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DRUG DISCOVERY AND DEVELOPMENT

HKB PUBLICATIONS

Review

https://doi.org/10.5530/ddd.2.1.4

A comprehensive review on the role of nanomedicine in chronic wound healing

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Chronic wounds remain a major global healthcare challenge due to delayed healing, frequent recurrence, high treatment costs, and reduced quality of life. Conditions such as diabetic foot ulcers, venous leg ulcers, pressure ulcers, and burn wounds often fail to heal effectively with conventional therapies, primarily due to poor drug penetration, inadequate local drug retention, persistent inflammation, infection, and impaired tissue regeneration. Nanomedicine has emerged as a promising approach to overcome these limitations by enabling targeted, controlled, and sustained delivery of therapeutic agents directly to the wound site. Nanocarrier-based systems improve antimicrobial efficacy, promote angiogenesis, regulate inflammation, support extracellular matrix remodeling, and enhance re-epithelialization, thereby accelerating the healing process and reducing scar formation. Preclinical and clinical studies demonstrate improved healing outcomes, reduced infection rates, and better patient compliance with nanomedicine-based wound care strategies compared to traditional treatments. Despite these advantages, challenges such as high production costs, limited large-scale clinical evidence, long-term safety concerns, and complex regulatory pathways remain. This review focuses on the role of nanomedicine in addressing the key pathophysiological barriers of chronic wound healing and discusses its translational potential in advancing regenerative and precision-based wound management.

Keywords: Nanomedicine, Wound, Healing, Chronic, Inflammation

INTRODUCTION

One of the body's largest organs, the skin serves as a vital barrier for perception, control, and protection. However, because of its constant exposure to the outside world, it is prone to damage and injury. The development of chronic wounds, such as diabetic foot ulcers, venous leg ulcers, and pressure ulcers, has grown due in large part to the rising prevalence of obesity, vascular insufficiencies, and chronic illnesses. These wounds are associated with high morbidity and economic burden[1]. Despite decades of improvements in wound dressings, conventional therapies place more emphasis on healing than true regeneration[2]. Traditional treatments can be helpful for acute wounds, but they are still ineffective for chronic wounds due to their limitations in medicine penetration, dosing accuracy, and extended therapeutic effectiveness. The latest developments underscore the increasing significance of medication-focused, precision-driven approaches in wound healing[3]. Nanoparticles' distinct physicochemical characteristics allow for targeted and regulated interventions at the molecular and cellular levels, making nanotechnology in particular a promising field[4]. For the treatment of complex wounds, such as large-area skin loss, burns, ulcers (pressure, diabetic, neuropathic, ischemic), traumas, and infected

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Received 2 December 2025 | **Revised** 18 February 2026 | **Accepted** 20 February 2026

wounds frequently brought on by microbial colonization, precise delivery of antimicrobials and bioactive substances is receiving attention[5,6].

This review offers a comprehensive overview of nanomedicine-based approaches to chronic wound healing, highlighting novel drug delivery methods, mechanisms of action, translational potential, current obstacles, and prospects for individualized and regenerative wound care in the future[7].

Epidemiology & burden of chronic wounds

A major public health concern that has a big social and economic impact is chronic wounds. About 2-2.5% of people worldwide suffer with chronic wounds, which impair movement, cause discomfort, and lower quality of life. Because of the aging population and rising comorbidities, the anticipated yearly cost of wound care in the United States has reached US$28-31.7 billion and is expected to continue to climb, reaching almost US$148 billion in 2022[8,9].

According to recent community-based studies, the frequency in India is between 1.9 and 4.5 per 1,000 people. With a median yearly out-of-pocket expense (OOPE) of almost Rs. 29,775 (USD 320) per patient, diabetic foot ulcers pose a serious financial burden. By resulting in chronic pain, limited mobility, disturbed sleep, and psychological discomfort, chronic wounds also have a significant negative impact on quality of life[10-12].

Wound categories and process of wound healing

Wound categories: A wound is defined as a skin rupture or irregularity brought on by trauma or medical/physiological conditions; in these situations, the skin's anatomical structure is typically harmed, and the unpleasant occurrence of skin physiologic capacities usually occurs. Injuries that cause the skin or other body tissues to break are called wounds. These include skin punctures, wounds, and scratches. Wounds can result from surgery or sutures, although accidents are the most frequent cause[13]. Even though minor wounds are typically not real, they nevertheless need to be cleaned. Acute and chronic wounds are the two categories into which the majority of injuries fall. While chronic wounds persist longer than three months and are often caused by diabetes, venous insufficiency, or infection, acute wounds are usually caused by trauma or surgery and heal in a predictable length of time. Chronic wounds typically occur from a few specific infections, such as diabetes, which is notorious for its severe ulcers. These wounds take longer to heal and are more likely to return if the underlying infection is not addressed. Typical wound types are listed in Table 1[14].

Wound healing mechanism

Wound healing is a dynamic and continuously regulated physiological process involving multiple cell types, proteinases, growth factors, and extracellular matrix (ECM) components[15]. In healthy skin, the epidermis (outer epithelial layer) and dermis (inner connective tissue layer) function as a protective barrier against external insults. Disruption of this barrier triggers a cascade of coordinated biological responses aimed at restoring tissue integrity.

Wound healing does not occur in a strictly linear manner; instead, it proceeds through overlapping phases, including hemostasis, inflammation, proliferation, and remodelling.

Table 1. Comparative table of major chronic wound types

Wound type	Etiology	Healing difficulty	Clinical challenge
Diabetic foot ulcer (DFU)	Peripheral neuropathy, ischemia, impaired angiogenesis, hyperglycemia	Very difficult; slow healing due to poor vascularization & infection risk	High recurrence, infection risk, limb amputation, requires strict glycemic control
Venous leg ulcer (VLU)	Chronic venous insufficiency, venous hypertension, edema	Moderate to difficult; recurrence common	Requires compression therapy, prone to chronic inflammation, high recurrence rate
Pressure ulcer (Decubitus ulcer)	Prolonged pressure, shear forces, ischemia in immobile patients	Difficult in advanced stages; delayed granulation	Often in elderly/bedridden patients, risk of infection, costly long-term care
Arterial ulcer	Atherosclerosis, arterial occlusion, ischemia	Very difficult; poor blood supply limits healing	Requires vascular intervention, severe pain, high risk of tissue necrosis
Burn wound	Thermal, chemical, or electrical injury	Healing varies by depth; deep burns heal poorly	Large surface area, fluid/ electrolyte imbalance, infection risk, scarring
Infected/Contaminated wound	Microbial invasion (bacterial, fungal, polymicrobial)	Healing severely delayed until infection resolved	Antimicrobial resistance, biofilm formation, recurrent infections

Hemostasis often overlaps with the early inflammatory phase rather than existing as an entirely separate stage, highlighting the dynamic nature of wound repair (Fig. 1)[16].

Inflammation stage

The period of inflammation following skin injury usually lasts between two and five days. Immediately after an injury, intravascular platelets start hemostasis to form a clot and stop death[17]. Furthermore, thrombin will activate platelets, which will release several growth factors, such as insulin-like growth factor 1 (IGF-1), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), transforming growth factors (TGF-α and TGF-β), and insulin-like growth factor 1 (IGF-1)[18]. These growth factors act as biological signalling molecules that recruit neutrophils, monocytes, leukocytes, and macrophages to the wound site. These inflammatory cells remove necrotic tissue and microbial contaminants, protect against infection, and secrete additional cytokines and growth factors that regulate subsequent phases of healing[19,20]. Persistent or excessive inflammation is a key factor contributing to impaired healing in chronic wounds.

Proliferative phase

The proliferative phase usually takes place three days to two weeks after injury and is characterised by cell migration and proliferation[21]. Eventually, proangiogenic chemicals such as PDGF, which are secreted by inflammatory cells and platelets inside the injury zone, develop modern blood arteries and capillaries. Apart from angiogenesis, the synthesis of PDGF and FGF by inflammatory cells initiates fibroblast migration to create granulation tissue[22,23]. The proliferation and aggregation of fibroblasts transport the extracellular matrix (ECM), which is made up of elastin, collagen, and proteoglycans. Fibroblasts synthesize and deposit extracellular matrix components such as collagen, elastin, and proteoglycans. Some fibroblasts differentiate into myofibroblasts, facilitating wound contraction.

Re-epithelialization occurs concurrently during this phase, wherein keratinocytes from the wound edges migrate and proliferate to restore the epidermal layer, ultimately contributing to wound closure[24].

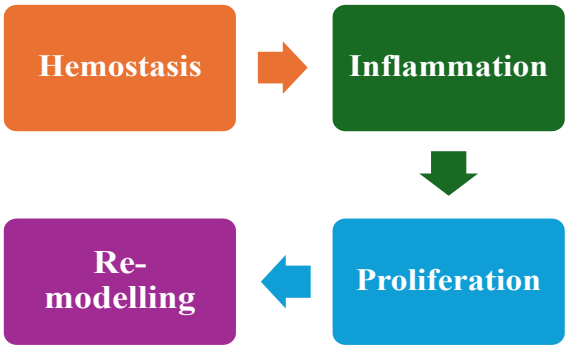

Figure 1. Mechanism of wound healing

Re-epithelialization stage

The remodelling (maturation) phase may persist for several weeks to up to two years following injury. During this stage, collagen type III is gradually replaced by collagen type I, and newly formed collagen fibers are reorganised into a stronger and more aligned structure, resulting in increased tensile strength of the healed tissue[25-27].

Re-epithelialization is essential for restoring the epidermal barrier but does not directly cause scar formation. Scar development primarily results from extracellular matrix remodelling and collagen reorganisation during the remodelling phase. Abnormal or excessive scarring is often associated with dysregulated remodelling and prolonged inflammation rather than re-epithelialization itself.

Drug delivery systems in wound healing

A significant worldwide issue at the moment is chronic and infected wounds. An excellent opportunity to stop illnesses or enhance the efficacy of already available treatments is presented via drug delivery systems (DDS) that deliver antibacterial and anti-inflammatory drugs as wounds heal. In order to treat wounds and deliver drugs to the wound site, a variety of biocompatible biomaterials have been extensively researched. Various biomaterials, such as hydrogels, scaffolds, lipid nanoparticles, polymeric microspheres and nanospheres, and nanofibrous structures, have been used in more extensive research to develop drug delivery methods[28,29] (Fig. 2).

Delivery of antibiotics

The wound healing process is complex and often requires the use of antibiotics to control or prevent bacterial infection. However, conventional antibiotic therapy may suffer from poor local drug retention, frequent dosing, and systemic side effects. To overcome these limitations, antibiotic drug delivery systems (DDS) have gained attention for improving the therapeutic efficiency of existing antibiotics.

Several antibiotics have been incorporated into wound delivery systems, including cefazolin[30], gentamicin sulphate, ceftazidime pentahydrate[31], ciprofloxacin[32], gentamicin[33], doxycycline hyclate[34], and the anti-inflammatory drug diclofenac. Biodegradable polymer-based scaffolds such as electrospun nanofibers, microspheres, composite matrices, and films have been widely explored for antibiotic delivery. These include electrospun poly(lactide-co-glycolide) (PLGA) nanofibers, porous polyamide and polyglycolide core-shell systems, polycaprolactone-tricalcium phosphate (PCL-TCP) networks, polyvinyl alcohol-based matrices, and chitosan (CS) gel composite films. These systems allow localized and sustained antibiotic release, thereby reducing dosing frequency and systemic exposure[35]. Other delivery components include antibacterial agents and

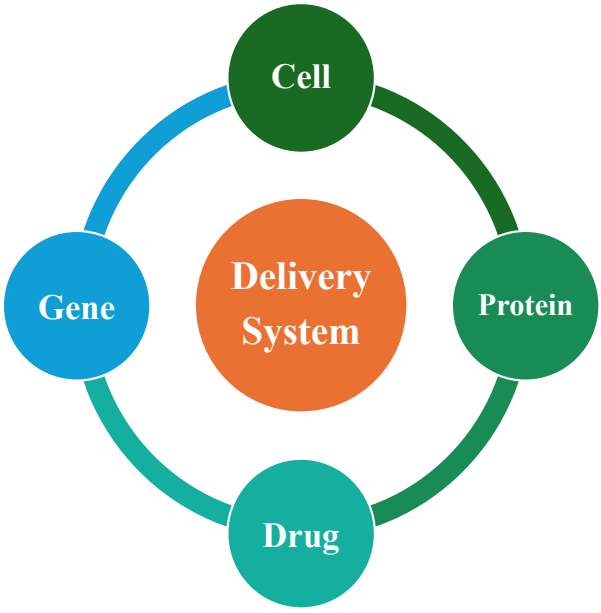

Figure 2. Delivery of drugs

antibiotic-loaded microspheres, such as β-cyclodextrin-linked hyaluronic acid hydrogels and electrospun poly(3-hydroxybutyrate) (PHB) fibers[36]. Despite their effectiveness, many antibiotics used in wound treatment are associated with adverse effects, including hemolysis caused by certain antibacterial polymers, cytotoxicity associated with ciprofloxacin, and nephrotoxicity linked to vancomycin. Encapsulation of antibiotics within polymeric carriers has been shown to reduce these toxic effects by limiting uncontrolled drug exposure[37]. Recent studies have reported the development of enzyme-responsive polymer vesicles designed to release antibiotics selectively in the presence of bacterial enzymes such as penicillin G amidase (PGA) and β-lactamase (BLA), which are commonly produced by drug-resistant bacterial strains. Such systems provide prolonged and controlled antibiotic release, improving drug stability and reducing adverse effects. Antibiotics delivered from BLA-degradable polymer vesicles demonstrated effectiveness against methicillin-resistant *Staphylococcus aureus* (MRSA) by enhancing wound healing and inhibiting bacterial growth in in vivo models[38].

Delivery of silver

Wound infections caused by drug-resistant bacteria represent a major challenge in chronic wound management. Silver has been widely used as a broad-spectrum antimicrobial agent due to its ability to inhibit bacterial growth through multiple mechanisms, thereby reducing the risk of resistance development. Silver does not function as an antibiotic but exerts its antimicrobial effect by disrupting bacterial cell membranes, interacting with proteins and enzymes, and interfering with DNA replication.

Various silver-containing wound dressings have been developed, including colloidal silver solutions, silver protein complexes, silver salts, silver sulfadiazine (SSD), and nanosilver formulations. These dressings have been shown to reduce microbial burden and support wound healing[39]. Silver nanoparticles (AgNPs), commonly referred to as nanosilver, can be synthesized using methods such as chemical reduction, microbial reduction, microwave-assisted photochemical reduction, and laser ablation.

AgNP-embedded poly(vinylpyrrolidone) (PVP) hydrogels prepared using gamma irradiation at doses of 25, 35, and 45 kGy have demonstrated strong antibacterial activity, with hydrogels containing 1 mM and 5 mM AgNPs achieving up to 99% bacterial reduction in vitro. Gamma-irradiated polyvinyl alcohol (PVA)/nanosilver hydrogels have also been developed for potential use in burn wound therapy. Additionally, Pluronic F127 gels containing 0.1% w/w AgNPs have shown enhanced wound healing activity[40].

Porous silver microparticles (AgMPs) with a high surface area have also been investigated as alternative antimicrobial agents. Highly porous AgMPs or AgNPs can be effectively incorporated into polylactic acid (PLA) nanofibers, allowing controlled silver ion release. These nanofiber dressings have demonstrated antibacterial activity against *Staphylococcus aureus* while supporting keratinocyte growth[41].

Chitosan, a natural polymer with intrinsic antibacterial, hemostatic, and immune-modulating properties, has been widely used in wound healing applications. Chitosan-based wound dressings can be fabricated as gels, sponges, and micro- or nanoparticles[42]. The combination of silver and chitosan has been shown to enhance antimicrobial effectiveness. Silver-containing chitosan-tripoly-phosphate (TPP) hydrogels form antibacterial barriers, where AgNPs are stabilized within the chitosan matrix. Biocompatibility studies using fibroblast (NIH-3T3) and keratinocyte (HaCaT) cell lines confirmed no significant cytotoxicity, while maintaining strong bactericidal activity. Composite scaffolds composed of nanosilver and chitin have also demonstrated effective blood clotting ability and antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*[43].

Delivery of other drugs

Silver's usefulness in combination with other drugs, such as astragaloside IV, an anti-scarring drug, to encourage wound healing. In a rat model of skin excision, the in vivo control of 9% astragal side IV-based solid lipid nanoparticle gel prevented scar formation in vivo by enhancing the rate of wound closure ($P < 0.05$), encouraging keratinocyte migration and proliferation, and boosting drug uptake in fibroblasts in vitro through the caveolae-endocytosis pathway ($P < 0.01$). Curcumin functions differently from most antibiotics, which promote bacteria that are resistant to them. Curcumin's antioxidant and anti-inflammatory

qualities enable it to have a complex and active regulatory role in inflammatory, neurological, cardiovascular, Alzheimer's, and cancer conditions. Wound healing is further aided by its natural antimicrobial properties. However, therapeutic application of natural curcumin is hindered by its limited solubility, physicochemical instability, lack of bioavailability, rapid metabolism, and poor pharmacokinetics; these problems could be addressed with an effective delivery system[44]. Using a biodegradable sponge made of sodium alginate (SA) and chitosan (CS), which has a 1000-4300% water absorption capacity, curcumin can be applied as a wound dressing for up to 20 days. Curcumin is found to be more effective than cotton gauze at enhancing the compound's surface in experiments conducted on SD rats, an in vivo animal model of the sponge[45]. The creation of Curc-np, a minuscule nanoparticle with a 222 ±14 nm normal diameter, has demonstrated effectiveness in lowering the load of bacteria and the antibacterial action of MRSA. Research using DNA culture on mice (Neomycin) confirmed this finding and shown how well it works to eradicate infections. *P. aeruginosa* may be a new topical antibacterial and emollient for wound healing in chronic scars along with other tissue lesions. It depends on the dosage. Drug loading and controlled release are two applications for bacterial cellulose (BC)[46]. Topical or transdermal drug delivery systems have been developed for two model medications: lidocaine hydrochloride and ibuprofen. Adding lidocaine hydrochloride to BC membranes reduced penetration rates when compared to conventional formulations, according to diffusion experiments conducted using Franz cells[47]. Due to poor angiogenesis caused by decreased HIF-1 alpha activation, patients with diabetes and severe pressure ulcers have a higher mortality rate. The term "hypoxi-inducible factor" refers to this.

Current wound treatment

The major objectives of wound care are to minimize pain and scarring, speed up the healing process, and prevent dangerous infections. Although there are other approaches to wound healing nowadays, the three primary ones are autolytic grafts, debridement, and the use of therapeutic medications (Table 2). Additionally, a variety of novel therapies, such as gene therapy, stem cell therapy, and photothermal and photodynamic therapy, are becoming increasingly important in the treatment of complex wounds.

Debridement

Traditional debridement may prolong inflammation, hinder wound healing, and prevent wounded tissue from contracting and re-epithelializing if necrotic or diseased tissue is removed[48]. In debridement treatments, such as mechanical, maggot, enzymatic, autolytic, and surgical methods, an extra wound dressing is typically employed[49]. Sharp debridement, in particular, is considered the gold standard for quickly removing necrotic tissue and preventing infection; however, it has a number of disadvantages, such as the requirement for a physician and the use of specialist materials to minimize secondary injury[50]. The method employed necessitates a thorough evaluation of the patient's traits, the unique features of the wound, and the available therapeutic options[51].

Autografts and allografts

Autografts and allografts remain the gold standard despite advancements in skin regeneration. Autografting uses tissue from the patient's own body, while allografting uses tissue from another individual. During autograft and allograft procedures, full-thickness fascia from the patient's or another donor's donor site is often removed and transplanted into the intended region[52]. Autografts are thought to have a very high incidence of wound adhesion, significantly lessen discomfort, and produce better cosmetic effects. Its application is limited by the severe extraction points requirements. Moreover, skin transplants of this type result in expensive hospitalization, significant skin contracture, and unfortunate scarring in the later phases of wound healing. The ability of allografts to temporarily stop the drying and polluting processes of wounds, as well as their great wound tolerance, are their main advantages. However, the resource-intensive transplant procedure carries a risk of infectious disease transmission and increased immunological rejection. While in-situ biofabrication of skin substitutes, such as tissue-engineered skin substitutes and cultured epithelial autographs, is showing promise, traditional autogenesis has limits[53].

Delivery of topical drugs

Topical drugs are still widely used in wound care to encourage healing and prevent infection. As a result, there is still much work to be done in developing new topical treatments for wound healing. Topical therapeutic medications that support wound healing and skin renewal include growth factors and antibacterial agents. These medications are quite effective. Development factors are strong and effective polypeptides that regulate cell migration, differentiation, and development, hence affecting all phases of wound healing. Growth factors have been shown in numerous clinical investigations to have a remarkable ability to promote wound healing and restore skin function without causing any noticeable side effects[54].

Gene delivery in wound healing

Gene transfer is a developing tissue repair strategy that can accelerate wound healing by delivering genes that promote angiogenesis, reduce fibrosis, or enhance cell proliferation. The main goals of gene delivery are to achieve sustained release, minimize side effects, and control spatial and

Table 2. Current wound treatments - benefits and limitations

Treatment	Benefit	Limitation	Clinical status
Debridement (surgical, enzymatic, autolytic, mechanical)	Removes necrotic tissue, reduces infection risk, promotes granulation	Painful, may damage healthy tissue, requires repeated sessions	Widely practiced; standard of care in chronic wounds.
Autograft (patient's own skin)	Gold standard; low risk of rejection, promotes natural healing	Donor site morbidity, limited availability, invasive procedure	Clinical gold standard for large/deep wounds.
Allograft (donor skin)	Provides temporary wound coverage, reduces fluid loss & infection risk	Risk of immune rejection, disease transmission, expensive	Used as temporary cover, especially in burns.
Topical drugs (antibiotics, antiseptics, growth factors, corticosteroids)	Easy application, localized effect, reduces systemic side effects	Poor penetration, drug resistance, short-term efficacy	Widely used but limited for chronic wounds.
Synthetic dressings (hydrogels, foams, alginates, collagen dressings)	Maintain moist environment, protect wound, aid autolysis	Expensive, may require frequent changes, limited bioactivity	Commercially available; supportive therapy
Negative Pressure Wound Therapy (NPWT)	Promotes angiogenesis, reduces edema, improves granulation	Requires device, costly, not suitable for all wounds	Approved for chronic & post-surgical wounds

temporal gene expression[55]. However, direct delivery of nucleic acids (DNA or RNA) is limited by poor stability, low cellular uptake, and potential toxicity, especially when viral vectors are used.

Nanocarrier-based systems, including hydrogels, scaffolds, micro/nanoparticles, and electrospun fibers composed of lipids or cationic polymers, protect the genetic material and allow controlled, localized delivery, making gene therapy more effective and safer.

Viral vectors in gene delivery

Viral vectors such as lentivirus and adenovirus have been used to deliver therapeutic genes. For example, mutant TGFβ3 (mutTGFβ3) delivered via lentiviral vectors reduced fibroblast density and scar formation in a mouse skin injury model[56]. Adenoviral vectors have been used to study gene kinetics in vivo, with luciferase expression peaking on day 7. Genes such as Ecrg4 have been delivered to the dermis, epidermis, and hair follicles to promote regeneration[57].

Non-viral vectors in gene transfer

Non-viral delivery uses biocompatible carriers to reduce toxicity and improve gene stability. Fibrin and collagen scaffolds can deliver microRNAs or plasmid DNA for regulating extracellular matrix remodelling and enhancing re-epithelialization[58]. Alginate gels allow sustained release of bioactive molecules such as VEGF for diabetic wound care.

• Nanoparticle-assisted delivery improves gene transfer efficiency. For example: Silver nanoparticles (AgNPs) functionalized with chitosan-g-polyacrylamide and PEG can carry DNA safely, and RGDS peptide modification enhances transfection efficiency in HeLa and A549 cells.

• Cationic dendrimers (PAM-RG4) and biodegradable poly(β-amino) esters (PBAE) have been used to deliver VEGF or KGF plasmids to mouse adipose-derived stem cells[59].

In summary, integrating gene delivery into nanocarrier-based approaches allows controlled, targeted, and safer gene therapy, which can improve wound healing outcomes while reducing side effects compared to traditional viral or naked gene delivery methods.

Types of nanocarriers & mechanism

The numerous wound healing mechanisms, such as antibacterial activity, scavenging of reactive oxygen species, promoting angiogenesis, extracellular matrix (ECM) remodelling, and sustained local medication delivery, have been proven by nanocarrier-based systems. Major nanocarriers, their payloads, methods, benefits, and drawbacks are compiled in the following table[60-61].

A comparative summary of nanotechnology-based drug delivery systems for wound healing, their therapeutic roles, advantages, and limitations is presented in Table 3.

Future directions and innovations

Novel approaches to treating chronic and infected wounds are being made possible by recent developments in nanotechnology, biomaterials, and regenerative medicine. Intelligent, multipurpose, and patient-specific wound management systems that can offer simultaneous therapeutic and diagnostic capabilities are the path this industry is headed toward in the future.

• One of the most fascinating areas is the development

Table 3. Nanotechnology-based drug delivery systems for wound healing[62]

Nanocarrier / Material	Drug / Agent Delivered	Therapeutic Role	Mechanism of action	Advantages	Limitations
Polymeric nanoparticles (PLGA, PCL, chitosan)	Antibiotics (ciprofloxacin, gentamicin), growth factors	Antimicrobial, angiogenesis, ECM remodeling	Protect drugs, enable controlled release, enhance cellular uptake at wound site	Controlled release, biocompatibility, reduced toxicity	Possible burst release, high cost
Lipid nanoparticles (SLNs, NLCs)	Silver sulfadiazine, curcumin, anti-scarring drugs	Antibacterial, antioxidant, scar prevention	Encapsulate drugs in lipid core, improve solubility, facilitate diffusion into tissue	High drug loading, sustained release, good stability	Limited penetration in deep wounds
Nanofibers (electrospun)	Antibiotics, silver NPs, herbal extracts	Infection control, moisture balance	Provide scaffold for cell growth and sustained drug release via high surface area	Large surface area, mimics ECM, customizable porosity	Mechanical fragility, scale-up challenges
Hydrogels (natural/ synthetic)	Growth factors (EGF, PDGF), antibiotics, AgNPs	Moist healing, cell migration, antibacterial	Swell to maintain moist environment, release drugs via diffusion or stimuli (pH, temperature)	Biocompatible, stimuli-responsive (pH, temperature)	Poor mechanical strength, dehydration risk
Microspheres / Microsponges	Corticosteroids, antibiotics	Sustained release, anti-inflammatory	Encapsulate drugs in porous structure for gradual diffusion	Long-term stability, controlled drug diffusion	Limited to small molecules
Silver nanoparticles (AgNPs)	Nanosilver incorporated into hydrogels or scaffolds	Broad-spectrum antibacterial, accelerates healing	Release silver ions that disrupt bacterial membranes, proteins, and DNA	High efficacy against resistant bacteria, cost-effective	Cytotoxicity risk at high dose
Gene delivery systems (viral & non-viral)	VEGF, TGF-β, siRNA, miRNA	Angiogenesis, scar reduction, ECM remodeling	Protect and transport nucleic acids into target cells, enabling gene expression or silencing	Long-term regeneration, personalized therapy	Safety issues, low efficiency (non-viral)

of intelligent wound dressings with biosensors that can continuously monitor wound parameters like pH, temperature, moisture content, and bacterial load. These systems can be used in conjunction with stimuli-responsive drug delivery platforms, such as pH-sensitive hydrogels, thermoresponsive polymers, or enzyme-triggered nanoparticles, which release therapeutic agents only in response to pathological changes, to reduce unnecessary drug exposure and side effects.

• Personalized wound care is an additional novel strategy that makes use of artificial intelligence (AI) and machine learning. Customized drug combinations, optimal dosages, and dressing compositions based on patient-specific information, including genetic background, comorbidities, and wound microbiota composition, could optimize therapeutic outcomes.

• True tissue regeneration, as opposed to merely repair, is possible when stem cell therapy is combined with cutting-edge delivery methods. When enclosed in protective nanofibrous scaffolds or injectable hydrogels, mesenchymal stem cells (MSCs) and triggered pluripotent stem cells (iPSCs) can release growth factors and cytokines continuously, stimulating angiogenesis, collagen synthesis, and epithelialization.

• It is anticipated that 3D bioprinting will be essential to wound care in the future because it will make it possible to fabricate skin substitutes on-site that include extracellular matrix components, numerous cell types, and implanted medication reservoirs for controlled release. While incorporating antibacterial and regenerative qualities, these bio-fabricated constructions could mimic the structural and functional complexity of natural skin.

• Finally, a path to environmentally friendly, highly biocompatible dressings with adjustable mechanical and biological properties is provided by the development of bioinspired and sustainable materials, such as silk fibroin,

marine polysaccharides, and plant-derived nanocellulose. The goal of these developments is to replace supportive treatment in wound care with active, regenerative, and adaptive therapy.

Case and success studies in wound healing with nanomedicines

Nanocrystalline silver dressings in burn wounds: In 2021, a single-center, randomized clinical trial in Brazil evaluated 1% silver sulfadiazine and nanocrystalline silver dressings for 100 adult burn patients. Both groups experienced similar wound re-epithelialization after 15 days (48% vs. 52%, $p = 0.56$). The nanocrystalline silver group required fewer dressing changes (mean 4.1 vs. 9.6, $p < 0.001$), reducing the treatment burden. There were no documented side effects, and both therapies were safe and well tolerated. The overall cost of nanocrystalline dressings was higher[63].

Silver colloid dressings in diabetic foot ulcers: A prospective, double-blind randomized trial (2024) compared silver colloid dressings with traditional saline dressings in 50 patients with non-ischemic diabetic foot ulcers. The silver group showed greater reduction in ulcer area (67.8% ± 17.8%) than the control group (21.7% ± 23.5%), and shorter mean healing time (23.2 vs. 48.4 days). By day 14, the ulcer area reduction was 48% in the silver group, compared to 10-12% in controls[64].

Chitosan nanogel in chronic diabetic foot ulcers: The CHITOWOUND study (2024) assessed a chitosan-based nanogel (ChitoCare®) in patients with chronic diabetic foot ulcers over 10 weeks. The nanogel group achieved a higher rate of complete wound closure than the placebo group, without any side effects, showing the promise of biopolymer-based nanomedicines for persistent wounds[65].

Limitations of nanomedicines in chronic wounds

Limited clinical evidence: The majority of studies that are currently accessible are pilot or single-center RCTs with brief follow-up periods and limited sample numbers. For instance, systematic evaluations found no discernible overall improvement in the healing effects of nanosilver dressings for diabetic foot ulcers[66].

High cost of advanced dressings: Although nanocrystalline silver dressings are less frequent than traditional dressings or silver sulfadiazine, they are nevertheless more costly. There is still uncertainty regarding cost-effectiveness in extensive clinical use.

Heterogeneity of study outcomes: Clinical trials employ a variety of endpoints, including as microbial load, wound size reduction, and epithelialization, which makes cross-study comparability challenging[67].

Unclear long-term safety: Inadequate information on systemic absorption, nanoparticle retention, and potential cytotoxicity with repeated usage. Changes in wound microbes and microbial resistance are causes for concern.

Patient and wound variability: Diabetes, vascular disease, infection, and inadequate perfusion are some of the multiple contributing factors to chronic wounds. This heterogeneity makes generalisation more difficult since it results in uneven reactions to nanomedicine treatments[68].

Conclusions

Chronic wounds continue to present a major burden to patients and healthcare systems worldwide, largely due to delayed healing and the shortcomings of conventional therapies. By making it possible for medicinal chemicals to be delivered in a targeted, regulated, and sustained manner, advances in nanomedicine have brought about creative solutions. Numerous nanocarriers, such as hydrogels, nanoparticles, nanofibers, and formulations based on silver, have shown great promise in hastening wound closure, lowering infection, and promoting tissue regeneration. Widespread clinical adoption is still hampered by issues like high production costs, complicated regulations, a lack of large-scale clinical data, and worries about long-term safety, despite promising preclinical and clinical results. Future directions suggest the creation of 3D bioprinted skin substitutes, smart, sensor-integrated dressings, and AI-guided tailored treatment plans, which could revolutionize wound care by making it more accurate and regenerative. All things considered, nanomedicine is a potential new area in the treatment of chronic wounds; however, more multidisciplinary research, strong clinical validation, and clear regulations are needed before it can be successfully implemented into everyday practice.

Conflict of interest

The authors declare no conflict of interest.

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