

*Review article*

**Nano formulation for wound healing**

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**Abstract:**

Skin injury is one of the most common lesions that people have to face, and some wounds, such as infected wounds and extensive burns, are notably difficult to heal. Nano formulations based wound healing has tremendous potential for treating and preventing wound infections with its multiple benefits compared with traditional treatment approaches. Nanotechnology presents a once-in-a-lifetime potential to revolutionize and invent new cures, as well as improve the efficacy of existing medical treatments. Nano-drug delivery methods, in particular, anchor bioactive molecules to the treated area, maintain drug release, and expressly improve drug therapeutic efficacies, making such a fine figure in the field of skin regeneration. This creates awareness regarding and addressed the existing nano-drug delivery systems with tremendous possibilities for wound healing and skin regeneration, with a focusing on liposomes, polymeric nanoparticles, inorganic nanoparticles, lipid nanoparticles, nanofibrous and nanohydrogel.

**Keywords**

Nano formulations, wound healing, nanofibers, nanoparticles.

**Introduction:**

**Wounds:** Wounds result from disruption of the normal anatomical epithelial lined tissue barriers and may be caused by trauma, tissue resection, or burns <sup>[1]</sup>. Some wounds are failed to heal in a less time and become chronic. This occurs in conditions such as diabetes or peripheral vascular disease. Failure to heal might also result from post-operative wound infections which are estimated to affect up to 4% of patients who undergo surgery. Chronic non-healing wounds

represent a growing health and economic burden and are associated with a high morbidity that adds significantly to the cost of medical care <sup>[2]</sup>. The gold standard for the treatment of non-healing skin wounds is the transplantation of autologous skin. Clearly, there is a need to develop strategies to promote wound healing and prevent scarring <sup>[3,4]</sup>.

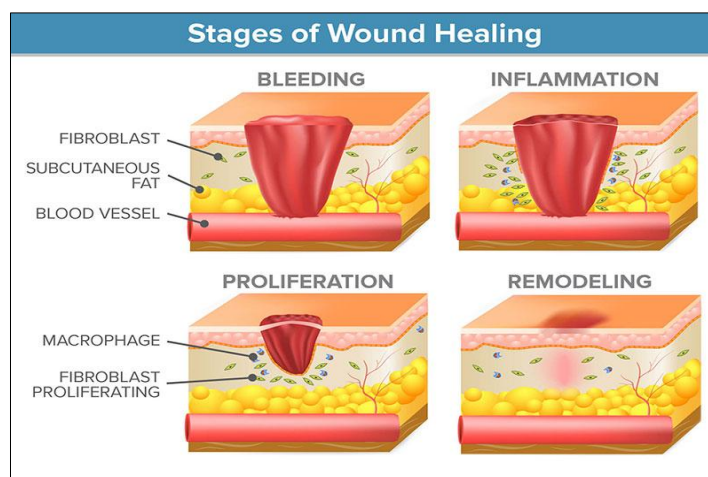
**Types of Wounds:** Wounds are classified into two categories: acute and chronic wounds <sup>[5]</sup> depending on the methods and duration of the healing process.

Acute wounds: Wounds resulting from corrosive chemicals, radioactivity, mechanical injury, heat, or electrical shock, they usually heal with proper wound-care treatment in a fairly short period of time. Chronic wounds are associated with specific diseases like diabetes mellitus, and do not follow the orderly set of stages and predictable amount of time that characterize the normal wound-healing process. Chronic wounds frequently remain in the inflammatory stage for a long time, and their duration is associated with factors like bacterial load, necrotic tissue, and moisture balance of the wound site. Later, the risks of this regeneration of chronic wounds are high, unless the root of the disease is cured <sup>[6]</sup>. Sometimes chronic wounds can never heal or it may take many years to heal.

Wounds classification according to wound depth:

- i) Superficial wounds, which lost a part of epidermis
- ii) Partial thickness wounds, here deeper dermal and epidermis layer are affected
- iii) Full thickness wounds, here the deeper tissue and subcutaneous fat are ruptured <sup>[7,8]</sup>.

**Wound healing:** Wound healing is a dynamic response to injury. In addition, mast cells and macrophages play a crucial role in repairing wounds <sup>[9]</sup>. Wound healing is divided into three stages which overlap in time (figure) - haemostasis and inflammation; proliferation; and remodelling and maturation. Irrespective of the cause of their infliction, all wounds go through these three phases <sup>[10]</sup>.



**Figure: stages of wound healing**

Haemostasis occurs just after the injury it utilizes clotting factors which prevent further blood loss from the wound site and structural foundation for the future formation of granulation tissue. The inflammation phase involving phagocytic cells that release reactive oxygen species, it may last for up to seven days in acute wounds and longer in the chronic wounds.

As inflammatory cells undergo apoptosis and wound healing progresses to the phase of proliferation, that is characterized by the formation of granulation tissue, wound contraction, angiogenesis (blood vessel formation) and the epithelialization process. The remodelling phase, that is characterized by the formation of scar tissue and it may occur over a period of months and or years, depending on the initial severity of the wound, method of treatment and location. <sup>[11]</sup>

**Nanotechnology:** By downscaling to nanometric range, a particle's surface increases exponentially, whereas its volume decreases, which leads to particular physicochemical characteristics that account for numerous medical applications. The shape and size of nanoparticles are important properties that determine their biological efficiency by influencing active substance delivery, penetrability and cellular responses.

Nano-drug delivery system in wound treatment and skin regeneration Nano-DDSs hold immense potential in enhancement of drug therapeutic efficacy for their capability of preventing drug degradation and sustaining drug release. Nano-DDSs including lipid nanoparticles, liposomes, nanohydrogel, polymeric nanoparticles, inorganic nanoparticles, nanofibrous structures <sup>[12-14]</sup>.

Nano-DDSs clearly speed wound healing and increase healing quality due to the numerous benefits they provide <sup>[4,5]</sup>:

- i) Nano-DDSs have been discovered to be non-toxic, skin-compatible, and to facilitate wound healing activation and acceleration by offering a moist environment.
- ii) Some nano-DDSs have the ability to overcome cellular barriers and reach the cytoplasmic space, as well as activate specific transport systems to promote drug retention.
- iii) When combined with bioactive molecules, nano-DDSs shield pharmaceuticals from protease-mediated degradation in wounds, significantly improving therapeutic efficacy.
- iv) Sustained drug release minimizes the frequency of administration, lowers expenditure, and appropriately address while extending the maintenance of an active therapeutic content. In this systematic review, nanotechnologies are examined with reference to wound healing.

**Recent researches of nano-DDSs are listed in following table**

**Table: Recent research of nano-drug delivery system in wound treatment and skin regeneration**

<b>Formulation</b>	<b>Drug</b>	<b>Administration</b>	<b>Outcome</b>
Deformable liposomes	Curcumin	Topical treatment, once a day for 18 days	Shorten inflammatory process, prevent infection and promoted fibrosis, angiogenesis, re-epithelialization and wound contraction [49].
Nanoparticles	Thrombin	Topical treatment	Advanced process of healing, improved skin tensile strength, reduced complications in surgery [28].
Hydrogel loading nanoparticles	Asiatic acid/ZnO/CuO	Topical treatment	Raised DNA, total protein, hexosamine and hydroxyproline content and rendered superior re-epithelization, collagen fibres arrangement and angiogenesis [53].
Microspheres /scaffold	Mupirocin	Applied topically, covered and tied	Combated infection and stimulated fibroblast proliferation and dermal collagenization [54].
SLNs	LL37 and A1	Applied topically	Promoted wound closure in fibroblast cells and keratinocytes, simultaneously enhanced antibacterial activity [40].

Nanofibers loaded with nanoparticles	Cefazolin/zinc oxide	Applied topically/single	Showed great anti-bacterial activity, enhanced cell adhesion and epithelial migration, contributed to faster and more efficient collagen synthesis [56].
Nanofibrous scaffold	Human bone marrow stem cells	Applied topically	Boosted cell growth rate and accelerated wound Recovery [56].
Hybrid nanostructures/hydrogels	Ag/Ag–AgCl/ZnO	Applied every 2 days for 14 days	Stimulated the immune function, produced the synergistic antibacterial effects and accelerated wound healing.
Nano hydrogel	Baicalin	Topically smeared every day for 4 days	Faster and more complete skin restoration and inhibition of specific inflammatory markers was noticed [52].

**Liposomes:** Liposomes are bilayer vesicles built by amphiphilic molecules such as phospholipids, emerging as one of promising nano-carriers for topical drug delivery [15]. They are nontoxic, biodegradable, biocompatible with skin, and capable of accommodating both hydrophilic drugs (example: growth factors) in inner water cavity and hydrophobic agent in bilayer [16, 17]. Furthermore, liposomes effectively cover wound and create moist environment on wound surface after application, which is very conducive to wound healing [18]. All these merits of liposomes have been universally applied in wound treatment and skin regeneration. Xu et al. [19] prepared a novel liposome with hydrogel core of silk fibroin which effectively encapsulated bFGF. The vehicles improved the stability of bFGF in wound fluids and maintained cell proliferation activity with respect to traditional liposomes.

**Polymeric nanoparticles:** Polymeric nanoparticles are biocompatible colloidal systems drawing increasing attention in both biomedicine and bioengineering fields [20]. When drugs are embedded with these polymeric devices, drugs get protected from degradation by the proteases presenting in the wound and released in a controlled manner so as to reduce administration frequency. The need of effectively delivering biomolecules such as antimicrobial agents, growth factors and genes, will be met with aid of nanoparticles [21, 22]. Currently most polymeric nanoparticles are prepared by poly lactic-co-glycolic acid (PLGA,

crowned as the mostly used polymers), alginate, gelatine, chitosan, as well as other polymer combinations [23, 24]. Dave et al. prepared a lipid polymer hybrid nanoparticle formulation which was able to sustained drug release to 24 h with favourable skin permeation and reduced the frequency of application [25].

To reduce more cytotoxicity of Amphotericin B, Sanchez et al. incorporated Amphotericin B into the silane- based hydrogel nanoparticles to replace the intravenous injection infusion (traditional). Amphotericin B nanoparticles resulted in equivalent or enhanced killing efficacy with 72.4–91.1% by 4 h for Clinical strains [26].

**Inorganic nanoparticles:** Inorganic nanoparticles refer to nanoparticles deprived from inorganic materials, including the metallic nanoparticles, carbon-based nanoparticles, ceramic nanoparticles etc. [27]. Inorganic nanoparticles exhibit similar merits in wound healing treatment and strong antibacterial effect. Ali et al. designed and synthesized ZnO<sub>2</sub> nanoparticles by coprecipitation method. Zinc oxide nanoparticles had good antibacterial activity for aspergillus and pseudomonas aeruginosa isolated from wound infected tissues of burn patients. Due to their antibacterial properties and low toxicity profile, metal nanoparticles such as silver, gold and zinc represent ideal candidates for integration in wound dressings [28].

### **i) Silver Nanoparticles**

Silver nanoparticles (AgNPs) is the metallic nanoparticle it overcome the limitations of standard silver compounds. Due to their high surface volume ratio, AgNPs are more potent at less concentration, thus lowering their toxicity. Pure AgNPs can modulate anti-inflammatory cytokine release in order to promote rapid wound closure without increasing scarring. By inducing the differentiation of myofibroblasts from normal fibroblasts, Silver Nanoparticles promote wound contractility thus accelerating the healing process. Moreover, AgNPs stimulate epidermal re-epithelialization through the proliferation and relocation of keratinocytes [31]. However, Szmyd et al. reported that high concentration of AgNPs decrease keratinocyte viability, migration, metabolism and differentiation of these cells, through the activation of caspase 7 and 3 and dose-dependent DNA damage [32]. For side effects reduction, silver nanoparticles can be used in low doses along with the antimicrobial drugs to achieve high efficiency. In a recent study it was demonstrated that AgNPs combined with tetracycline significantly decreased bacterial load both in superficial and deep tissue layers in a mouse model, thus accelerating healing [33]. This nanomaterial proved a high bacteria-killing performance against Gram negative pathogens and promoted wound healing [34, 35].

## **ii) Gold Nanoparticles**

Gold nanoparticles (AuNPs) represent a option when it comes to wound therapy due to their capacity of absorbing near infrared light, while, at the same time and chemical stability, being relatively easy to synthesize<sup>[30]</sup>. Gold Nanoparticles can either directly target the bacterial cell wall, or they can bind to bacterial DNA, blocking the double-helix from uncoiling during replication or transcription, thus exerting bactericidal and bacteriostatic properties. As a result, they can inhibit multidrug resistant pathogens like *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Moreover, AuNPs prevent the formation of reactive oxygen species, thus acting as antioxidants, aiding the healing process<sup>[31]</sup>.

## **iii) Zinc Oxide Nanoparticles**

Zinc oxide nanoparticles (ZnONPs) itself represent a reliable antibacterial agent by inducing the bacterial cell membrane perforations. Moreover, when incorporated in hydrogel-based wound dressings, the overall contact time is increased, promoting keratinocyte migration, thus improving re-epithelialization<sup>[31]</sup>. In addition, in a recent study, a microporous chitosan hydrogel/ZnONPs dressing presented a high capacity of absorbing wound exudates and enabled the formation of haemostatic blood clots, while also displaying antibacterial properties with little cytotoxicity<sup>[29]</sup>.

**Lipid nanoparticles:** Nanostructured lipid carriers (NLCs) and Solid lipid nanoparticles (SLNs) are the lipid nanoparticles to overcome the limitation of liposomes. Lipid nanoparticles were generally prepared with physiological lipids or lipid molecules and their preparation process requires no involvement of any potentially toxic organic solvents<sup>[36-40]</sup>.

**Nanofibrous structures:** Nanofibers are fabricated from natural and synthetic polymer chains which are able to act as nanofibrous sheets or 3D-scaffolds applied in the tissue engineering<sup>[41, 42]</sup>. These nanofibrous structures are designed to mimic the ECM, provide favourable condition for cell attachment and elevate cell-drug interaction, serving as a replacement for artificial dermal analogues<sup>[42, 43]</sup>. Electrospinning is mostly used technique for production of nanofibers. An electrical charge is taken as driving force to draw fibres from a polymer solution so as to fabricate nanometric continuous fibres<sup>[44]</sup>. Due to its high area and volume ratio the nanofibers enhance transfer of the variety of therapeutic agents include diverse antimicrobial agents, nucleic acids, growth factor<sup>[45, 47, 57]</sup>.

**Nanohydrogel:** Nanohydrogel is the three dimensional polymeric networks considered as best formulation for the wound treatment, the porous three dimensional structure enrich it with the ability of preventing wound dehydration, aqueous fluid absorption<sup>[48]</sup> and creating a beneficial moist environment for wound healing<sup>[49]</sup>, its non-adhesive nature allows it to preserve the wound bed while maintaining the penetration of oxygen, which is necessary for the wound healing<sup>[50]</sup>; Texture (soft) of nanohydrogel provides comfortable experience in the course of treatment<sup>[51]</sup>. Nanohydrogel is able to encapsulate many drugs with efficacy and perfect compatibility exerting an impressive effect on skin regeneration<sup>[52]</sup>.

### **Conclusions and Future Perspectives:**

The main purpose of this review was to highlight the advantages of nano formulations for the wound-healing process. The wound-healing process based on nanomaterial also proved to be more effective than the conventional wound therapy. Nanomaterials alter wound healing phases of the wound healing process since they possess anti-proliferative, antibacterial, anti-inflammatory properties.

Wound healing is an intricate three-staged process involving inflammation, proliferation and remodelling. However, chronic wounds still remain a challenge due to multidrug-resistant microorganisms, bacteria biofilms and because of current therapies mostly failed to provide favourable outcomes of wound healing, due to the Superior surface to volume ratio of nanoparticle can be efficiently employed in medical applications including wound therapy. Inorganic nanoparticles such as silver, gold and zinc possess good properties like antibacterial activity and low toxicity for integration in wound dressings. Moreover, nano compounds which encapsulate growth factors, genes or stem cells are currently under development, thus offering new treatment modalities in the near future. The nano-DDSs in recent years has brought new insight for skin regeneration of wounds, benefits like drug carriers prolong drug release, protect drug from degradation and improve skin retention, so as to realize augment of the therapeutic power of biological and synthetic molecules (example: reduction or eradication of the wound bacterial load and improvement of re-epithelialization).

In current times, huge progress has been made in discovering the mechanisms underlying the wound healing process. In current clinical treatments of wounds, medications such as topical antimicrobial agents are still relevant. Moreover, applying nanotechnology and incorporating knowledge of cellular, subcellular events occurring during the typical healing process, could obviously get better future therapeutic interventions. Nanotechnology offers high opportunities



for improving wound treatments. The nanometre scale opens the way for the development of novel materials for use in highly advanced medical technology.

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