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Emerging Nanoformulation For Topical Wound Care: Challenges And Opportunities

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Abstract

Topical wound care is moving from passive coverage toward biologically active, microenvironment-responsive therapy. Conventional dressings protect the wound surface and absorb exudate, but they often fail to address the interacting causes of delayed repair: persistent inflammation, microbial biofilm, oxidative stress, protease excess, impaired angiogenesis, pain, and repeated trauma during dressing changes. Nanoformulations offer an attractive strategy because particle size, surface charge, composition, and architecture can be engineered to localize therapeutic action at the wound interface while reducing systemic exposure. This review examines emerging nanoformulation platforms for topical wound care, including lipid vesicles, solid lipid nanoparticles, nanostructured lipid carriers, polymeric nanoparticles, nanofibers, nanoemulsions, nanogels, nanoparticle-loaded hydrogels, metallic and metal oxide nanoparticles, exosome-inspired systems, and stimuli-responsive hybrid dressings. The article synthesizes current opportunities in antimicrobial delivery, anti-inflammatory modulation, moisture-balanced healing, oxygen and nitric oxide support, growth factor stabilization, phytochemical delivery, scar reduction, and smart monitoring. Particular attention is given to chronic wounds, diabetic foot ulcers, burns, pressure injuries, venous ulcers, and surgical wounds, where impaired perfusion and infection amplify the need for multifunctional topical systems. Nanoformulations can improve drug solubility, protect labile bioactives, prolong residence time, enable controlled release, and combine therapeutic and diagnostic functions in a single dressing platform. However, clinical translation remains limited by safety uncertainties, batch reproducibility, sterilization constraints, unclear regulatory classification, cost, environmental concerns, inadequate large-animal and human evidence, and the absence of standardized wound-relevant release and toxicity assays. A publishable research agenda should therefore prioritize clinically meaningful endpoints, infection and biofilm models, wound-fluid simulated testing, scalable green manufacturing, transparent reporting of physicochemical characterization, and comparative trials against advanced standard care rather than against gauze alone. The future of topical nanomedicine is likely to depend less on novelty of the particle and more on fit-for-purpose design: a formulation must match wound type, exudate level, microbial risk, patient usability, manufacturing feasibility, and regulatory expectations. Overall, emerging nanoformulations provide substantial opportunities to modernize wound care, but their promise will be realized only through careful risk-benefit evaluation, interdisciplinary formulation science, and evidence generation that is relevant to real clinical practice.

Keywords: nanoformulation; topical wound care; nanomedicine; wound healing; antimicrobial dressing; hydrogels; nanofibers; nanoparticles; chronic wound

1. Introduction

Wound care has entered a period of rapid technological transition. For many years, topical management was dominated by simple coverings, antiseptic solutions, absorbent pads and occlusive dressings. These approaches remain important because the first duty of a wound dressing is to provide protection, reduce contamination, maintain a favorable moisture balance and permit observation of healing progress. Nevertheless, the contemporary wound-care burden is increasingly driven by chronic wounds, burns, diabetic foot ulcers, venous leg ulcers, pressure injuries and complicated surgical wounds in which passive coverage is not sufficient. Such wounds are not merely breaks in the skin; they represent disturbed tissue ecosystems involving inflammatory cells, extracellular matrix, vascular supply, oxygen gradients, bacteria, biofilm, proteases and patient-level factors such as diabetes, malnutrition, immobility, smoking, vascular disease and immune suppression [1,12,17].

Topical nanoformulations are being developed to address this complexity by placing functional materials directly at the wound surface. The term nanoformulation in wound care includes nanoscale drug carriers, nanostructured matrices and nanomaterial-enabled dressings that are engineered to improve residence time, drug stability, wound penetration, antimicrobial performance or cellular response. Their value is not limited to being small. At the nanoscale, materials may show increased surface area, tunable surface chemistry, altered solubility, controlled release behavior and capacity for multifunctional design [2,3,8]. A topical system can be designed to hydrate the wound, release an antimicrobial agent, reduce oxidative stress, deliver a growth-promoting molecule and respond to pH or enzyme changes in wound fluid. This multifunctionality creates opportunities unavailable to many conventional preparations.

The interest in nanoformulations is also driven by limitations of topical drugs. Many antibiotics, antiseptics, anti-inflammatory compounds, plant-derived molecules and growth factors are chemically unstable, poorly soluble, irritating at effective concentrations or rapidly cleared by exudate. In chronic wounds, protease-rich fluid may degrade therapeutic proteins, while bacterial biofilm reduces drug susceptibility and delays epithelial migration. Nanocarriers can protect labile cargo, increase dispersibility, concentrate drug at the wound interface and release it over a clinically useful period [4,21,24]. For example, lipid vesicles can encapsulate hydrophilic and lipophilic agents; polymeric nanoparticles can provide sustained release; nanofibers can mimic extracellular matrix; and nanoparticle-loaded hydrogels can combine moisture retention with antimicrobial and regenerative effects [2,5,11,22].

Despite the excitement, the field must be evaluated cautiously. A promising result in an in vitro scratch assay or small animal excision model does not guarantee clinical benefit in infected diabetic ulcers or ischemic wounds. The wound bed contains dynamic fluid, variable pH, necrotic tissue, host enzymes and microbial communities that are difficult to reproduce in laboratory systems. A nanomaterial that accelerates closure in a clean rodent wound may fail in a biofilm-rich chronic wound, and a formulation that kills bacteria may damage keratinocytes or fibroblasts if the dose and release profile are not optimized. Therefore, a publishable review on emerging topical nanoformulations must balance opportunity with translational challenges [6,7,9].

This review aims to present a publication-style synthesis of emerging nanoformulations for topical wound care, focusing on their rationale, formulation categories, therapeutic mechanisms, clinical opportunities and barriers to translation. The review is narrative rather than a systematic review, and it emphasizes recent developments while retaining foundational concepts of wound healing and drug delivery. The central argument is that future success will depend on fit-for-purpose formulation design rather than novelty alone. A useful wound-care nanoformulation should match a real clinical problem, possess reproducible physicochemical properties, show safety in relevant models, survive sterilization and storage, and demonstrate superiority or added value compared with existing advanced dressings [3,20,39].

2.Wound-healing biology and topical formulation targets

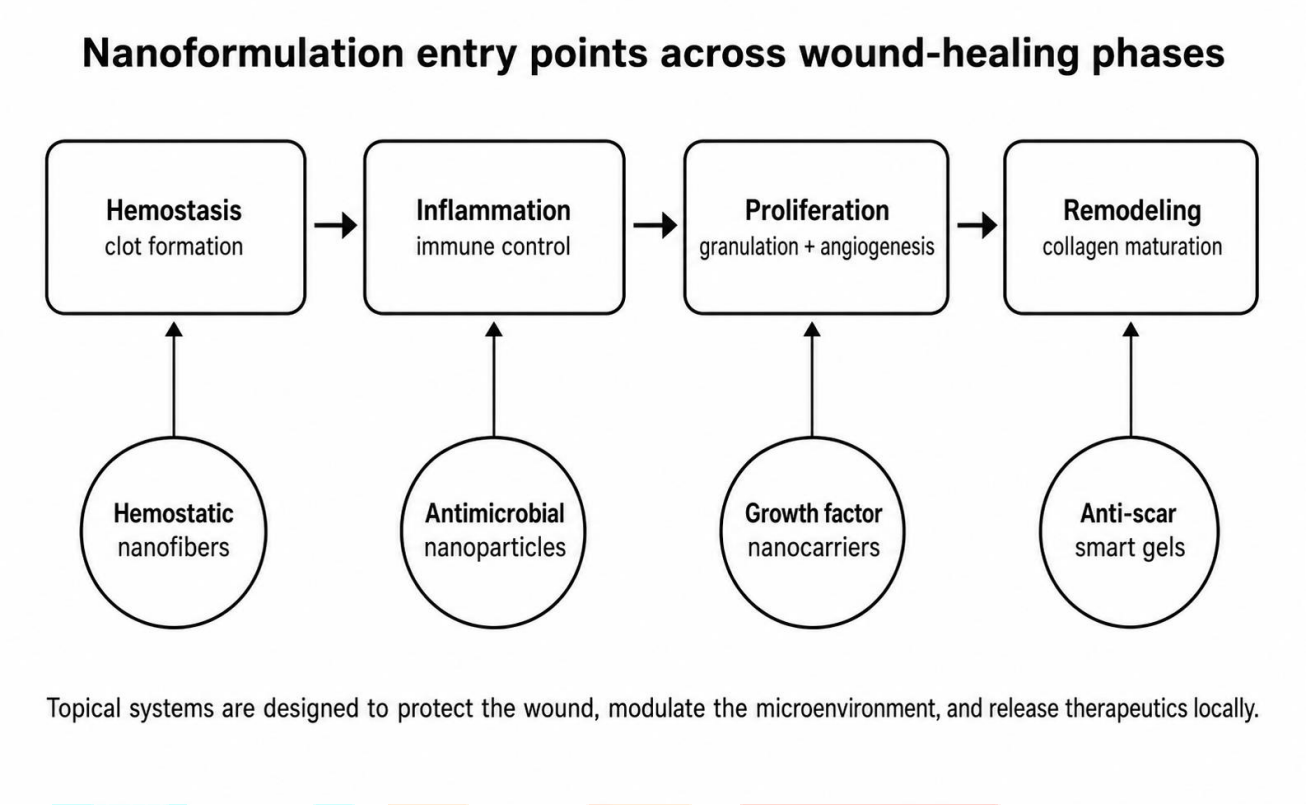

Figure 1. Nanoformulation entry points across the major phases of wound healing. Original schematic prepared for this review.

Normal cutaneous wound healing is usually described as a sequence of overlapping phases: hemostasis, inflammation, proliferation and remodeling [1,14,15]. Hemostasis begins immediately after injury with vasoconstriction, platelet activation and fibrin clot formation. The clot provides temporary protection and a provisional matrix for cell migration. The inflammatory phase recruits neutrophils and macrophages to clear debris and microbes, but excessive or persistent inflammation can damage tissue and block transition to repair. During proliferation, fibroblasts deposit extracellular matrix, endothelial cells form new vessels, keratinocytes migrate to close the surface and granulation tissue develops. Remodeling then reorganizes collagen and gradually improves tensile strength, although healed skin rarely regains the full strength of uninjured tissue [14,15].

Nanoformulation design should begin with an understanding of which wound-healing process requires support. In a clean acute wound, the primary needs may be protection, moisture control and pain reduction. In a diabetic foot ulcer, impaired angiogenesis, neuropathy, biofilm, oxidative stress and chronic inflammation may dominate. In a burn wound, high exudate, infection risk, pain and scarring may be major concerns. In a pressure injury, mechanical unloading and perfusion restoration are as important as local therapy. Thus, no single nanocarrier is universally optimal. A rational formulation is one that aligns a therapeutic mechanism with the stage, depth, microbial burden and patient context of the wound [1,12,18].

The wound microenvironment offers both obstacles and opportunities. Chronic wound fluid often contains elevated proteases, pro-inflammatory cytokines, bacterial metabolites and reactive oxygen species. These factors can degrade growth factors, injure cells and perpetuate tissue breakdown [12,17,32]. However, the same microenvironment can be used as a trigger. pH-responsive carriers may release drugs in alkaline infected wounds; enzyme-responsive systems may respond to matrix metalloproteinases; redox-sensitive materials may react to oxidative stress; and thermoresponsive gels may transform from liquid to gel at skin temperature [2,3,39]. Such responsiveness is attractive because topical therapy can be synchronized with pathological conditions rather than relying only on passive diffusion.

The barrier function of skin also affects topical nanomedicine. Intact stratum corneum restricts penetration of many substances, whereas open wounds expose dermis and wound fluid. This means that a topical wound formulation is not the same as a cosmetic or transdermal formulation. For open wounds, the formulation interacts with blood proteins, exudate, extracellular matrix and inflammatory cells. Particle aggregation, protein corona formation and altered release may occur. For partial-thickness wounds and burns, the remaining skin barrier may still influence distribution. Therefore, wound-specific evaluation should include exudate compatibility, dressing adherence, removal trauma, local retention and cytocompatibility with keratinocytes, fibroblasts, endothelial cells and immune cells [7,9,28].

The goals of topical wound-care nanoformulations can be organized into five broad categories. First, barrier and moisture functions maintain a warm, moist environment while avoiding maceration. Second, antimicrobial functions reduce planktonic bacteria and biofilm. Third, immunomodulatory functions resolve excessive inflammation without suppressing necessary defense. Fourth, regenerative functions support angiogenesis, extracellular matrix deposition and epithelialization. Fifth, user-centered functions improve comfort, dressing-change interval, transparency, conformability and acceptability. The most promising emerging products are not isolated particles but integrated systems that combine these functions in dressings, gels, films, foams, sprays or electrospun matrices [2,11,21,22].

3. Classification of emerging topical nanoformulations

Table 1. Major topical nanoformulation platforms for wound care

Platform	Typical components	Main wound-care opportunity	Key limitation
Lipid vesicles and lipid nanoparticles	Liposomes, transfersomes, solid lipid nanoparticles, nanostructured lipid carriers	Solubilize lipophilic molecules, protect labile drugs, improve local retention [3,5]	Oxidation, leakage, vesicle instability and sterilization sensitivity
Polymeric nanoparticles	Chitosan, alginate, PLGA, gelatin, polycaprolactone	Sustained release, adhesion, incorporation into films or gels [21,22]	Residual solvent, burst release, polymer variability
Metal/oxide nanoparticles	Silver, zinc oxide, gold, copper, cerium oxide, iron oxide	Antimicrobial, antioxidant, angiogenic or photothermal functions [2,7]	Dose-dependent cytotoxicity and environmental persistence
Nanofibers	Electrospun natural/synthetic polymers with drugs or nanoparticles	ECM-like architecture, exudate handling, staged release [11,31]	Scale-up, fiber shedding, mechanical fragility
Nano-hydrogels and hybrid gels	Self-healing, adhesive, injectable, sprayable or stimuli-responsive gels	Moist wound healing, conformability, local drug release [2,39]	Sterility, storage, mechanical consistency

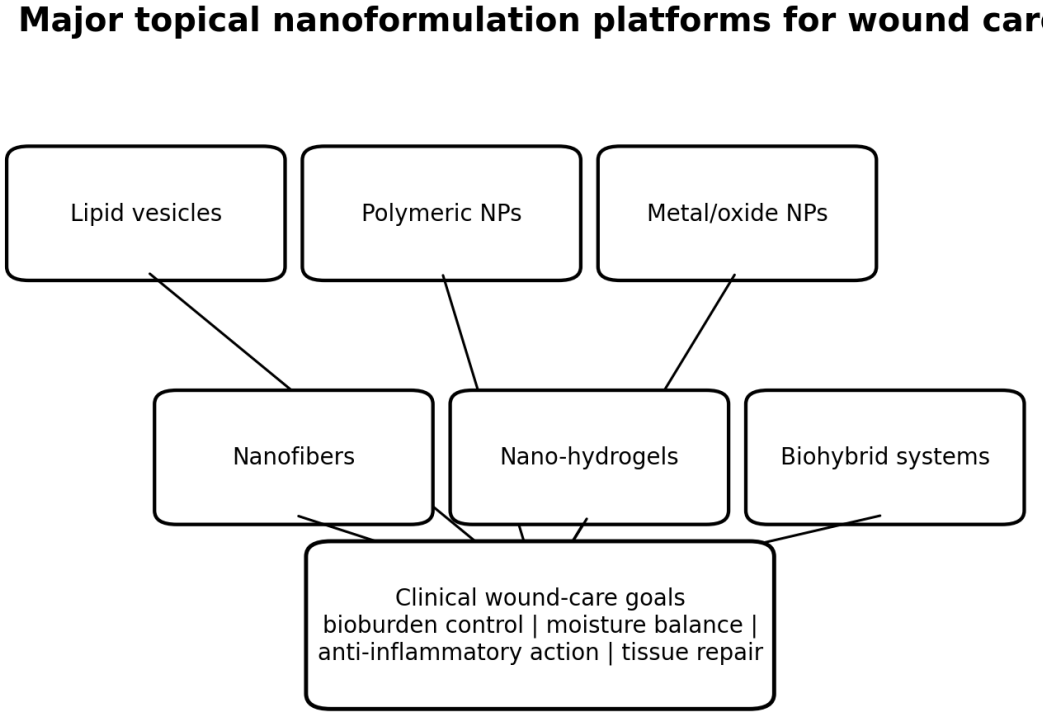

Figure 2. Major topical nanoformulation platforms and their convergence toward clinical wound-care goals. Original schematic prepared for this review.

Lipid-based nanoformulations include liposomes, ethosomes, transfersomes, solid lipid nanoparticles and nanostructured lipid carriers. Their popularity arises from biocompatibility, ability to host both hydrophilic and lipophilic molecules, and potential to merge with biological membranes [3,5]. Liposomes can carry antibiotics, antioxidants, anesthetics, anti-inflammatory drugs, peptides and plant-derived compounds. Elastic vesicles may enhance distribution across superficial skin layers or damaged tissue interfaces. Solid lipid nanoparticles and nanostructured lipid carriers can improve stability of poorly soluble drugs and provide sustained release. In wound care, lipid systems are attractive for anti-inflammatory molecules and phytochemicals that would otherwise degrade or irritate tissue [4,5].

Polymeric nanoparticles are prepared from natural or synthetic polymers such as chitosan, alginate, gelatin, poly(lactic-co-glycolic acid), polycaprolactone and other biodegradable materials. Chitosan-based systems are especially relevant because chitosan itself can show hemostatic, mucoadhesive and antimicrobial properties. Polymeric carriers can be engineered for sustained release, surface functionalization and incorporation into hydrogels or films [21,22,28]. Their limitations include possible burst release, residual solvent concerns, sterilization sensitivity and variability in polymer quality. For clinical translation, polymer identity, molecular weight, degree of deacetylation or functionalization, degradation products and release kinetics need transparent reporting [3,9].

Metal and metal oxide nanoparticles, especially silver, zinc oxide, gold, copper, cerium oxide and iron oxide, have drawn attention because they can provide antimicrobial, antioxidant, pro-angiogenic or imaging-related functions [2,7,33,34]. Silver nanoparticles are among the most studied due to broad antimicrobial activity, but their safety depends strongly on dose, particle size, coating, ion release and local exposure. Zinc oxide nanoparticles may combine antimicrobial and anti-inflammatory effects, while cerium oxide nanoparticles are studied for redox-modulating behavior. Gold nanoparticles can serve as drug carriers or photothermal agents. Copper-containing systems may stimulate angiogenesis but require careful dose control. These materials illustrate a central challenge: the same physicochemical reactivity that provides therapeutic activity may also cause cytotoxicity if uncontrolled [7,33,35].

Nanofiber dressings are commonly produced by electrospinning polymers into fibers with high surface area and extracellular-matrix-like architecture. They can absorb exudate, permit gas exchange, support cell migration and deliver drugs in a controlled fashion [11,31]. Nanofibers may be loaded with antibiotics, antiseptics, growth factors, antioxidants, analgesics or herbal molecules. Layered or core-shell fibers can separate incompatible agents and provide staged release. The fibrous structure can also be combined with nanoparticles to add antimicrobial or conductive functions. Important translational issues include mechanical strength, sterilization, residual solvent, scale-up, reproducibility and prevention of fiber shedding into the wound [11,31].

Nanoemulsions and nanoemulgels are useful when topical delivery involves hydrophobic drugs, essential oils or phytochemicals. Their small droplets increase apparent solubility and distribution, while a gel phase can improve residence time and patient acceptability. Nanoemulsions may be particularly attractive for plant-derived antimicrobial or anti-inflammatory compounds, but formulation stability, irritation potential, surfactant concentration and oxidation must be controlled [4,24]. Nanogels and nanoparticle-loaded hydrogels occupy a prominent position because they combine wound-friendly moisture retention with nanoscale delivery. Hydrogels can be injectable, sprayable, self-healing, adhesive, transparent, conductive, antibacterial or responsive to wound stimuli [2,21,22,39].

Biohybrid and cell-derived nanosystems are emerging as a newer frontier. Exosomes and extracellular vesicles derived from stem cells, immune cells or platelets may carry proteins, lipids and nucleic acids that influence inflammation and regeneration. Biomimetic nanoparticles can be coated with cell membranes to improve biological interaction or immune evasion. These systems are appealing because wound healing is a biological process, not only a chemical one. However, they raise additional challenges related to source variability, characterization, potency assays, contamination risk, storage, cost and regulatory classification. In topical wound care, their future may depend on robust manufacturing and clear evidence that bioactivity survives incorporation into dressings [3,6,26].

4. Antimicrobial and ant biofilm opportunities

Table 2. Therapeutic opportunities and formulation logic

Therapeutic target	Nanoformulation approach	Potential benefit	Evaluation requirement
Biofilm and infection	Silver, zinc oxide, antibiotic nanoparticles, photodynamic nanocarriers	High local antimicrobial exposure with controlled release	Mature biofilm models and cytocompatibility testing
Oxidative stress	Cerium oxide, antioxidant-loaded lipid/polymeric carriers	Reduction of excessive reactive oxygen species	ROS markers plus keratinocyte/fibroblast safety
Impaired angiogenesis	Copper, nitric oxide, oxygen-generating or VEGF-protective systems	Improved vascular support in diabetic or ischemic wounds	Diabetic/ischemic animal models and dose-response data
Pain and dressing trauma	Local anesthetic nanogels, non-adherent nanofiber/hydrogel surfaces	Reduced pain and fewer traumatic dressing changes	Patient-reported pain and removal-force testing
Excess exudate	Absorptive nanofibers, alginate/chitosan hybrid gels	Moisture balance without maceration	Fluid uptake, retention and vapor transmission tests

Infection is one of the most important reasons for delayed wound healing. Acute contamination can progress to colonization, local infection, spreading infection and systemic illness. Chronic wounds often contain polymicrobial biofilms embedded in extracellular polymeric substances, which protect bacteria from antibiotics, antiseptics and host immunity. Nanoformulations provide several possible antimicrobial advantages: high local surface area, controlled release, improved penetration into biofilm matrix, combination therapy, reduced systemic exposure and capacity to integrate antimicrobials into dressings [7,13,32].

Silver nanoparticle systems remain prominent because silver ions and silver-containing surfaces can disrupt bacterial membranes, proteins and DNA. In wound care, silver-containing dressings already exist, but nanosilver formulations aim to improve release control and reduce unnecessary exposure [7,34]. A key opportunity is dose economy: a well-designed nanocarrier may deliver sufficient antimicrobial activity while using less total silver than traditional dressings. Yet this benefit must be proven, not assumed. Excessive silver exposure may impair keratinocyte and fibroblast function, delay epithelialization or raise environmental concerns. Future studies should report silver content, particle size, ionic release, cytotoxicity and comparative performance against standard silver dressings [7,34].

Antibiotic-loaded nanoparticles are another strategy, especially for agents limited by poor penetration, instability or local toxicity. Encapsulating mupirocin, gentamicin, vancomycin, ciprofloxacin or other antibiotics may improve wound retention and reduce dosing frequency. Combination nanosystems may pair an antibiotic with a biofilm-disrupting agent, quorum-sensing inhibitor, enzyme or photothermal material. However, antibiotic stewardship is essential. A topical nanocarrier should not encourage indiscriminate antibiotic use or subtherapeutic release that promotes resistance. Clinical development should define intended indications, microbial targets and duration of therapy [13,37].

Photothermal and photodynamic nanoformulations are receiving attention for infected wounds. Gold, carbon-based, copper sulfide and other photothermal materials can generate localized heat after light exposure, while photosensitizer-loaded nanoparticles can produce reactive oxygen species under specific illumination. These systems may help disrupt biofilm and kill resistant organisms. Their practical limitations include light penetration depth, heat control, patient discomfort, device requirements and risk of damaging healthy tissue. For superficial infected wounds, they may become useful adjuncts, but protocols must be standardized before widespread adoption [3,6].

Antimicrobial peptides, nitric oxide donors, essential oils and plant-derived molecules can also be incorporated into nanoformulations. These agents may offer broad mechanisms and lower resistance pressure, but they often suffer from instability, volatility, irritation or rapid degradation. Nanoemulsions, liposomes, nanofibers and hydrogels can protect and localize them [4,24]. The opportunity is not merely to replace antibiotics but to design multi-mechanism wound dressings that reduce bacterial burden while preserving host repair. In this context, antibiofilm outcomes should be measured using mature biofilm models, relevant wound pathogens and endpoints such as viable cell count, matrix disruption, inflammatory response and healing rate [7,13].

5. Regenerative, immunomodulatory and antioxidant opportunities

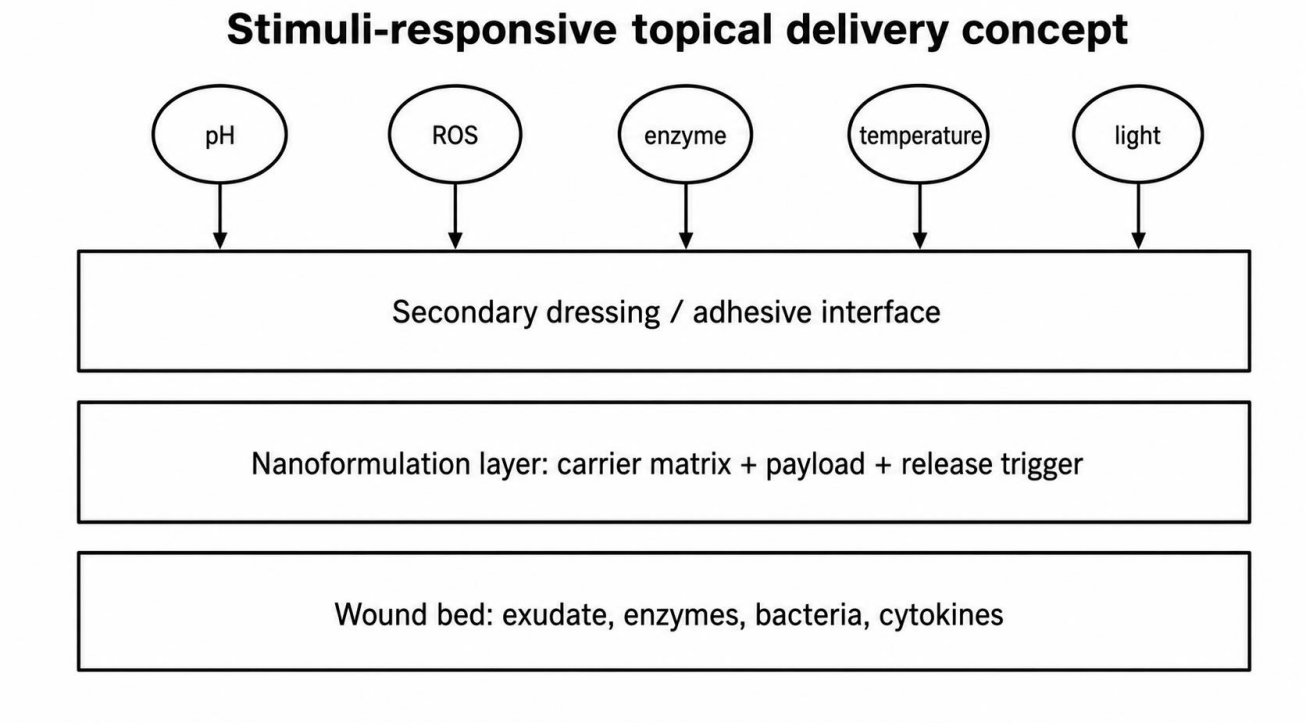

Figure 3. Stimuli-responsive topical release concept using wound pH, enzymes, reactive oxygen species, temperature or light as triggers. Original schematic prepared for this review.

Chronic wounds frequently remain trapped in a prolonged inflammatory state. Macrophage phenotype imbalance, neutrophil persistence, elevated proteases and oxidative stress contribute to tissue destruction and delayed closure [12,17,32]. Nanoformulations can be engineered to modulate these signals locally. For example, antioxidant nanoparticles may scavenge reactive oxygen species, anti-inflammatory drugs can be released gradually, and nucleic-acid-based approaches can target molecular pathways involved in impaired repair [26,35]. Local delivery is especially attractive because systemic immunosuppression would be undesirable in infected or colonized wounds.

Growth factor therapy has long been appealing, but clinical use is limited by instability, short half-life, high cost and protease degradation in chronic wound fluid. Nanocarriers can protect growth factors such as epidermal growth factor, vascular endothelial growth factor, fibroblast growth factors and platelet-derived growth factor, while hydrogels and nanofibers can provide sustained release [28,29]. The challenge is biological timing. A growth factor released too early, too late or in excessive concentration may be ineffective or even counterproductive. Therefore, smart release systems that respond to wound enzymes or pH may be more rational than simple loading into a dressing [2,3].

Angiogenesis is another major target, particularly in diabetic and ischemic wounds. Copper-containing, oxygen-generating, nitric-oxide-releasing and growth-factor-loaded materials have been studied to support microvascular repair [2,38]. Oxygen delivery is attractive because hypoxia impairs collagen synthesis, bacterial killing and epithelialization, but oxygen-generating systems must avoid oxidative injury. Nitric oxide has antimicrobial and vasoregulatory effects, but controlled release is necessary because excessive levels may be harmful. Nanotechnology offers ways to tune these signals, yet translation requires careful dose-response testing in compromised wound models rather than healthy animals alone [1,38].

Extracellular matrix repair can be supported by nanofiber scaffolds and bioactive hydrogels that mimic aspects of native tissue structure. Electrospun matrices provide topographical cues for cell migration and can be designed with collagen, gelatin, chitosan, silk fibroin or synthetic polymers [11,31]. Self-healing and adhesive hydrogels can conform to irregular wounds and reduce trauma during movement. Transparent hydrogels allow wound inspection without frequent removal. Conductive

hydrogels and piezoelectric materials are being explored to interact with endogenous electrical signals involved in healing, although clinical evidence remains early [2,39].

Phytochemical nanoformulations represent a growing opportunity because many plant-derived compounds have antioxidant, anti-inflammatory, antimicrobial or collagen-modulating properties but poor water solubility and stability [4,24]. Curcumin, quercetin, resveratrol, asiaticoside, aloe constituents and essential oils have been incorporated into lipid carriers, nanoemulsions, nanofibers and hydrogels. Their appeal is high, especially for low-cost topical products, but quality control is demanding because plant extracts vary by source, extraction method and composition. Publication-quality studies should identify active markers, quantify loading and release, test cytocompatibility and compare against clinically accepted dressings [4].

6. Formulation design and characterization requirements

A topical nanoformulation cannot be judged only by its biological effect. It must be characterized as a pharmaceutical or medical-device product. Core physicochemical parameters include particle size distribution, polydispersity index, zeta potential, morphology, surface chemistry, drug loading, encapsulation efficiency, pH, viscosity, spreadability, swelling, degradation, mechanical strength, adhesiveness and release kinetics [3,8,9]. For nanofibers, fiber diameter, porosity, tensile strength and residual solvent are essential. For hydrogels, rheology, gelation time, water vapor transmission, exudate absorption and adhesive strength matter. For metallic nanoparticles, ion release and aggregation in wound fluid are important [2,7,11].

Release testing should be wound-relevant. Many studies use simple phosphate buffer, but real wound fluid contains proteins, salts, enzymes and variable pH. The release profile in buffer may not predict release in exudate. Simulated wound fluid and enzyme-containing media can provide better insight, although they also require standardization. A useful topical formulation may show an initial therapeutic concentration followed by sustained maintenance, but burst release may be acceptable for hemostatic or early antimicrobial needs. Therefore, desired release kinetics should be linked to clinical purpose rather than judged abstractly [2,3].

Sterility and preservation are critical. Open wounds are vulnerable sites, and topical products may be used repeatedly by patients or healthcare workers. Sterilization by gamma irradiation, electron beam, ethylene oxide, filtration or aseptic manufacturing can alter nanoparticle size, polymer structure, drug stability or hydrogel mechanics. A formulation that performs well before sterilization may fail afterward. Therefore, sterilization compatibility should be investigated early. Multidose containers also need microbial preservation strategies, but preservatives may irritate wounds or interact with nanocarriers [9,20].

Biocompatibility testing must go beyond a single cell line. Keratinocytes, fibroblasts, endothelial cells, macrophages and red blood cells may respond differently. A silver nanoparticle concentration that kills bacteria may impair fibroblast proliferation. A cationic nanoparticle may adhere strongly but damage cell membranes. A surfactant in a nanoemulsion may cause irritation even if the active compound is safe. Cytotoxicity, hemocompatibility, inflammatory cytokine response, oxidative stress and genotoxicity may be relevant depending on material class [3,7,8]. Animal studies should include wound models that reflect intended use, such as diabetic, infected, burn or ischemic wounds when relevant.

Manufacturing feasibility is a decisive but underreported issue. Laboratory batches often use small-scale sonication, solvent evaporation, electrospinning or mixing conditions that are difficult to reproduce at industrial scale. Batch-to-batch variability in size, loading and release can undermine regulatory approval and clinical trust. Green synthesis and solvent-free processes are attractive, but they must still deliver consistent quality. For publication-quality formulation research, authors should report process parameters, raw material specifications, stability data and storage conditions. Without these details, a promising material remains a laboratory curiosity rather than a wound-care product [3,8,20].

7. Clinical translation: challenges

Table 3. Translational challenges for topical wound-care nanoformulations

Challenge	Why it matters	Practical mitigation
Nontoxicity	Open wounds may permit local tissue exposure and systemic absorption	Dose-response cytotoxicity, inflammation, hemocompatibility and repeated-application testing
Sterilization	Heat, radiation or chemicals may alter particle size, release or gel strength	Evaluate final sterilized product, not only laboratory prototype
Manufacturing scale-up	Small batches may not predict industrial reproducibility	Define critical quality attributes and process controls
Regulatory classification	Drug-device-biologic combinations create complex dossiers	Engage early with regulatory expectations and document mechanism
Clinical evidence	Rodent closure data rarely proves patient benefit	Randomized trials using advanced standard-care comparators

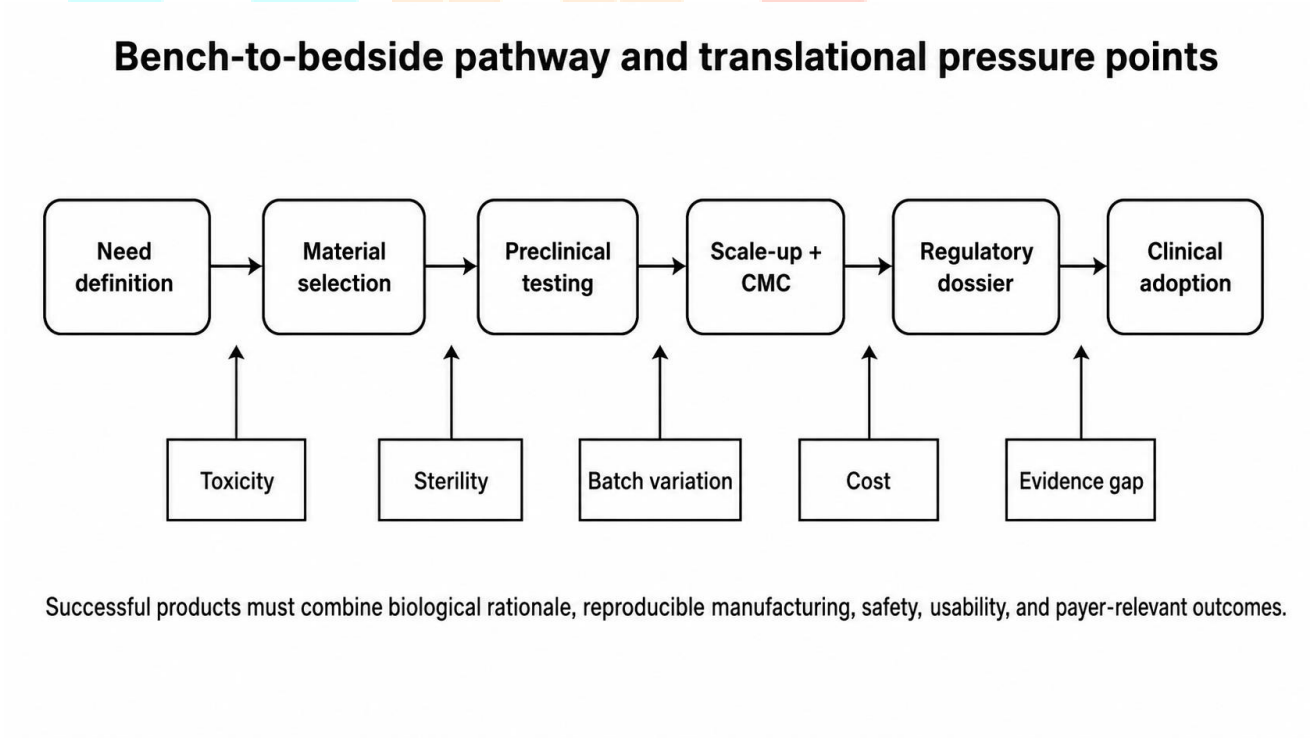

Figure 4. Bench-to-bedside pathway and common translational pressure points for nanoformulation-based wound products. Original schematic prepared for this review.

The gap between experimental success and clinical adoption is wide. Wound healing is influenced by debridement, off-loading, compression, revascularization, glycemic control, nutrition, infection control and nursing practice. A topical nanoformulation cannot overcome untreated ischemia or continuous pressure. Therefore, clinical trials must position the formulation as part of comprehensive wound care rather than as a standalone cure. Endpoints should include time to closure, percentage area reduction, infection control, pain, exudate management, dressing-change frequency, quality of life, cost and recurrence [18,19,20].

Regulatory classification can be complex because many nanoformulation products are combination products. A nanoparticle-loaded hydrogel may function as a device, drug and antimicrobial material at the same time. If it contains a biologic, exosome or growth factor, additional requirements apply. Regulators may request detailed characterization of nanoscale attributes, release behavior, toxicology, degradation, impurities and manufacturing controls. For metallic or persistent nanomaterials, long-term local retention and environmental release may become important. Developers should engage regulatory expectations early rather than designing studies that cannot support approval [3,9].

Safety uncertainty remains a central challenge. Topical application may reduce systemic exposure, but open wounds can permit absorption into tissue or circulation, especially in large burns or ulcers. Particles may be taken up by immune cells, persist in tissue or interact with proteins. Chronic wounds may require repeated application for weeks or months, increasing cumulative exposure. Pediatric, elderly, diabetic, vascular and immunocompromised patients may have altered risk. Safety evaluation should therefore consider intended wound size, duration of use, frequency of application and removal method [1,7,40].

Evidence quality is another limitation. Many published studies compare advanced nanoformulations with blank controls or gauze, which can exaggerate apparent benefit. Clinically relevant comparisons should include standard advanced dressings, antimicrobial dressings, hydrocolloids, alginates, foams, negative pressure therapy adjuncts or approved topical agents where appropriate. Randomized controlled trials are still limited for many emerging platforms. In addition, publication bias favors positive results, and negative safety or scale-up findings are less visible. A realistic review should therefore describe nanoformulations as promising but not yet universally established [2,6,7].

Cost and usability may determine adoption as much as efficacy. A dressing that requires refrigeration, light activation, complex preparation or specialized disposal may not be practical in routine outpatient wound clinics or low-resource settings. Conversely, a stable sprayable nanogel or transparent adhesive hydrogel that reduces dressing changes could provide meaningful value even if its biological mechanism is modest. Patient comfort, odor control, pain during removal, compatibility with compression or off-loading, and ease of nursing use should be incorporated into product design. Opportunities are greatest where nanoformulations solve practical problems that clinicians and patients already recognize [19,20].

8. Opportunities for specific wound categories

Diabetic foot ulcers represent a major target because they combine neuropathy, impaired perfusion, infection risk, oxidative stress and defective angiogenesis. Nanoformulations for this setting may need antimicrobial, pro-angiogenic and anti-inflammatory functions. Transparent hydrogels could permit monitoring, while adhesive systems may reduce trauma. However, diabetic foot management also requires off-loading, vascular evaluation, debridement and glycemic control. Trials should measure wound closure alongside infection, recurrence, amputation-related outcomes and compatibility with standard podiatric care [1,18,32].

Burn wounds require rapid protection, pain control, infection prevention and scar management. Nanofiber mats, silver or zinc nanoparticle dressings, hydrogel sheets and growth-factor carriers have been explored for burns [6,40]. The opportunity is high because burn wounds may have large surface area and heavy exudate, but safety requirements are also high because systemic absorption can occur. Materials must be non-adherent or atraumatic, flexible, sterile and capable of maintaining moisture without encouraging infection. Scar reduction and pigmentation outcomes may require long-term follow-up beyond initial closure [6,40].

Venous leg ulcers and pressure injuries highlight the importance of mechanical and vascular context. A nanodressing cannot replace compression therapy for venous disease or pressure relief for pressure injury. However, nanoformulations may help manage bioburden, exudate, inflammation and pain while standard etiological therapy is applied. Hydrogels, alginates with nanoparticles, and antimicrobial nanofibers may be useful when exudate and bacterial burden are problematic. Clinical studies should report compression or off-loading protocols to avoid confounding [18,20].

Surgical wounds and traumatic wounds may benefit from hemostatic nanofibers, antimicrobial films, adhesive hydrogels and scar-modulating systems. In clean surgical wounds, the threshold for introducing reactive nanomaterials is high because baseline healing is often good. The most useful applications may be high-risk incisions, contaminated wounds, reconstructive procedures and wounds requiring secondary intention healing [10,27]. Endpoints may include surgical-site infection, dehiscence, pain, cosmetic outcome and patient satisfaction. Nanoformulations for surgical use must integrate with sutures, staples, tissue adhesives and postoperative dressings.

Resource-limited settings offer both opportunity and caution. Chronic wound care is expensive, and advanced dressings may be inaccessible. Low-cost nanoformulations based on chitosan, cellulose, natural polymers or phytochemicals could improve care if they are stable, safe and easy to manufacture. However, introducing poorly regulated nanoproducts without adequate quality control could harm patients. The public-health opportunity lies in affordable, standardized, locally manufacturable products supported by transparent evidence rather than in expensive novelty [4,23,36].

9. Future research agenda

Table 4. Suggested reporting checklist for publishable studies

Domain	Minimum details to report	Reason
Nanomaterial identity	Composition, grade, supplier/source, synthesis route, purification	Enables reproducibility and safety interpretation
Physicochemical profile	Size, PDI, zeta potential, morphology, loading, release, pH	Defines critical quality attributes
Wound-relevant testing	Simulated wound fluid, biofilm model, exudate interaction, cytocompatibility	Improves translation beyond simple buffer assays
Product performance	Adhesion, swelling, water vapor transmission, mechanical strength, removability	Connects material function to dressing usability
Clinical pathway	Comparator, endpoints, intended wound type, sterilization, stability, cost considerations	Supports eventual clinical and regulatory adoption

The next phase of topical wound nanomedicine should move from demonstration studies to problem-driven development. Researchers should begin with a defined clinical wound type and unmet need, then select materials and release behavior accordingly. For example, an infected diabetic ulcer requires different design criteria from a clean donor-site wound. Study protocols should include clinically relevant controls, standardized wound area measurement, infection assessment, histology, inflammatory markers and safety endpoints. Where possible, large-animal models or human ex vivo wound models should bridge the gap between rodents and patients [2,6,9].

Standardization is urgently needed. Journals should require complete reporting of nanoparticle size, polydispersity, morphology, charge, loading, release, sterilization, stability and cytotoxicity. Wound-specific release media and biofilm models should be described in detail. For plant-derived nanoformulations, phytochemical standardization is essential. For exosome-inspired systems, source, isolation method, marker profile, potency and storage must be defined. Without such reporting, studies cannot be reproduced or compared [3,4,8].

Combination design should be rational rather than overloaded. It is tempting to add an antibiotic, metal nanoparticle, antioxidant, growth factor and phytochemical to a single dressing, but each

component adds risk, cost and regulatory complexity. A better approach is modular design based on wound phenotype. High-bioburden wounds may receive antimicrobial modules; ischemic wounds may receive angiogenic support; highly exudative wounds may require absorptive matrices; and scar-prone wounds may receive remodeling-focused therapy. Personalized wound dressings may eventually be selected based on wound pH, protease level, bacterial profile and perfusion status [3,20].

Digital and diagnostic integration is an emerging opportunity. Smart dressings incorporating nanosensors could monitor pH, temperature, oxygen, moisture, bacterial metabolites or inflammatory markers. Such data may help clinicians decide when to change dressings or escalate therapy. However, sensor-enabled dressings must be reliable, affordable and interpretable. A sensor that produces data without actionable thresholds may increase complexity without improving outcomes. Combining therapeutic nanoformulations with simple visual or smartphone-readable indicators may be more practical than highly complex electronics in many settings [3,20].

Sustainability and environmental safety deserve greater attention. Nanomaterials released during manufacturing, disposal or dressing changes may enter wastewater or clinical waste streams. Silver and other persistent materials raise particular concerns. Green synthesis, biodegradable carriers, reduced metal loading and safe disposal guidance should become part of product design. The future market is likely to favor formulations that demonstrate not only efficacy and safety for patients but also responsible manufacturing and environmental stewardship [7,8,37].

10. Conclusion

Emerging nanoformulations have the potential to transform topical wound care by shifting treatment from passive coverage to active, localized and responsive therapy. Lipid vesicles, polymeric nanoparticles, metallic nanoparticles, nanofibers, nanoemulsions, nanogels and nanoparticle-loaded hydrogels can improve drug stability, release, antimicrobial performance, moisture balance and regenerative signaling. Their greatest value lies in multifunctional design that matches the biology of difficult wounds, especially infected, diabetic, burn and chronic inflammatory wounds [2,3,6].

At the same time, translation requires discipline. Not every nanoscale material is clinically useful, and novelty does not replace safety, reproducibility or comparative evidence. The most important challenges include cytotoxicity, long-term biocompatibility, sterilization, scale-up, regulatory classification, cost and lack of robust human trials. Future products should be developed through a fit-for-purpose framework that begins with a defined clinical need, uses wound-relevant testing, reports full characterization and compares outcomes with advanced standard care. If these requirements are met, topical nanoformulations can become an important component of modern wound management rather than remaining primarily experimental platforms [2,7,9,20].

Evidence coverage note

This manuscript uses a sequential Vancouver reference list combining foundational wound-healing biology with recent nanoformulation reviews and representative formulation studies. Recent references emphasize nanoparticle-infused hydrogels, lipid vesicles, phytochemical nanoformulations, nanomaterial-enabled wound repair and pharmaceutical nanoformulation design [2-9]. Foundational references support wound physiology, chronic wound burden, extracellular matrix repair, nanofiber delivery, antimicrobial materials and clinical dressing design [10-40].

Declarations

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