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Recent advances in SLN and NLC-based lipid nanoparticles for cosmetic, dermal, and transdermal drug delivery: A comprehensive review

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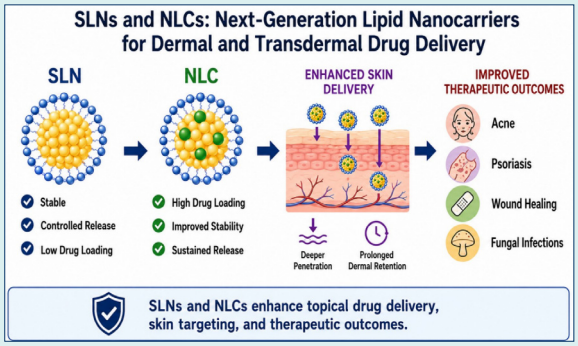
Abstract



Recent advances in nanotechnology have positioned solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) as promising platforms for dermal and transdermal drug delivery. This review critically highlights emerging breakthroughs that go beyond the conventional advantages of lipid nanoparticles. SLNs, composed of physiologically compatible solid lipids, provide improved drug stability and controlled release; however, their clinical utility is often constrained by limited drug loading, drug expulsion during storage, and highly ordered crystalline structures. To overcome these drawbacks, second-generation NLCs incorporate both solid and liquid lipids, creating an imperfect lipid matrix that significantly enhances loading capacity, minimizes drug leakage, and enables tunable release kinetics. Recent formulation innovations including precision high-pressure homogenization, microfluidic-assisted production, and optimized hot/cold homogenization approaches have enabled tighter particle size control, improved batch reproducibility, and better long-term stability. In parallel, surface engineering strategies such as ligand functionalization, polymer coating, and incorporation of natural bioactives have demonstrated enhanced skin targeting, deeper stratum corneum penetration, and prolonged dermal retention. Notably, recent preclinical and translational studies report improved therapeutic outcomes in acne, psoriasis, fungal infections, inflammatory disorders, wound healing, hyperpigmentation, and melanoma-related skin conditions when compared with conventional topical systems. Despite these advances, important translational gaps remain, including large-scale manufacturing challenges, regulatory uncertainties, and limited clinical validation. By integrating recent technological breakthroughs with application-focused evidence, this review provides a forward-looking perspective on the evolving role of SLNs and NLCs as next-generation lipid nanocarriers for dermatological therapy and advanced skin care.

Introduction

The skin is a highly specialized and multifunctional organ that functions as the primary protective interface between the human body and the external environment. Its outermost layer, the stratum corneum, is composed of a well-organized lipid protein matrix that effectively minimizes trans epidermal water loss and restricts the penetration of exogenous substances. Although this barrier is essential for physiological protection, it significantly hinders dermal and transdermal drug delivery. Consequently, therapeutic effectiveness relies not only on the pharmacological potency of the active compound but also on formulation-related parameters such as physicochemical stability, compatibility with skin components, residence time, and penetration enhancement strategies.[1] Conventional topical formulations, including creams and gels, often provide limited regulation of drug release and may result in

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Research Highlights

What is the current knowledge?

- SLNs and NLCs enhance dermal drug delivery through occlusion, lipid interaction, and controlled release mechanisms.
- NLCs improve drug loading and stability compared to highly crystalline SLN matrices.
- Surface modification strategies improve nanoparticle stability, skin retention, and targeted delivery efficiency.

What is new here?

- This review integrates recent advances in ligand-functionalized and stimuli-responsive lipid nanocarriers for precision dermatology.
- It critically discusses translational barriers including polymorphic instability, scale-up reproducibility, and regulatory challenges.
- Emerging applications in melanoma therapy and multifunctional transdermal systems are comprehensively evaluated.

inconsistent permeation across the skin.

To address these limitations, nanocarrier-based drug delivery systems were developed. Liposomes and nano emulsions enhance the solubility of lipophilic drugs; however, they frequently face challenges such as physical instability and premature drug leakage. Polymeric nanoparticles offer sustained drug release, yet concerns related to biodegradability, residual organic solvents, and potential toxicity can restrict their broader application. These shortcomings necessitated the development of more stable and physiologically acceptable lipid-based nanocarrier systems.

Nanostructured lipid carriers (NLCs)[2] and Solid lipid nanoparticles (SLNs)[3] were subsequently introduced to combine improved structural stability with biocompatibility. SLNs are prepared by replacing the liquid lipid component of traditional emulsions with a solid lipid matrix, thereby enhancing drug protection, occlusive effects, skin hydration, and controlled drug release.[4,5] Because they are composed of physiological lipids, SLNs present a lower risk of irritation and toxicity compared with polymeric nanoparticulate systems.[6-9] However, their highly ordered crystalline lattice may limit drug loading capacity and contribute to drug expulsion during polymorphic transitions.[10-13]

To overcome these drawbacks, NLCs were developed by incorporating both solid and liquid lipids within the matrix, generating structural imperfections that improve drug accommodation and reduce expulsion.[14] In contrast to nanoemulsions, both SLNs and NLCs maintain a solid lipid matrix at physiological temperature, allowing sustained drug release. Furthermore, unlike liposomes, these systems exhibit superior storage stability.[14] Drug incorporation patterns and lipid polymorphism are critical determinants of their performance characteristics.[15,16]

Therefore, SLNs and particularly NLCs offer significant advantages over other nanoparticulate delivery systems due to their physiological compatibility, controlled release capability, enhanced stability, and adaptable matrix architecture, making them promising carriers for optimized dermatological and transdermal drug delivery.[17-19]

Development of solid lipoprotein nano-particles and nanostructured lipoprotein carriers: an historical background

Initial research in Zurich led to the development of the first lipid particles,[20] prepared by high-speed stirring of a melted lipid phase with a hot aqueous surfactant solution to form an oil-in-water (o/w) emulsion. Upon cooling, the lipid solidified into particles. However, this method resulted in broad particle size distribution and required high surfactant concentrations. Speiser termed these systems "lipid nanopellets" for oral use, but despite patenting, they were not commercially pursued. Similarly, Domb developed "lipospheres"[21] using sonication, though these also did not achieve significant pharmaceutical application.

The first SLNs were described in a 1991 patent using high-pressure homogenization (HPH)[22] and microemulsion techniques.[23] HPH, widely applied in pharmaceutical products such as Intralipid®, Lipofundin®, and Lipovenoes®,[24-26] enabled scalable production with improved particle uniformity and physical stability compared to earlier polymeric nanoparticles. Two main approaches exist: hot and cold HPH.

In hot HPH, the drug is dispersed in melted lipid (5–10°C above melting point), emulsified in a hot surfactant solution, and homogenized (200–500 bar). Cooling induces recrystallization and nanoparticle formation. Cold HPH involves solidifying the drug–lipid mixture, milling it into microparticles, dispersing in cold surfactant solution, and homogenizing to form nanoparticles.

The microemulsion method forms nanoparticles by diluting and cooling a lipid–surfactant–cosurfactant microemulsion.[27,28] However, it yields highly diluted dispersions (< 1% lipid), requiring further water removal.

Alternative techniques adapted from polymeric nanoparticle production include solvent emulsification–evaporation,[29] solvent displacement,[30] emulsification diffusion,[31] and phase inversion methods.[32-34] These methods provide versatile approaches for the preparation of lipid nanoparticles and enable the successful incorporation of both hydrophilic macromolecules and conventional therapeutic agents into lipid matrices.[35] Solvent injection has emerged as an effective technique for manufacturing lipid nanoparticles with controlled process parameters and particle characteristics.[36] Recent formulation strategies have further optimized SLNs and NLCs by improving drug loading, stability, and formulation versatility.[37] Solvent diffusion and solvent emulsification–diffusion techniques have been widely employed to induce lipid precipitation and nanoparticle formation, resulting in controlled particle size, high encapsulation efficiency, and reproducible formulations.[38-40] These

advances have significantly enhanced the applicability of SLNs and NLCs for diverse pharmaceutical drug delivery systems.[40] Instead of just particle generation, more recent developments have concentrated on process optimization and functional performance. Reproducibility and industrial viability have increased thanks to advanced production techniques, such as solvent-free procedures, phase inversion techniques, and optimized high-pressure homogenization.[41] At the same time, surface modification, targeted skin delivery, controlled release behavior, and integration with enhancing technologies like microneedles and stimuli-responsive devices are becoming more and more important in current research. Therefore, while the technological basis was laid by early historical developments, the main goals of current SLN and NLC research are to overcome biological barriers, enhance clinical predictability, and facilitate successful translation into cosmetic and transdermal therapeutic products.

The focus has switched to intelligent and multipurpose lipid nanocarriers in the most recent stage of research. To achieve site-specific delivery and enhanced skin penetration, researchers are investigating ligand-decorated, PEGylated, and stimuli-responsive SLN/NLC systems.[42] Green manufacturing techniques, the use of natural bioactive lipids, and hybrid lipid–polymer nanoparticles are also gaining traction to improve sustainability and biocompatibility. Furthermore, formulation robustness and regulatory preparedness are being strengthened by the use of advanced solid-state characterisation, in silico modeling, and quality-by-design (QbD) principles. All of these recent developments point to a distinct shift away from traditional lipid nanoparticles and toward more advanced, clinically focused nanoplatforms for transdermal medication administration and next-generation cosmetics.[43]

Structure and molecular makeup of solid lipoidal nanoparticles and nanostructured lipoidal carriers

In literature, various models for integrating active molecules into SLNs and NLCs have been presented.[44] There are three fundamental types of carriers for each (Fig. 1).

Chemical composition of lipid and active ingredient, surfactant variety and volume, in addition to solubility of its components in condensed lipid, manufacturing temperature, and type of HPH (cold vs. hot) all affect kind of SLNs. Consequently, three models for inclusion have been put out[45]:

1) Homogeneous matrix models (SLN Type I),
2) Drug-enriched shell models (SLN Type II),
3) Drug-enriched core models (SLN Type III).

Solid lipid mixture and main component is used to create SLN Type-I. Cold homogenization process of producing SLNs can result in a solid solution. The active ingredient can be present in a lipid blend in a form that is molecularly distributed. To prevent or minimize enrichment of active chemicals in various regions of lipid nanoparticle, this blend is crushed in its solid form after solidification.

A low amount of main ingredient in melted lipid & formulation of SLNs using hot HPH process result in SLN Type-II. Lipid will precipitate first during cooling phase of hot o/w nano-emulsion, which will cause proportion of lipid solidified to increase along with amount of active compounds in lipids melt that is still present.

As drug approaches complete absorption in rest of residual melt, an exterior layer made up of both lipid and active will constrict, creating an inactive lipid core. The particles outer region is enriched, which results in burst release. By changing production conditions, amount of active component that is located in outer shell can be regulated. Coenzyme Q10's inclusion is a common illustration of an active-enriched shell concept.[46,47]

A high amount of main ingredient in melted lipid, at or

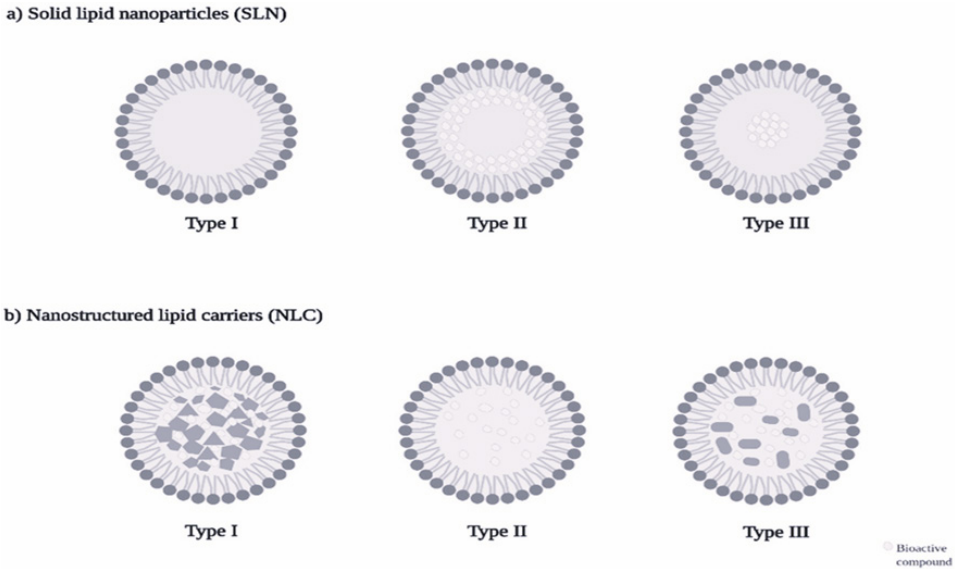

Fig. 1. Primary forms of nanostructured lipid carriers and solid lipid nanoparticles.

near its saturation solubility, can result in SLN Type-III. In most cases, cooling down heated oil droplets will make active less soluble in melt; active substances dissolve when saturation retention is achieved.

The types of NLCs are displayed in (Fig. 1), additionally displays three distinct structures:

1) NLC Type I, also known as imperfect crystal model,
2) NLC Type II, also known as amorphous model,
3) NLC Type III, also known as multiple model.

Since active molecules can be accommodated by numerous defects present in its matrix, NLC type I. This model is produced by combining modest amounts of liquid lipids (oils) with solid lipids. A highly ordered structure cannot be formed by matrix of NLCs because of mixing of mono-, di-, and triacylglycerols and varying chain lengths of fatty acids.

Several medications, including those which is easier to dissolve in fluid lipids than in solid ones, can have their loading capacity increased by using this model.[48,49] Water in oil in water emulsions, which are made up of an oil-in-fat-in-water dispersion, are source of this kind. Phase-separation technique produces very tiny oil nano compartments inside solid lipid matrix of nanoparticles.

When solid and liquid-lipids are mixed in proportion that exceeds. Solid lipids absorption in fatty acids, this model is produced. Since heated oil and melted lipid are mixed, there must be a miscibility gap between two lipids at used concentrations, which are around 40°C. Lipid droplets are cooled after a hot oil/water nano-emulsion created at elevated temperature. The oil precipitates and forms microscopic oil droplets in melted solid lipid when it reaches miscibility gap. Fixation of oily nano compartments results from solid lipid's subsequent solidification as a solid nanoparticle matrix.

Controlled Drug Release from SLNs and NLCs

SLNs and NLCs are designed to achieve sustained and controlled drug delivery through their solid or semi-solid lipid matrices. Since the lipid core remains solid at body temperature, drug diffusion is restricted, and release predominantly occurs via Fickian diffusion, where the drug slowly migrates from the lipid matrix into the surrounding medium.

SLNs possess a highly ordered crystalline structure that acts as a strong barrier to drug movement, promoting prolonged release. However, changes in lipid polymorphism during storage may lead to drug expulsion and altered release profiles. In contrast, NLCs incorporate both solid and liquid lipids, generating a less ordered matrix with structural imperfections. This design enhances drug incorporation and allows more adaptable and stable release behavior, while minimizing the risk of drug leakage.

Drug release from these systems may result from matrix diffusion, redistribution of drug during cooling (causing an initial burst effect), or gradual lipid degradation. Furthermore, the internal localization of the drug whether uniformly dispersed, core-enriched, or shell-enriched significantly influences whether the release pattern is sustained, biphasic, or burst-dominated.

Factors influencing drug release

Drug release SLNs and NLCs is governed by formulation composition and processing conditions.

1) Lipid composition and crystallinity strongly determine release kinetics. Highly crystalline lipids form compact matrices that limit drug diffusion and promote sustained release, whereas the imperfect structures in NLCs created by blending solid and liquid lipids enhance molecular mobility and enable adjustable release behavior.
2) Drug solubility and lipophilicity also play a key role. Lipophilic drugs with strong lipid affinity are retained within the core, supporting prolonged release. In contrast, drugs with some aqueous solubility may localize near the surface during preparation, resulting in an initial burst effect.
3) Drug loading influences the diffusion gradient. Moderate increases in loading generally accelerate release, but excessive drug content can cause crystallization within the matrix, which may slow diffusion.
4) Surfactant concentration affects nanoparticle stabilization and drug partitioning. Higher surfactant levels can increase drug solubilization in the aqueous phase and promote surface-associated drug, thereby enhancing burst release.
5) Preparation method, particularly hot versus cold homogenization, determines drug distribution. Hot methods may cause drug redistribution during cooling and increase burst release, while cold homogenization supports more uniform incorporation.
6) Particle size impacts release rate, as smaller particles provide larger surface area and shorter diffusion pathways, leading to faster release compared with larger particles.
7) Storage conditions influence lipid polymorphism and matrix stability. Structural transitions over time can alter crystallinity, affect drug retention, and modify release profiles, emphasizing the importance of controlled storage for maintaining consistent performance.

Formulation of transdermal and cosmetic products using SLNs and NLCs

This section is included to provide a clear understanding of the significance of formulating SLNs and NLCs in transdermal and cosmetic applications. It is important because the formulation strategy directly influences the stability, performance, and effectiveness of lipid-based nanocarriers. By discussing established formulation approaches, this section explains how SLNs and NLCs can be successfully incorporated into semisolid dosage forms such as gels and creams. The information presented helps to justify the selection of formulation techniques and

highlights their role in enhancing controlled drug release, product stability, and overall therapeutic or cosmetic efficacy.

Numerous methods for creating goods based on SLNs and NLCs are reported in scientific literature.

Integrating SLNs and NLCs to semisolid formulations

Like liposomes, polymeric nanoparticles, and microsponge systems, semisolid preparations like lotions, creams, and hydrogels can be enhanced with aqueous SLN or NLC dispersions.[50,51] This method has benefit of combining a number of appealing benefits of lipid nanoparticles with a well-known topical formulation in a single finished product.

SLNs or NLCs are incorporated into creams by adding nanoparticles of lipid as highly saturated dispersion, meaning they contain 50 percent solid content, to a freshly made oil in water cream or while cream is being made.[52] Elevated concentration of SLN/NLCs dispersion is used in first instance to partially replace water in cream formulation. Production process is then carried out as usual. Because of their adequate stabilization, lipid nanoparticles do not merge with emulsion's inner oil droplets. Lipid nanoparticles will melt if temperatures throughout their melting point are used to create emulsions, but they will recrystallize when process cools down. The second method, which is more sophisticated, involves producing cream normally but with less water to make up for water that was introduced with aqueous SLN or NLC dispersion. Saturated SLN/NLC dispersion is incorporated and agitated at normal temperature until cream is produced. By preventing nanoparticles from melting, this method prevents undesirable alterations to interior particle structure.

It is significantly easier to do if goal is to add SLNs or NLCs to hydrogels. After hydrogels have been created, semisolid formulation can be diluted with SLN or NLC dispersion. Concentrated SLN/NLC dispersion alternatively introduced prior to gelation procedure. Electrolytes, which are commonly utilized to soften artificial polymers, have potential to break down lipid nano-particles. Aggregation of suspended particles results from a decrease in surface electrical charge, or zeta potential. For instance, this phenomenon should be taken into account when adding sodium hydroxide electrolytes to carbomer gel production. Tristan® and Neutrol® TE are two neutralizing agents that can prevent or reduce aggregation of SLNs and NLCs, which is influenced by type of neutralizing agent used. After gel is created, SLNs and NLCs will be psychologically stable and confined within gel network., preventing aggregation. In general, after being included into hydrogels, SLN and NLC dispersions that have become instable due to an inadequate surfactant composition may often be stabilized. This makes it possible to apply stabilizers, which are permitted by regulations but are not very effective in ensuring aqueous dispersion's long-term stability. Only a few hours are required for SLN and NLC dispersions to remain stable before they are added to semisolid formulation, where gel network will stabilize them.

Formulation of gels using NLCs and SLNs

Topical formulations used to produce gels based on SLNs and NLCs are composed solely of lipid nanoparticles. Prior to adding gelling agent preferably nonelectrolyte substances as forms of cellulose or other organically produced gums[53] (as shown in Table 1), a lipid nanoparticle dispersion is made. An amount of 4% to 10% lipid nanoparticles is adequate for a lot of gel formulations. It is possible to generate a concentrated particle suspension (for example, 40%–50%) and then dilute it to required final concentration in order to increase production profitability. This method has several benefits, like actives' release being solely regulated by lipid nanoparticle matrix. Attenuation of lipid nanoparticle characteristics allows for a highly regulated adjustment of required attributes.

Formulation of Creams Using NLCs and SLNs

Lipid nanoparticle dispersions in water at elevated concentrations, either 50 or 60 percent, are produced in order to produce creams based on SLNs and NLCs. Higher lipid concentrations will result in formation of ointments with a bicontinuous structure; in other words, homogenization process produces distinct particles rather than an ointment-like system.

As lipid concentration rises, preparations' viscosity is known to increase; at roughly Formulations resemble cream between 40 and 45 percent; at 50 percent, they resemble paste., and at 80% or 90% solid content, they become solid and knife-cuttable. Cream-based and paste-based preparations are suitable for cutaneous utilization of ingredients, whereas solid-based methods are frequently crucial for lipid fragments which are orally administered that capitalizes on boosting intestinal activity.[54] In order to produce such formulations, HPH first prepares a highly concentrated stock suspension that contains between 50% and 60% lipid nanoparticles. Concentration of solid material is then increased to 80% or 90% by gradually adding more melted fat and dispersing it once more. The resultant substance remains liquid & exhibits comparatively less viscosity when it is melted. When system cools, it takes on consistency of cream, paste, or solid (as mentioned in Table 2).

Characteristics of SLNs, NLCs, and their effects on skin

Physical stability of creams and aqueous dispersions

In order to formulate pharmaceutical and cosmetic goods as per SLNs & NLCs, liquid SLN and NLC dispersions must be physically inert, meaning they must not aggregate or cream. Lipid nanoparticles are inherently stable due to tiny size, hence deposition of small particles or blending of fluid dispersions might not occur. Water molecules Brownian motion maintains particles in suspension. Particles are stabilized by electrostatic repulsion due to their surface electrical charge, and chemically maintaining polymers improves their external durability even further,

Table 1. Different properties profile of SLNs and NLCs

Formulation Component/Step	Description	Key Points/Advantages	References
Base composition	Gels consist entirely of SLNs or NLCs.	Ensures even distribution and controlled release of actives.	50
Preparation step 1	Make a lipid nanoparticle dispersion first.	Maintains uniformity and stability of nanoparticles before gelling.	49
Gelling agent	Use non-electrolyte agents like cellulose derivatives or natural gums.	Prevents destabilization of lipid nanoparticles caused by electrolytes.	49,53
Lipid nanoparticle concentration	Gel usually contains 4%–10% lipid nanoparticles.	Sufficient for gel formation and therapeutic effect.	49,53
Concentrated suspension option	Prepare a 40%–50% concentrated suspension, then dilute as needed.	Increases production efficiency and profitability.	49,53
Controlled release	Drug release is regulated solely by the lipid nanoparticle matrix.	Provides sustained and predictable drug release profile.	49,53
Adjustability	Modifying lipid nanoparticles helps adjust gel properties.	Allows adjustment of texture, viscosity, and release.	50

Table 2. Summary of various components used in SLNs and NLCs

Lipid concentration (% w/w)	Type of formulation	Consistency/Appearance	Application	References
40–45%	Cream-like	Moderate viscosity	Suitable for dermal application	51,54
50–60%	Paste-like	High viscosity	Suitable for dermal application	51,54
80–90%	Solid / Ointment-like	Solid, knife-cuttable	Suitable for oral delivery	54

like poloxamer or Tween 80, are added to formulation as surfactants. There have been reports of strong durability of lipid nanoparticles in a mixture of water for more than 3 years.[55] As mentioned above, if necessary, SLN and NLC can be added to skincare products to increase their solidity.

Lipid nanoparticle dispersion in fluid oil of previously mentioned semisolid compositions may be regarded as an additional type of instability in addition to aggregation and creaming. Benefit of SLNs and NLCs over liposomes is that their durability can be accurately demonstrated using differential scanning calorimetry. To determine overall proportion of nanoparticles remaining in formulation, melting power at specific day, nano-particles were added to cream & melting energy acquired after specific amount of time of storage can be compared. Using liposomes to accomplish this is impossible. The presence of liposomes in a product can be easily demonstrated by electron microscopy after a specific amount of storage time, but quantifying their quantity is either impossible or very challenging (using precise microscopy using electrons evaluation, for instance, in this instance). This is a significant barrier to Japanese market introduction of a liposomal cosmetic product. This is not a significant issue with SLNs and NLCs, though, as DSC can readily do a quantitative analysis of precise amount after a specific storage period.[56]

Drug loading, entrapment efficiency, and physicochemical characterization of SLNs and NLCs

The capacity of lipid nanoparticle systems to incorporate therapeutic agents and the efficiency with which these agents are retained within the carrier matrix are critical parameters when assessing the suitability of lipid-based nanocarriers such as SLNs and NLCs. These delivery systems have been extensively explored for the incorporation of numerous model drugs, highlighting their adaptability for different pharmaceutical applications. A recently published compilation summarized a wide range of active compounds successfully integrated into SLN and NLC formulations.[57] For instance, tetracaine and etomidate have demonstrated drug loading levels between approximately 10–20% relative to the lipid mass while maintaining satisfactory nanoparticle stability.[58] In most studies, loading capacity is expressed as the percentage of drug present compared with the total amount of lipid used in the formulation.

Additional investigations have reported that SLN systems incorporating lipid-soluble vitamins such as vitamins A and E, along with their derivatives, can achieve loading capacities approaching 25%. Attempts to further increase the drug content in these systems were unsuccessful because higher concentrations did not yield additional stable lipid particles. Nevertheless, increasing the proportion of molten lipid during formulation can enhance drug loading. When the active compound exhibits complete miscibility with the lipid phase, loading capacities exceeding 50% may be obtained. In certain situations where the drug itself is highly lipophilic and solid in nature, theoretical loading capacities approaching 100% have been suggested.

Entrapment efficiency (EE) refers to the proportion of the drug that becomes successfully incorporated within the lipid nanoparticle structure during formulation. For lipophilic drugs, EE values in SLN and NLC systems are generally very high, typically ranging from 90% to 98%. However, some compounds demonstrate slightly lower efficiencies. For example, tetracaine[59] and clotrimazole[60] have been reported to exhibit entrapment efficiencies of about 80%, which still reflects considerable drug incorporation within the lipid matrix. In contrast, hydrophilic compounds often show lower loading and

entrapment values due to their greater affinity for the aqueous phase during nanoparticle preparation. A commonly cited example is the hydrophilic radiocontrast agent Iotrolan, which shows an EE of approximately 50%.[61] Because of its extremely high-water solubility approximately two parts dissolving in one part water it is frequently used as a model compound for studying the loading of hydrophilic molecules in lipid nanoparticles.

Beyond small-molecule drugs, macromolecules such as proteins and peptides have also been incorporated into SLN systems. Lysozyme, often used as a model protein, has been successfully encapsulated within SLNs. Experimental studies demonstrated that the protein retained both its chemical stability and biological activity following incorporation into the lipid matrix.[62] In biological models designed to study prolonged in-vivo drug release, loading capacities of approximately 20% have been reported for certain hydrophilic peptides.

Comprehensive physicochemical characterization is essential to verify successful nanoparticle formation and efficient drug incorporation in SLN and NLC systems. Commonly employed analytical techniques include particle size determination, differential scanning calorimetry (DSC), and X-ray diffraction (XRD). Particle size is particularly important because it influences formulation stability, drug release behavior, and biological interactions. Dynamic light scattering measurements generally report mean particle diameters between 50 and 300 nm with polydispersity index (PDI) values typically below 0.3. Such values indicate relatively narrow particle size distribution and good colloidal stability. Nanoparticles within this size range also offer a high surface area, which can enhance drug delivery efficiency.

Differential scanning calorimetry is frequently applied to analyze the thermal characteristics and crystallinity of lipid nanoparticle formulations. Bulk lipids generally exhibit melting transitions between 60 and 80 °C depending on the lipid type. However, in SLN systems the melting temperature often decreases slightly, typically by about 2–10 °C compared with the bulk lipid. This reduction can be attributed to nanoparticle size effects and interactions between the lipid and surfactant molecules. In many cases, DSC thermograms show the disappearance or substantial reduction of the drug's melting peak after encapsulation. This observation indicates that the drug is molecularly dispersed or solubilized within the lipid matrix rather than existing in a crystalline form.

XRD analysis further provides insight into the crystalline structure of lipid nanoparticles. Crystalline lipids generally produce characteristic diffraction peaks within a 2θ range of approximately 19°–24°. After drug loading, these peaks often become broader or decrease in intensity, suggesting a reduction in lipid crystallinity. Such changes indicate that drug molecules are incorporated within the lipid matrix, disrupting the ordered crystal arrangement. In NLC formulations, the presence of liquid lipid components introduces structural imperfections into the crystal lattice of the solid lipid, resulting in lower crystallinity and creating additional space for drug incorporation.

The drug release behavior of lipid nanoparticles is strongly influenced by formulation composition and internal structure. Because SLNs possess a highly ordered and crystalline lipid matrix, drugs encapsulated within them are generally more tightly retained. In contrast, NLCs contain both solid and liquid lipids, creating a less ordered internal structure. As a result, drugs incorporated into NLCs are typically less strongly bound compared with those in SLNs. For example, clotrimazole incorporated into NLC formulations is less firmly embedded than in SLNs, where the highly crystalline lipid structure restricts drug diffusion. Consequently, SLNs often exhibit slower and more sustained drug release profiles.

Controlled drug release from lipid nanoparticles is largely governed by diffusion processes described by Fick's law of diffusion. However, the diffusion coefficient within the lipid matrix is not constant because it depends on the concentration of the drug present. High drug loading may sometimes reduce diffusion rates due to steric hindrance effects, where numerous drug molecules compete for diffusion pathways within the lipid structure. Earlier SLN incorporation models also support this phenomenon. Therefore, drug loading plays an important role in determining the release kinetics. In general, increasing the drug content accelerates drug release; however, in certain formulations higher drug loading may reduce release rates if drug crystallization occurs inside the nanoparticles.

During SLN production using the high-pressure homogenization (HPH) technique, redistribution of the drug between phases can occur (Fig. 2). When the drug-containing lipid melt is emulsified in a hot aqueous surfactant solution, the drug partitions between the lipid and aqueous phases according to its solubility characteristics and partition coefficient. Increasing the surfactant concentration in the aqueous phase may enhance the solubility of hydrophobic drugs in water, leading to greater migration of the drug from the lipid phase into the aqueous medium. Similarly, higher processing temperatures can further increase drug solubility in the aqueous phase, promoting this redistribution effect. As the nanoemulsion cools, the lipid phase crystallizes to form the solid nanoparticle core, which now contains a reduced amount of drug. During

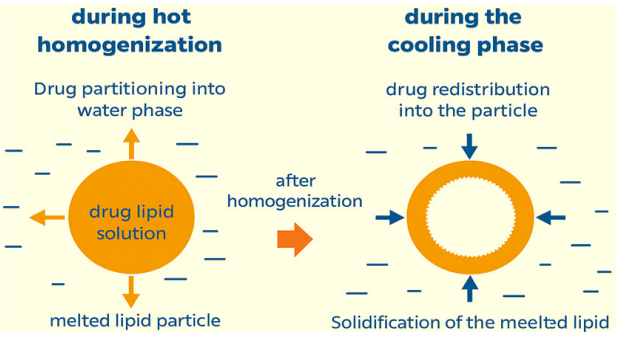

Fig. 2. Drug partitioning during the high-pressure homogenization process used to create lipid nanoparticles.

further cooling, drug solubility in the aqueous phase decreases and some drug molecules migrate back toward the lipid particles. However, because the lipid core has already solidified, the drug primarily accumulates in the outer shell region of the nanoparticles. This phenomenon may lead to an initial burst release of the drug. Adjusting formulation variables such as surfactant concentration, processing temperature, or employing cold high-pressure homogenization can help minimize this burst release effect.[63,64]

Protecting integrated substances chemically

Chemically labile actives can be stabilized against degradation (such as hydrolysis and oxidation) by employing a solid matrix, like that of polymeric particles.[65] Lipid nanoparticles are no exception. Incorporating retinol and coenzyme Q10 in nanoparticles of lipid composed of blend of Compritol®888 ATO and Miglyol®812 may improve their stability.[66,67] Using same lipid, ketoconazole could also be somewhat protected.[68]

Active components will separate between liquid oil and water phases due to fluid nature of carriers like liposomes and emulsions. Nondegraded compounds will separate from oil to aqueous phase concurrently with permanent interchange of particles within these 2 phases, which break down active particles in aqueous phase (according to coefficient of partitioning of Nernst). We will continue to maintain partitioning ratio between degraded and nondegraded active (Fig. 3A). The main ingredient would be set within lipid molecules in this instance as opposed to solid matrix. The interchange across inside and outside phases will be minimal (Fig. 3B). These observations highlight protective and chemical stabilizing properties of active ingredients added to SLNs and NLCs.[69]

Effects of occlusion and hydration of Skin

Due to their small particle sizes, SLNs and NLCs exhibit sticky qualities,[70] which have also been noted when liposomes are used. Lipid nanoparticles, when they come into touch with skin, form a thin layer with extremely small gaps between them. Applying an SLN or NLC formulation to skin allows one to feel creation of this film. Lipid nanoparticles in a cream, even in comparatively tiny levels (e.g., 5%), can form this film.

Comparing lipid nano-particles by lipid micro-particles (Fig. 4) with same lipid portion reveals that comparatively high occlusivity is a unique characteristic of former. The wide gaps between micro-meter carriers that yet let water evaporation are cause of relatively poor occlusivity of microparticles. Water loss is limited by hydrodynamically unfavorable tiny spaces (capillaries) between nanoparticles. Because this film prevents liquid from evaporating, it has an occlusive effect that increases skin hydration.

When using placebo SLNs or NLCs for skin protection during day, this feature may be highly intriguing. Numerous chemicals that are typically found in atmosphere are continually in contact with skin. These consist of ambient gasses, water & melted mineral-salts that are exist as free ions. Permeability of skin to various chemicals changes greatly. Increased hydration and consequent wrinkle smoothing are results of occlusion of skin, an effect that is used in many cosmetic treatments. Based on this characteristic, products containing SLN & NLC were anticipated having anti-aging properties as well, particularly made with skin-care active substances including ceramides and other vitamins. The skin's damaged protective lipid layer can be restored by applying ceramides, which combined with elevated melting lipids to create solid nano-particles.

Enhancing penetration of added substances

Lipid nanoparticles' occlusion qualities and resulting

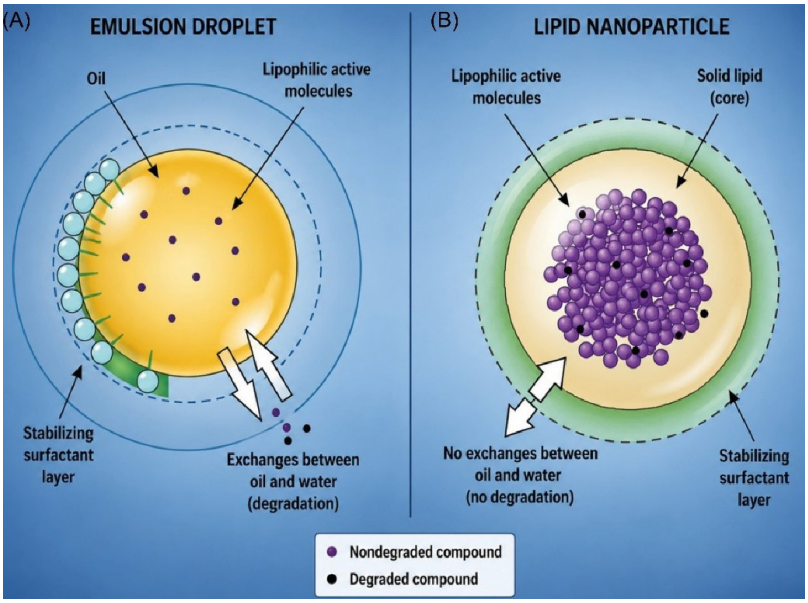

Fig. 3. Chemical protection of unstable active compounds: In emulsions (A), both intact and degraded molecules can freely partition, whereas in lipid nanoparticles (B), the solid lipid matrix restricts such diffusion, enhancing stability.

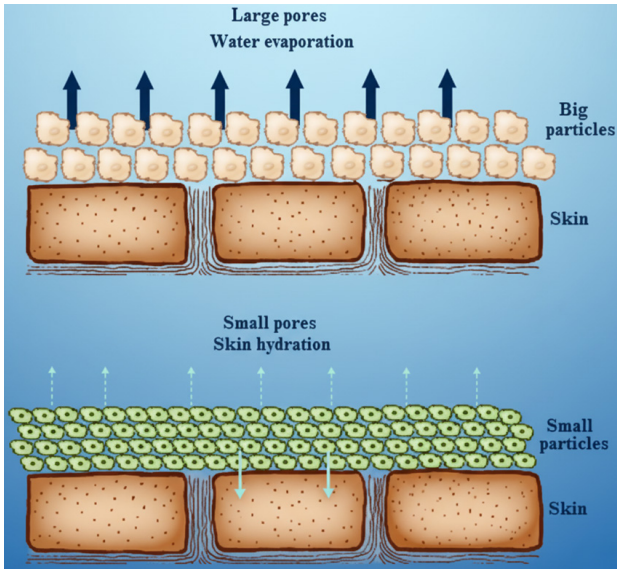

Fig. 4. Mechanism of the occlusion effect as influenced by particle size. Comparison between a solid lipid microparticle dispersion (1 μm, top) and an aqueous solid lipid nanoparticle or nanostructured lipid carrier dispersion (230 nm, bottom).

increase in skin moisture allow these carriers to enhance integrated actives' skin penetration. Lipid nanoparticles' penetration-enhancement impact has been evaluated using tocopherol and tocopherol acetate. By using an extraction test, which measures overall permeation as a result of lot of strips, lipid nano-particles containing active ingredients were used on skin & their comparison of permeation to that of an alcoholic solution of similar compounds. The penetration rate of lipid nanoparticle formulations was double that of alcoholic solution that was used as a reference. Furthermore, when applied to skin, these data showed demonstrated that active compounds included in lipid nanoparticles were clearly liberated from carriers.

Vehicles for cosmetic, dermal & transdermal activities: SLNs and NLCs

Lipid particles are said to have been included into pharmaceutical technology for a very long time, and cosmetic and pharmaceutical companies have recently attempted to bring lipid nanoparticles to market. With Yamanouchi patent[71] protecting it, first product is already available on market and was released by Yamanouchi company in Poland (e.g., Nanobase®). This product is designed to be used cosmetically and contains active-free lipid nanoparticles.

Despite not necessarily having any physiological purpose, cosmetic formulations share many characteristics with topical dermatological applications. As an illustration, lipstick serves primarily as a cosmetic, yet it contains several excipients that are frequently found in pharmaceutical products. It is only essential to look at how these procedures are modified for use in cosmetic industry after taking into account how therapeutic applications are created, paying particular attention to scent, feel, freshness, appearance, and skin persistence. When consumers buy product, factors like fashion and personal taste also play a significant role. A good product must therefore have both functional qualities and aesthetic appeal in its formulation.

In addition to lipsticks, lipid nanoparticle-containing face cosmetic items could be created. They help to provide a smooth matt finish, conceal flaws, add fresh color, and increase coloring uniformity. Since face was part of body most exposed to climate change, protection is absolutely necessary given significant aesthetic value of its appearance. The facial epidermis' relative thinness makes this kind of protection even more crucial. It is also possible to develop cleaning creams using SLNs and NLCs. These oil-miscible preparations are beneficial for removing makeup remnants. While lipid nanoparticles stick to skin to protect it, dispersion's aqueous phase contains surfactant qualities that help remove makeup. Additional examples include skin powders for a base pigmentation or concealing to cover small flaws.

Merchandise research indicates that appearance of formulation itself is just as significant as visually appealing packaging when it comes to cosmetic's purchasing. Consumers prefer white products, and lipid nanoparticles can be utilized to diminish yellowish active ingredients like vitamin C and coenzyme Q10. Even if degradation products don't affect product quality, this lightening impact is particularly interesting for main ingredient that broken down by color-containing degradation products. Research is currently being done on whitening and lightening capabilities of lipid nanoparticles.[71-74]

Lipid nanoparticles have emerged as valuable carriers in cosmetic formulations because they enhance the stability of bioactive ingredients, promote prolonged skin retention, and enable controlled release of encapsulated compounds. They have also been incorporated into deodorant and antiperspirant formulations containing antiseptic agents such as trichlorophane and hexachlorophene to improve their residence time on the skin and enhance formulation performance.[75] Skin aging is influenced by hormonal changes; however, chronic exposure to ultraviolet (UV) radiation plays a major role by accelerating the degradation of collagen and elastin within the skin.[76,77] As a result, SLNs and NLCs have been widely investigated as carriers for UV-filtering agents in sunscreen products, where they improve photoprotective efficiency, enhance skin localization, minimize systemic exposure, and increase the overall effectiveness of sun-protective formulations.[78,79] Owing to their favorable biocompatibility, occlusive characteristics, and ability to improve the delivery and stability of cosmetic actives, SLNs and NLCs are considered promising platforms for the development of advanced photoprotective and cosmetic products.[80]

Skin irritation or allergic responses might result from these sunscreens' penetration into skin.[81] Titanium dioxide particles, which are likewise placed into NLCs, are often employed particulate UV blockers.[82] Another contentious issue is whether and how much titanium dioxide particles

enter skin,[83,84] where they may have an impact on immune system.[85] Once molecular UV blockers were included into lipid nanoparticles, it was shown that UV absorbance of molecular sunscreen and UV scattering from SLN itself worked in concert.[86] This begs question of how to maintain UV protection level while lowering molecular sunscreen's concentration and any potential negative effects. This outcome has commercial significance for pricey UV blockers in addition to lowering adverse effects. Additionally, when SLNs were compared to conventional oil in water emulsion of comparable formulation, it was discovered that absorption of sunscreens within skin was decreased.[87]

Almost all cosmetic products use perfume to add a pleasant scent, which is one thing they have in common. Comparing lipid nanoparticles to oil in water emulsions and Eau de Toilettes, latter shall be employed for longer-lasting releases of odors, perfumes, and insect repellents.[87] If scent is incorporated into solid matrix rather than liquid-lipid particle, release can be slowed down. If goal is to design an application that lasts for a day, this is quite intriguing. Majority of formulas still heavily rely on natural oils, which are basic source of essential oils with botanical origins. Because NLCs have an inner liquid core in their structure, they can therefore deliver greasy fragrances. Despite their high cost, oily perfumes can be utilized in soaps and other less costly items by using an extended-release technology like NLC, which requires less oil. Insect repellents like lemon oil also showed prolonged release.[88-90]

Functional appropriateness is primary factor that determines whether to use a specific dose form.[91] Degree of drug absorption via skin affects how well topical and transdermal devices work. As a result, there is a propensity to consider these systems to be functionally closely connected. SLNs and NLCs, for example, can operate in three different ways when applied to skin: (i) in local tissues directly underneath application site; (ii) in deep areas around application site; and (iii) in systemic circulation.[92] It goes without saying that drug delivery problem gets worse as you proceed down this path. Long-term medication release is necessary to achieve systemic circulation. Lipid nanoparticles designed for transdermal and cutaneous medication delivery are mostly known for their controlled-release characteristics. Lipid nanoparticles' structure determines release profile they achieve. The release characteristics might be very quick, medium, or exceedingly extended, depending on matrix structure. The dissolving characteristics of pharmaceuticals during production process, which depend on lipid, surfactant, and production temperature, may account for burst release, for instance, intended for dermal applications. Comprehending this mechanism enables regulated synthesis of lipid nanoparticles with a specified starting dosage.

A significant quantity of medication must pass through skin from application site to circulation in order for transdermal therapy to achieve pharmacologically appropriate systemic levels. The ointments and adhesives used in conventional transdermal systems are properly sized, and ideally there is no local accumulation.[92] In certain situations, nevertheless, transdermal system's contact area defines a little diffusional window that drug molecules must enter. The underlying system may therefore exhibit sensitizing and/or irritating effects. Given that they are made of physiological and widely recognized lipids, usage of lipid nanoparticles may be helpful in resolving this problem. Additionally, fatty acids and ceramides found in skin can potentially contribute to composition of lipid nanoparticles. Apart from chemical stability of integrated medicines, occlusion and additional hydration effects can enhance drug penetration.

Fig. 5 illustrates how lipid nanoparticles, including SLNs and NLCs, serve as effective carriers for enhancing cosmetic skin therapy and transdermal delivery.

Surface modification and targeting strategies

In cosmetic, dermal, and transdermal drug administration, surface modification and targeting techniques have become important technological developments for enhancing the therapeutic performance of SLNs and NLCs.[93] Despite being biocompatible, native lipid nanoparticles frequently have drawbacks such nonspecific dispersion, short skin residence times, and early drug leakage. By modifying the nanoparticles' external interface to alter their physicochemical behavior and biological interactions, surface engineering overcomes these limitations. Researchers can optimize interaction with the stratum corneum, avoid particle aggregation, increase colloidal stability, and encourage deeper penetration into specific skin layers by designing surfaces logically. Crucially, these changes also increase the overall bioavailability of encapsulated actives and allow for improved control over drug release kinetics.[93]

To improve SLN and NLC performance, a number of surface modification techniques have been studied. Polyethylene glycol chain attachment, or PEGylation, is frequently employed to improve formulation stability during storage, decrease opsonization, and offer steric stabilization.[94] Chitosan, hyaluronic acid, alginate, and carbopol are examples of polymer coatings that have been used to enhance mucoadhesion, skin hydration, and residence time at the application site. Another useful tactic is charge modulation. For instance, positively charged nanoparticles can interact more strongly with the negatively charged skin surface, increasing adherence and penetration. Furthermore, lipid-polymer hybrid coatings are being investigated more and more to combine the benefits of both systems, leading to better mechanical stability and regulated drug diffusion. Together, these surface-level modifications aid in overcoming the inherent drawbacks of traditional lipid nanoparticles.[95]

Active, receptor-mediated distribution is made possible by targeting methods, especially ligand functionalization, which is a more advanced kind of surface engineering. In order to identify and attach to overexpressed receptors

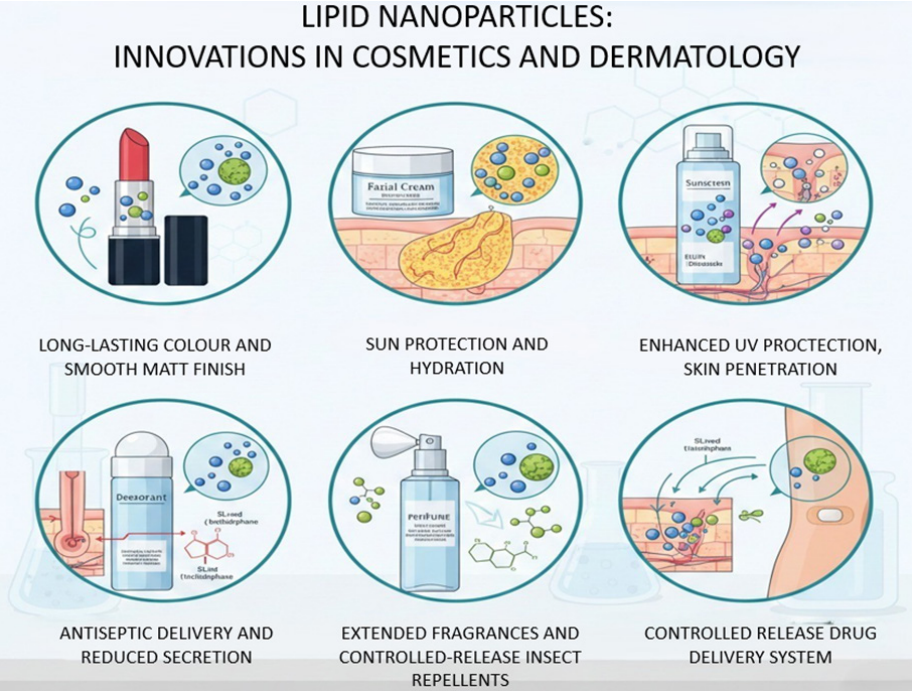

Fig. 5. Lipid nanoparticles including SLNs and NLCs effective carriers that improve cosmetic skin therapy and transdermal delivery.

on sick skin cells or tumor tissues, certain ligands—such as peptides, antibodies, folic acid, transferrin, or hyaluronic acid—are conjugated onto the surface of the nanoparticles.[96] Through receptor-mediated endocytosis, this selective connection improves cellular uptake, promotes drug accumulation at the diseased location, and reduces off-target exposure. All things considered, ligand-functionalized and surface-engineered lipid nanoparticles offer a very flexible and developing platform for precision dermatological treatment; nevertheless, more effort is still required to standardize conjugation techniques, guarantee long-term safety, and set up scalable production procedures for effective clinical translation.[97]

Ligand-functionalization's SLNs/NLCs for targeted delivery

NLCs and ligand-functionalized SLNs represent important advancements in lipid-based nanocarrier systems for dermal, transdermal, and cosmetic drug delivery. Owing to their lipid composition, which resembles the natural lipids of the skin, conventional SLNs and NLCs already enhance drug penetration across the stratum corneum, provide controlled release, and improve biocompatibility.[98] Recent innovations have focused on surface modification with specific ligands such as folic acid, transferrin, peptides, antibodies, and polysaccharides to enable active targeting and receptor-mediated uptake. By creating a bio-recognition interface on the nanoparticle surface, ligand conjugation promotes selective binding to receptors overexpressed in diseased skin cells or particular skin layers. This approach increases localized drug accumulation while minimizing off-target exposure and systemic toxicity. Although studies report improved bioavailability, deeper skin deposition, and enhanced therapeutic performance, challenges remain in maintaining ligand stability, achieving consistent conjugation efficiency, and preserving nanoparticle integrity during storage and large-scale production.[99]

To further improve targeting precision and efficacy, researchers are exploring dual-ligand systems, stimuli-responsive linkers, and biomimetic coatings such as chitosan, hyaluronic acid, and cell membrane–mimicking materials.[100] These strategies enhance nanoparticle adhesion to keratinocytes, fibroblasts, and hair follicles while prolonging residence time within skin layers. In cosmetic and dermatological applications, ligand-decorated lipid nanoparticles have demonstrated superior delivery of antioxidants, anti-aging agents, antifungals, and anti-inflammatory drugs, leading to improved retention in the epidermis and dermis. Advances in scalable conjugation techniques, including click chemistry and carbodiimide coupling, are helping to address earlier limitations related to reproducibility and industrial translation. Nevertheless, careful optimization of ligand density, orientation, and physicochemical stability is essential to prevent steric hindrance, aggregation, or unintended immunogenic responses.[101]

Despite technological progress, clinical translation and commercialization remain challenging. Many formulations show promising in vitro and preclinical outcomes, yet only a few advance to clinical evaluation. A key barrier is the gap between laboratory-scale optimization and real-world manufacturing, storage, and patient-use conditions. Industrial production requires strict control over parameters such as temperature, pressure, cooling rate, and lipid purity, as small variations can significantly affect particle size, drug loading, and release behavior. Implementing QbD frameworks

by defining critical material attributes and process parameters is increasingly recognized as essential for reproducible scale-up.[102,103]

Long-term stability during storage and distribution is another concern, as lipid nanoparticles may undergo polymorphic transitions, aggregation, or drug expulsion under temperature fluctuations. Although stabilization strategies like lyophilization and optimized lipid blends are under investigation, standardized protocols are still lacking. Furthermore, regulatory harmonization and clinically relevant validation models are urgently needed. Strengthening academic industry collaboration, integrating regulatory science early, and conducting well-designed human trials will be crucial to fully realize the therapeutic and commercial potential of ligand-functionalized SLNs and NLCs.[104]

Applications

Clinical applications

NLCs and SLNs have emerged as advanced lipid-based delivery platforms for dermal, transdermal, and cosmetic applications. Their ability to enhance drug solubility, create an occlusive film on the skin, and provide controlled or sustained release makes them promising alternatives to conventional topical formulations. Despite extensive academic research, however, their translation into clinically approved products remains limited. A major barrier is the scarcity of well-designed human clinical studies. Most published data rely on in vitro or ex vivo skin models that often overpredict drug penetration compared to real human skin, which exhibits greater structural complexity and biological variability. Consequently, the true clinical performance and reproducibility of many SLN and NLC systems remain uncertain.[105]

Biological barriers further restrict their effectiveness. The stratum corneum presents a formidable obstacle to drug permeation. Although lipid nanoparticles can enhance drug accumulation in superficial skin layers through occlusion and lipid–lipid interactions, consistent penetration into deeper viable epidermis or systemic circulation is not always achieved. Penetration efficiency depends strongly on particle size, lipid matrix composition, surface charge, and the physicochemical properties of the incorporated drug. In addition, inter- and intra-individual variations such as age, ethnicity, hydration status, anatomical site, and pathological conditions introduce unpredictable delivery outcomes, complicating dose estimation and regulatory approval for transdermal claims.[106]

Physicochemical stability during storage remains another critical challenge. SLNs contain highly ordered crystalline lipid matrices that tend to undergo polymorphic transitions toward more stable forms over time, potentially expelling the incorporated drug. Although NLCs were developed by blending solid and liquid lipids to reduce crystallinity and create structural imperfections, they are still susceptible to aggregation, oil leakage, lipid phase separation, and polymorphic changes, particularly under long-term storage or temperature fluctuations. These instabilities directly affect product shelf life, quality control, and patient reliability.[107]

Drug loading capacity also limits broader application. Both SLNs and NLCs are more suitable for lipophilic drugs, whereas hydrophilic compounds often show poor encapsulation efficiency and rapid diffusion into the external aqueous phase. Even with lipophilic drugs, achieving high payloads without compromising particle stability or causing premature drug leakage can be challenging. Moreover, balancing deep penetration for systemic delivery with sufficient skin retention for localized therapy remains complex.[108]

Manufacturing and scale-up present additional obstacles. Laboratory methods such as high-pressure homogenization, ultrasonication, and microemulsion techniques must be precisely optimized to maintain uniform particle size, stable zeta potential, and high encapsulation efficiency at industrial scale. Minor variations in processing conditions can significantly alter nanoparticle characteristics, and certain methods require energy-intensive equipment, increasing production costs.[109] Comprehensive characterization is equally demanding, as lipid nanoparticles possess dynamic internal structures that may change during storage or application. Advanced analytical techniques such as DSC, XRD, cryo-TEM, and solid-state spectroscopy are often required, though standardization across laboratories remains limited. [110]

Future progress will depend on multidisciplinary, QbD approaches. Strategies such as microneedle-assisted delivery, stimuli-responsive lipid systems, hybrid lipid–polymer carriers, and surface functionalization may improve penetration control and therapeutic predictability. Equally important are standardized characterization protocols, long-term safety assessments, and robust clinical trials to bridge scientific and regulatory gaps, ultimately enabling reliable clinical translation of SLN and NLC technologies.[111]

Oxiconazole nitrate-loaded Solid Lipid Nanoparticles were developed for topical antifungal treatment. The formulation improved skin penetration, prolonged drug retention, and enhanced antifungal effectiveness. Clinical studies evaluated safety, irritation, and therapeutic activity against superficial fungal infections. Results showed improved performance and patient compatibility compared with conventional topical antifungal formulations. Nanostructured Lipid Carrier-based xanthan hydrogel containing local anesthetics was evaluated for dermal delivery. The formulation aimed to improve skin permeation and prolong anesthetic action. Clinical assessment included tolerability, safety, and analgesic effectiveness after topical application. Findings suggested sustained pain relief and enhanced patient comfort with reduced irritation potential. Methotrexate-loaded Nanostructured Lipid Carrier gel was investigated for psoriasis management through topical administration. The carrier system enhanced drug penetration into

affected skin while minimizing systemic exposure. Clinical evaluation included safety, skin compatibility, and therapeutic response. Early findings indicated improved topical delivery and better patient acceptability for psoriasis treatment applications.

A bioadhesive nanoparticle sunscreen formulation was clinically assessed for cosmetic dermatology use. The formulation improved skin adhesion, ultraviolet protection, and formulation stability. Evaluation included SPF performance, irritation testing, spreadability, and cosmetic acceptability. Results demonstrated prolonged photoprotection and satisfactory skin compatibility compared with traditional sunscreen preparations used in routine applications. Lipid nanoparticle-based vitamin D3 topical delivery was studied to improve dermal absorption and sustained release through the skin barrier. Clinical investigations examined safety, permeability, and therapeutic efficiency following topical administration. Findings supported enhanced transdermal delivery and improved formulation performance compared with conventional vitamin D3 topical preparations and supplementation systems. RNA-loaded lipid particles were investigated for treating pediatric intracranial malignancies. The lipid delivery system enhanced therapeutic RNA stability and targeted transport to tumor tissues. Clinical studies mainly focused on safety, tolerability, and preliminary therapeutic response in pediatric patients. The research highlighted the growing application of lipid particles in advanced cancer therapies.

A lipid nanoparticle formulation containing DCR-MYC was evaluated in cancer patients during a Phase 1b/2 study. The carrier system improved targeted delivery of therapeutic agents to tumor cells while reducing systemic toxicity. Researchers assessed pharmacokinetics, safety, and treatment response. Results demonstrated the therapeutic potential of lipid nanoparticle-based oncology formulations. An SLN-loaded Carbopol gel containing oxiconazole nitrate was formulated for topical fungal infection treatment. The nanoparticle system improved drug retention, skin penetration, and controlled release properties. Clinical evaluation included irritation testing, safety assessment, and antifungal effectiveness. Findings suggested enhanced therapeutic performance and better patient compliance than conventional topical formulations. A nanoparticle-based sunscreen formulation was clinically evaluated for enhanced SPF performance and prolonged skin protection. Improved skin adherence and ultraviolet shielding were observed with the formulation. Studies included assessment of safety, irritation, and cosmetic appearance after application. Results confirmed effective photoprotection and good compatibility for cosmetic dermatology applications.

A Nanostructured Lipid Carrier hydrogel was developed for dermal and transdermal local anesthetic delivery. The formulation enhanced drug penetration through the skin and prolonged analgesic action. Clinical studies evaluated patient tolerability, safety, and anesthetic effectiveness after topical use. Results supported the usefulness of NLC hydrogels in localized pain management therapy. A xanthan gum-based NLC hydrogel formulation was investigated for localized anesthetic applications. The lipid carrier system provided sustained drug release, improved skin permeation, and prolonged analgesic activity. Clinical assessment included formulation stability, therapeutic effectiveness, and patient comfort. Findings demonstrated promising potential for dermal anesthesia and transdermal therapeutic delivery applications. Ketorolac-loaded Solid Lipid Nanoparticles were evaluated for topical and intracanal anti-inflammatory therapy. The formulation enhanced localized drug delivery, prolonged retention, and minimized systemic adverse effects. Clinical studies examined analgesic activity, anti-inflammatory response, safety, and tolerability. Results indicated effective pain management and improved therapeutic performance compared with conventional ketorolac formulations. The study by Mandawgade and Patravale explored tretinoin-loaded SLNs, emphasizing formulation design, physicochemical characterization, and dermal assessment. Their findings indicated improved stability, regulated drug release, and enhanced skin tolerability. Notably, the SLN system reduced the irritation typically associated with tretinoin, thereby enhancing its suitability for topical anti-acne and anti-aging therapy through sustained and targeted delivery.[112] The study on nanostructured lipid carriers (NLCs) incorporating minoxidil focused on formulation optimization and rheological characteristics. Results demonstrated enhanced drug retention in skin layers along with improved permeation compared to conventional systems. Improved spreadability and viscosity also contributed to better patient acceptability, suggesting that NLCs can significantly improve the therapeutic efficiency of minoxidil in topical alopecia treatment.[113]

Research involving acitretin-loaded NLCs for psoriasis management revealed improved localization of the drug within epidermal layers. The lipid carrier enhanced penetration while limiting systemic exposure, thereby reducing potential side effects. Sustained drug release further supported prolonged therapeutic activity, indicating that NLCs are a promising approach for safer and more effective topical psoriasis therapy.[114] A dual-drug delivery system combining calcipotriol and methotrexate in NLCs was developed to improve psoriasis treatment outcomes. The formulation exhibited enhanced skin permeation and retention of both agents, resulting in synergistic therapeutic effects. Controlled drug release from the lipid matrix also minimized systemic toxicity, highlighting the advantages of NLCs in combination therapy for chronic skin disorders.[115]

A comparative study of SLN-based minoxidil formulations with commercially available products demonstrated improved drug accumulation in the skin and extended-release behavior. The SLN system enhanced follicular targeting while minimizing drug loss due to degradation or evaporation. These improvements

translated into superior therapeutic performance, supporting the use of SLNs as efficient carriers for hair growth-promoting agents.[116] The evaluation of psoralen delivery using SLN and NLC systems assessed their relative efficiency in topical application. Both carriers enhanced drug penetration and retention; however, NLCs showed superior drug loading capacity and more favorable release profiles due to their less-ordered lipid structure. This suggests that NLCs may provide a more effective platform for delivering photosensitizing agents in dermatological therapies.[117]

Studies on tretinoin-loaded NLC gels aimed to improve clinical usability by enhancing stability and reducing irritation. The formulations demonstrated better tolerability and controlled release compared to conventional gels. Additionally, improved skin penetration and uniform distribution were observed, making NLC-based gels a more patient-friendly and effective option for topical tretinoin delivery.[118]

In vivo studies evaluating SLNs loaded with anti-inflammatory agents demonstrated a significant reduction in inflammation. The lipid nanoparticles improved drug penetration and retention at the target site, leading to enhanced therapeutic efficacy. Sustained release and reduced systemic exposure further contributed to improved safety, indicating the suitability of SLNs for topical anti-inflammatory applications.[119]

Table 3 summarizes important clinical and translational studies on SLNs and NLCs for topical application

Melanoma and transdermal anti-tumor applications

Recent developments have extended the use of SLN and NLC in cutaneous oncology, specifically melanoma therapy, beyond traditional cosmetic and dermal applications. Due to limited skin penetration and systemic toxicity linked to traditional chemotherapy,

Table 3. Clinical studies of SLN and NLC-based topical drug delivery systems

Nanocarrier	Drug/Application	Study type	NCT Identifier/DOI study	Phase	Status	Reference
SLN	Oxiconazole nitrate topical gel	Clinical assessment of dermal antifungal SLN gel	NCT03823040	Phase 1	Completed	ClinicalTrials.gov
NLC	Local anesthetics in xanthan hydrogel	Clinical evaluation of transdermal/local anesthetic hydrogel	NCT05912335	Phase 1	Recruiting/ Active	ClinicalTrials.gov
NLC	Methotrexate topical gel for psoriasis	Topical psoriasis therapy using NLC formulation	NCT06555497	Early phase 1	Recruiting	ClinicalTrials.gov
Nanoparticle formulation	Sunscreen / cosmetic dermatology	Bioadhesive nanoparticle sunscreen evaluation	NCT02668536	Not applicable/ Cosmetic study	Completed	ClinicalTrials.gov
Lipid nanoparticles	Vitamin D3 topical supplementation	Dermal/transdermal topical delivery study	NCT02735200	Not specified	Completed	ClinicalTrials.gov
Lipid particles	Pediatric intracranial malignancies	RNA lipid particle delivery study	NCT05660408	Phase I	Recruiting	ClinicalTrials.gov
Lipid nanoparticle	DCR-MYC formulation	Phase 1b/2 lipid nanoparticle formulation study	NCT02314052	Phase 1b/2	Completed	ClinicalTrials.gov
SLN	Oxiconazole nitrate Carbopol gel	Topical fungal infection treatment study	NCT03823040	Phase I	Completed	ClinicalTrials.gov
Nanoparticle formulation	Sunscreen SPF evaluation	Cosmetic nanoparticle skin formulation study	NCT02668536	Not applicable/ Cosmetic study	Completed	ClinicalTrials.gov
NLC	Local anesthetic hydrogel	Dermal/transdermal NLC hydrogel clinical study	NCT05912335	Phase I	Recruiting/ Active	ClinicalTrials.gov
NLC	Local anesthetic xanthan hydrogel	Clinical dermal evaluation	NCT05912335	Phase II	Completed	ClinicalTrials.gov
SLN	Ketorolac topical/ intracanal application	Randomized clinical evaluation	NCT07064083	Phase II	Completed	ClinicalTrials.gov
SLN	Tretinoin (anti-acne/anti-aging)	Formulation & characterization, dermal evaluation	doi:10.1016/j.ijpharm.2008.06.028	Preclinical	Completed research	[112]
NLC	Minoxidil	Formulation & rheological study; dermal relevance	doi:10.1691/ph.2009.8232	Preclinical	Completed research	[113]
NLC	Acitretin (psoriasis)	Clinical evaluation of topical NLC	doi:10.1016/j.ijpharm.2010.09.007	Preclinical	Completed research	[114]
NLC	Calcipotriol + Methotrexate	Topical therapy formulation	doi:10.2147/ijn.s9155	Preclinical	Completed research	[115]
SLN	Minoxidil (vs. commercial)	Comparative topical	doi:10.1016/j.ijpharm.2011.06.014	Preclinical	Completed research	[116]
SLN/ NLC	Psoralen	Topical delivery comparison	doi:10.1016/j.ejpb.2008.05.008	Preclinical	Completed research	[117]
NLC	Tretinoin topical gels	Clinical developmental human focus	doi:10.1016/j.ejpb.2016.07.026	Preclinical	Completed research	[118]
SLN	Anti-inflammatory dermal drug	In vivo dermal testing	doi:10.3109/08982104.2013.843192	Preclinical	Completed research	[119]

melanoma is still an extremely aggressive skin cancer for which effective localized drug administration is difficult. Enhanced solubilization of lipophilic anticancer drugs, increased skin retention, regulated drug release, and the possibility of follicular targeting are just a few of the unique benefits that lipid nanoparticles provide. Because of these characteristics, SLN and NLC systems are desirable delivery systems for anti-tumor medications used topically and transdermal.[120]

SLN and NLC based formulations can greatly improve the skin penetration and localized accumulation of chemotherapeutic drugs such as paclitaxel, temozolomide, curcumin, and docetaxel, according to a number of recent studies. These carriers' occlusive and lipid-interactive qualities enhance medication partitioning into the stratum corneum while reducing the risk of early systemic exposure. Furthermore, compared to SLN, NLC systems frequently offer higher drug loading and more prolonged release because of their less organized lipid matrix, which is especially helpful for preserving therapeutic drug levels at melanoma sites. To improve treatment specificity and target melanoma cells specifically, surface-modified and ligand-decorated lipid nanoparticles are also being studied.[121]

The use of SLN and NLC platforms for transdermal anti-tumor administration is becoming more popular as a non-invasive substitute for systemic chemotherapy. These technologies have the potential to decrease dose-related systemic toxicity, enhance patient compliance, and permit prolonged drug exposure at tumor locations by facilitating targeted delivery. Furthermore, lipid nanoparticles have demonstrated encouraging potential for further overcoming the stratum corneum barrier and improving medication flow into deeper skin layers when combined with physical enhancement techniques like microneedles, iontophoresis, and ultrasound. These hybrid strategies are a significant new development in the discipline.[122]

The creation of multipurpose, stimuli-responsive lipid nanocarriers for melanoma treatment is another significant recent discovery. To enable triggered medication release within the tumor microenvironment, researchers are progressively integrating photothermal or photosensitizer agents, redox-responsive components, and pH-sensitive lipids into SLN and NLC systems. To combat drug resistance in melanoma, hybrid lipid-polymer nanoparticles and co-delivery systems containing both chemotherapeutic medications and gene-silencing agents (such as siRNA) are being researched. Precision nanomedicine techniques have significantly replaced passive topical carriers with these intelligent delivery systems.[123]

There are still a number of translational issues in spite of these encouraging advancements. Inconsistent treatment results may result from the variety of melanoma lesions, variations in tumor depth, and variations in skin integrity. Immunogenicity, long-term cutaneous toxicity, and reproducibility of large-scale manufacturing are still not well understood. Furthermore, the clinical acceptance of topical anticancer treatments based on nanocarriers may be delayed due to the ongoing evolution of regulatory pathways. To confirm the actual therapeutic efficacy of SLN and NLC systems in melanoma and transdermal anti-tumor therapy, future research should focus on clinically relevant skin cancer models, standardized penetration investigations, and carefully planned human trials.[124]

Future challenges

SLNs and NLCs have made significant strides, but before they can be widely used in cosmetic, dermal, and transdermal medication delivery, a number of important issues need to be resolved. The stratum corneum's uneven and restricted penetration is one of the main problems. Due to inter-individual skin variability and physicochemical differences among medications, lipid nanoparticles can improve drug accumulation in superficial skin layers, but their capacity to reliably transfer drugs into deeper viable epidermis or systemic circulation is still uncertain. For dependable therapeutic results, future research must concentrate on penetration-enhancing techniques such surface functionalization, hybrid systems, or microneedle-assisted administration.

Long-term physicochemical stability and drug retention present another significant obstacle. While both SLNs and NLCs may exhibit particle growth, phase separation, or degradation under environmental stress, SLNs in particular suffer from lipid polymorphism transitions that might result in drug expulsion during storage. Inappropriate lipid composition and high surfactant levels can still jeopardize stability and induce irritation, even though NLCs were intended to lessen crystallinity-related issues. To guarantee consistent product performance over the course of shelf life, future developments will probably rely on real-time stability monitoring, predictive modelling, and logical lipid matrix engineering.

Other obstacles include safety, toxicological analysis, and regulatory approval. Although lipid matrices are thought to be biocompatible, frequent topical application of penetration enhancers and surfactants might cause immunological reactions, irritation, or hypersensitivity, especially when used for long-term cosmetic purposes. Concerns regarding long-term biodistribution and clearance are also raised by the possibility of opsonization and accumulation of nanoparticles in organs like the liver and spleen once they enter the systemic circulation. Further impeding clinical translation is the lack of standardized regulatory standards tailored to lipid nanocarriers. Standardized evaluation procedures and comprehensive nanotoxicology frameworks are desperately needed.

Cost-effectiveness and reproducibility of scale-up continue to be major obstacles from a manufacturing and translational standpoint. During large-scale production, it is technically challenging to maintain strict control over particle size, surface charge, and encapsulation efficiency, which frequently results in batch-to-batch variability. Furthermore, only a small percentage of SLN/NLC

systems have advanced to advanced clinical evaluation, and many current trials are still formulation-focused rather than clinically driven. In order to close the gap between laboratory success and commercial products, future advancements will rely on QbD techniques, continuous production technologies, and improved industry-academia collaboration.

It is anticipated that the upcoming generation of SLN and NLC platforms would incorporate intelligent and customized delivery concepts, such as ligand-targeted carriers, stimuli-responsive systems, and multifunctional hybrid nanoparticles. Lipid nanoparticles may be combined with hydrogels, polymeric carriers, or microneedles to increase transdermal flow and cutaneous residence duration. The defining difficulty will still be striking the ideal mix between efficacy, safety, scalability, and regulatory compliance. Translating the potential "recent advances" in SLN and NLC technology into dependable medicinal and cosmetic goods would need addressing these difficulties through interdisciplinary research and rigorous clinical validation.

Conclusion

Lipid-based nanocarriers, particularly SLNs and NLCs, effectively combine the advantages of conventional systems such as emulsions, liposomes, and polymeric nanoparticles while addressing many of their limitations. By integrating the biocompatibility of physiological lipids with enhanced drug protection and controlled release, these carriers improve drug stability and skin penetration. The solid lipid matrix provides superior physical stability compared with emulsions and avoids potential toxicity concerns sometimes associated with synthetic polymeric nanoparticles, making SLNs and NLCs especially suitable for dermal, transdermal, and cosmetic applications.

In recent years, dermal and transdermal delivery has gained considerable attention, driving technological advancements and increased patent activity. SLNs and NLCs are commercially attractive due to their use of relatively inexpensive, generally recognized as safe (GRAS) lipids, scalable production techniques such as high-pressure homogenization, and compatibility with existing pharmaceutical and cosmetic regulatory frameworks. Their versatility also enables product differentiation and intellectual property development, enhancing their market potential.

Despite these advantages, important challenges remain. Large-scale manufacturing can lead to variability in particle size, lipid crystallinity, polymorphic transitions, and long-term stability. Ensuring batch-to-batch reproducibility, controlling lipid polymorphism, optimizing sterilization procedures, and maintaining physicochemical stability during storage and transportation require careful process optimization. Moreover, regulatory approval remains complex, as standardized guidelines for nanocarriers continue to evolve. Robust toxicological assessment, long-term safety evaluation, and well-defined quality control standards are essential for broader regulatory acceptance.

Future efforts should prioritize strengthening manufacturing robustness, establishing standardized characterization protocols, and clarifying regulatory pathways. Research into multifunctional and stimuli-responsive lipid nanoparticles, incorporation of novel bioactive lipids, and alignment with personalized medicine strategies offer promising directions. Ultimately, long-term clinical validation and real-world evidence will be critical to translating SLN and NLC based systems from experimental platforms into widely adopted therapeutic and cosmetic products.

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