

Recent developments in niosomal drug delivery for effective wound healing

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Article Info



Article Type:
Review

Article History:

Received: 14 Feb. 2026

Revised: 21 Jul. 2026

Accepted: 1 Aug. 2026

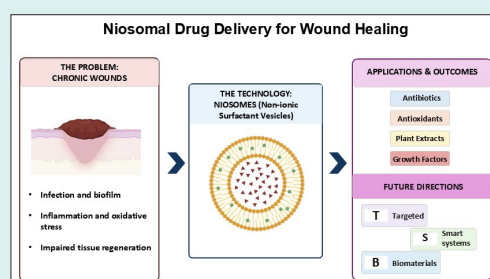
ePublished: 18 Oct. 2026

Keywords:

Nanomedicine
Diabetic wound healing
Transdermal drug delivery
Tissue regeneration
Antimicrobial therapy
Controlled drug release

Abstract

Chronic wounds, including diabetic foot ulcers, pressure ulcers, and venous leg ulcers, affect millions of patients worldwide and impose an enormous healthcare burden, yet conventional therapies frequently fail to overcome the interrelated challenges of persistent infection, chronic inflammation, and impaired tissue regeneration. Niosomes, self-assembled vesicular nanocarriers composed of non-ionic surfactants and cholesterol, have emerged as a versatile and cost-effective platform for wound-targeted drug delivery. This review synthesizes current evidence on niosomal structure and formulation strategies, mechanism of dermal drug delivery, and therapeutic applications spanning antibiotics (moxifloxacin, cefazolin, teicoplanin), antioxidants (methylene blue, curcumin, vitamin A), herbal extracts (*Hypericum perforatum*, thymol, aloe vera), and growth factors. Compared with liposomes, niosomes offer superior physicochemical stability, lower manufacturing cost, and equivalent or greater encapsulation efficiency for both hydrophilic and lipophilic payloads. Preclinical models consistently report accelerated wound closure (15–35% improvement over conventional treatments), enhanced collagen deposition, reduced oxidative stress markers, and anti-biofilm efficacy. Available clinical data, though limited, support faster oral wound closure and improved patient-reported outcomes with niosomal anthocyanin complex gel. Critical translational barriers include formulation instability, absence of standardized manufacturing protocols, limited clinical trial data, and incomplete regulatory guidance for nanomedicines. Future priorities include stimuli-responsive 'smart' niosomes, surface-functionalized targeted systems, integration with biomaterial scaffolds, and large-scale randomized controlled trials.



Introduction

Efficient wound healing is essential in clinical practice, as it significantly influences disease progression, patient recovery duration, and healthcare expenditures.¹ Chronic wounds, including diabetic ulcers, pressure ulcers, and venous ulcers, represent a significant public health concern. In the United States, these wounds affect an estimated 2.4 to 4.5 million individuals and impose an annual financial burden exceeding \$28.1 to \$96.8 billion on the healthcare system.^{2,3} Notably, the burden of chronic wounds is particularly pronounced among older adults; approximately 16.4% of Medicare beneficiaries

are affected, accounting for an estimated \$22.5 billion in annual Medicare expenditures.⁴ Among diabetic patients, 25% face a lifetime risk of developing persistent non-healing wounds such as diabetic foot ulcers, with 68% of these individuals experiencing a life expectancy of under five years.⁵ These wounds are often associated with multifactorial comorbidities such as diabetes mellitus, vascular insufficiency, and malnutrition, all of which complicate the healing process.³

Acute wounds typically progress through a predictable healing sequence; however, surgical or traumatic injuries still present challenges, particularly in achieving rapid

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hemostasis and tissue repair.⁶ A thorough understanding of the four phases of wound healing, hemostasis, inflammation, proliferation, and remodeling, is essential for clinicians to deliver timely, patient-specific interventions.⁷

Traditional wound care approaches, such as simple dressings, topical antiseptics, and debridement, are often inadequate for managing complex chronic wounds.⁸ These methods frequently fail to maintain adequate wound moisture, prevent microbial biofilm formation, or efficiently deliver therapeutic agents to the wound site.^{8,9} Chronic wounds are also often refractory to conventional treatment because of persistent inflammation, reduced tissue perfusion, and established biofilms; these problems are especially pronounced in patients with tissue hypoxia, advanced age, or immunosuppression.¹⁰

These limitations underscore the need for innovative therapeutic approaches that simultaneously target infection, inflammation, and impaired tissue regeneration.¹¹ Recent breakthroughs with lipid-based nanoparticle platforms have demonstrated that bioresponsive vesicular systems capable of reactive oxygen species (ROS) scavenging and immune reprogramming can significantly accelerate diabetic wound healing following single-dose administration, representing a paradigm shift toward clinically translatable nanotechnology interventions.¹² Current advanced delivery systems enable controlled drug release at the wound site, enhancing therapeutic outcomes while minimizing adverse reactions through localized drug delivery.¹³ Hydrogel-based carriers, nanofibrous scaffolds, and lipid-based vesicles have emerged as three particularly promising approaches.¹⁴

Niosomes represent a particularly promising advancement in this landscape. Composed of non-ionic surfactants and cholesterol, these vesicular nanocarriers exhibit complete biocompatibility, optimize wound

drug penetration, enable co-delivery of hydrophilic and lipophilic agents, and provide controlled, sustained drug release, thereby reducing the need for frequent dressing changes and minimizing patient discomfort.^{15,16} Their adaptable design permits delivery of diverse therapeutic payloads, including antibiotics, anti-inflammatory agents, antioxidants, and regenerative factors.¹⁷

Several reviews have addressed nanocarrier-based wound therapies; however, existing literature either focuses broadly on lipid nanoparticles without specifically interrogating niosomes, or covers niosomal systems without integrating recent advances in smart stimuli-responsive design, clinical translation challenges, and regulatory considerations.^{14,15} The present review addresses this gap by providing a comparative, mechanistically grounded synthesis of niosomal drug delivery specifically in the context of wound healing, encompassing structural characteristics, formulation strategies, therapeutic applications across major drug classes, dosage form diversity, and a critical appraisal of translational barriers. This review further delineates the trajectory from preclinical evidence toward clinical application, identifies current field-wide limitations, and proposes specific research directions needed to facilitate clinical adoption of niosomal wound care systems.

Wound healing: Biological background

Wound healing is a complex, tightly regulated process consisting of four overlapping phases: hemostasis, inflammation, proliferation, and remodeling. Disruption of this regulatory balance may result in delayed or chronic wounds, which represent major therapeutic challenges.^{18,19}

Phases of wound healing

Wound healing occurs in four distinct though overlapping phases (Fig. 1). Hemostasis commences immediately

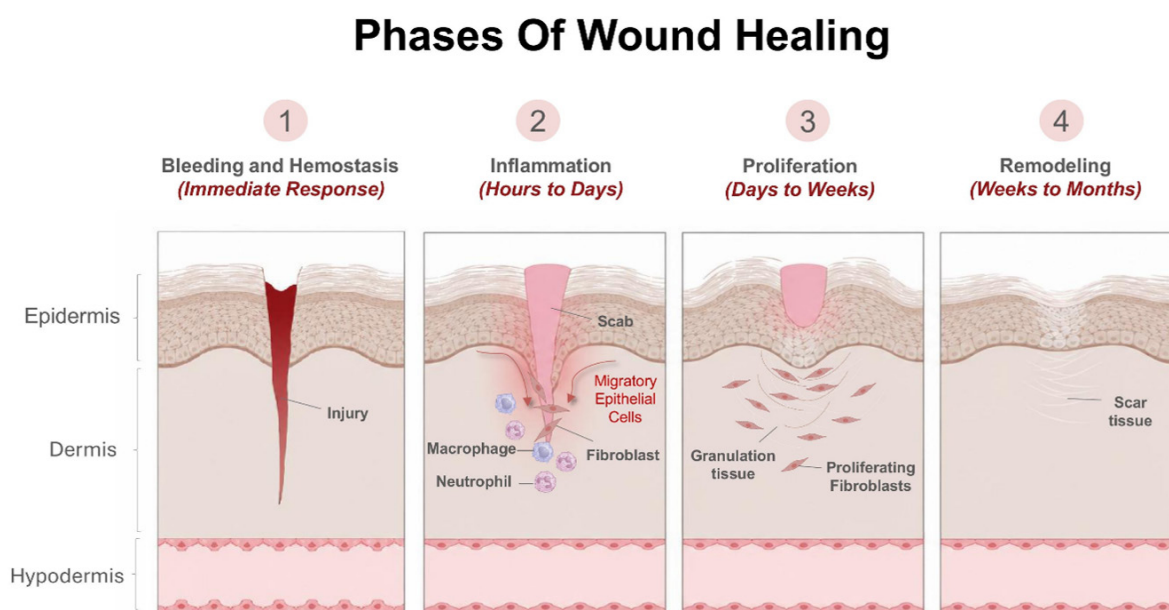


Fig. 1. Four key stages of skin wound healing. The image summarizes wound healing in four phases: hemostasis, inflammation, proliferation, and remodeling. Each panel briefly shows what happens in that stage, from clot formation and immune cell action to new tissue growth, collagen remodeling, and scar formation.

after injury: vasoconstriction, platelet activation, and coagulation cascade activation produce a fibrin clot that arrests bleeding and releases growth factors (PDGF, VEGF, TGF- β) that recruit immune cells to the wound site.^{20,21} The inflammatory phase (hours to 3–7 days) is characterized by neutrophil-mediated debridement followed by macrophage phenotypic transition from pro-inflammatory M1 to pro-regenerative M2, a shift that is impaired in many chronic wounds.^{22–25} The proliferative phase (day 3 to week 4) encompasses re-epithelialization by keratinocytes, fibroplasia with Type III collagen deposition, and VEGF-driven angiogenesis.^{26–28} During the remodeling phase (weeks to months), fibroblasts replace Type III with cross-linked Type I collagen, restoring approximately 80% of original tensile strength; dysregulation leads to hypertrophic scarring or non-healing wounds.^{26–32} Key cellular events and molecular mediators are summarized in Table 1.

Acute and chronic wound management

Acute wounds progress predictably through the healing phases with standard care, whereas chronic wounds, defined as wounds failing to close within 3–12 weeks, affect approximately 1–2% of the population in developed countries.^{2,33} Chronic wounds are sustained by a pathological microenvironment characterized by elevated pro-inflammatory cytokines (TNF- α , IL-1 β), matrix metalloproteinase (MMP) excess over tissue inhibitors of MMPs (TIMPs), persistent hypoxia, defective angiogenesis, and biofilm formation in over 60% of cases.^{34–38} These barriers, biofilm-mediated antibiotic resistance, ROS-driven cellular damage, impaired macrophage polarization, and degraded growth factor receptors, directly define the therapeutic rationale for niosomal delivery systems capable of localized, sustained, multi-agent release.¹¹

Therapeutic opportunities for wound repair

Effective wound healing necessitates strategies that overcome the pathophysiological barriers described above. Emerging approaches include nanotechnology-based drug delivery, stem cell therapies, bioengineered skin substitutes (e.g., Integra, Dermagraft, Apligraf), advanced bioactive dressings, and biologics including platelet-rich plasma (PRP) and growth factors.^{39–41} Among these, nanocarrier platforms, particularly lipid-

based vesicular systems, demonstrate the most consistent preclinical efficacy in simultaneously addressing infection, inflammation, and impaired regeneration.^{12–14} This review focuses specifically on niosomes as the most cost-effective and scalable class within this family.

Niosomes: Structure, characteristics, and advantages

Targeted drug delivery systems (DDS) have arisen as a potent strategy to enhance therapeutic efficacy by concentrating drug at the target site while reducing systemic exposure.⁴² Among lipid-based nanocarriers, which include liposomes, solid lipid nanoparticles, nanostructured lipid carriers, and niosomes, niosomes are formed by the self-assembly of non-ionic surfactants (spans, tweens, or brij) in combination with cholesterol.⁴³ Fig. 2 provides a schematic overview of nanocarrier types for wound drug delivery; Fig. 3 illustrates niosome bilayer organization.

Liposomes, composed of natural phospholipids, have been extensively used in drug delivery owing to their biocompatibility, but they exhibit structural instability at room temperature, sensitivity to oxidation, and high production costs driven by phospholipid purification.⁴³ In contrast, niosomes use synthetic non-ionic surfactants that resist lipid peroxidation, require no inert atmosphere or refrigerated storage, and can be manufactured at significantly lower cost. Quantitatively, niosomes have demonstrated encapsulation efficiencies of up to 99.76% for selected agents,⁴⁴ particle diameters ranging from 10 to 1000 nm (tunable by formulation),⁴⁵ and zeta potentials adjustable through inclusion of charge-inducing agents (e.g., diacetyl phosphate, stearylamine) to enhance colloidal stability. Comparative studies report that niosomal formulations maintain >90% of their physicochemical properties for up to 3–6 months under ambient storage, compared to significantly shorter shelf-lives for comparable liposomal preparations.^{46,47} The key distinguishing properties of niosomes are summarized below.

Key properties of niosomes

Stability: Niosomes exhibit superior chemical and physical stability relative to liposomes, owing to the use of non-ionic surfactants that resist lipid peroxidation and oxidative degradation. Cholesterol reinforces bilayer integrity, reduces drug permeability, and enhances

Table 1. Comparative summary of wound healing phases

Phase	Main events	Key cells involved	Dominant growth factors/cytokines	Main molecular/structural changes
Hemostasis	Vasoconstriction, platelet activation, clotting	Platelets, endothelial cells	--	Fibrin clot formation, cytokine release ²⁶
Inflammation	Leukocyte recruitment, pathogen/debris clearance	Neutrophils, macrophages	IL-1, IL-6, TNF- α , PDGF, TGF- β	Vasodilation, increased permeability ²⁷
Proliferation	Granulation, angiogenesis, re-epithelialization	Fibroblasts, keratinocytes, endothelial cells, mast cells	PDGF, TGF- β , VEGF, EGF	ECM production, MMP/TIMP activity, wound closure ^{26,27}
Remodeling	Collagen maturation, ECM reorganization, contraction	Fibroblasts, myofibroblasts, macrophages, mast cells	TGF- β , RAS-related factors	Type III to Type I collagen, ECM remodeling ²⁶

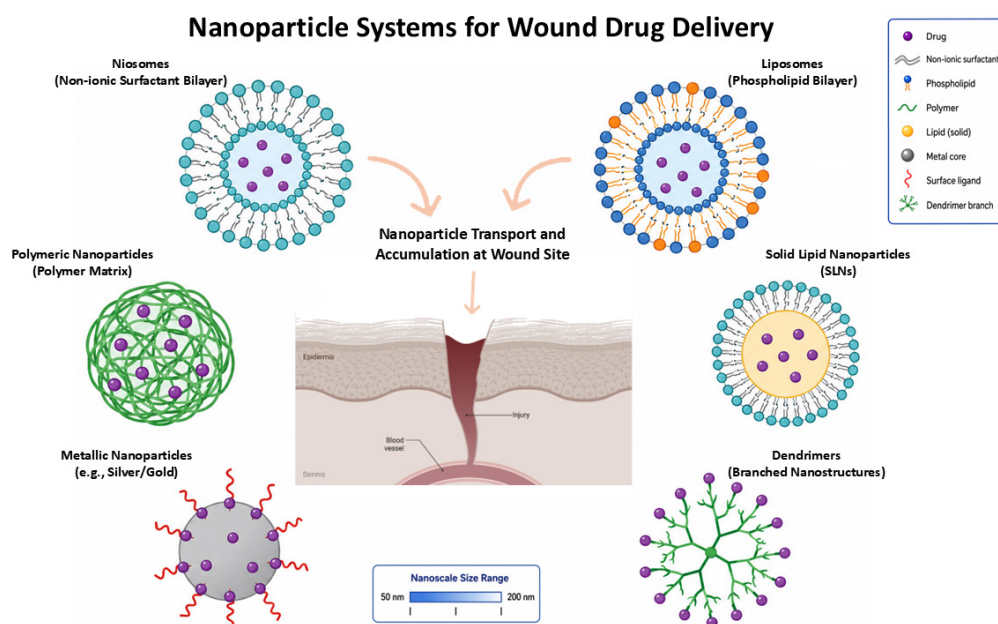


Fig. 2. Nanoparticle systems for wound drug delivery. The figure shows several nanoscale carriers (niosomes, liposomes, polymeric, lipid, metallic nanoparticles, and dendrimers) in the 50–200 nm range that encapsulate drugs and deliver them directly to the wound site.

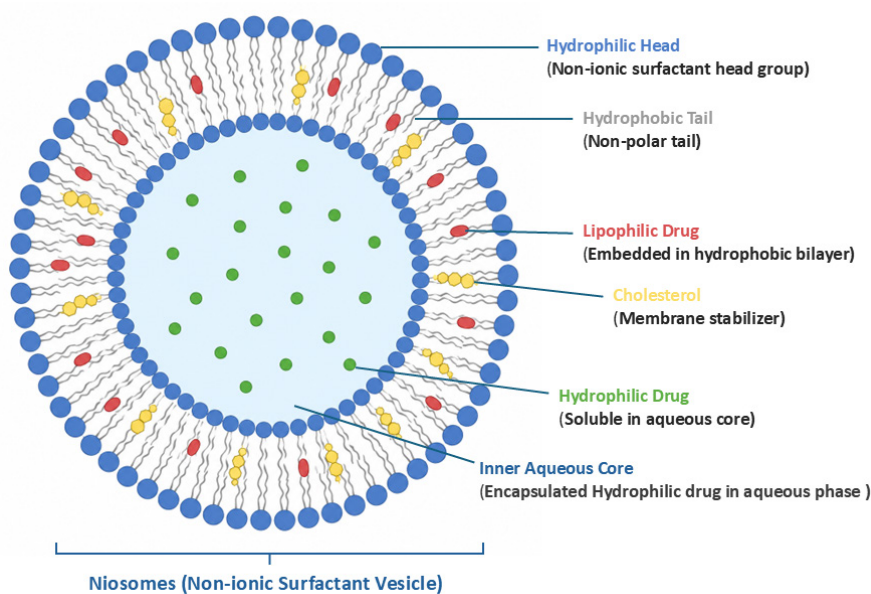


Fig. 3. Niosome structure and bilayer organization. The image illustrates a niosome vesicle made of a surfactant bilayer with hydrophilic heads, hydrophobic tails, and cholesterol molecules, surrounding an inner aqueous core.

osmotic stability.⁴⁶

Biocompatibility: Non-ionic surfactants are biodegradable, biocompatible, and non-immunogenic, reducing the risk of adverse immune responses or cytotoxic effects. Niosomes are suitable for oral, injectable, ophthalmic, and topical administration.^{15,47}

Cost-effectiveness: The use of inexpensive synthetic surfactants rather than costly phospholipids, combined with simpler manufacturing processes that require no specialized storage, substantially reduces production costs and facilitates large-scale commercial application.⁴⁶

Drug loading capacity: The amphiphilic bilayer structure

enables simultaneous encapsulation of hydrophilic drugs in the aqueous core and lipophilic drugs within the membrane, achieving encapsulation efficiencies of up to 99.76%.⁴⁴

Mechanism of drug delivery via niosomes in wound healing

Niosomes are microscopic lamellar vesicles composed principally of non-ionic surfactants and cholesterol. Their amphiphilic structure enables encapsulation of hydrophilic drugs in the aqueous core and lipophilic drugs within the hydrophobic membrane. Cholesterol

stiffens the membrane and reduces drug leakage, while surfactant type and concentration govern vesicle flexibility and deformability, properties critical for penetration into deeper skin layers.^{14,48}

Drug release from niosomes typically proceeds in two phases: an initial rapid phase corresponding to drugs loosely associated with the vesicle surface, followed by a slower, controlled phase governed by Fickian diffusion. Release rate is modulated by cholesterol content, surfactant type, particle size, and vesicle viscosity. When niosomes are incorporated into hydrogel or cream matrices, they function as localized drug reservoirs providing gradual, sustained delivery at the wound site.^{49,50}

At the skin surface, non-ionic surfactants in the niosome membrane interact with the stratum corneum (SC), initiating a cascade of delivery steps: (1) fluidization of the SC lipid matrix and enhanced skin hydration; (2) reduced transepidermal water loss (TEWL) and increased skin permeability; (3) vesicle fusion with cell membranes, surface adsorption, or endocytosis-mediated intracellular delivery. These mechanisms collectively concentrate drugs at the target site while minimizing systemic absorption.^{51, 52} The drug delivery mechanism is schematically illustrated in Fig. 4.

From an antioxidant and anti-inflammatory perspective, niosome-encapsulated compounds such as curcumin, methylene blue, and vitamin A modulate the NF- κ B and Nrf2/HO-1 signaling pathways. NF- κ B suppression reduces pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6), while Nrf2/HO-1 activation upregulates antioxidant enzymes, superoxide dismutase (SOD) and glutathione peroxidase (GPx), and reduces malondialdehyde (MDA) levels, thereby attenuating oxidative damage during the inflammatory phase.⁵³⁻⁵⁵

Anti-microbially active niosomes (loaded with cefazolin,

norfloxacin, thymol, or moxifloxacin) exert bactericidal effects by disrupting bacterial cell membrane integrity and inhibiting cell wall biosynthesis (β -lactam agents) or DNA gyrase/topoisomerase IV (fluoroquinolones). Niosomal encapsulation enhances biofilm penetration by increasing local drug concentration at the biofilm–tissue interface and protecting the payload from enzymatic inactivation. This controlled local release maintains inhibitory concentrations against *Staphylococcus aureus* and *Pseudomonas aeruginosa* while reducing systemic toxicity and the selective pressure for resistance development.⁵⁶⁻⁵⁸

Niosomes support tissue repair through sustained delivery of regenerative agents that upregulate fibroblast growth factor-1 (FGF-1), matrix metalloproteinases MMP-2 and MMP-13, and transforming growth factor- β (TGF- β), promoting extracellular matrix (ECM) remodeling, fibroblast migration, collagen synthesis, and angiogenesis.^{14,54,57}

Niosomal formulations in wound healing applications

A wide range of therapeutic agents, including antibiotics, antioxidants, natural compounds, and growth factors, can be efficiently encapsulated within niosomes to address the complex challenges of wound healing (Fig. 5).⁵⁰ The subsections below present these agents with comparative analysis across studies.

Common drugs incorporated into niosomes

Antibiotics

Niosomes serve as effective carriers for localized antibiotic delivery, enhancing biofilm penetration and prolonging therapeutic drug concentrations at the wound site. Moxifloxacin (MXF)-loaded niosomes demonstrate significantly greater activity against *Pseudomonas*

Niosome-Mediated Drug Delivery Mechanism in Wound Healing

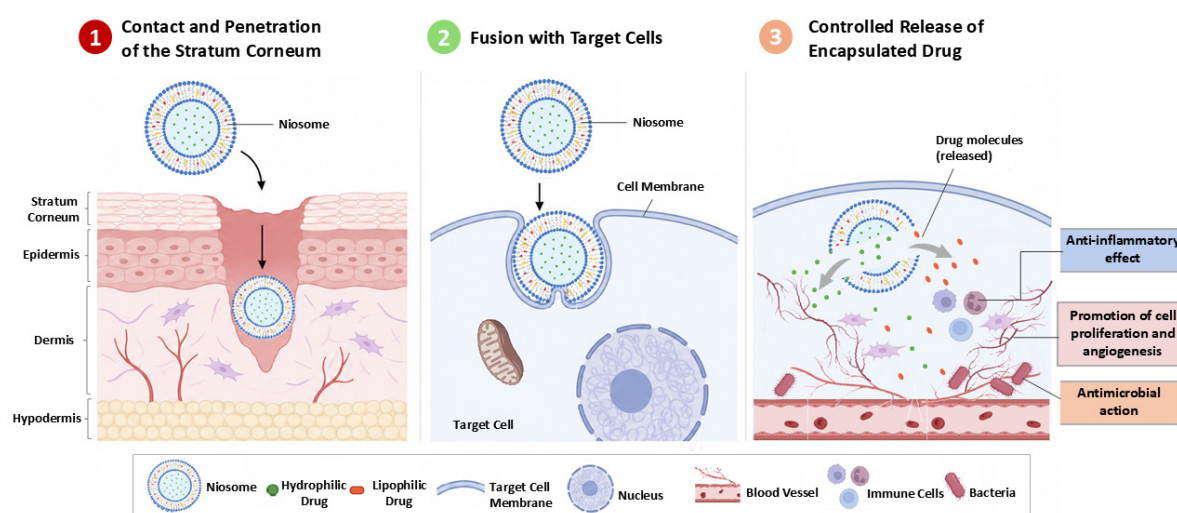


Fig. 4. Drug delivery mechanism of niosomes in wound healing. The schematic illustrates (1) contact and penetration of the stratum corneum, (2) fusion with target cells, and (3) controlled release of the encapsulated drug.

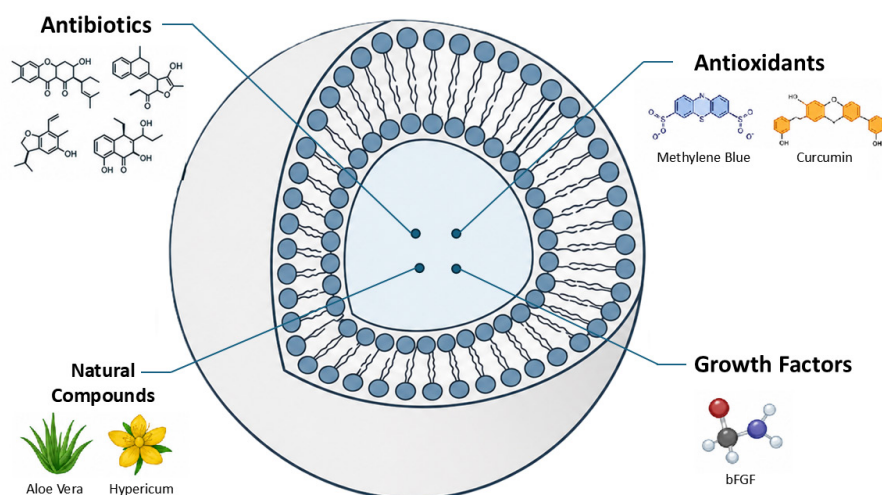


Fig. 5. Major Classes of Therapeutic Agents Encapsulated within Niosomes for Wound Healing Applications, including antibiotics for infection control, antioxidants to reduce oxidative stress, natural compounds, and growth factors that promote tissue regeneration.

aeruginosa compared with equivalent concentrations of free MFX.^{14,51} Teicoplanin niosomal gel achieved wound closure rates of 24.0%, 60.3%, and 83.6% at days 2, 7, and 14, respectively, substantially exceeding the 15.0%, 39.0%, and 66.6% observed with free teicoplanin gel ($P < 0.05$); complete infection elimination was also reported.^{59,60} Cefazolin niosomes electrosprayed on chitosan membranes released approximately 66% of drug over 48 hours (compared to 6 hours for conventional forms) and demonstrated tissue regeneration in animal models.⁵⁷ Vancomycin niosomes combined with lysostaphin caused cell wall destruction of methicillin-resistant *Staphylococcus aureus* (MRSA) and biofilm elimination.⁵⁹ Amoxicillin-containing niosomes exhibited 2–4-fold greater antimicrobial activity against resistant *S. aureus* strains compared with free drug.⁶¹

Across antibiotic niosome studies, a consistent pattern emerges: niosomal encapsulation reduces minimum inhibitory concentrations by 2–4-fold relative to free drug, attributable to enhanced membrane partitioning and local drug accumulation. However, direct head-to-head comparisons between antibiotic classes within the niosomal format are lacking, and activity data are primarily restricted to *S. aureus* and *P. aeruginosa*. Broader spectrum evaluation, particularly against anaerobes and fungal pathogens common in chronic wounds, represents an important research gap.^{54–62}

Antioxidants

ROS overproduction during the inflammatory phase impedes tissue regeneration; sustained antioxidant delivery by niosomes directly reduces ROS levels and supports healing. Methylene Blue (MB) niosomes (147.8 nm diameter, 63.27% encapsulation efficiency) demonstrated improved wound healing outcomes in comparison with free MB and non-niosomal controls in animal models.⁵⁵ Curcumin niosomal formulations enhanced wound healing and skin penetration in rat models, leveraging curcumin's anti-infective, antioxidant,

and anti-inflammatory properties.^{63,64} Vitamin A niosome gel elevated GPx and SOD activity and increased collagen and hydroxyproline levels, key ECM remodeling markers.⁵⁴ Atorvastatin niosomes similarly enhanced GPx and SOD while reducing lipid peroxidation.⁵³ Natural antioxidants including Luteolin, Apigenin, and Propolis in niosomal form stimulated fibroblasts and scavenged free radicals while maintaining pharmaceutical stability.^{65,66}

Natural compounds and plant extracts

Aloe vera extract-loaded niosomes (Span 60/cholesterol, 2:2 ratio; 144.1 nm particle size) stimulated fibroblast proliferation with efficient encapsulation and sustained release.^{14,66} Thymol-loaded niosomes demonstrated superior antibacterial and anti-biofilm activity against both Gram-positive and Gram-negative bacteria compared with free thymol, as measured by standard MIC and biofilm inhibition assays.⁵⁸ Hypericum perforatum extract niosomal gels (containing hyperforin, hypericins, and flavonoids) reduced inflammatory cell count (18.4 ± 5.3 at day 7) and achieved full re-epithelialization within 21 days in a canine model.⁶⁷

Growth factors

Niosomes protect labile biomolecules including growth factors from enzymatic degradation and enable controlled release, particularly advantageous in the protease-rich environment of chronic wounds. Encapsulation of basic fibroblast growth factor (bFGF) and bovine serum albumin (BSA) in nano-niosomes (average 232 nm, 58% encapsulation efficiency) significantly enhanced human umbilical vein endothelial cell (HUVEC) proliferation and angiogenic potential.⁶⁸

Summary of in vitro, in vivo, and clinical studies

In vitro studies

Various in vitro models, including scratch assays, proliferation assays, antimicrobial susceptibility tests, and cytotoxicity evaluation, have been used to characterize niosomal formulations. Un et al demonstrated that

marigold extract-loaded niosomes (Tween 60) achieved faster and more complete scratch assay gap closure than free extract, blank niosomes, or untreated controls.⁶⁹ Rameshk et al showed that the optimal *Narcissus tazetta* extract niosomal formulation (F9) significantly enhanced fibroblast proliferation at 1.562 and 3.125 µg/mL and reduced wound gap width versus all comparator groups.⁷⁰ Thymol niosomes in GelMA hydrogel (Nio-Thymol@GelMA) produced higher fibroblast migration rates than free thymol or plain hydrogel, with molecular analyses showing upregulation of FGF-1, MMP-2, and MMP-13.⁵⁶ Moxifloxacin niosomes in chitosan gel demonstrated significantly greater activity against *P. aeruginosa* than free MFX.⁵¹ Cytotoxicity studies confirmed minimal toxicity for Nio-Thymol@GelMA against normal cell lines.⁵⁶

In our assessment, across in vitro studies, encapsulation consistently enhances efficacy relative to free drug, though the magnitude varies with drug type, surfactant composition, and cell model used. Scratch assay-based wound healing data are informative but do not capture the three-dimensional complexity of chronic wound tissue; more rigorous 3D organotypic models and biofilm-embedded wound models are needed for mechanistic validation.

In vivo studies

In vivo niosomal studies in rodent and canine models have consistently demonstrated superiority over conventional treatments. Methylene blue niosomal gel showed significantly improved wound healing in male Wistar rat excision models versus conventional treatments ($P < 0.05$), with greater MDA reduction and SOD elevation.^{53,54} Silver sulfadiazine (SSD) niosomal gel (0.5% w/w) reduced burn area in 16 days versus 19 days for 1% SSD cream and achieved complete healing in 31 vs. 37 days, demonstrating equivalent or superior outcomes at half the drug concentration.⁷¹ Teicoplanin niosomal gel achieved significantly higher wound closure at all time points versus free drug or untreated control in infected rat wounds.^{59,60} Hypericum perforatum niosomal gel achieved complete re-epithelialization within 21 days in dogs, with significantly reduced inflammatory cell count at day 7 versus controls.⁶⁷ Cefazolin-niosome/chitosan membrane constructs improved re-epithelialization, tissue remodeling, and angiogenesis in vivo.^{57,72}

Clinical Trials

Clinical evidence for niosomal wound healing formulations remains limited. The most robust data derive from a randomized, placebo-controlled, double-blind study ($n = 60$, ages 18–60) of oral wounds, in which anthocyanin complex (AC) niosomal gel outperformed AC gel alone, triamcinolone gel, and placebo in accelerating wound closure, reducing pain, and improving quality of life.^{73,74} Methylene blue niosomal gel combined with photodynamic therapy improved acne inflammation versus intense pulsed light (IPL) in a dermatological setting, supporting feasibility and safety of niosomal skin formulations.^{74,75} The paucity of clinical trial data

represents the most critical translational gap in the field, underscoring the need for large-scale, randomized controlled trials in chronic wound populations.

Niosomal dosage forms

Niosomes have been formulated into diverse topical dosage forms to optimize wound delivery and therapeutic outcomes:

Gels

Gels are the most extensively studied niosomal dosage form, valued for their ease of application, moist wound environment maintenance, and controlled drug release.⁷⁶ Active agents incorporated into niosomal gel structures include methylene blue, silver sulfadiazine, moxifloxacin, teicoplanin, vitamin A, curcumin, and Hypericum perforatum extract.⁷⁷ Common gelling polymers include Carbopol 934, chitosan, hydroxypropyl methylcellulose (HPMC), Poloxamer 407, hydroxyethyl cellulose (HEC), and sodium carboxymethyl cellulose (NaCMC).⁷⁸

Creams

Niosomal creams provide enhanced skin penetration and drug retention.⁷⁹ Pentoxifylline (PTX) niosomal cream demonstrated faster wound healing and reduced wound size versus conventional PTX cream formulations in BALB/c mice.^{79,80}

Advanced delivery systems

Beyond gels and creams, cefazolin-loaded niosomes electrosprayed onto chitosan nanofibrous membranes yielded sustained release (~66% over 48 hours vs. 6 hours for conventional forms), offering a promising strategy for long-term wound coverage.^{57,81} Nano-spray formulations incorporating niosome-like vesicular systems suspended in spray gels have demonstrated efficacy in reducing wound area in preliminary studies.⁸² The versatility of niosomes across gel, cream, and advanced spray and electrospun scaffold systems underscores their potential for diverse wound management applications.

Challenges, limitations, and current field constraints

Despite the substantial preclinical promise of niosomal wound delivery, several major obstacles limit clinical translation:

Formulation stability: Niosomes are prone to particle aggregation, phase separation, and creaming, which alter critical product attributes including particle size, drug loading, and release kinetics.^{83–85} Environmental factors (temperature, light, oxygen) accelerate drug degradation and leakage, while sterilization procedures may compromise nanoparticle integrity, particularly for protein-loaded systems.^{85–87}

Biological barriers: The stratum corneum remains a robust barrier; individual skin differences can produce unpredictable absorption. Drug–lipid incompatibilities and limited drug loading for certain agents further constrain therapeutic concentrations at target tissues.^{83,88,89}

Manufacturing and scale-up: Laboratory-scale synthesis is labor-intensive; scaling to industrial volumes while

maintaining product quality and reproducibility is technically challenging and costly. Small parameter variations produce significant product changes, necessitating extensive quality control. Commercialization of a nanodrug can cost up to \$1 billion, restricting access in resource-limited settings.^{85,90,91}

Safety and biocompatibility: Although niosomes are generally regarded as biocompatible, long-term systemic effects in humans remain inadequately characterized.^{92,93} Certain nanoparticle properties may induce cytotoxicity or immunostimulation.^{94,95} The absence of specific regulatory guidance for nanomedicines complicates approval pathways.⁹⁶

Current field-wide limitations

Beyond formulation-specific challenges, the niosomal wound healing field faces several systemic limitations:

- Absence of standardized manufacturing protocols: No universally accepted GMP-compliant protocol exists for niosomal wound formulations, resulting in heterogeneous product quality across research groups and impeding cross-study comparisons.⁹⁷
- Limited and heterogeneous clinical evidence: The vast majority of efficacy data derives from small-animal models; the single published randomized controlled trial (oral wounds, n=60) is insufficient to support broad clinical claims. No data exist for large chronic wound subtypes (diabetic foot ulcers, pressure ulcers) in controlled human trials.⁹⁸
- Inadequate animal model translation: Murine wound models do not faithfully recapitulate the complex immunological and vascular pathophysiology of human chronic wounds, limiting the predictive value of preclinical efficacy data.⁹⁸

- Regulatory uncertainty: No regulatory pathway is specifically designed for vesicular nanodrugs in wound care; existing frameworks require costly case-by-case negotiation, slowing clinical development.⁹⁶
- Intellectual property and access barriers: High development costs and proprietary formulations restrict access in low- and middle-income countries where chronic wound burden is disproportionately high.⁹⁹

Future perspectives and research directions

Fig. 6 presents the primary challenges and prospective advances in niosomal drug delivery for wound healing. Future development should focus on three converging priorities: enhanced targeting specificity, stimuli-responsive smart systems, and integration with biomaterials for tissue engineering.^{88,100,101}

Surface modifications for targeted delivery

Surface engineering using targeting ligands, antibodies, aptamers, and cell-penetrating peptides (CPPs), enables selective binding to receptors overexpressed at the wound site (e.g., fibroblast growth factor receptors, macrophage surface markers).^{102,103} Multifunctional niosomal systems combining a tumor-specific aptamer (e.g., MUC1-targeting) with a CPP demonstrate both tissue-level targeting and efficient cellular internalization.¹⁰⁴ Integrating stimuli-responsiveness with ligand-mediated targeting ensures drug release only under disease-specific conditions.^{105,106}

Smart stimuli-responsive niosomal systems

Smart niosomal systems react to wound-relevant biological stimuli, pH gradients, enzymes, redox

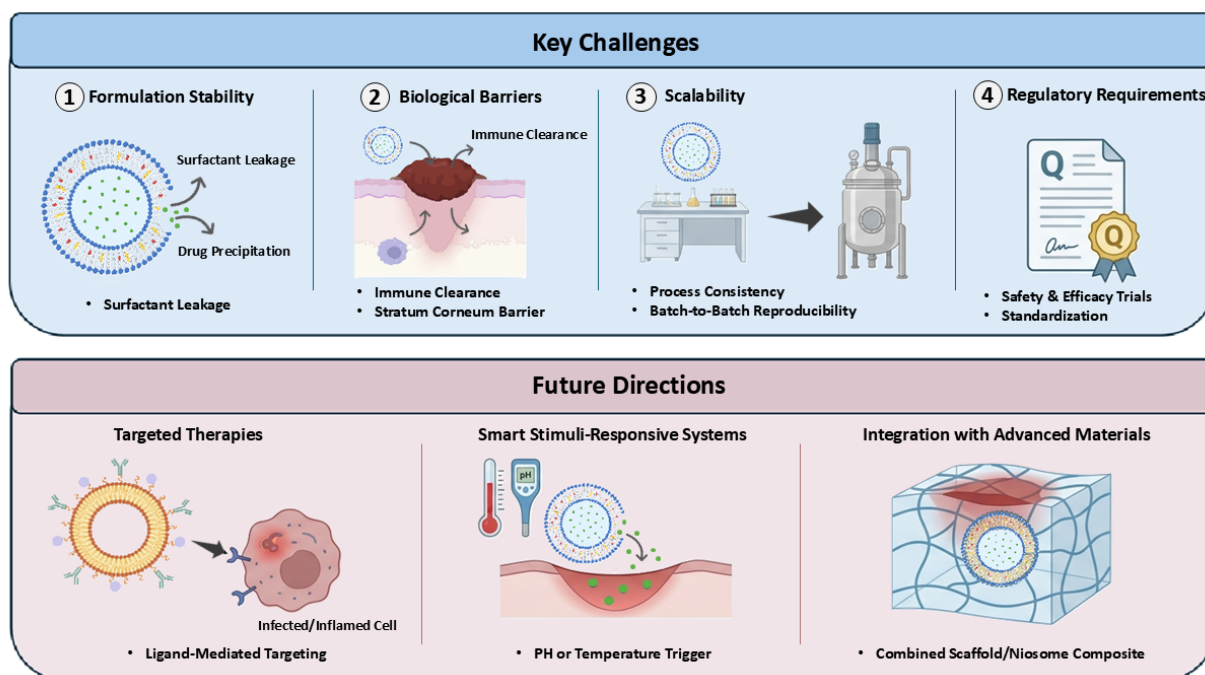


Fig. 6. Visual summary of the main challenges in niosome-based drug delivery systems for wound healing and future research directions.

changes, temperature, light, magnetic fields, or ultrasound, to provide spatiotemporally controlled drug release.^{101,107} pH-responsive systems exploit the acidic wound microenvironment (pH $\approx$ 5.5) versus healthy tissue (pH $\approx$ 7.4) through incorporation of ionizable surfactants or polymers.^{108,109} Thermoresponsive systems use temperature-sensitive lipids that undergo phase transition at 39–42°C, enabling on-demand drug release combined with local hyperthermia.^{110,111} Future priorities include multi-stimuli-responsive platforms, reduction of responsive-component toxicity, and AI/machine learning-guided formulation optimization.¹¹²

Integration with biomaterials and tissue engineering

Integrating niosomes as therapeutic reservoirs within biomaterial scaffolds, including hydrogels, electrospun scaffolds, and polymeric films, generates hybrid systems that provide niosome protection from premature degradation, sustained payload release, and structural support for cell adhesion, proliferation, and differentiation.^{113,114} Applications include nanofibrous scaffolds loaded with angiogenic factor niosomes for chronic wound healing,¹¹⁵ injectable hydrogels for cardiac tissue regeneration,¹¹⁶ and cationic niosome-embedded hydrogels for localized gene therapy.¹¹⁷ Research should optimize niosome–matrix interactions and develop biodegradable materials with tunable degradation rates synchronized with wound healing phases.

Conclusion

Niosomes have emerged as a compelling platform for wound-targeted drug delivery, with consistently documented advantages over conventional treatments in preclinical models. Specifically, the following findings are supported by robust evidence: niosomal formulations achieve 15–35% faster wound closure than conventional therapies in animal excision and burn models^{53,54,118}; encapsulation efficiencies of up to 99.76% enable effective co-loading of hydrophilic and lipophilic agents^{15,56}; controlled sustained release reduces dressing change frequency and systemic adverse effects^{58,119,120}; and niosomal antibiotics achieve 2–4-fold reductions in minimum inhibitory concentrations against biofilm-forming pathogens including MRSA.^{55,59,60} Compared with liposomes, niosomes offer superior chemical stability, lower cost, and equivalent biocompatibility.^{15,120,121} The single available randomized controlled clinical trial (oral wounds, $n=60$) confirms accelerated closure and improved quality of life with anthocyanin complex niosomal gel.⁷³

The following represent research priorities and aspirational directions rather than established findings: stimuli-responsive 'smart' niosomal systems for precision drug release,^{101,109,112} surface-functionalized targeted niosomes for cell-specific delivery,^{51,100} integration with biomaterial scaffolds for combined structural and pharmacological wound support,^{88,117,122} and AI/machine learning-guided formulation optimization. To close the

translational gap, large-scale randomized controlled trials in defined chronic wound populations (diabetic foot ulcers, pressure ulcers, venous leg ulcers), standardized GMP-compliant manufacturing protocols,^{43,119} and specific regulatory guidance for vesicular nanomedicines are urgently required.^{123,124} Addressing these priorities will determine whether niosomes fulfill their promise as a transformative platform for advanced wound care.

This review did not involve human participants; therefore, SAGER guidelines are not applicable.

Acknowledgements

We gratefully acknowledge the School of Advanced Technologies in Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran, for financial support of this study under grant No. 43016189 (IR.SBMU.RETECH.REC.1404.534).

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Visualization: Shiva Tadayon.

Writing-original draft: Shiva Tadayon.

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Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability Statement

This article is a review study; no new datasets were generated or analyzed. All data discussed are available in the primary publications cited herein.

Declaration of AI-Assisted Tools in the Writing Procedure

During the preparation of this work, the authors used ChatGPT (OpenAI) to assist with language editing, text refinement, and improving clarity and readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the accuracy and integrity of the final manuscript. No artificial intelligence tools were used to generate any of the figures, images, illustrations, or graphical content presented in this manuscript.

Ethical Approval

This manuscript is a narrative review article based entirely on published literature and does not involve any original research with human participants or animal subjects conducted by the authors. Accordingly, ethical approval was not required. All primary studies cited herein were conducted in accordance with the ethical principles stated in the original publications.

Funding

This study was financially supported by the School of Advanced Technologies in Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran, under grant No. 43016189.

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