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REVIEW

Nanostructured Lipid Carrier-Gels for Wound Healing: A Narrative Review of Formulation Strategies, Mechanisms, and Translational Potential

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Abstract: Wound healing is a complex process involving hemostasis, inflammation, proliferation, and remodeling of tissues or cells. In chronic conditions, such as diabetic wounds, this process is often disrupted. Nanostructured lipid carriers (NLCs) are advantageous topical drug delivery systems because of their ability to improve stability, bioavailability, and controlled drug release. The incorporation of NLCs into a gel matrix (NLC-gel) enhances the formulation with bioadhesive properties, skin hydration, and drug retention in the wound area. This accelerates healing and reduces the risk of infections. While these findings highlight the potential of NLC–gel systems to improve local drug bioavailability and promote tissue regeneration, most available evidence is derived from in vitro and animal studies, and clinical data remain limited. This review critically summarizes recent advances in NLC–gel formulations for wound healing, with particular emphasis on the relationship between formulation strategies and biological mechanisms, including modulation of inflammation, angiogenesis, fibroblast and keratinocyte proliferation, collagen deposition, and antimicrobial and antioxidant activities. Additionally, translational considerations such as long-term safety, formulation scalability, and clinical prospects are discussed. Recent in vivo and in vitro studies have shown that NLC gels containing active ingredients, such as simvastatin, curcumin, quercetin, moxifloxacin, or other therapeutic proteins, can accelerate wound healing, particularly in wounds caused by metabolic disorders. These results suggest that NLC gels have great potential as therapeutic platforms for wound care. However, further research is required to optimize its formulation and clinical translation.

Keywords: nanostructured lipid carriers, gel, hydrogel, wound healing

Introduction

Wound healing is a tightly regulated biological process involving hemostasis, inflammation, proliferation, and tissue remodeling to replace damaged components. Anti-inflammatory agents are used to reduce complications caused by an excessive immune response at the wound site.[1] This process involves the migration and proliferation of blood cells, production of extracellular matrix, endothelial cells, cytokines, release of growth factors, angiogenesis, and fibroblasts.[2] Pharmacological agents can aid in accelerating the wound-healing process.[3,4] Acute wounds generally progress through the healing phases in a timely and coordinated manner, whereas chronic wounds are characterized by delayed or arrested healing, often associated with persistent inflammation, impaired angiogenesis, and metabolic disorders such as diabetes, making them the primary target for advanced drug delivery approaches, including nanocarrier-based systems.[5,6] Conventional topical wound treatments often face limitations such as poor drug penetration and stability, rapid

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uncontrolled release, low wound retention, microbial colonization, oxidative stress, and inadequate vascularization. Topical drug delivery systems enable localized and sustained drug release at wound sites, reducing systemic effects. However, conventional hydrophilic bases often fail to maintain moisture and control drug release, resulting in frequent reapplication, suboptimal local concentrations, and inconsistent healing outcomes.[7–9] Conventional gels provide hydration and ease of use but lack controlled drug release, offer limited protection against degradation, and are ineffective for delivering lipophilic drugs, reducing their therapeutic potential in complex wounds.[10,11] Beyond hydrogel-based matrices, decellularized extracellular matrix (dECM) scaffolds have emerged as bioactive platforms for wound repair and tissue regeneration, owing to their preserved structural, biochemical, and signaling components that actively regulate cell migration, angiogenesis, and tissue remodeling.[12] Recent advances in dECM processing and functionalization further highlight its role as a benchmark scaffold in tissue engineering, providing a useful reference framework for evaluating synthetic and hybrid delivery systems, including NLC–gel formulations. Therefore, nanocarrier-based topical systems, especially nanostructured lipid carriers (NLCs), offer improved bioavailability, drug protection, and tissue repair. Their mixed solid–liquid lipid matrix provides higher drug loading capacity and lower drug expulsion compared to solid lipid nanoparticles (SLNs).[13] NLC increase the stability and effectiveness of drugs by protecting them, increasing drug loading capacity, controlling drug release, improving drug release kinetics, and facilitating better absorption.[11,14] When incorporated into gel formulations, NLCs further enhance skin hydration and adhesion, protect the drug within the lipid matrix, and enable direct delivery to the wound site. NLC-based gels maintain local drug concentrations for a longer period, reduce systemic absorption, and provide anti-inflammatory, antioxidant, and pro-healing effects, making them a promising strategy for improving wound healing outcomes.[9,15] Several review articles have previously discussed lipid-based nanocarriers, including solid lipid nanoparticles (SLNs) and nanostructured lipid carriers, for wound healing applications. However, most of these reviews either broadly cover multiple nanocarrier systems or focus predominantly on formulation aspects without critically linking formulation parameters to biological mechanisms and therapeutic outcomes. In addition, the specific advantages and challenges of NLC-based gel systems, particularly regarding wound retention, local bioavailability, mechanistic pathways, and translational potential, remain insufficiently explored. Therefore, the present review aims to fill this gap by providing a focused and mechanistically oriented overview of NLC–gel systems for wound healing, integrating formulation strategies, physicochemical and biological characterization, mechanistic insights, and emerging therapeutic directions.

Nanostructured Lipid Carriers (NLCs): Fundamentals and Applications

Composition and Key Components of NLCs

Nanostructured Lipid Carriers (NLCs) are advanced lipid-based nanocarriers composed of a mixture of solid and liquid lipids stabilized by suitable surfactants. The combination of solid and liquid lipids forms an imperfect crystalline matrix that enhances the drug loading capacity and prevents drug expulsion during storage, which is a limitation of first-generation solid lipid nanoparticles (SLNs).[16,17] Solid lipid components, such as glyceryl monostearate, stearic acid, and beeswax, provide structural integrity and modulate the release rate of the encapsulated drug.[18,19] Liquid lipids, such as oleic acid, medium-chain triglycerides, and natural oils, introduce structural imperfections into the solid matrix, improving drug accommodation and controlling polymorphic transitions.[20] This can be combined with liquid lipids or oils (eg, argan oil, oleic acid, medium-chain triglycerides) to create the structural "imperfections" necessary for higher encapsulation efficiency of lipophilic active ingredients.[21] The selection of surfactants is crucial for the formation of NLCs to obtain a skin application size range (150–300 nm), colloidal stability, and biocompatibility. Surfactants and co-surfactants, such as Tween 80, Poloxamer 188, and lecithin, stabilize the dispersion and influence the droplet size and zeta potential.[22] In addition, there are polysorbates for topical and dermal applications, sucrose esters (sucrose monostearate (SS) and sucrose monopalmitate (SM)) as biodegradable non-ionic surfactants, so they are better tolerated and less irritating than polyethoxylated surfactants, α-Tocopheryl Acetate (αTA) to chemically stabilize lipids, pentylene glycol (PG) as a preservative to ensure antimicrobial stability of the formulation, with good skin tolerability and suitability of NLC formulations.[23,24] The proper selection of these components determines the physicochemical stability, entrapment efficiency, and release kinetics of NLC systems.[25] Analysis of the formulations summarized in Table 1

Table 1 Formulation Components And Preparation Methods Of NLC-Gel Systems For Wound Healing Applications

No	Active Substance	Solid/Liquid Lipid	Surfactant/Co-Surfactant	Gel Base	Manufacturing Method	References
1	Hyperforin	Glyceryl behenate (compritol 888 ATO) + Almond/Borage oil	Polysorbate 80, Sorbitan monooleate	Bigel combining Hydrogel (Poloxamer 407) + Organogel (Sorbitan monostearate + Borage oil)	Hot homogenization + sonication	[26]
2	Genistein + Dexamethasone + Moxifloxacin	Compritol 888 ATO + MCT	Kolliphor HS15, Cremophor EL	Thermoresponsive in situ Hydrogel (Pluronic F127/F68)	Hot emulsification + sonication	[27]
3	Dexamethasone + Moxifloxacin	Soybean Lecithin + Cholesterol (Liposome)	–	Composite Hydrogel (Collagen, gelatin, sodium alginate)	Thin film hydration + ionic gelation	[25]
4	Phenytoin	Compritol 888 ATO + Capryol 90	Poloxamer 188	Carbomer 934 Hydrogel	Hot homogenization + ultrasonication	[28]
5	Melatonin	Compritol 888 ATO + Miglyol 812N	Pluronic F127	Chitosan microsphere in-situ Hydrogel	Hot homogenization + spray drying	[29]
6	Phenytoin	Compritol 888 ATO + Capryol 90	Poloxamer 188	Carbopol 934 Hydrogel	High shear + sonication	[30]
7	Chlorhexidine	Lipoid S100	–	Chitosan hydrogel	One-pot + sonication	[31]
8	Rutin	Beeswax + Sesame oil	Tween 80	Dual responsive Hydrogel: Pluronic F127 + Carbopol 940	High shear + ultrasonication	[18]
9	Doxycycline + Aloe-emodin	Stearic acid + Oleic acid	Tween 80	Carbopol 934 Gel	Box–Behnken optimized NLC	[32]
10	Astaxanthin	Glycerol monostearate (GMS) + Oleic acid	Span 60 + Tween 60	Carbopol 940 Gel	Hot homogenization + sonication	[7]
11	Lidocaine	Apifil + Miglyol 812	Kolliphor RH40	Carbopol 971P Gel	High shear + optimization	[33]
12	Simvastatin	Stearic acid + Capryol PGMC + cholesterol + triolein	Brij 35 and 72	Carbomer 934 + NaCMC Gel	Solvent diffusion, evaporation	[34]
13	Mupirocin	Precirol ATO 5 + Oleic acid	Kolliphor RH40	Emulgel base	Phase inversion temperature	[35]
14	5-Fluorouracil + Cannabidiol	(Gelucire 50/13, Gelucire 44/14, Precirol ATO 5, Geleol, Compritol 888 ATO) + (Coconut oil, Labrasol, Campul, Capryol 90, Oleic acid, Olive oil, Castor oil)	Smix (2:1)	Carbopol 934 Gel	CCD-optimized	[36]
15	Propolis	Glycerol monostearate (GMS) + Capric acid	Lecithin + Tween 80	Carbopol 942 Gel	Emulsion, evaporation, solidification	[37]
16	Zerumbone	Hydrogenated palm oil + Olive oil, Lipoid S100	Sorbitol + Tween 80 + Thimerosal	Carbopol 940 Gel	Hot homogenization	[15]
17	Recombinant human thrombomodulin (rhTM)	Precirol ATO5 + Miglyol 812	Poloxamer 188	Carbopol 940 Gel	Hot homogenization + sonication	[17]
18	Quercetin + Resveratrol	Labrafil M 2130 CS + Labrafil M 2125 CS	Cremophor RH40	Carbopol 934 Gel	Melt emulsification + ultrasonication	[19]
19	Mentha pulegium essential oil (MPEO)	Precirol ATO5 + Miglyol 812	Poloxamer 407	Aqueous gel	Hot homogenization + sonication	[38]
20	Zerumbone	Natural lipids	–	Carbopol 980 Gel	High-pressure homogenization	[22]
21	20 (S) Protopanaxadiol (PPD)	Glyceryl monostearate (GMS) + Medium-chain triglycerides (MCT)	Tween 80 + Pluronic F68	Silicone elastomer Gel	Emulsion–evaporation–solidification	[20]
22	Rosemary essential oil	Precirol ATO5 + Miglyol 812	Poloxamer 407	Aqueous Gel	Hot homogenization + sonication	[39]
23	Thymol	Illipe butter + Calendula oil	Pluronic F68	Carbopol 940 Hydrogel	Hot emulsion + sonication	[40]
24	Retinyl palmitate	Tristearin + Caprylic/capric triglyceride	–	Hyaluronic acid Gel	NLC standard	[41]

Abbreviations: ATO, all triglycerides; MCT, medium-chain triglyceride; HS15, hydroxystearate; EL, ethoxylated lytic; GMS, glycerol monostearate; S100, soybean; F127, poloxamer; F68, poloxamer; N, neutral; RH40, castor oil; CCD, central composite design; rhTM, recombinant human thrombomodulin; MPEO, mentha pulegium essential oil; CS, capsule shell; PPD, protopanaxadiol; NLC, nanostructured lipid carriers.

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reveals a consistent preference for mixed solid–liquid lipid matrices, typically combining lipids such as glyceryl behenate, precirol ATO 5, stearic acid, or glycerol monostearate with oils including medium-chain triglycerides, oleic acid, or Miglyol derivatives. This strategy is applied across a wide range of wound-healing actives, indicating its versatility for topical delivery. Non-ionic surfactants, particularly Tween 80, Poloxamers, and Kolliphor derivatives, dominate the formulations, reflecting their favorable skin compatibility, although surfactant selection and ratios vary considerably among studies. Carbopol-based hydrogels emerge as the most frequently used gel matrix, followed by thermoresponsive poloxamer and chitosan-based systems, highlighting the importance of tunable rheology and bioadhesion for wound applications. Preparation methods are predominantly based on hot homogenization combined with sonication, with some studies incorporating experimental design approaches to optimize formulation variables. Overall, while recurring formulation trends are evident, the heterogeneity in formulation composition and processing underscores the need for more standardized, design-driven strategies to improve comparability and translational relevance.

Mechanisms of Enhanced Drug Loading, Controlled Release, and Skin Permeation

The inclusion of solid and liquid lipids allows NLCs to encapsulate a wide range of hydrophilic and lipophilic drugs with an enhanced entrapment efficiency compared to solid lipid nanoparticles.[39] NLCs are typically composed of a mixture of solid and liquid lipids, resulting in a less ordered (amorphous) core compared to fully crystalline solid lipid nanoparticles (SLNs). This disordered matrix provides more space (imperfections) to accommodate drug molecules. Amorphous regions in the lipid core reduce drug crystallization, allowing for a higher loading capacity and prolonged release.[40,42] Controlled release is achieved through lipid diffusion and degradation, which can be modulated by the lipid composition and surfactant concentration. Controlled and sustained release from NLCs arises from the slow diffusion of drug molecules through the lipid matrix and the gradual reorganization/crystallization of lipids, which has been shown to prolong local drug availability in wound models.[15,16] Mechanistically, the nanometric size (typically < 200 nm) and lipid composition of NLCs may enhance skin permeation and surface area by increasing drug partitioning into skin lipids and temporarily disrupting the stratum corneum lipid domain processes, as demonstrated in ex vivo permeation and in vivo wound studies, as well as promoting passive diffusion of the drug across the skin barrier.[34,43] The nanoscale size of NLCs increases their surface area and allows direct contact with the skin surface, facilitating a higher concentration gradient and enhancing the drug flow into the skin.[44] The lipid composition of NLCs not only protects labile bioactives from environmental degradation (oxidation and enzymatic hydrolysis) but also imparts an occlusive effect on lipid nanoparticles, which improves skin hydration and permeability by reducing transepidermal water loss and helps maintain a moist wound microenvironment that supports re-epithelialization. This occlusion slows drug release from the skin surface, effectively creating a reservoir. Increased hydration can disrupt the dense lipid structure of the stratum corneum, thereby increasing its permeability.[11,45] Together, these mechanisms ensure the sustained and localized delivery of therapeutic molecules directly to the wound site.[21,30]

Pharmaceutical and Herbal Compounds for Wound Healing: Rationale for Incorporation into NLC–Gel Systems

Various bioactive compounds have been successfully incorporated into NLCs for wound-healing applications. Synthetic drugs, such as doxycycline hydrate,[32] simvastatin,[34] phenytoin,[30] and lidocaine,[33] have demonstrated enhanced dermal retention and controlled release from NLC formulations. Natural compounds and herbal active ingredients, including curcumin, resveratrol,[19] aloin, astaxanthin,[7] zerumbone,[15,22] and rosemary essential oil,[39] have demonstrated potent antioxidant and anti-inflammatory properties when delivered via NLCs. Curcumin-loaded NLCs accelerated full-thickness wound closure and reduced oxidative/inflammatory markers in animal models, whereas simvastatin-loaded NLC gels improved ulcer healing and histological regeneration in vivo.[34,43] In addition, the encapsulation of propolis[37] and St. John's Wort extracts[26] in lipid carriers enhanced antimicrobial activity and promoted faster epithelialization than free extracts. Many of these compounds exhibit high lipophilicity, poor aqueous solubility, and susceptibility to oxidative or enzymatic degradation, which limit their effectiveness in conventional hydrophilic gel formulations. Encapsulation

within the imperfect lipid matrix of NLCs enhances drug solubilization, protects labile compounds from degradation, and enables sustained release at the wound site. The gel matrix further complements NLCs by improving wound adhesion, hydration, and local drug retention, thereby creating a synergistic delivery platform that enhances the therapeutic performance of both pharmaceutical and herbal bioactives in complex wound environments. Finally, recent primary research has demonstrated that formulation variables (lipid type, surfactant concentration, and production method) and processing conditions (homogenization/sonication parameters and cooling profile) critically determine NLC physicochemical attributes and their subsequent wound-healing performance, which underscores the importance of systematic optimization in translational development and the versatility of NLCs in delivering pharmaceutical and phytochemical agents for comprehensive wound management.[46]

NLC–Gel Hybrid Systems for Topical Wound Healing

Role of Gel Matrices in NLC-Gel Hybrid Systems

Gel matrices are widely used in topical wound therapy due to their ability to form hydrophilic three-dimensional networks that maintain a moist wound environment. As semisolid systems, gels provide appropriate viscosity and spreadability.[29,46] Common polymers such as carbopol, poloxamer, sodium alginate, and chitosan[17,25] form cross-linked networks capable of retaining large amounts of water and therapeutic agents, thereby sustaining the microenvironment required for effective wound healing.[31,47] Carbopol-based hydrogels are particularly valued for their transparency and spreadability, whereas poloxamers exhibit thermoresponsive sol–gel transition at skin temperature, facilitating in situ application and improved retention.[48] In addition, natural polymer-based gels such as chitosan and alginate contribute intrinsic biocompatibility and biological activity, including antimicrobial and hemostatic properties, which further support wound repair.[49] From a formulation perspective, gel matrices also offer practical advantages as topical dosage forms. Their semisolid consistency improves handling, ease of application, and dose reproducibility compared with liquid dispersions, while reducing discomfort during application and removal.[19] The bioadhesive nature of gels prolongs residence time at the application site and minimizes dosing frequency, contributing to improved patient compliance.[38,40] Hydrogels maintain sustained hydration at the wound surface, which favors fibroblast migration and granulation tissue formation,[21] and often exhibit shear-thinning behavior that facilitates spreading while allowing the formulation to remain in place after application.[50] Moreover, the hydrophilic polymer network protects incorporated actives from environmental and thermal degradation, enabling the inclusion of thermolabile compounds and improving formulation stability during storage.[22,25] Gel matrices also reduce physical instability such as aggregation and sedimentation, resulting in more stable and user-acceptable topical systems.[46] Beyond these vehicle- and dosage-form-related functions, the integration of nanostructured lipid carriers within gel matrices generates synergistic effects that enhance therapeutic performance beyond that achievable by either component alone.[18,28] The gel network immobilizes NLCs, improving mechanical stability and enabling more controlled drug release at the wound site.[51] This synergistic interaction supports sustained local bioavailability and prolonged wound contact, translating into enhanced wound healing outcomes compared with gel-based or NLC-based systems alone. In vivo studies consistently report accelerated wound closure and improved tissue regeneration with NLC–gel formulations, highlighting the therapeutic advantage of this hybrid approach.[33,52] Importantly, the extent of synergy depends on the choice of gel polymer, as polymer composition influences mechanical strength, release kinetics, and permeation behavior; therefore, gel selection should be tailored to the intended wound environment and therapeutic objective.[53]

Formulation Strategies

Analysis of NLC-Gel and Other Topical Nanocarriers

Nanostructured lipid carriers (NLCs) are versatile topical systems for wound healing, offering enhanced drug stability, controlled release, higher drug loading, and reduced drug expulsion compared to solid lipid nanoparticles (SLNs), while also improving hydration and adhesion to support sustained therapeutic levels and faster tissue repair. In addition to lipid carriers like NLCs, other topical nanocarriers such as polymeric nanoparticles (PNPs), nanoemulsions, and ethosomes have been extensively investigated for wound healing applications. A semi-quantitative comparison of topical

nanocarrier systems based on particle size and entrapment efficiency (EE) revealed formulation- and manufacturing-method-dependent differences relevant to wound healing performance. Nanostructured lipid carriers (NLCs) typically exhibit particle sizes in the range of approximately 80–300 nm, with high entrapment efficiencies generally reported between 70% and 95%, due to the imperfect solid-liquid lipid matrix, which allows for higher drug loading and minimizes unwanted release during storage.[54] Solid lipid nanoparticles (SLNs) typically exhibit particle sizes in the range of approximately 100–1000 nm, with more variable and often lower %EE values, typically in the range of 50–85%, due to lipid crystallization and polymorphic transitions that can promote drug release over storage.[54,55] Polymer nanoparticles (PNPs), such as chitosan- or PLGA-based systems, typically range in size from approximately 100–400 nm and exhibit moderate to high entrapment efficiencies, generally reported between 60–90%, depending on the polymer composition, molecular weight, and drug-polymer interactions.[56]

Nanoemulsions generally have droplet sizes of approximately 100–200 nm and exhibit good solubilization capacity for lipophilic drugs, with reported %EE values typically ranging from 60–85%. However, the absence of a solid matrix results in faster drug diffusion and less controlled release compared to lipid nanoparticle systems, although their ability to enhance skin permeation has been well documented.[57] Ethosomes, which consist of ethanol-rich phospholipid vesicles, typically have particle sizes between approximately 120–400 nm with %EE values often exceeding 70–90%, and are highly effective in enhancing dermal and transdermal penetration, although formulation durability and potential ethanol-related irritation remain issues to consider.[54,58] Overall, this semi-quantitative comparison demonstrates that while SLNs, PNPs, nanoemulsions, and ethosomes each offer specific advantages, NLC-based systems provide a more balanced combination of nanoscale size, consistently high capture efficiency, and controlled release behavior, supporting their growing relevance in advanced topical wound healing strategies.

Polymeric nanoparticles, composed of biodegradable polymers such as PLGA, chitosan, or collagen, can encapsulate therapeutic agents to protect them from premature degradation and provide controlled release, often resulting in improved drug stability and retention at the wound site with relatively high loading capacities; however, their formulation typically involves complex synthesis steps and purification that can increase production costs and manufacturing complexity, which has hindered clinical translation despite strong preclinical interest.[59,60] Nanoemulsions are oil–water dispersions stabilized by surfactants that enhance skin permeation by altering barrier properties and can be simpler and cheaper to produce than polymeric systems; they also offer moderate drug loading and kinetic stability, though they may be prone to physical instability (eg, droplet coalescence) under certain conditions and may require additional gelling agents to improve retention at wound sites.[61] Ethosomes are soft phospholipid vesicles containing high concentrations of ethanol, increasing lipid fluidity and facilitating deeper penetration of both hydrophilic and lipophilic drugs through the stratum corneum, often outperforming conventional liposomes in skin delivery; while ethosomes can achieve high entrapment efficiency and enhanced penetration, the presence of ethanol can pose formulation challenges such as potential irritation and requires careful optimization, and their manufacturing is generally more complex than that of simple nanoemulsions.[45] Collectively, these platforms demonstrate varied advantages and limitations: polymeric nanoparticles excel in controlled release and stability but at higher cost and complexity, nanoemulsions offer ease of production and good penetration enhancement with moderate stability, and ethosomes provide superior permeation at the expense of formulation challenges and potential irritation. All of which should be weighed when selecting a nanocarrier for topical wound healing.

Lipid and Surfactant Selection Strategy

The selection of appropriate lipids and surfactants is crucial for developing stable and effective NLC formulations and creating an imperfect crystalline matrix that maximizes encapsulation of the intended active molecule.[17] The goal is to select a solid and liquid lipid that can form a stable NLC matrix and effectively dissolve the active pharmaceutical ingredient (API).[62] Screening is typically performed by evaluating the solubility of the active compound in various solid and liquid lipids, such as glyceryl monostearate, stearic acid, beeswax, oleic acid, and caprylic triglyceride, by measuring drug solubility/partitioning in candidate lipids, thermal behavior (DSC), and solubility of solid/liquid lipid mixtures because drug solubility in the lipid matrix significantly determines entrapment and release efficiency.[18,19] Experimental studies periodically performed solubility testing (drug in lipid), DSC/pXRD to check crystallinity, and short-term

stability screening to select the optimal lipid mixture.[63,64] Surfactants and co-surfactants are essential for stabilizing NLC dispersions and lowering interfacial tension and HLB. Various surfactants/co-surfactants were tested for their ability to form a stable pre-emulsion with the selected lipid mixture and aqueous phase.[65] Surfactants such as Poloxamer 188, Tween 80, and lecithin were selected based on their ability to maintain colloidal stability during homogenization or ultrasonication and to achieve a stable nanoparticulate dispersion with the desired particle size and zeta potential for topical application, emulsification ability, skin toxicity/compatibility, and the hydrophile-lipophile balance (HLB) required to form stable NLC nanoemulsions/dispersions.[47,66] The combination of solid and liquid lipids, along with the choice of surfactant, determines the particle size, zeta potential, and encapsulation efficiency. Compatibility studies are often performed to ensure chemical stability and to prevent phase separation or drug leakage over time.[20] The visual representation of the NLC formulation loaded into the gel is shown in Figure 1.

Application of Experimental Design in NLC Optimization

NLC formulation parameters are generally optimized using statistical tools such as Design of Experiment (DoE) or Response Surface Methodology (RSM), which allow for the systematic evaluation of variables such as lipid ratio, surfactant concentration, and homogenization rate.[25] The widespread use of DoE in early research involved factorial designs, Box-Behnken designs (BBD), Central Composite Designs (CCD), and D-optimal designs to study factors such as lipid percentage (solid:liquid ratio), surfactant concentration, sonication/homogenization time, and temperature.[68,69] This approach efficiently identifies the critical formulation and process parameters, minimizes the number of experiments while identifying the optimal formulation with the desired particle size, polydispersity index (PDI), and entrapment efficiency, and helps achieve the desired product quality attributes at a lower cost and time than traditional methods.[70] Some experimental groups combine elements of QbD (defining CQAs, risk assessment, and DoE) to allow optimization to be transferred to scale-up and to define design space boundaries for process robustness.[71] For example, an optimized NLC-gel formulation of doxycycline and aloin achieved a uniform size distribution and high drug loading, thereby accelerating the healing of diabetic wounds. Similarly, a curcumin–resveratrol combination NLC gel developed using RSM demonstrated enhanced antioxidant activity and tissue regeneration in skin wounds. Thus, statistical optimization ensures the production of reproducible and scalable, high-performance NLC systems. Processing parameters, such as high-pressure homogenization or probe sonication, temperature during emulsification, and cooling profile during lipid

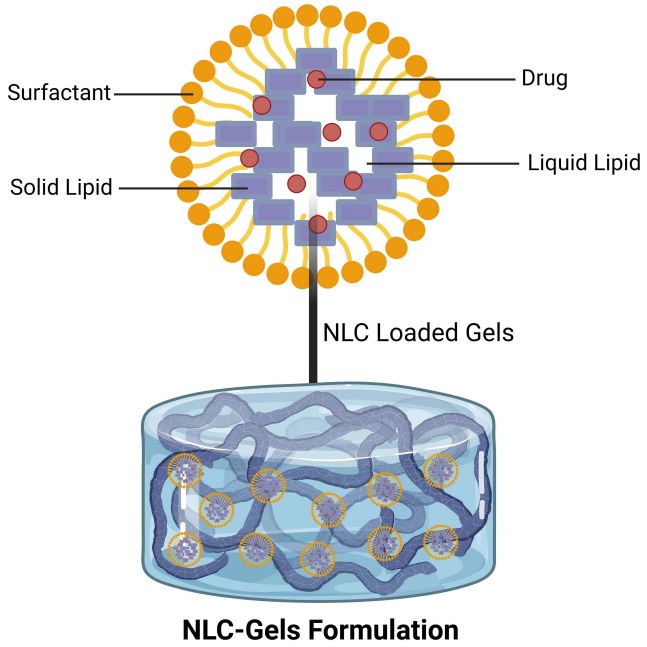

Figure 1 NLC consists of a solid–liquid lipid matrix stabilized by surfactants, enabling high drug loading and controlled drug release.[67] Embedded within a hydrogel network, the NLC-gel provides enhanced skin penetration, prolonged retention, and improved wound-healing performance.[47]

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solidification, strongly influence the particle size distribution, polydispersity, and entrapment efficiency, and must be systematically optimized.[19,22]

Incorporation of Active Pharmaceutical Ingredients into NLC Systems

The incorporation of actives into a nanostructured lipid carrier (NLC) gel involves a two-step process: first, loading the active agent into the NLC particles and second, dispersing these loaded nanoparticles into a gel base.[72] Various preparation methods have been developed for nanostructured lipid carriers (NLCs), and the choice of technique strongly influences particle characteristics, drug loading, and suitability for topical gel formulations. High-pressure homogenization, in both hot and cold variants, is the most widely used method due to its scalability, solvent-free processing, and ability to produce particles with narrow size distributions; however, exposure to elevated temperatures in the hot process may compromise thermolabile active ingredients.[73] Melt emulsification represents a simple and reproducible approach that avoids organic solvents, although it may result in broader particle size distributions and limited control over lipid polymorphism.[73] Solvent-based methods, such as emulsification–evaporation or diffusion, enable efficient incorporation of poorly water-soluble drugs at relatively low processing temperatures but require careful removal of residual solvents to ensure safety and regulatory compliance.[73] Microemulsion-based techniques offer excellent control over particle size through the formation of thermodynamically stable precursors, yet they often rely on high concentrations of surfactants and co-surfactants, which may limit their applicability in topical formulations.[74] Phase inversion methods, including phase inversion temperature approaches, allow NLC formation with relatively low energy input and are particularly attractive for heat-sensitive compounds; nevertheless, these methods typically exhibit narrow processing windows and strong dependence on formulation composition.[74] Collectively, these preparation strategies, as summarized in recent comprehensive reviews, highlight the need for rational method selection based on the physicochemical properties of the active ingredient and the intended performance of NLC-based gel systems.[73,74]

Herbal active ingredients such as propolis, rosemary essential oil, and St. John's Wort extract, have been successfully integrated into NLCs to maintain biological activity and enhance penetration into deeper skin layers.[37,39] For example, zerumbone-loaded NLCs and astaxanthin-loaded chitosan-coated NLCs exhibited enhanced antioxidant and anti-inflammatory effects in a diabetic wound model.[7,15] Appropriate incorporation techniques are crucial for achieving homogeneous drug distribution, high entrapment efficiency, and stability during storage.[32] The polarity and solubility of an active compound determine the optimal lipid composition and preparation method. NLCs protect the incorporated active ingredients from chemical degradation (eg, hydrolysis and oxidation), thereby extending the product shelf life. The NLC dispersion is physically compatible with gel excipients (polymers, surfactants, etc.) to prevent the aggregation of nanoparticles or other instabilities.[75] While formulation strategies define the rational design and compositional framework of NLC–gel systems, they do not inherently guarantee optimal biological performance. The translation of lipid selection, surfactant optimization, and processing conditions into therapeutic efficacy requires systematic physicochemical and mechanical characterization. Therefore, characterization parameters serve as a critical bridge between formulation design and biological function, providing measurable indicators of stability, skin interaction, drug release behavior, and wound-healing potential. In this context, parameters such as particle size, surface charge, entrapment efficiency, morphology, and gel rheology are not merely descriptive attributes, but functional determinants that govern the in vivo performance of NLC–gel systems.

Characterization Parameters

Particle Size, Polydispersity Index, and Zeta Potential

Particle size, polydispersity index (PDI), and zeta potential are the primary characterization metrics because they correlate with colloidal stability and skin interaction.[46,76] The particle size and Polydispersity Index are important indicators of NLC uniformity and stability, which are usually measured by dynamic light scattering (DLS), and are critical because smaller, uniform nanoparticles favor good skin penetration, stability, and controlled release.[17] Optimal wound-healing formulations typically exhibit particle sizes below 200 nm with narrow PDI values (<0.3), thus ensuring better penetration and minimal aggregation.[52] For example, simvastatin-loaded NLCs used for wound healing have an average diameter of ~100 nm.[34] The

zeta potential reflects the surface charge and electrostatic stability of the nanoparticles; values greater than ±30 mV are generally considered stable against aggregation.[25] For example, zerumbone-loaded NLC gels exhibit a zeta potential of approximately −35 mV, which contributes to their excellent colloidal stability and sustained release.[15,22] In NLC studies, the influence of process parameters (lipid composition, homogenization, etc.) on particle size and stability was characterized by dynamic light scattering (DLS), which showed that particle sizes of ~60–80 nm and zeta potential reaching ~−30 mV indicated good colloidal stability.[77] Another formulation (NLC-containing albendazole) reported optimized particles with a size of ~176.5 nm, a PDI of 0.41, and a zeta potential of −22.7 mV, indicating a relatively narrow size distribution and stable charge.[78] The physicochemical data summarized in Table 2 indicate that most NLC–gel formulations for wound healing exhibit particle sizes predominantly below 200 nm with relatively narrow polydispersity indices (PDI < 0.3),

Table 2 Physicochemical Characterization Parameters Of NLC-Gel Formulations For Wound-Healing Applications

No	Particle Size (nm)	PDI	Zeta (mV)	Entrapment Efficiency (EE%)	Morphology (SEM/TEM)	References
1	125–146	–	−36 to −42	>70%	–	[26]
2	39.47	0.213	−4.32	92.75%	–	[27]
3	~150	0.12	−5	Dexamethasone 82% Moxifloxacin 81%	–	[25]
4	178.2	<0.2	–	–	Spherical (TEM)	[28]
5	199–228	≤0.24	+13 to +27.7	99.3%	–	[29]
6	172.5	0.19	−24.1	91.7%	Spherical (TEM)	[30]
7	150–260	0.18–0.32	+12 to +79	≤79%	Spherical (TEM)	[31]
8	176	0.21	−21.3	82%	–	[18]
9	124.3	0.28	−21.4	Doxycycline 88% Aloe-emodin 91%	Spherical (TEM)	[32]
10	80	–	–	85.45%	Spherical (TEM)	[7]
11	124–132	0.23–0.27	−29.8	85–89%	–	[33]
12	132.3	0.478	−16.6	Curcumin 94.21% Resveratrol 84.61%	–	[79]
13	100–140	<0.3	−25	>80%	Spherical, smooth (TEM)	[34]
14	128.8	0.283	−24.2	–	–	[35]
15	100–140	<0.3	−25	>80%	Spherical, smooth (TEM)	[36]
16	41–44	0.29–0.39	−31 to −43	83–87%	Spherical (SEM)	[37]
17	52.7	0.29	+25	99%	–	[15]
18	200–300		−25 to −45	>92%	TEM	[17]
19	191	0.33	−10.00	Quercetin 92.85% Resveratrol 89.05%	Spherical (TEM)	[19]
20	100–250	0.335	−18.8	91%	Spherical (SEM)	[38]
21	111.4	0.21	−33.2	97.9%	Spherical, uniform (SEM)	[20]
22	100–250	0.335	−15.7	92%	Spherical, smooth (SEM)	[39]
23	107	<0.25	−11.6	89.1%	Spherical, uniform	[40]

Abbreviations: PDI, polydispersity index; EE, entrapment efficiency; SEM, scanning electron microscopy; TEM, transmission electron microscopy.

reflecting generally uniform nanoscale dispersions suitable for topical application. Entrapment efficiency values are consistently high across studies, frequently exceeding 80% and in several cases approaching or surpassing 90%, particularly for lipophilic and phytochemical actives. These findings support the suitability of NLC-based systems for efficient drug incorporation within semisolid topical matrices. Zeta potential values span a broad range from moderately negative to strongly positive, indicating diverse stabilization strategies depending on lipid composition and surfactant selection. Notably, both negatively and positively charged systems demonstrate high entrapment efficiency and acceptable particle size distributions, suggesting that surface charge alone does not dictate encapsulation performance or dispersion quality. Morphological analyses, where reported, consistently describe spherical and smooth nanoparticles, further supporting the physical integrity of NLCs within gel systems. However, the lack of standardized reporting particularly for long-term stability and complete surface charge characterization limits direct comparison across studies and highlights the need for harmonized physicochemical evaluation in future formulation design.

Entrapment Efficiency and Drug Loading

Entrapment efficiency (EE%) and drug loading (DL%) were measured to quantify the extent of activity associated with the lipid matrix versus free in the aqueous phase, and these values directly influenced the release kinetics and in vivo efficacy.[80] The entrapment efficiency (EE) and drug loading (DL) indicate the proportion of active compounds successfully encapsulated in the lipid matrix.[30] High EE values (>80%) are desirable for sustained release and reduced wastage of bioactive ingredients.[27] The lipid composition, surfactant concentration, and preparation method significantly influenced these parameters. In NLCs made with different liquid lipid types (eg, black seed oil and coconut oil), researchers compared entrapment efficiency among formulations, measured EE, and drug loading, and found that the choice of lipid significantly influenced EE.[81] In the albendazole-NLC system (RSC study), the entrapment efficiency reached ~89.85%, and the drug loading capacity was ~3.19%, indicating that a high proportion of the drug can be stably incorporated.[78] Studies involving simvastatin and doxycycline have reported high EE and DL values due to the partial crystallinity of NLCs, which provides sufficient space for drug incorporation.[32,52] Maintaining high entrapment while preventing burst release is crucial for achieving prolonged therapeutic effects in the wound environment.

Morphological Characterization (SEM/TEM)

Morphological characterization using Scanning Electron Microscopy (SEM) or Transmission Electron Microscopy (TEM) confirmed the shape, surface texture, surface characteristics, and structural integrity of NLCs, which can help explain the release phenomena and skin deposition observed in ex vivo and in vivo studies, thereby ensuring a stable and effective drug delivery system.[46,82] Most wound-healing NLCs exhibited a spherical or oval morphology with smooth surfaces, indicating successful lipid stabilization and minimal aggregation. For instance, melatonin-loaded microspheres[29] and phenytoin-loaded[30] NLCs exhibited uniform spherical shapes, which correlated with their controlled drug release profiles and improved bioadhesion on to wound bed. TEM images often reveal a dense core–shell structure, confirming the encapsulation of bioactive compounds within the lipid matrix.[39] In the clobetasol propionate NLC gels, SEM was used to observe the morphology, which predominantly exhibited spherical to slightly oval shapes, indicating the formation of uniform lipid droplets within the nanostructured matrix. The particles appeared to have a smooth surface, indicating the proper encapsulation of clobetasol propionate within the lipid mixture without surface crystallization or drug efflux.[83] In the curcumin-NLC formulation for skin regeneration, SEM showed an irregular spherical shape, and TEM confirmed the nanoparticle structure, supporting a uniform morphology.[43]

Gel Properties and Rheological Behavior

The physicochemical evaluation of NLC gels ensures compatibility with skin physiology and user acceptability.[38] The ideal pH range (5.5–7.0) prevents irritation while maintaining the stability of the drug. Viscosity influences the retention time and release rate of the drugs. Liquid NLCs are formulated into semi-solid forms (gel formulations) because of their low viscosity and poor adhesiveness upon topical application. An appropriate concentration of the gelling agent was selected to provide optimal organoleptic properties and viscosity was selected.[84] Formulations using carbopol or chitosan

exhibit shear-thinning behavior, which is suitable for topical applications.[31] Spreadability and extrudability determine the ease of application and the uniform distribution over the wound site.[25] Texture profile analysis provided insights into the firmness, cohesiveness, and adhesiveness, which directly affect the bioadhesive performance of NLC gels. Overall, these parameters ensured optimal consistency, aesthetic appeal, and therapeutic efficiency of the final formulation.[18,30] In a study of ibuprofen-containing NLC gels, Texture Profile Analysis (TPA) was used to measure hardness, adhesion, cohesiveness, and firmness, which are highly relevant to the texture profile. A reverse extrusion test was also performed to assess extrudability, with spreadability measured using a more precise instrument-based texture analyzer that correlated with firmness and consistency.[85] In a study of NLC-mediated transdermal aceclofenac hydrogels, the texture properties were characterized using a texture analyzer, and firmness (gel strength), spreadability (shearing effort), and adhesion (adhesion effort) were measured to remove the texture probe.[86] In a recent study on amphotericin B-containing NLC gels, pH, extrusion ability, and spreadability were measured. A gel with a pH of 6.3, which is relatively skin-friendly, extrudability of 9.5 ± 0.12 g/cm^2, and spreadability of ~6.4 cm^2 was produced.[87]

Mechanisms of Enhanced Wound Healing

Sustained Drug Release and Prolonged Local Bioavailability

Nanostructured lipid carriers (NLCs), bigels, and hybrid hydrogels enhance wound healing by providing sustained and controlled release of active compounds. This mechanism reduces sudden release, ensuring that therapeutic molecules remain at the wound site for a longer period, reducing the need for repeated applications while maintaining effective drug concentrations, including drugs such as simvastatin,[34] phenytoin,[30] melatonin,[29] astaxanthin,[7] zerumbone,[22] and St. John's Wort extract.[26] This controlled release accelerated re-epithelialization or tissue repair, enhanced angiogenesis, and increased collagen synthesis/deposition in both acute and chronic wounds. In preclinical biodistribution studies, topically administered NLCs remained localized in the skin for up to 24 h with minimal systemic absorption, preventing nanoparticle penetration, thus supporting a prolonged and safe local effect after topical application to wounds.[88] In another study, NLC encapsulated hydrophobic and hydrophilic active ingredients in a solid-liquid lipid matrix containing epidermal growth factor and curcumin. The results showed that NLC can slow diffusion, protect the payload from rapid clearance or degradation, accelerate wound closure, and enhance the antioxidant enzyme activity. Thus, it has the potential to accelerate the healing of chronic wounds.[89] When integrated into gels, such as carbopol-based hydrogels or collagen/chitosan scaffolds, the lipid + polymer gel matrix provides a depot effect that releases the drug over hours to days, maintaining therapeutic concentrations in the wound bed, reducing dosing frequency, and increasing tissue exposure for repair.[90] It should be noted that the majority of biological effects observed in NLC–gel formulations arise from the pharmacological activity of the incorporated agents, while the primary contribution of the NLC–gel carrier lies in enhancing drug stability, local bioavailability, and sustained exposure at the wound site, thereby potentiating these effects rather than acting as a therapeutic entity on its own.

Enhanced Skin Penetration and Dermal Drug Deposition

Many drugs experience limited skin permeation because of the barrier properties of the stratum corneum. NLCs enhance drug permeation by mimicking the lipid architecture of the skin through the combination of solid and liquid lipids, thereby increasing fluidity and dermal absorption. Enhanced skin penetration and dermal deposition in NLCs and hybrid hydrogels as visualized in Figures 2 and 3 have been shown to be effective demonstrated for difficult-to-administer combination drugs such as curcumin,[46] quercetin-resveratrol,[19] astaxanthin,[7] mupirocin,[35] doxycycline,[32] and lidocaine.[33] Enhanced systems allow drugs to pass through the stratum corneum or reach deeper tissue layers more effectively by utilizing the occlusive effect of small particle which enhance hydration and transfollicular entry. This allows small molecules and phytochemicals to reach deeper dermal layers, where inflammation, bacterial infection, and impaired angiogenesis commonly occur. This could result in improved therapeutic strategies for wound healing. Nanometric lipid particles (NLCs) interact with stratum corneum lipids, disrupting the barrier, and act as penetration enhancers by enhancing drug partitioning and retention within the epidermis/dermis. Small particle size and lipid composition (solid + liquid lipids, surfactants) support closer contact and better dermal absorption than conventional

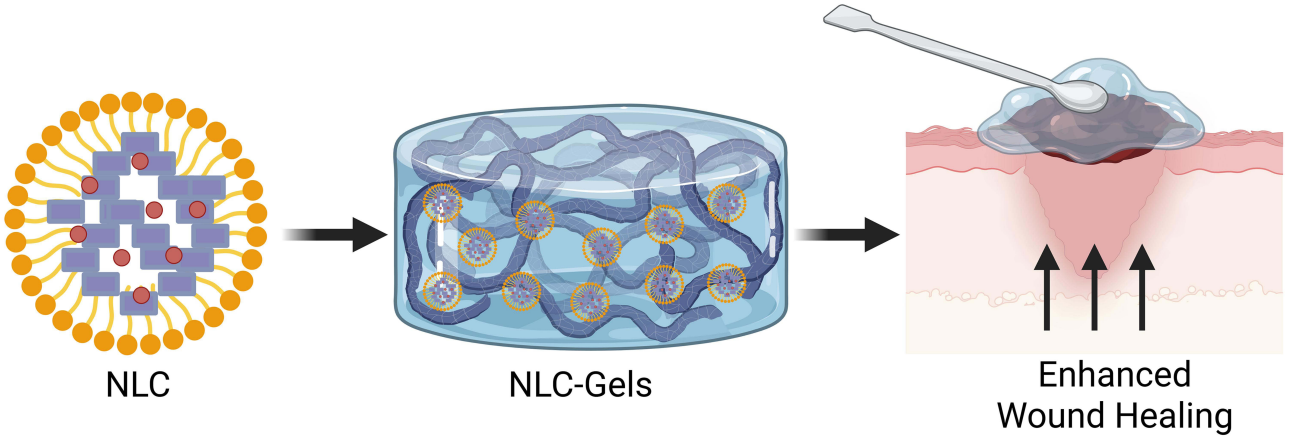

Figure 2 Formation of NLCs, their incorporation into hydrogels to create NLC-gels, and the resulting enhancement in wound healing through improved penetration, sustained drug release, and accelerated tissue repair.[51] The upward arrows indicate enhancement of key wound healing processes, including improved cellular infiltration, angiogenesis, and tissue regeneration at the wound site.

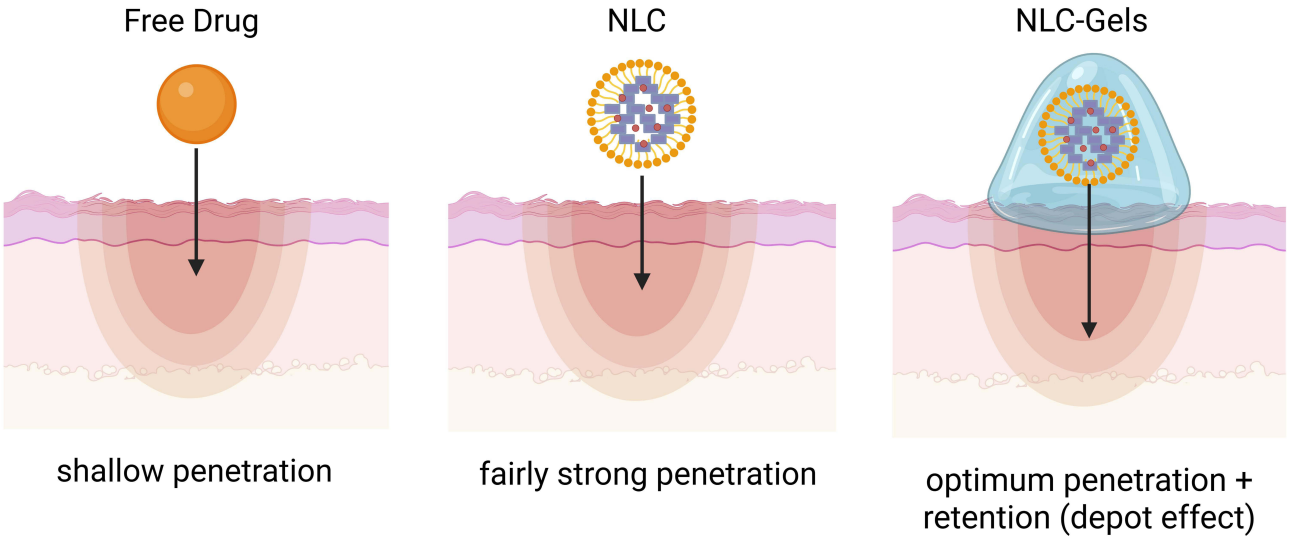

Figure 3 Comparative skin penetration profile of free drug, nanostructured lipid carriers (NLC), and NLC-gel.[93] Free drugs show minimal and superficial penetration due to rapid clearance and low affinity for the stratum corneum. NLC enables deeper dermal penetration through lipid–lipid compatibility and nanoparticle-mediated transport.[94] NLC-gel provides the most optimal penetration and retention due to its combination of nanoscale penetration enhancement and hydrogel-mediated depot effect, resulting in prolonged drug availability at the wound site.[51]

formulations. In NLC gel studies using lidocaine, higher dermal deposition and better local effects were demonstrated when NLC was administered owing to increased skin permeation and higher local drug levels.[91] In NLC studies using idebenone, significant improvements in stability and skin permeation were achieved, thus potentially becoming an alternative wound treatment.[92]

Anti-Inflammatory, Antioxidant, and Antimicrobial Mechanisms

Many nanoformulations possess anti-inflammatory, antioxidant, and antimicrobial activities, regardless of the drug itself (quercetin, resveratrol,[19] and mupirocin),[35] natural active substances (rosemary essential oil,[39] thymol,[40] propolis,[37] and mentha pulegium oil[38]), or lipid excipients, which contribute to wound infection control by suppressing colonization, inhibiting microbial growth, and reducing oxidative stress. Thus, these mechanisms can synergistically accelerate epithelialization, reduce cytokine levels, collagen deposition, and granulation tissue formation, and accelerate the healing of infected or chronic wounds. Furthermore, the combination of NLCs with biologics (eg, growth factors) and polymeric

scaffolds potentiated neovascularization and organized matrix formation in full-thickness models.[95] NLC gel delivery with anti-inflammatory active ingredients (zerumbone,[15] simvastatin,[34] and pioglitazone) resulted in a greater reduction in inflammatory markers and faster histological wound repair in animal wound models, consistent with better local availability and sustained exposure. NLC, which simultaneously deliver antioxidants (curcumin and growth factors), increase the activity of antioxidant enzymes (SOD, catalase, GPx), which contribute to accelerated healing and improved tissue remodeling.[89] The controlled release of NLC helps to maintain antioxidant levels in the wound. Topical antimicrobials incorporated into NLC demonstrated improved wound retention and sustained antibacterial action against wound pathogens, resulting in better infection control. The composition of the NLC (certain lipids/surfactants) may also contribute to membrane interactions that enhance antimicrobial efficacy.[96]

Evaluation Models

In vitro Evaluation of Cytocompatibility and Wound-Healing Activity

In vitro studies are essential for validating the safety and wound-healing potential of this formulation. These tests include cell viability, scratch assay (cell migration), DAPI staining, and cell cycle analysis (assessing cell proliferation), which are commonly used to evaluate the cytocompatibility of NLC formulations containing genistein-dexamethasone-moxifloxacin,[27] curcumin-resveratrol,[79] simvastatin,[34] astaxanthin,[7] and recombinant thrombomodulin.[17] This ensured their regenerative potential before in vivo testing. Cell viability assays generally examine the cytotoxicity of NLCs or NLC gel formulations in relevant skin cell lines (keratinocytes and fibroblasts). In studies on NLCs containing allopurinol and HaCaT cells (human keratinocytes), cell viability was maintained up to a certain concentration.[97] In scratch assays (wound healing), cell migration during wound closure was mimicked by scratching a confluent monolayer of fibroblasts or keratinocytes, and the effect of NLCs or NLC gels on the rate of gap closure was measured. In studies on NLCs containing thymoquinone (TQ-NLC), migration in 3T3-L1 fibroblasts was significantly increased compared to that of free TQ in a scratch assay.[98] DAPI staining was used to visualize the nucleus and sometimes the morphology of the nucleus to assess cell health, proliferation, and apoptosis after treatment. In studies of apigenin-loaded NLC formulations, DAPI was used to stain the nucleus and localize the NLC in relation to the cell.[99] In cell cycle analysis (flow cytometry), NLCs influenced cell cycle-dependent proliferation or cytotoxicity. In a study on zerumbone-loaded NLCs, cell cycle analysis (flow cytometry) showed G_2/M phase arrest in Jurkat cells treated with ZER-NLCs, indicating its effect on proliferation/apoptosis.[100] The in vitro studies summarized in Table 3 collectively demonstrate that NLC–gel formulations consistently enhance key biological processes relevant to wound healing, including cell migration, antimicrobial activity, antioxidant protection, and modulation of inflammatory responses. Scratch assays using keratinocytes and fibroblasts frequently report accelerated cell migration and improved viability, indicating favorable interactions between NLC–gel systems and skin-related cell lines. In parallel, strong antibacterial activity against common wound pathogens such as *Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa* is repeatedly observed, supporting the potential of NLC–gel platforms for managing infected or chronic wounds. Notably, these biological benefits are not restricted to a single class of active compounds but span small molecules, phytochemicals, essential oils, and recombinant proteins, underscoring the versatility of NLC–gel systems. However, substantial heterogeneity exists in the employed in vitro models, endpoints, and evaluation protocols, which limits direct comparison across studies. Furthermore, several studies extend beyond classical wound-healing models to include anticancer or antipsoriatic applications, emphasizing the need for more standardized, wound-specific in vitro assays to strengthen translational relevance.

Ex vivo Permeation, Retention, and Deposition Studies

Ex vivo Franz diffusion studies assess drug permeation/penetration, retention, and deposition through excised skin (animal or human) in a Franz diffusion cell to measure the amount of drug that penetrates or is retained in the skin from the gel application. This allows for quantification of transdermal delivery efficiency, which is widely used in formulations such as lidocaine permeation enhancers,[33] quercetin-resveratrol NLC,[19] thymol,[40] doxycycline–aloe-emodin,[32] and mupirocin.[35] This validates the ability of NLC to deliver drugs more effectively than conventional gels and creams. In

Table 3 Summary Of in vitro Wound-Healing Studies Evaluating NLC Gel Formulations

No	in vitro Model	Main Results	Role of NLC Gel	References
1	Antibacterial activity and biocompatibility on L929 fibroblast cells	Antibacterial *E. coli* and *S. aureus*; good biocompatibility	Sustained release of simvastatin, antibacterial activity, and moisture balance	[52]
2	Scratch assay (lens epithelial cells); Western blot; IF	Acceleration of cell migration; reduction of fibrosis/PCO markers	Thermoresponsive NLC hydrogel: sustained multi-drug release post-cataract	[27]
3	Human Corneal Epithelial Cells (HCEC); antibacterial; anti-inflammatory	Effective against *S. aureus* and *P. aeruginosa*; histocompatible	Liposome–hydrogel supports corneal epithelialization, anti-infection, and anti-inflammatory	[25]
4	Keratinocyte/fibroblast viability; antibacterial; antibiofilm	Powerful antimicrobial; histocompatible; antibiofilm MRSA	Chitosan microsphere NLC: Controlled release melatonin, antimicrobial, moisture retention	[29]
5	HaCaT; keratinocytes; macrophage; antibacterial (*S. aureus* and *S. epidermidis*)	Fast antibacterial; suppresses inflammation	Chitosomes-in-gel enhances Chlorhexidin penetration and effect	[31]
6	Antibacterial; antioxidant	Bacteria reduction; high antioxidant activity	Dual-responsive hydrogel enhances routine effects	[18]
7	Antibacterial; antioxidant	Effective against *S. aureus* and *P. aeruginosa*; powerful antioxidant	NLC-gel maximizes the combination of doxycycline + aloe-emodin	[32]
8	L929 fibroblast migration; antioxidant; antibacterial	Accelerate fibroblast migration; high antioxidant	Chitosan coated nanostructure lipid carriers (CS-AST-NLC) improves astaxanthin skin permeation, stability, and antioxidant	[7]
9	Permeation test; raman imaging	Increased skin penetration: 2–3× flux	NLC as a lidocaine enhancer (not a wound model)	[33]
10	Ex vivo permeation; dermatokinetic	Increased retention and permeation	Curcumin and reseveratrol NLC gel dermal targeting	[79]
11	Antibacterial; drug release	Antibacterial activity is maintained	Increased permeation and controlled release of mupirocin NLC-gel	[35]
12	A431 cytotoxicity (human epidermoid carcinoma); scratch assay	Inhibition of cancer cell migration/proliferation	Anti-skin cancer	[36]
13	Antimicrobial assays; antioxidant	Effective vs bacteria; high antioxidant activity	Propolis NLC-gel enhances regenerative potential activity	[37]
14	Antioxidants; inflammatory cytokines (in vitro)	Reduction of ROS; suppression of inflammation	Zerumbone-NLC-gel acts as an anti-inflammatory–antioxidant	[15]
15	HaCaT migration; cytokine assays	Increase keratinocyte migration	rhTM-NLC-gel increases angiogenesis and tissue granulation	[17]
16	A431 cell cytotoxicity; wound assay; release and permeation	Inhibition of cancer cell migration	Quercetin-Resveratrol NLC-gel as an anti-skin cancer agent	[19]
17	Antibacterial (diffusion, MIC/MBC)	Bacteria are strongly suppressed	Mentha pulegium essential oil-NLC-antibacterial and pro-healing gel	[38]
18	Anti-inflammatory RAW264.7, NO assay; angiogenesis HUVEC migration, tube formation	NO inhibition; increased angiogenesis	PPD-NLC-gel pro-angiogenic and anti-inflammatory early phase wound	[20]
19	Antibacterial assay (diffusion, MIC/MBC)	Effectively kills bacteria	Rosemary essential oil-NLC-gel accelerates angiogenesis and collagen deposition	[39]
20	HaCaT cells viability; release permeation (Franz cells)	Non-toxic; good permeation	Thymol NLC-gel: anti-inflammatory and antiproliferative for psoriasis (antipsoriatic)	[40]
21	Drug diffusion studies (Franz cell); HaCaT keratinocytes scratch assay	24-hour closure acceleration	Retinyl palmitate + hyaluronic acid: wound closure synergistic effect	[41]

Abbreviations: *E. coli*, *Escherichia coli*; *S. aureus*, *Staphylococcus aureus*; L929, laboratory; IF, Immunofluorescence; NLC, nanostructured lipid carriers; PCO, polycystic ovary; HCEH, human corneal epithelial cells; *P. aeruginosa*, *pseudomonas aeruginosa*; MRSA, Methicillin-resistant *Staphylococcus aureus*; *S. epidermidis*, *Staphylococcus epidermidis*; CS, chitosan; AST, astaxanthin; HaCaT, human keratinocyte cell line; ROS, reactive oxygen species; rhTM, recombinant human thrombomodulin; MIC, minimum inhibitory concentration; MBC, minimum bactericidal concentration; NO, nitric oxide; HUVEC, human umbilical vein endothelial cells; PPD, protopanaxadiol.

a study of lidocaine-containing NLC gels, a Franz diffusion cell with human epidermis and a coated membrane was used to compare the skin penetration.[91] Another study reported that NLC-based chitosan hydrogels demonstrated a sustained release of simvastatin and improved skin permeation in an ex vivo drug release study using rat abdominal skin mounted on a Franz diffusion cell for diabetic wound healing. Wound healing in diabetic rats was faster and superior to NLC-based hydrogels compared to drug-loaded hydrogels and plain hydrogels, confirming the enhanced drug permeation at the wound site due to the enhanced absorption of nanosized lipid particles from the chitosan gel matrix through the skin.[101]

In vivo Wound Healing Models and Therapeutic Evaluation

In vivo wound models, including excisional, incisional, burn, and diabetic wound models, have been consistently used in various studies. Studies of excisional or diabetic wound models, specifically those using zerumbone,[15] beeswax-based hydrogels,[18] doxycycline–aloe-emodin,[32] silicone-elastomer–ginseng,[20] melatonin microspheres,[29] and rosemary–NLCs,[39] have been conducted to assess therapeutic outcomes. Similarly, NLCs containing growth factors, such as recombinant human thrombomodulin (rhTM), have been tested in diabetic rat wound models for wound closure, histological granulation tissue, collagen deposition, and angiogenesis.[17] These in vivo models provide valuable data, including histopathological and macroscopic validation of collagen formation, re-epithelialization, wound contraction rate, tissue architecture, reduction of inflammation, angiogenesis, and infection control. Biodistribution and toxicology studies have demonstrated limited systemic absorption after topical NLC application and a favorable local safety profile in preclinical settings.[88] Studies in porcine and rodent full-thickness wound models have consistently demonstrated faster epithelial regeneration and collagen formation with topical NLC. NLC containing EGF achieved better wound closure than the standard cream in a porcine excisional model.[95] Burn or incision wound models are less common but possible in NLC gel wound studies. Although many published NLC wound healing studies use excisional models, formulations designed for burns or incisions can be evaluated similarly in animal burn or incision models by treating the wound and assessing healing through reduction in wound size, histology, and biochemical markers.[102] The in vivo studies summarized in Table 4 consistently demonstrate superior wound-healing outcomes for NLC–gel formulations across a range of animal models and wound types, including normal, diabetic, chronic, and infected wounds. Enhanced wound closure, increased tensile strength, improved re-epithelialization, and greater collagen deposition are recurrent findings, particularly in metabolically compromised models such as STZ induced diabetic rats and db/db mice, where delayed healing is clinically relevant. Several studies further report modulation of inflammatory and angiogenic markers such as reduced pro-inflammatory cytokines and increased CD31 or VEGF expression suggesting that NLC–gel systems promote not only faster closure but also improved healing quality. Despite these encouraging trends, direct comparisons between different NLC–gel formulations remain limited due to substantial heterogeneity in animal species, wound models, and evaluated endpoints. Moreover, a subset of studies focuses primarily on dermal delivery or anticancer applications rather than wound healing per se, which complicates cross-study interpretation. Collectively, the data indicate that NLC–gel systems offer robust in vivo efficacy; however, standardized wound models, longer-term outcome assessment, and head-to-head comparative studies are required to strengthen translational relevance and guide rational formulation selection.

Taken together, the collective evidence across Tables 1–4 indicates that the therapeutic performance of NLC–gel systems for wound healing is governed by the interplay between formulation composition, physicochemical stability, and biological response, rather than by isolated parameters such as particle size or entrapment efficiency alone. These findings emphasize the need for rational, design-driven formulation strategies to achieve reproducible and translatable wound-healing outcomes.

Therapeutic Potential

Acceleration of Wound Closure in Preclinical Models

Numerous studies using NLC-based systems or NLC gels have consistently demonstrated faster wound closure in preclinical models through increased epithelial migration, fibroblast proliferation, collagen deposition, and extracellular matrix remodeling in skin. NLC containing simvastatin,[34] zerumbone,[15] mupirocin,[35] astaxanthin,[7] and Mentha pulegium

Table 4 Summary Of in vivo Wound-Healing Studies Evaluating NLC Gel Formulations

No	Animal Models	Wound Type	Parameters Assessed	Main Results and Role of NLC Gel	References
1	Wistar male rats	Incisional	Tensile strength	HP-NLC bigel increases tensile strength compared to control	[26]
2	Rabbit corneal infection	Corneal epithelial wound	Healing rate; histology, bacterial count	Liposome-hydrogel accelerates corneal regeneration and anti-infection	[25]
3	Clinical DFU patients	Diabetic foot ulcer	Wound area % reduction	Phenytoin NLC is better than regular gel and control	[28]
4	Rat excision model	Full-thickness excision	Wound closure, histology	PHT-NLC gel accelerates epithelization vs plain gel	[30]
5	STZ diabetic rats	Diabetic foot ulcer	Wound closure, histology, masson	NLC-gel increases powerful antioxidant and antibacterial	[18]
6	STZ diabetic rats	Diabetic wound	Wound contraction, collagen	Doxy + aloe-emodin NLC-gel accelerates healing	[32]
7	Wistar rats	Full-thickness excision	Wound closure, collagen; histology	CS-AST-NLC gel enhances re-epithelialization and antioxidant	[7]
8	Human skin (ex vivo)		Permeation	Not for wound healing (dermal delivery of lidocaine)	[33]
9	Rat/goat skin ex vivo	Wound related indirectly	Permeation and dermatokinetic	CUR-RSV gel enhances dermal targeting	[79]
10	Rats (pressure ulcer model)	Pressure ulcer (chronic)	Histology, closure, collagen	Simvastatin NLC-gel accelerates healing and deposition	[34]
11	Wistar rats	Contaminated full-thickness wound	Wound contraction, bacterial load; closure	Mupirocin NLC-gel is more effective than ointment; sustained anti-infection	[35]
12	Rabbits	Full-thickness skin wound	Histology, collagen	Propolis NLC-gel enhances skin regeneration	[37]
13	STZ diabetic rats	Full-thickness excision	Wound contraction; SOD/CAT; cytokines	ZER-NLC-gel antioxidant, anti-inflammatory, increases SOD/CAT	[15]
14	STZ diabetic mice (O-ring)	Chronic diabetic wound	Granulation tissue CD31; collagen; angiogenesis	rhTM-NLC-gel increases CD31, collagen, epithelialization, angiogenesis	[17]
15	Ex vivo + irritation test	Skin cancer model	Cytotoxicity	NLC-gel is optimized for anticancer, not wound healing	[19]
16	Infected mouse excision (*S. aureus* and *P. aeruginosa*)	Infected wound excision	Wound closure, bacterial load; cytokines VEGF	MPEO-NLC-gel is very effective against bacterial infections + pro-healing	[38]
17	Rat full-thickness excision	Normal excisional wound	Histology, cytokines; COX-2 qPCR	ZER-NLC-gel promotes scar-free healing (decreases TNF-α/IL-6; increases IL-10)	[22]
18	db/db diabetic mice	Diabetic ulcer	CD31, collagen I/III, cytokines	PPD-NLC-gel promotes ordered, scar-free healing (pro-angiogenic)	[20]
19	Infected mouse wound	Infected excision	Bacterial load, VEGF, collagen	REO-NLC-gel accelerates healing + strong antibacterial	[39]
20	BALB/c mice (psoriasis and inflammation)	Inflammatory skin lesions	Edema; erythema, scaling	Thymol NLC-gel anti-inflammatory and anti-psoriatic	[40]

Abbreviations: HP, hyperforin; DFU, diabetic foot ulcer; PHT, phenytoin; STZ, streptozotocin; NLC, nanostructured lipid carriers; DOX, doxycycline; CS, chitosan; AST, astaxanthin; CUR, curcumin; RSV, resveratrol; ZER, zerumbone; sod, superoxide dismutase; cat, catalase; CD31, cluster of differentiation; rhTM, recombinant human thrombomodulin; *S. aureus*, *Staphylococcus aureus*; *P. aeruginosa*, *pseudomonas aeruginosa*; MPEO, mentha pulegium essential oil; VEGF, vascular endothelial growth factors; COX-2, cyclooxygenase-2; qPCR, quantitative polymerase chain reaction; TNF-α, tumor necrosis factor-alpha; IL, interleukin; db, diabetic; PPD, protopanaxadiol; REO, rosemary essential oil encapsulate; BALB, bagg and albino.

essential oil[38] significantly accelerated epithelialization and collagen maturation, and demonstrated significantly faster wound contraction compared to conventional treatments, making it a promising candidate for clinical use in both acute and chronic wounds. For example, NLC encapsulated with EGF+curcumin accelerated wound closure and increased

antioxidant enzyme activity in a rat model of chronic diabetes.[89] Similarly, zerumbone NLC gel resulted in faster wound contraction and improved histological healing in STZ-treated diabetic rats.[15] In previous studies, topical systems based on curcumin-containing NLCs accelerated wound closure and enhanced histological regeneration in rabbit and rodent wound models. Carvacrol NLCs have recently been shown to significantly accelerate wound closure in diabetic wounds, possessing stronger antioxidant, anti-inflammatory, and antibacterial activities than free carvacrol, thus increasing the local bioavailability and sustained release of pro-healing activities.[43,103]

Infection Control and Enhanced Tissue Regeneration

Many nanoformulations also demonstrate superior infection reduction and potent bacterial inhibition, particularly those containing antimicrobial drugs (moxifloxacin and mupirocin), plant-derived antibacterial oils (rosemary,[39] thyme, and propolis[37]), and immunomodulatory agents such as recombinant thrombomodulin. This resulted in improved healing of infected wounds. Multidrug dual-function systems, such as dexamethasone-moxifloxacin hydrogels, exhibit anti-inflammatory and antibacterial activities.[25] Tissue regeneration is further enhanced by antioxidants such as curcumin, resveratrol, melatonin, and astaxanthin, which reduce oxidative stress, inflammation, and support matrix remodeling.[19,29] In diabetic wound models, composite devices combining NLCs with polymer scaffolds (collagen-chitosan) or silicone dressings have demonstrated significantly increased contraction rates, decreased protease activity (MMP-9), and improved tissue quality compared with controls.[104] The formulation of antibiotics or antimicrobial phytochemicals into NLCs improves skin retention and provides longer-lasting antimicrobial activity in the wound bed, reducing bacterial bioburden and secondary inflammation. Studies on mupirocin (antibiotic) NLC gels and essential oil/tea tree oil NLCs have demonstrated stronger antibacterial activity and improved in vivo wound outcomes (less infection, better granulation, and collagen deposition) compared to conventional formulations.[35,105] In parallel, allopurinol-NLCs (an antioxidant/ROS modulator) promoted lesion regeneration and histological improvement in treated animals.[97] Bioadhesive NLCs encapsulating antioxidants and antimicrobials: Studies have developed NLCs with α-tocopherol and quercetin (antioxidants) plus tea tree oil (antimicrobial) were modified with chitosan or alginate for encapsulation bioadhesion, which retained antimicrobial activity against *S. aureus* and *P. aeruginosa* and enhanced fibroblast migration, demonstrating infection control and pro-regenerative action.[106]

Translational Potential for Chronic Wounds, Diabetic Ulcers, and Burn Injuries

Many studies have specifically focused on diabetic wound models that pose major clinical challenges. These findings highlight the translational potential of NLC-based gels and hybrid hydrogels, which have shown promising results for chronic and difficult-to-heal wounds, including diabetic ulcers, corneal tissue injuries, moderately exudative wounds, infected or burn wounds, and postoperative wounds. Beeswax-based hydrogels,[18] recombinant thrombomodulin NLC gels,[17] and silicone-elastomer-ginseng NLC dressings demonstrated excellent results in diabetic rats with strong regenerative effects, improved perfusion, reduced inflammation, and potent antioxidant properties.[20] Other formulations such as phenytoin-NLCs, rosemary-NLCs, and thymol nanoparticles have demonstrated efficacy in burn or infected wound models.[30,107] Propolis-based NLC-α-Mangostin (NLC-P-αM), in alloxan-induced diabetic rats, provided a very high wound closure rate, with histology showing reduced inflammation and better tissue regeneration compared to free α-mangostin treatment.[108] This demonstrates a strong potential for application in the treatment of chronic, non-healing wounds, as it helps reduce wound healing time by delivering drugs at a sustained level. Recent studies have confirmed that controlled release, protection of labile active ingredients, and enhanced penetration provided by lipid carriers result in measurable improvements in preclinical wound endpoints.[109,110]

Challenges and Future Directions

Clinical Translation and Commercialization Challenges of NLC-Gel Systems

Despite promising preclinical performance, the clinical translation and commercialization of NLC–gel systems are limited by several interrelated challenges.[26] One clinically relevant study was reported[28] who evaluated a topical NLC-based gel formulation for wound treatment and demonstrated significantly enhanced wound contraction and faster

healing compared with conventional formulations. The improved therapeutic outcome was attributed to enhanced drug penetration, sustained release, and prolonged residence time at the wound site, highlighting the translational potential of NLC–gel systems in clinical wound care. Nevertheless, the limited number of clinical investigations underscores several barriers to clinical translation. These include the need for standardized large-scale manufacturing processes, long-term stability assurance of NLC–gel formulations, and clear regulatory pathways for topical nanomedicines. Additionally, the design of well-controlled clinical trials with standardized wound healing endpoints remains challenging due to variability in wound etiology, patient comorbidities, and treatment protocols. Future clinical studies should focus on robust trial design, long-term safety evaluation, and comparative effectiveness against established wound dressings to fully realize the clinical potential of NLC–gel systems. A key issue is batch-to-batch reproducibility, particularly in complex hybrid formulations containing multiple lipids, surfactants, and gel polymers.[31] Small variations in processing conditions such as homogenization energy, lipid crystallization behavior, or gel rheology can markedly affect particle size, entrapment efficiency, and release profiles, leading to inconsistent product quality.[111] Similar scale-up challenges have been reported for lipid nanocarriers, where laboratory-optimized processes fail to maintain critical quality attributes at pilot or industrial scale, especially when transitioning between ultrasonication and high-pressure homogenization approaches.[112] Long-term physical stability represents another major barrier. Polymorphic lipid transitions, drug expulsion, and particle aggregation during storage have been widely documented for lipid nanoparticles and related systems.[113] In NLC–gel hybrids, time-dependent interactions between nanoparticles and polymer networks may further alter rheological properties and release behavior. Comparable stability limitations observed in nanoemulsions and solid lipid nanoparticles highlight the broader relevance of crystallization and phase behavior to shelf life. Although stabilization strategies such as optimized lipid blends, surfactant selection, antioxidants, cryoprotectants, and lyophilization can improve stability, they also increase formulation complexity and cost,[114,115] extend shelf life and allow storage at room temperature.[80,116] From a commercialization standpoint, cost-effectiveness remains a nontrivial concern. Compared with conventional topical formulations, NLC–gels require specialized excipients, energy-intensive manufacturing, and extensive characterization, potentially limiting market feasibility unless clear therapeutic benefits are demonstrated, particularly for chronic wound indications.[117] Finally, regulatory challenges specific to nano-topical products further complicate translation. NLC–gel systems require comprehensive physicochemical characterization and formulation-specific safety evaluation under a risk-based regulatory framework.[118] Although preclinical studies generally report good dermal tolerability and minimal systemic exposure, long-term safety data addressing chronic exposure and nanoparticle accumulation remain limited. Consequently, formulation-specific toxicological assessment and clearer regulatory guidance are essential to advance nano-enabled topical therapies toward clinical and commercial implementation.[119]

Regulatory Considerations and Safety/Toxicological Profiles

Although preclinical studies have demonstrated high biocompatibility, regulatory concerns regarding the safety of topical exposure remain. Long-term safety, particularly involving nanoparticle accumulation, potential skin irritation, systemic absorption, and steroid-containing formulations, requires rigorous evaluation. The regulatory pathway for nanomedicines is more complex than that of conventional topical agents. Formulations containing the active ingredients, dexamethasone, simvastatin, essential oils, or lipid carriers, must undergo rigorous and extensive toxicological evaluation.[25,27,39] Preclinical toxicology and biodistribution studies of topically applied NLCs have demonstrated their tolerability, local retention, low systemic absorption, route of administration, dose, particle size, and surface properties. Many formulations are non-irritating and non-sensitizing in animal models, thereby determining systemic exposure and organ accumulation.[88,120] However, the results depend on the composition and precise lipid/surfactant loading, and long-term safety data and immunogenicity remain limited. Therefore, each NLC gel candidate requires formulation-specific GLP safety testing (skin irritation/sensitization, repeated dose skin toxicity, appropriate genotoxicity), excipient GRAS status for regulatory acceptance, and risk-based characterization (size, surface chemistry, degradation products).[118,121]

Integration of Growth Factors, Peptides, and Multi-Drug Loading Strategies

Future wound therapies are expected to combine multiple therapeutic functions simultaneously, increasing the complexity of formulations (different solubility, release kinetics, and stability), encompassing biological challenges (growth

factors, peptides) that are labile and susceptible to denaturation or enzymatic degradation, and delivery of multi-drugs or gene modulators, which have already been explored in multi-drug NLC systems (genistein-dexamethasone-moxifloxacin)[27] and combination phytochemical therapies (curcumin–resveratrol, quercetin–resveratrol).[19,79] Experimental studies have demonstrated the successful encapsulation and delivery of peptides (antimicrobial peptide LL-37, EGF) and co-encapsulation of small molecules and growth factors in NLCs. However, these studies highlight the need for gentle production methods, bioactivity preservation, and controlled/sequential release. Adaptations to mild manufacturing (low-temperature emulsification and protective excipients), core-shell or layered NLC designs, and combinations of NLCs with protective hydrogels/scaffolds to stabilize biomolecules and tailor release are also possible. Emerging evidence indicates that peptide-based interventions may provide regenerative benefits beyond conventional small molecules. For example, the ultra-short cyclic peptide Cy RL-QN15 accelerates wound closure by antagonizing TLR4-mediated inflammatory signaling and enhancing epithelial proliferation, suggesting a novel immunomodulatory mechanism that could complement NLC–gel delivery platforms.[122] Additionally, the cyclic peptide FZ21 promotes angiogenesis via integrin αvβ3-dependent activation of FAK–AKT/ERK pathways, enhancing endothelial proliferation and vessel formation, which are critical for tissue regeneration in chronic wounds. These findings support the integration of peptide cargoes with tailored nanocarrier systems such as NLC–gels to address both inflammatory and regenerative deficits in complex wound environments.[123] Other preclinical studies using rhEGF-NLC and peptide-loaded NLCs have demonstrated improved feasibility and healing in animal models with hydrophilic biomolecules (rhEGF) or peptides alongside small hydrophobic drugs and have demonstrated improved healing in preclinical wound models.[95,124,125] However, biocargos present additional challenges, such as maintaining bioactivity during processing, preventing burst release/degradation, and demonstrating sustained local activity and stability (cold chain/lyophilization considerations). Sequential or dual-drug NLCs demonstrate proof of principle for combination therapy but require further translational research to demonstrate reproducible manufacturing and predictable release kinetics in vivo. Advanced NLC systems enable the co-loading of anti-inflammatory, antimicrobial, and regenerative agents, thus enabling synergistic therapy for complex wounds.[89,125,126]

Personalized and 3D-Printed Wound Dressings Incorporating NLC System

The integration of personalized wound dressings with 3D-printed medications or theranostic sensors using NLC-infused hydrogels tailored to a patient's specific size, dimensions, wound depth, and healing needs represents a promising area for modern approaches. This requires compatible bioinks, predictable release from the printed matrix, and retention of nanoparticle integrity during printing (shear, light-curing, and temperature). This is particularly relevant in diabetes and chronic wound management models. Although numerous studies have demonstrated 3D-printed hydrogel dressings containing inorganic nanoparticles or drug-loaded nanomaterials, combining NLCs with 3D printing remains limited in the literature, indicating translational gap remains.[127,128] This integration is still in its infancy and has been further highlighted in recent studies focusing on the integration of advanced biomaterials and prioritizing well-designed translational studies (GLP toxicology, stability studies, followed by randomized clinical trials) to bridge the gap between robust preclinical efficacy and clinical adoption.[110] Experimental efforts should focus on developing NLC-enriched bioinks/hydrogel inks to maintain the NLC structure and charge, demonstrate controlled release and bioactivity after printing (in vitro and in vivo), and validate manufacturing reproducibility for personalized geometries. Recent original research incorporating NLC-enriched hydrogels for topical delivery and separate studies on nanoparticle-loaded 3D-printed dressings have demonstrated individual feasibility, continued integration, and in vivo validation.[16,127] Other preclinical studies have demonstrated the feasibility (drug-loaded lipid carriers in collagen sponges or 3D-printed matrices for burn/wound wounds), challenges include ensuring uniform NLC distribution, maintaining nanoparticle integrity during printing, controlling release from the bulk scaffold, and meeting sterility and regulatory requirements for device-drug combination products. This hybrid approach represents a promising translational direction, but requires standardized fabrication protocols and device/drug combination regulatory strategies.[129,130]

Conclusion

Nanostructured lipid carrier-based gels (NLC-gels) represent a new generation of topical therapeutic platforms for wound healing, combining the advantages of biocompatible lipid nanoparticles (such as sustained release, skin retention, and moisture-occlusive properties) with an easy-to-use gel matrix. Combined with natural bioactives (eg, zerumbone, rosemary oil, propolis, thymol, astaxanthin, and aloe-emodin), small-molecule drugs (eg, simvastatin, mupirocin, quercetin, resveratrol, melatonin, and doxycycline), or multifunctional combinations (eg, dexamethasone-moxifloxacin), NLC-gels consistently improve drug stability, skin penetration, and sustained release while maintaining biocompatibility. These benefits result in faster wound closure, increased collagen deposition, enhanced re-epithelialization, reduced inflammatory markers, and better control of microbial infections in various wound models, including acute, chronic, infected wounds, and diabetic ulcers. Studies, particularly those using diabetic models, provide strong evidence that NLC gels can address impaired angiogenesis, oxidative stress, and persistent inflammation characteristics of diabetic wounds, making them more effective than conventional formulations. The use of hybrid systems, such as beeswax-based constructs, chitosan-coated NLCs, chitosome platforms within hydrogels, or silicone gel matrices, further highlights the versatility of NLCs in supporting moisture balance, mechanical protection, and targeted delivery in complex wound environments. Despite promising preclinical results, most evidence remains at the in vitro and in vivo animal levels, with very limited early stage clinical data. Therefore, their future applications will depend on robust toxicological profiles, standardized manufacturing and characterization protocols, and a regulatory framework that reflects the use of lipid-based nanocarriers for topical administration. Only through well-designed clinical investigations can NLC-based wound healing therapies progress towards routine medical use.

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