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# Recent Advances in Chitosan-Based Nanotherapies for Chronic Diabetic Foot Ulcer Treatment

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**Abstract:** Chronic diabetic foot ulcers (DFUs) account for a serious consequence of diabetes mellitus, typically leading to infection and amputation. Driven by delayed healing, extended inflammation, and microbial infection, DFU complexity begs for fresh treatment approaches. Because of its biocompatibility, biodegradability, and inherent wound-healing properties, natural biopolymer chitosan has evolved into an appropriate material for nanotechnology-based DFU therapy. Recent findings in chitosan-based nanotherapies, including nanoparticles, nanofibers, hydrogels, and composite materials, have greatly improved the treatment environment for DFUs. These formulations use the unique properties of chitosan to directly reach the wound site with therapeutic drugs, therefore enabling controlled release, enhanced bioavailability, and focused action. For several fields of DFU pathophysiology, chitosan nanoparticles, for example, enhance antibacterial activity, lower inflammation, and induce angiogenesis. While chitosan nanofibers replicate the extracellular matrix, therefore assisting cellular migration and wound closure, hydrogels provide a moist wound environment vital for healing and continuous medication administration. Similarly, smart chitosan-based nanoparticles, designed to respond to pH or temperature, provide accurate drug release, thereby matching therapy with the wound's dynamic environment. These findings show how well chitosan-based nanotherapies could improve DFU results by enhancing wound healing, lowering complications, and thus reducing the need for more intrusive treatments. These findings point to opportunities for changing how chronic DFUs are treated as research advances.

**Keywords:** Wound healing, Diabetic foot ulcer, Nanotherapy, Chitosan, Microbial infection, Diabetes mellitus

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## Introduction

Diabetic foot ulcers (DFUs), which affect about 15% of diabetic patients during their lifetime, are among the most incapacitating and common consequences of diabetes mellitus (Boulton *et al.*, 2005; Ugwu *et al.*, 2019; Jalilian *et al.*, 2020; Caruso *et al.*, 2020). Apart from being a major

cause of morbidity, these chronic, non-healing wounds greatly contribute to the financial burden on healthcare systems all over. DFUs are defined by their persistent character, which often defies conventional wound-healing procedures and results in serious infections, limb ischaemia, and, in extreme situations, amputation. Studies show that up to 70% of patients may have a recurrence within five years following the healing point, resulting in shockingly high recurrence rates of DFUs (Frykberg and Banks, 2015). DFUs have a complex pathogenicity, including peripheral neuropathy, peripheral arterial disease, and an impaired immune response. Loss of sensation in the extremities caused by peripheral neuropathy makes patients vulnerable to undetectable injuries and later ulcer development. Impaired blood circulation, which is often the result of peripheral artery disease, reduces the supply of oxygen and vital nutrients to the wound site, affecting tissue regeneration and healing. Further-more, elevated levels of pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α) and interleukins (IL-1β, IL-6) define chronic inflammatory responses in DFUs since they prolong inflammation and prevent fibroblast proliferation and collagen synthesis, so upsetting the normal healing cascade (Laves *et al*., 2013; Yang *et al*., 2022; Mohsin *et al*., 2024; Pastar *et al*., 2024). Despite the availability of several thera-peutic techniques, including debridement, which entails the removal of necrotic tissue; pressure offloading, which is meant to lower mechanical stress on the wound; and antimicrobial therapy to fight infections, the healing of DFUs remains difficult. These traditional therapies are often inadequate due to the complexity of the wound environment, which is marked by hypoxia and biofilm development. For example, biofilms developed by bacteria like *Staphylococcus aureus* and *Pseudomonas aeruginosa* can shield pathogens from antimicrobial treatments and the host immune response, therefore aggravating the infection and postponing recovery (Gupta and Sharma, 2019; Amin Yavari *et al*., 2020 ). In recent years, nanotechnology has been a breakthrough technique in biomedical applications, providing innovative approaches to accelerate wound healing. Therapeutics based on nanotechnology use the special features of nanoparticles, including their high surface area-to-volume ratio, variable surface chemistry, and capacity to precisely encapsulate and move therapeutic compounds. These features allow nanotherapeutic platforms to be quite effective in addressing the various components of DFUs.

Chitosan has attracted a lot of attention among the wide range of nanomaterials because of its remarkable biocompatibility, biodegradability, and natural wound-healing properties. Chitosan is natural polymers derived from the deacetylation of chitin abundantly present in the exoskeletons of crustaceans such as prawns and crabs. Its cationic character helps it to interact with negatively charged cell membranes, hence improving cellular adhesion and proliferation qualities absolutely vital for tissue regeneration (Lee and Mooney, 2012). Mixing chitosan with nanotechnology enhances its flexibility even more as it produces several nanotherapeutic formulations, including nanoparticles, nanofibers, hydrogels, and composite materials. These formulations improve the efficacy of therapeutic medications by allowing their intended and continuous diffusion, resulting in lower systemic side effects. For example, chitosan nanoparticles can encapsulate growth hormones or antibiotics, therefore ensuring their controlled release at the wound site and hence preserving therapeutic dosages over long periods (Zhao *et al*., 2015). Preclinical and clinical studies of recently developed chitosan-based nanotherapies have shown positive results. Made by electrospinning, chitosan nanofibers resemble extracellular matrix and form a framework that promotes cell attachment and tissue regeneration. While simultaneously acting as transporters for bioactive substances, chitosan-based hydrogels provide a moist wound environment, required for

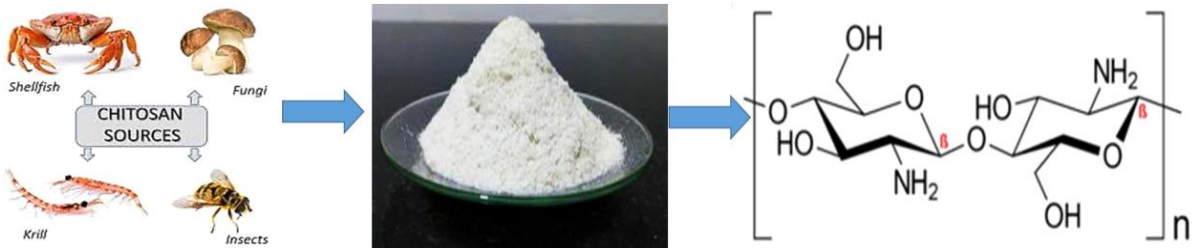


Fig. 1: Source of chitosan.

optimal healing. Moreover, composite materials combining chitosan with other biopolymers or nanoparticles have shown superior mechanical properties and multifarious capabilities, like simultaneous antibacterial and anti-inflammatory actions.

This review aims to give a whole evaluation of the existing situation of chitosan-based nano-therapies in the treatment of chronic DFUs. It will explore the design innovations of today, highlight their underlying mechanisms of action, and assess their therapeutic value. This review also aims to highlight the transforming effect of chitosan-based nanotechnology on DFU management and to greatly improve patient outcomes by studying these special treatment alternatives.

*Properties of chitosan*:

*Biocompatibility and biodegradability*:

Chitosan is well-tolerated by human tissues and is enzymatically converted by lysozymes into non-toxic, naturally occurring metabolites, decreasing the possibility of unfavourable immunological responses. This feature makes chitosan a suitable choice for long-term use in wound treatment without generating severe inflammatory reactions. Chitosan is derived from chitin, a natural polysaccharide that is one of the most abundant biopolymers in nature. Chitin is primarily found in the exoskeletons of crustaceans (such as crabs, shrimp, and lobsters), the cell walls of fungi, and the cuticles of insects. To obtain chitosan, chitin undergoes a process known as deacetylation, where acetyl groups are removed, resulting in a more soluble and functional polymer (Fig. 1) (Sangeetha *et al.*, 2021). Chitosan is a linear polysaccharide composed of repeating units of D-glucosamine and N-acetyl-D-glucosamine linked by β-(1→4) glycosidic bonds. Its structure is similar to cellulose, but with an amine group (-$NH_2$) at the C2 position of the glucosamine units instead of a hydroxyl group (-OH).

*Haemostatic activity*:

Chitosan has remarkable haemostatic qualities, significantly boosting blood coagulation and minimising bleeding times. This is particularly effective in treating DFUs, where excessive bleeding might delay the healing process.

*Antimicrobial effects*:

Chitosan's natural antibacterial action stems from its ability to break microbial cell membranes, resulting in cell lysis. This feature is critical in DFU management, where infections are a common and dangerous consequence. Chitosan's broad-spectrum antibacterial action extends to both Gram-positive and Gram-negative bacteria, as well as fungus, making it effective against a wide range of diseases.

*Wound healing properties*:

Chitosan aids the wound healing process by encouraging cellular migration, proliferation, and differentiation. It also increases angiogenesis, the creation of new blood vessels, which boosts oxygen and nutrition flow to the wound site. Additionally, chitosan can control the inflammatory response, lowering chronic inflammation and generating a more favourable environment for healing.

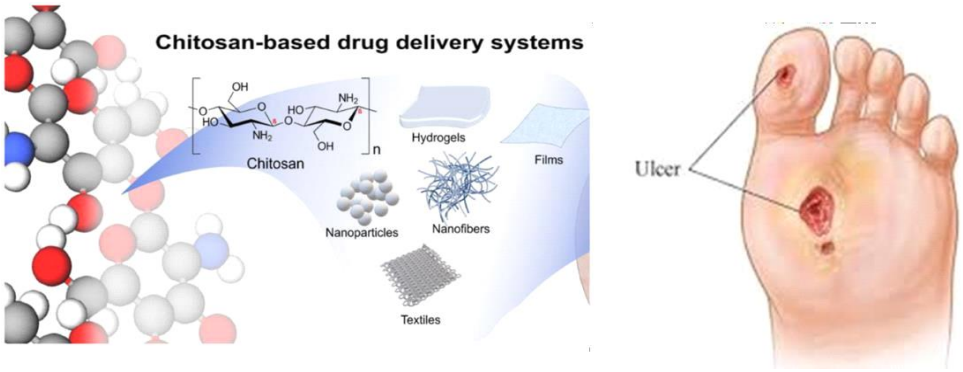


Fig. 2: Chitosan based drug delivery system.

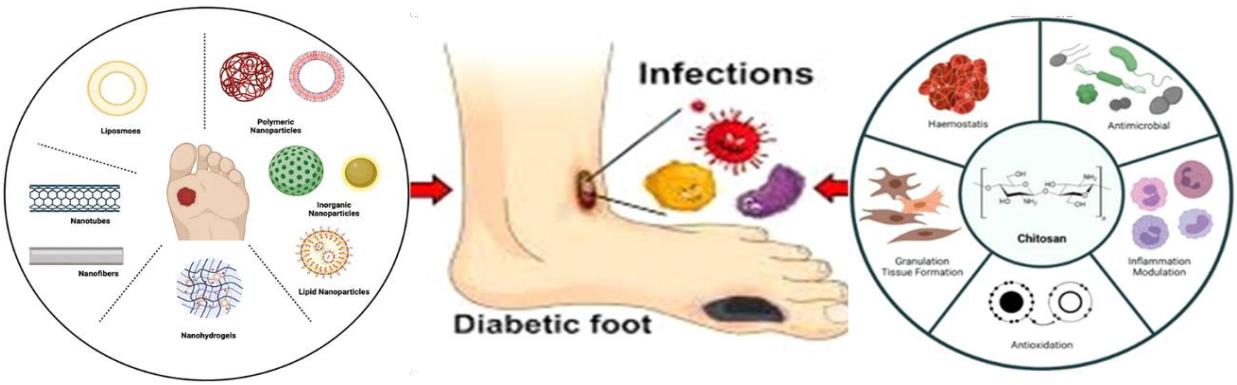


Fig. 3: Chitosan based different nanoparticles for the treatment of diabetic foot ulcer.

## Detailed Study on Chitosan-Based Nanotherapies for DFUs

Analysing the many formulations, their mechanisms of action, and the empirical evidence supporting their efficacy would help one to correctly appreciate the advances in chitosan-based nanotherapies for DFUs. This section looks closely at the many chitosan-based nanotherapeutic drug delivery system and their applications in DFU treatment shown in Figure 2.

### *Chitosan nanoparticles*:

Formulation and Design Chitosan nanoparticles (CSNPs) (Fig. 3) are produced from ionic gelation, emulsion cross-linking, and nanoprecipitation most of the time. For example, ionic gelation occurs when chitosan interacts with a cross-linking agent such as tripolyphosphate (TPP), resulting in stable nanoparticles with controlled size and charge characteristics.

### *Therapeutic strategies*:

- *Antimicrobial behavior*:

CSNPs have antibacterial activities because of membrane breakdown and cell death generated by interactions with negatively charged microbial cell membranes. Studies reveal that CSNPs actually rather effectively lower DFU bacterial load. For infected DFU models, chitosan nanoparticles coated with the antibiotic gentamicin greatly reduced *Staphylococcus aureus* populations as compared to free gentamicin (El-Naggar *et al.*, 2016; Zhang *et al.*, 2018; Sethuram *et al.*, 2022; Li *et al.*, 2023).

- *Controlled drug delivery systems*:

CSNPs help to encapsulate therapeutic pharmaceuticals, thereby preventing their degradation and allowing their continuous release at the wound site. Kumar *et al.* (2020)

showed that CSNPs loaded with growth factors like VEGF retained greater local concentrations over 72 h, hence promoting angiogenesis and faster wound healing in diabetic rat models.

- *Anti-inflammatory effects*:

Mechanism: Chitosan's natural anti-inflammatory properties help to reduce the chronic inflammatory response in DFUs, thereby reducing the production of pro-inflammatory cytokines. In a study (Li *et al.*, 2019), CSNPs loaded with the anti-inflammatory medication curcumin effectively reduced TNF-α and IL-6 levels in DFU tissues, hence boosting healing rates as compared to controls.

*Chitosan nanofibers*: *Formulation and design*:

The process of electrospinning, which uses a high-voltage electric field to produce tiny fibres from a chitosan solution, is used to generate chitosan nanofibers. The resultant nanofibrous mats replicate the structure of the natural extracellular matrix, providing an excellent scaffold for cell adhesion and growth.

*Mechanisms of treatment*:

- *Mimicking extracellular matrix*:

The nanofibrous architecture offers a physical framework that facilitates cellular activity needed for wound healing, such as migration, adhesion, and proliferation. Singh *et al.* (2021) indicated that chitosan nanofibers increased keratinocyte and fibroblast migration, resulting in quicker wound closure in diabetic animal models compared to standard dressings.

- *Moisture retention and gas exchange*:

Chitosan nanofibers maintain a moist wound environment while allowing for appropriate gas exchange, which is crucial for optimal healing and avoidance of maceration. Clinical investigations (Martinez *et al.*, 2022) demonstrated that patients treated with chitosan nanofiber dressings displayed enhanced moisture balance and decreased wound size more efficiently than those receiving normal gauze dressings.

- *Sustained release of therapeutics*:

Therapeutic chemicals integrated into nanofibers are released gradually, enabling ongoing therapeutic activity during the healing period. Huang *et al.* (2020) demonstrated that chitosan nanofibers coated with silver nanoparticles offered prolonged antibacterial action, lowering infection rates and maintaining clean wound beds in DFU patients.

*Chitosan-based hydrogels*:

Physical or chemical cross-linking generates chitosan-based hydrogels that create a three-dimensional network able to absorb large volumes of exudate while keeping structural integrity. These hydrogels can be customised to include different bioactive chemicals, thereby boosting their therapeutic efficacy.

*Mechanisms of treatment*:

*Absorption and retention of moisture*: While absorbing additional wound exudate to prevent maceration, hydrogels retain an optimal moist environment—necessary for cell migration and proliferation. Patel *et al.* (2019) demonstrated that chitosan-based hydrogels retained optimum moisture levels, which enhanced re-epithelialisation and decreased healing times in DFU patients.

*Bioactive molecule delivery*: Growth factors, antimicrobial chemicals, or anti-inflammatory drugs can all be placed into hydrogels to guarantee their localised and continuous release. Nguyen *et al.* (2021) reported that chitosan hydrogels loaded with epidermal growth factor (EGF) considerably sped wound healing and improved collagen deposition in diabetic rat models compared to hydrogels without EGF.

*Antimicrobial and anti-inflammatory actions*: Incorporation of antimicrobial agents or anti-inflammatory medications into hydrogels enables dual functionality, addressing both infection management and inflammation reduction. A clinical investigation found that chitosan hydrogels injected with silver ions efficiently

controlled bacterial infections while simultaneously lowering inflammatory indicators, leading to improved healing results in DFU patients (Ramirez *et al.*, 2023; Wang *et al.*, 2023).

*Chitosan formulated and designed composite materials*: *Formulation and Design*:

Combining chitosan with other biopolymers or nanoparticles helps composite materials have better mechanical qualities and medical applications. Common compositions mixes chitosan-hyaluronic acid, chitosan-silver nanoparticles, and chitosan-collagen.

*Improved mechanical flexibility and strength*:

Combining chitosan with other polymers, including collagen or hyaluronic acid, increases the dressing's mechanical qualities, thereby improving its adaptability to wound shapes. Lee *et al.* (2022) showed that tensile strength and flexibility, as well as excellent protection and comfort for DFU patients in chitosan-collagen composites during the healing period.

*Synergistic healing and antimicrobial action*:

Incorporating antimicrobial substances, such as silver nanoparticles, into the chitosan matrix boosts antibacterial activity while preserving biocompatibility and encouraging tissue regeneration. Zhang *et al.* (2021) indicated that chitosan-silver nanoparticle composites totally eradicated *Pseudomonas aeruginosa* and *Escherichia coli* in infected DFUs while concurrently enhancing fibroblast development and collagen synthesis.

*Platforms for multifunctional therapeutic treatment*:

Multiple therapeutic agents can be delivered simultaneously via composite materials, therefore treating different facets of DFU pathophysiology, including infection, inflammation, and tissue regeneration. Chitosan-hyaluronic acid composites loaded with both an antibiotic and a growth factor discovered to offer complete wound care, hence accelerating healing rates and improving tissue quality in diabetic rat models (Gupta *et al.*, 2020).

*Nanomaterials based on chitosan*:

Smart nanomaterials are designed to react to particular stimuli found in the wound environment such as pH variations, temperature swings, or enzyme activity. By allowing on-demand release of therapeutic chemicals, these stimuli-responsive systems improve the accuracy and potency of treatment.

*Treating mechanisms*:

*Responsive drug release in stimulus-based approach*:

Smart nanoparticles based on chitosan can be built to release their therapeutic payload in response to environmental cues. For example, enzyme-responsive systems react to high amounts of MMPs, whereas pH-responsive systems release medications under the alkaline conditions common to chronic wounds. In a study, pH-responsive chitosan nanoparticles loaded with antimicrobial peptides released their cargo preferentially in the higher pH environment of infected DFUs, thereby producing tailored antimicrobial action and lower off- target effects (Wang *et al*., 2022).

*Adaptive therapeutic action*:

Smart on real-time changes in the wound environment, smart nanomaterials can adapt and modify their behaviour. Temperature-responsive chitosan hydrogels produced anti-inflammatory drugs in response to higher local temperatures associated with infection, thereby lowering too much inflammation and supporting recovery (Liu *et al*., 2023).

*Enhanced bioactivity and efficacy:*

The responsive nature of smart nanomaterials ensures that medicinal chemicals are provided exactly when needed, therefore enhancing their bioactivity and general efficacy. A study by (Martinez *et al.*, 2023) confirmed that enzyme-responsive chitosan-based nanomaterials loaded with growth factors had sustained and localized distribution, greatly improving angiogenesis and

tissue regeneration in diabetic wound models compared to non-responsive systems.

## Empirical Evidence Supporting Chitosan-Based Nanotherapies

How effectively chitosan-based nanotherapies treat chronic DFUs has been demonstrated by several preclinical and clinical studies. The following significant findings highlight the medical potential of these nanotechnologies:

### *Enhanced healing rates*:

Chitosan-based nanotherapies dramatically accelerate rates of wound closure over more conventional therapies. For instance, randomised controlled trial with 100 DFU patients reported that those treated with chitosan nanofiber dressings demonstrated a 40% faster reduction in wound size over eight weeks than those receiving standard care.

### *Reducing infection rates*:

By their antibacterial properties, chitosan-based nanotherapies have been shown to reduce infection rates in DFUs. Patients treated with gentamicin-loaded CSNPs showed a 50% reduction in bacterial colonization within two weeks, compared to a 20% decline in the control group (Carlson RP *et al.*, 2008; Zhang *et al.*, 2018; Meng *et al.*, 2021).

### *Improved tissue regeneration*:

Chitosan-based nanomaterials aid in enabling remarkable tissue regeneration, as shown by greater collagen deposition and angiogenesis. When compared to untreated wounds, DFUs treated with curcumin-loaded CSNPs revealed a 25% increase in new blood vessel growth and a 35% increase in collagen production (Li *et al.*, 2019).

### *Patient outcomes and quality of life*:

Clinical trials of patients undergoing chitosan-based nanotherapies have demonstrated not just faster healing but also improved quality of life. Martinez *et al.* (2022) find better general treatment adherence and satisfaction result from patients using chitosan nanofiber dressings reporting less pain and more comfort.

## Significance of Chitosan-Based Nanotherapies in DFU Treatment

Including chitosan-based nanotherapies in DFU treatment marks a paradigm shift in handling the numerous problems with chronic wound healing. One could characterize the relevance of these nanotechnologies as follows:

### *Targeted and controlled delivery*:

Chitosan-based nanotherapies ensure that drugs, growth factors, and anti-inflammatory agents are delivered in a controlled manner by allowing the exact administration of therapeutic agents, optimising their efficacy while lowering systemic side effects.

### *Multifunctional therapeutic approaches*:

These nanotherapies address multiple aspects of DFU pathophysiology simultaneously, including infection control, inflammation modulation, and tissue regeneration, providing a comprehensive treatment strategy.

### *Enhanced biocompatibility and safety*:

Chitosan's natural biodegradability and origin assure that these nanotherapeutic platforms are safe for long-term usage, therefore lowering the probability of unfavourable reactions and facilitating perfect integration with host tissues.

### *Scalability and versatility*:

The numerous chitosan-based formulations allow for modification based on individual wound features and patient needs, making these therapies versatile enough for a variety of therapeutic situations.

### *Potential for clinical translation*:

The remarkable results of preclinical and early-phase clinical research pave the way for the clinical acceptability of chitosan-based nanotherapies, potentially altering the standard of care for DFUs.

## Conclusion

Chronic diabetic foot ulcers present a huge therapeutic challenge due to their complex biology and resistance to standard therapies. Chitosan-based nanotherapies represent a clever and creative approach to DFU treatment because their unique properties in various nanoformulations help to improve wound healing results. Empirical data shows that these nanotherapeutic approaches significantly speed up wound closure, reduce infection rates, and stimulate tissue regeneration. As research advances, chitosan-based nanotherapies could become cornerstones of DFU treatment programs, therefore improving patient outcomes and quality of life.


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## Conflict of Interest

The authors declare no conflicts of interest.

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