxypropyl methylcellulose hydrogel	(45)
Simvastatin	SLNs	*In* situ-forming poloxamer hydrogel	(46)
Atorvastatin	NLCs	Polycaprolactone-coated gelatin/hyaluronic acid scaffold	(47)
Pioglitazone	NLCs	Collagen/chitosan dressing	(48)
Phenytoin	NLCs	Carbopol hydrogel	(49)
Melatonin	NLCs	Chitosan microspheres	(51)
Allopurinol	NLCs	Aqueous nanodispersion	(50)
Semi-synthetic APIs			
Tetrahydrocurcumin	NLCs	Carbopol hydrogel	(52)
Naturally-Occurring APIs			
Individual Bioactive Molecules			
Asiaticoside	SLNs	Carboxymethyl chitosan/oxidized sodium alginate hydrogel	(53)
Retinoic acid	SLNs	Chitosan films	(54)
Lacticin 3147	SLNs	Carbopol hydrogel	(56)
Nisin	SLNs	Gellan gum scaffold	(55)
Zerumbone	NLCs	Carbopol hydrogel	(57)
20(S)-protopanaxadiol	NLCs	Silicone elastomer gel	(58)
Thymoquinone	NLCs	Aqueous nanodispersion	(59)
Essential Oils			
Melaleuca alternifolia	SLNs	Cellulose nanofiber gel	(63)
Mentha longifolia, *Mentha pulegium*, and *Zataria multiflora*	SLNs	Polycaprolactone/alginate dressing	(65)
Matricaria chamomilla	SLNs	Aqueous nanodispersion	(64)
Carum carvi	NLCs	Xanthan gum hydrogel	(69)
Mentha × *piperita*	NLCs	Xanthan gum hydrogel	(67)
Mentha pulegium	NLCs	Carbopol hydrogel	(66)
Rosmarinus officinalis	NLCs	Carbopol hydrogel	(68)
Extracts			
Hibiscus rosa sinensis	SLNs	Carbopol hydrogel	(70)
Hypericum perforatum	NLCs	Poloxamer/borage oil-sorbitan monostearate bigel	(71)
Propolis	NLCs	Aqueous nanodispersion	(72)
Combined Formulations			
Curcumin and ampicillin	SLNs	Petroleum ointment and Carbopol emulgel	(73)

Mupirocin and tinidazole	SLNs	Sodium alginate hydrogel	(74)
Curcumin and resveratrol	NLCs	Carbopol hydrogel	(75)
Epidermal growth factor and curcumin	NLCs	Aqueous nanodispersion	(76)
Ferulic acid and *Lavandula officinalis* oil	NLCs	Aqueous nanodispersion	(77)

good skin retention, penetration, and non-cytotoxicity (50). A novel dry powder wound dressing was developed by incorporating melatonin-loaded NLCs into chitosan-based microspheres. The biocompatible vehicle exhibited antibacterial activity, occlusive properties, and effective fluid uptake when exposed to simulated wound fluid (51).

Semi-Synthetic Molecules Loaded in Lipid Nanoparticles

Evidence for a semi-synthetic molecule encapsulated in LNPs was found for tetrahydrocurcumin. This hydrogenated curcumin derivative was incorporated into SLNs and included in a hydrogel as a final formulation. The semisolid was found to be stable and non-irritating, and *in vitro* and *ex vivo* investigations indicated a significant increase in skin permeation compared to free tetrahydrocurcumin gel. Pharmacodynamic evaluation in an excision wound mice model revealed the enhanced anti-inflammatory effect of the nanodispersion-loaded hydrogel, which was confirmed by biochemical and histopathological studies (52).

Lipid Nanoparticles as Carriers of Single Natural Compounds

This section highlights the utilization of LNPs as carriers of individual natural molecules in wound healing. Researchers have explored the potential of these nanosystems to enhance the therapeutic properties and bioavailability of various compounds. Lipid nanoparticles have proven to be versatile nanocarriers for delivering natural compounds, showing significant potential in wound care.

In their study, Kumar aimed to investigate the wound-healing potential of an asiaticoside-SLN-enriched hydrogel. The prepared vehicle showed sustained asiaticoside release for 8 h and an optimal water vapor transmission rate, indicating adequate moisture without risk of wound dehydration (53). Arantes et al. developed all-trans retinoic acid-loaded SLNs and achieved homogeneous drug distribution and controlled release by incorporating the nanosystem in chitosan films. *In vivo* experiments showed accelerated wound closure, reduced leukocyte infiltration, improved collagen deposition, and reduced scar tissue without any observed skin irritation (54). Two antibacterial peptides produced by *Lactobacillus lactis* were encapsulated in SLNs, and their wound-healing potential was investigated. Reczyńska-Kolman et al.'s nisin-SLN composite scaffold was cytocompatible and did not hinder cell migration while promoting wound healing (55). The hydrogel obtained by Ryan et al., containing lacticin 3147-loaded SLNs, demonstrated sustained API release and was proven active against a *Staphylococcus aureus* infection (56).

Zerumbone, a natural compound found in *Zingiber zerumbet*, was incorporated into NLCs and applied topically in the form of hydrogel. The semisolid promoted wound healing by reducing inflammation and increasing granulation in wound tissues (57). Again, a gel was employed as a vehicle for NLCs in the study of Sun et al. The authors investigated the therapeutic potential of nanoencapsulated 20(S)-protopanaxadiol: anti-inflammatory and pro-angiogenic properties were demonstrated *in vitro*, and significantly improved scarless wound healing was achieved *in vivo* (58). Nanostructured lipid carriers were also used to enhance the bioavailability of thymoquinone, a bioactive compound with wound-healing potential. The nanocarriers developed by Alexander et al. had a triple effect: they boosted cell proliferation and migration, reduced the number of necrotic and apoptotic cells while increasing the population of healthy ones, and acted as an antioxidant to decrease reactive oxygen species (59).

Essential Oil-Loaded Lipid Nanoparticles

Essential oils have gained significant attention in recent years due to their antimicrobial, anti-inflammatory, antioxidant, and analgesic activities, among others (60). However, these volatile plant ex-

tracts also exhibit stability limitations, such as oxidation, photodegradation, and evaporation, which can affect their efficacy and shelf life (61). Some other disadvantages include poor aqueous solubility, low bioavailability, rapid metabolism, and potential toxicity at high concentrations (62). To address these challenges, researchers have explored various strategies, including utilizing LNPs as carriers.

A nanolipogel comprising SLN-encapsulated tea tree oil was fabricated by Kamel et al. to overcome its hydrophobicity. *In vivo* studies showed accelerated skin regeneration, as confirmed by histopathological examination and quantitative assessment of the inflammatory infiltrate (63). To facilitate its tissue permeability, chamomile oil was encapsulated in SLNs: an *in vivo* study demonstrated improved skin restoration owing to its anti-inflammatory effect and its ability to enhance wound contraction and collagen production (64). Valizadeh et al. conducted a comparative study in which SLNs containing essential oils of *Mentha longifolia*, *Mentha pulegium*, and *Zataria multiflora* were developed, transformed into gels, and impregnated onto nanofiber scaffolds. The dressing containing gelled SLNs of *Zataria multiflora* essential oil showed the highest antibacterial activity against all standard and clinical bacterial strains, with a notable reduction in the growth of *Staphylococcus aureus* and *Pseudomonas aeruginosa* (65).

Volatile oil from *Mentha pulegium* was also incorporated into NLCs to explore its potential in wound management. Antibacterial activity against Gram-positive and Gram-negative bacteria was proven by microdilution assay and the promotion of wound healing by reducing the inflammatory phase and accelerating the proliferative phase in animal experiments (66). The authors have also developed NLCs loaded with peppermint and rosemary oil, and their antimicrobial properties were demonstrated in both *in vitro* and *in vivo* studies. The latter also showed a reduction in the wound size, with increased collagen deposition and promoted neo-angiogenesis, and enhanced epidermal restoration (67,68). Other essential oil-loaded NLCs that promoted the proliferative phase of wound healing were developed by Tazehjani et al. Furthermore, the elaborated nanosystem containing caraway oil was found to reduce bacterial colonization and shorten the inflammatory phase (69).

Extracts Incorporated into Lipid Nanoparticles

The incorporation of extracts into lipid nanoparticles has emerged as a promising approach in wound-healing research. Several studies have investigated the wound-healing properties of lipid nanoparticles loaded with natural extracts. For instance, Vijayanand et al. explored the potential of SLNs loaded with *Hibiscus rosa sinensis* extract. In their *in vivo* experiments, wounds treated with a nanodispersion-enriched hydrogel regenerated faster than those treated with crude extract and resembled healing with a marketed preparation (70). Similarly, in another *in vivo* comparative study involving a commercial herbal semisolid and a control group, a bigel formulation enriched with St. John's wort extract-loaded NLCs exhibited a superior wound-healing effect, as evidenced by the highest tear resistance of restored skin (71). When applied to full-thickness skin wounds in rabbits, the propolis-loaded NLCs, elaborated by Elkhateeb et al., demonstrated significantly higher closure rates than extract alone or control treatments. These nanocarriers also exhibited a more substantial inhibitory effect on various microbes, including bacteria and fungi, than raw propolis (72).

Multiple API-loaded Lipid Nanoparticles

In recent years, there has been growing interest in the development of LNPs loaded with more than one API at once in wound healing applications. Ghaffari et al. developed semisolid formulations containing curcumin and ampicillin SLNs, which were non-toxic, exhibited antibacterial properties, and improved wound healing (73). The use of SLNs as an approach to drug delivery was also explored for the simultaneous application of mupirocin and tinidazole to wounds. The nanodispersion was developed into a topical gel, whose antibacterial activity was found to be comparable to that of the standard drug gentamycin against aerobic bacteria (74).

Singh et al. developed NLCs containing curcumin and resveratrol and converted them to a gel for dermal application. The prepared semisolid had a higher permeability for both compounds and presented a longer retention time and better therapeutic efficacy for wound healing than a plain gel (75). Another study employed curcumin-loaded NLCs to promote wound healing but in combination with

an epidermal growth factor. These nanocarriers enhanced cell migration, accelerated wound closure, and increased the activity of antioxidant enzymes (76). The NLCs fabricated by Carbone et al., containing ferulic acid and lavender oil, significantly promoted cell taxis as well. Moreover, the presence of both APIs increased the stability of colloidal carriers and improved their cytocompatibility (77).

DISCUSSION

Undoubtedly, today, SLNs and NLCs are perceived as promising delivery platforms for biologically active compounds. Their participation in the wound healing process is also especially valued. Encapsulation of synthetic and semi-synthetic molecules in such lipid-based nanosystems has yielded favorable results: enhanced anti-inflammatory activity, antimicrobial properties, and wound-healing effects. This drug-delivery approach has also been successfully utilized to improve the therapeutic properties and bioavailability of individual natural compounds and essential oils. The incorporation of extracts and co-encapsulation of multiple APIs in these systems has shown a generally beneficial effect on wound healing, including more rapid re-epithelialization and increased tear resistance. Or, to put it another way, all these advances make LNPs a valuable tool for promoting "proper" tissue regeneration.

CONCLUSION

Ever since their invention at the end of the twentieth century, SLNs and NLCs have been introduced into a range of therapeutic areas, including wound management. The outgrowing interest in their employment as drug delivery systems lies in their customizable properties and ability to encapsulate a wide range of bioactive molecules. Similar yet different, both types of lipid nanoparticles have been proven to offer a versatile and effective approach to aiding wound healing. With further advancements and research, these nanocarriers have great potential for transforming the landscape of wound management, offering enhanced therapeutic options and improved patient outcomes.

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