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Nanoparticles for Diabetic Foot Ulcers: A New Frontier in Targeted Drug Delivery and Regenerative Therapy

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Abstract: ***Diabetic foot ulcer (DFU) is one of the most severe complications of diabetes mellitus, affecting nearly 25% of patients during their lifetime and frequently leading to infection, amputation, and increased mortality. Impaired wound healing in diabetes necessitates advanced therapeutic strategies. Nanotechnology-based drug delivery systems have emerged as promising tools to enhance wound healing and tissue regeneration in DFUs. Nanoparticles, alone or in combination with scaffold-based systems, enable targeted drug delivery, antimicrobial action, angiogenesis promotion, and controlled release of bioactive agents. These nano-enabled approaches offer significant advantages over conventional therapies and represent an emerging frontier in DFU management. Given the current medical advancements, the application of nanoparticles in diabetic foot ulcer treatment presents a highly effective and in-demand therapeutic strategy. These nano-delivery systems offer a targeted and efficient method to promote wound healing, ultimately improving patient outcomes.***

Keywords: Diabetic foot ulcer, Nanoparticles, Wound healing, Nanotechnology, Scaffolds

1. Introduction

Diabetes Mellitus (DM) is one of the most common chronic and metabolic diseases. Among its complications, diabetic foot ulcers represent a significant concern, as they are highly susceptible to microbial infections, leading to an increased risk of hospitalization and lower limb amputation. In industrialized countries, diabetic foot complications are the primary cause of non-traumatic lower extremity amputations. The risk of amputation in diabetic patients is estimated to be 15 to 46 times higher compared to individuals without diabetes[1,2]. Effective management of diabetic foot complications requires a comprehensive understanding of the major risk factors for amputation, regular clinical assessments, and meticulous preventive care.

Foot ulcers can develop in anyone and typically present as areas of broken skin, most commonly on the lower legs or feet. Both Type 1 and Type 2 diabetes patients are susceptible to diabetic foot ulcers (DFUs)[3]. These ulcers are frequently colonized by pathogenic bacteria, including *Staphylococcus aureus*, *Streptococcus* group B, *Enterococcus*, *Clostridium perfringens*, and *Enterobacteriaceae*. Among them, *S. aureus*, particularly methicillin-resistant *S. aureus* (MRSA), is the most commonly identified pathogen in DFU infections[4].

Diabetic foot infections are often severe due to the accumulation of bacteria in both superficial and deep tissues, sometimes extending to the bone[4]. As a result, symptoms can be particularly severe in certain patients, leading to a significantly high rate of lower limb amputations. It has been reported that, globally, a person with diabetes undergoes a foot amputation every 20 seconds.

Additionally, diabetic wounds tend to remain in a moist state, making proper surgical dressing a critical component of treatment. Inadequate wound management increases the risk of complications, including infections, neuropathy, and peripheral arterial disease (PAD), all of which contribute to the progression of foot ulcers. Even minor injuries can trigger the development of foot ulcers, leading to changes in wound pH, typically ranging from 6.0 to 8.0[5]. Studies have also indicated that individuals with chronic leg ulcers release approximately 5 grams of exudate per 10 cm^2 every 24 hours, further emphasizing the importance of appropriate wound care strategies.

Researchers at the Icahn School of Medicine at Mount Sinai have developed a therapy using lipid nanoparticles to deliver mRNA that encodes for anti-inflammatory proteins. In mouse models, this treatment effectively reduced inflammation and accelerated wound healing. Copper-containing nanoparticles have shown promise in expediting diabetic wound healing. Their antimicrobial properties help reduce infection risks, while their role in promoting angiogenesis aids in tissue regeneration. Combining nanoparticles with hydrogel systems has led to the development of advanced wound dressings. For instance, a hydrogel incorporating disulfiram-loaded nanovesicles demonstrated enhanced wound closure and tissue regeneration in diabetic models. Hydrogels containing chitosan-modified gold nanoparticles (CS-AuNPs) have demonstrated significant improvements in healing methicillin-resistant *Staphylococcus aureus* (MRSA)-infected diabetic wounds in rat models. This combination leverages the antimicrobial properties of gold nanoparticles and the biocompatibility of chitosan to enhance wound healing. In the study of Selenium Nanoparticles Combined with Platelet-Rich Plasma, the integration of selenium nanoparticles (Se NPs) with platelet-rich plasma (PRP) has shown a synergistic effect in diabetic wound

healing. Se NPs offer antioxidant and antimicrobial properties, while PRP provides growth factors that promote tissue regeneration, collectively enhancing the healing process in diabetic mice.

Researchers have engineered trisulfide-derived lipid nanoparticles (TS LNPs) to deliver mRNA encoding interleukin-4 (IL-4). This approach targets macrophages at the wound site, promoting their transition to an anti-inflammatory state, thereby accelerating tissue repair in diabetic mouse models. Cerium oxide nanoparticles (CeO_2 NPs) have been utilized to mitigate oxidative stress and inflammation in diabetic wounds. When conjugated with microRNA-146a and delivered via an amphoteric ionic hydrogel, these nanoparticles significantly improved wound healing rates in diabetic mouse models.

These emerging nanotherapeutic approaches highlight the potential of nanoparticles in addressing the complex challenges of diabetic wound healing, offering promising avenues for future clinical applications. Also these developments highlight the potential of nanoparticle-based therapies to improve outcomes in diabetic wound care.

1.1 Diabetic Foot Ulcer

A diabetic foot ulcer is an open sore or wound that develops on the foot due to diabetes. It affects approximately 15% of diabetes patients, most commonly appearing on the bottom of the foot, as shown in Figure 1.

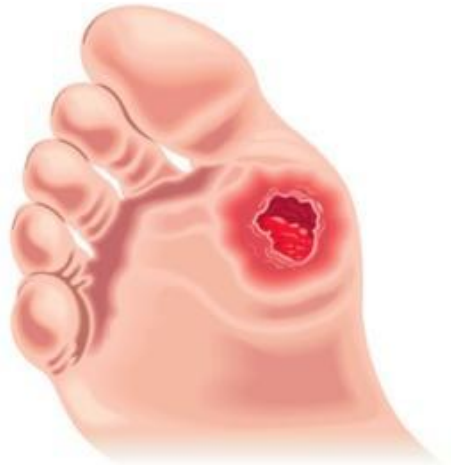


Figure 1: Diabetic Foot Ulcer

When blood glucose levels are elevated or fluctuate, skin wounds may struggle to heal or repair themselves. Even a minor injury can trigger the formation of an ulcer, leading to changes in the wound's pH, typically ranging from 6.0 to 8.0[6].

Recent studies have provided valuable insights into the treatment and management of diabetic foot ulcers (DFUs). A study published in *Diabetologia* reported high short-term mortality rates among patients with new DFUs, with 14.4% mortality at 52 weeks, particularly in older individuals with cardiovascular or renal comorbidities. In therapeutic advancements, a study published in the *New England Journal of Medicine Evidence* demonstrated that fish-skin grafts significantly outperformed standard care, achieving a 44% healing rate at 16 weeks compared to 26.4% with standard treatment. Additionally, research from Michigan State University revealed that combining injectable insulin with orally administered metformin increases metformin concentration at wound sites, potentially accelerating healing. Furthermore, a study highlighted in *Medical Xpress* introduced a pressure-alternating shoe insole designed to cyclically relieve pressure on different foot areas, aiming to prevent DFUs by enhancing blood flow and reducing tissue stress. These findings underscore the multifaceted approach required to effectively manage and treat DFUs.

1.2 Nanoparticles in Diabetic Wound Healing

1) Silver nanoparticles

Silver nanoparticles (AgNPs) are widely used in various fields, including healthcare, food, medicine, and, most importantly, wound healing. They are valued for their unique physical and chemical properties. Silver is commonly used as an antibacterial agent, aiding in the treatment of open wounds, burns, and other skin injuries. Silver nanoparticles are well known for their broad-spectrum antimicrobial activity. AgNPs disrupt bacterial membranes, generate reactive oxygen species (ROS), and inhibit biofilm formation. Their ability to release silver ions gradually provides sustained antimicrobial effects. Recent clinical studies have demonstrated that AgNP-based dressings accelerate wound closure rates in DFU patients.

AgNPs have demonstrated antimicrobial activity against strains of *Bacillus subtilis*, *Escherichia coli*, *Staphylococcus aureus*, and other skin pathogens. Studies suggest that silver nanoparticles attach to the cell membrane and release silver ions[9]. Due to their distinctive chemical and physical properties, AgNPs present a promising alternative to conventional antibacterial agents for treating diabetic foot infections[10]. For this reason, they are often referred to as "topical bullets."

Recent studies have investigated the efficacy of silver nanoparticles (AgNPs) in the treatment of diabetic foot ulcers (DFUs), yielding mixed results:

- **Comparative Study on AgNP Dressing vs. Conventional Dressing**: A randomized controlled trial assessed the effectiveness of SilvrSTAT Gel, an AgNP dressing, compared to conventional dressings in non-ischemic DFUs. The study found that the healing rate was significantly higher in the AgNP group, with 55% of ulcers completely healed by the 6th week, compared to 50% in the conventional group by the 8th week.
- **Systematic Review and Meta-Analysis**: A comprehensive analysis of randomized controlled trials evaluated the therapeutic effect of AgNPs in managing diabetic ulcers. The review concluded that there was no significant difference in DFU healing rates between AgNP treatments and other methods, indicating insufficient clinical evidence to support the superiority of AgNPs in DFU healing.

These findings suggest that while some individual studies report positive outcomes with AgNPs in DFU treatment, the overall clinical evidence remains inconclusive. Further large-scale, well-designed randomized controlled trials are

necessary to establish the definitive efficacy of silver nanoparticles in diabetic foot ulcer management.

Characteristics of Silver Nanoparticles

- They can be easily synthesized using several simple, economical, safe, and reliable methods.
- They exhibit strong antibacterial effects against a wide range of bacterial species.
- Bacterial resistance to elemental silver is extremely rare, indicating the presence of multiple bactericidal mechanisms working in synergy.
- They can be easily incorporated into cotton fabrics and dressings without causing any adverse effects.
- They possess efficient anti-inflammatory properties, which help promote wound healing by reducing cytokine release and decreasing lymphocyte and mast cell infiltration.

2) Gold Nanoparticles (AuNPs)

Due to their unique properties and multifunctional surface characteristics, gold nanoparticles (AuNPs) are highly useful in bionanotechnology. They are considered promising biologically active materials[11]. Gold nanoparticles exhibit antioxidant, anti-inflammatory, and antimicrobial properties. Functionalized AuNPs can be conjugated with therapeutic agents, enhancing drug delivery to the wound site. AuNPs have also been utilized in photothermal therapy to eradicate multidrug-resistant infections in DFUs.

Studies suggest that AuNPs combined with epigallocatechin gallate and α-lipoic acid significantly accelerate wound healing[12]. AuNPs containing antioxidant agents have also been shown to enhance diabetic wound healing. Additionally, AuNPs can bind or interact with other therapeutic agents. For detecting target biomolecules, AuNPs can be conjugated with antibodies or oligonucleotides[13,14,15]. Drug loading in AuNPs can be achieved through either covalent conjugation or non-covalent interactions[16,17]. AuNPs have been utilized to deliver therapeutic agents effectively. A notable example is the conjugation of toluidine blue to chitosan-coated gold–silver core–shell nanoparticles, which, when used in photodynamic therapy, showed efficacy against multidrug-resistant bacterial infections commonly found in DFUs. In addition to their antimicrobial properties, AuNPs have been incorporated into hydrogel systems to enhance their wound-healing potential. A study reported the synthesis of AuNPs using a hydrogel extracted from *Cydonia oblonga* seeds, resulting in nanoparticles with significant antimicrobial activity and improved wound healing in vivo.

3) Copper Nanoparticles

Copper nanoparticles exhibit unique properties such as catalytic activity and antifungal/antibacterial effects, which are not present in commercial copper. These nanoparticles, ranging in size from 1 to 100 nm, play a significant role in wound healing. Copper nanoparticles promote angiogenesis and fibroblast proliferation. They stimulate the expression of vascular endothelial growth factor (VEGF) and hypoxia-inducible factor-1 alpha (HIF-1α), crucial for neovascularization and wound healing. Clinical studies show that copper-infused dressings reduce bacterial load and significantly shrink wound sizes. Copper (Cu) also plays a crucial role in various cellular functions, modulating cytokines and growth factor mechanisms. It is actively involved in all stages of the wound healing process[18]. Copper nanoparticles (CuNPs) have garnered attention for their potential in treating diabetic foot ulcers (DFUs) due to their antimicrobial, anti-inflammatory, and angiogenic properties. A systematic review highlighted that CuNPs promote angiogenesis and skin regeneration, thereby accelerating the wound healing process.

In a clinical case study, the application of copper nanoparticle–infused dressings resulted in a 63% reduction in wound size over eight weeks, suggesting their efficacy in reducing bacterial bioburden and promoting healing in recalcitrant DFUs. Furthermore, research indicates that copper plays a crucial role in skin regeneration and angiogenesis by inducing vascular endothelial growth factor (VEGF) and enhancing hypoxia-inducible factor-1-alpha (HIF-1α) expression, both vital for effective wound healing. These findings suggest that incorporating copper nanoparticles into wound care strategies may offer a multifaceted approach to managing DFUs, addressing microbial infection, inflammation, and impaired tissue regeneration.

4) Other Nanoparticles

Cerium Oxide Nanoparticles (CeO2 NPs) Cerium oxide nanoparticles (CeO2 NPs) have garnered significant attention in diabetic wound healing due to their potent antioxidant and anti-inflammatory properties. CeO2 NPs possess a unique ability to switch between Ce3+ and Ce4+ oxidation states, enabling them to scavenge reactive oxygen species (ROS) effectively. This redox activity helps to mitigate oxidative stress, a major contributor to delayed wound healing in diabetes.

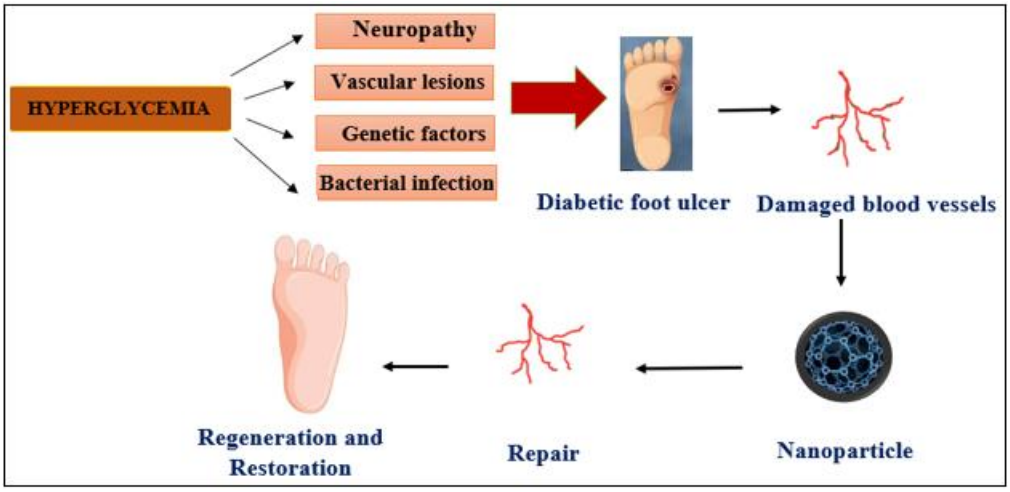
CeO2 NPs promote cellular proliferation, migration, and angiogenesis, essential steps for tissue regeneration. They have been shown to upregulate vascular endothelial growth factor (VEGF) expression, enhancing neovascularization in the wound bed. Furthermore, CeO2 NPs can modulate macrophage polarization from a pro-inflammatory (M1) to an anti-inflammatory (M2) phenotype, thereby facilitating the resolution of inflammation and promoting tissue repair. In experimental models, CeO2 NPs incorporated into hydrogels or scaffolds have significantly accelerated wound closure rates, reduced inflammatory markers such as TNF-α and IL-6, and enhanced collagen deposition. Moreover, when conjugated with bioactive molecules like microRNA-146a, CeO2 NPs have demonstrated synergistic effects in improving diabetic wound healing outcomes. Their biocompatibility and ability to sustain therapeutic effects over extended periods make CeO2 NPs a promising candidate for clinical applications in chronic wound management.

1.3 Angiogenesis in Diabetic Wound Healing

Wound healing is a critical aspect of the proliferative phase of tissue repair. Diabetic neuropathy and peripheral arterial disease play significant roles in various stages of ulcer development. The formation of new blood capillaries within a wound site following injury is referred to as angiogenesis.

Silver nanoparticles have demonstrated effectiveness in promoting diabetic wound healing. All types of nanoparticles possess scavenging properties that counteract oxidative stress[21]. By integrating the functionalities of nanoparticles with recombinant DNA technology, this issue can be further addressed.

Reduced angiogenesis in diabetic wounds is primarily attributed to inadequate oxygen supply in the granulation tissue[23, 24]. Nanoparticles can stimulate various cellular and molecular processes within the wound microenvironment, thereby transforming non-healing wounds into healing ones. Gold nanoparticles (AuNPs) exhibit inherent antibacterial properties and facilitate wound healing by contributing to hemostasis and the inflammatory phases. The mechanism and treatment of diabetic foot ulcers are illustrated in Figure 2.



1.4 Polymeric Materials in Wound Healing

Polymers are the suitable materials for drug delivery because of their biocompatible nature. In case of diabetic wound healing they can act as skin substitutes. their flexibility for chemical modifications, resulting in a chemical composition suitable for creating defined 3D structures and customized surface functionality[25]. There are two class of polymers;

1) Natural Polymers
2) Synthetic Polymers

1) Natural Polymers

Compared to synthetic ones natural polymers used in nanotechnology offer number of advantages. they are obtained from natural sources, from vegetables, microbial sources etc. They shows a high level of biocompatibility, biodegradability, and/or biological activity. They produce by products when subjected to enzymatic degradation. By using natural polymers, can produce some versatile materials also[26]. compared to other polymer materials they have high chances of degradation[27]. For diabetic injuries, wound dressing materials based on polymers have attracted much attention. The most used natural polymers in wound healing process are shown in Table 1[28,29,30].

Table I: Natural Polymers in Wound Healing

Polymer	Role in Wound Healing	Advantages
Gelatin	Expedite cell adhesion and proliferation	Biodegradable Cost effective Non-antigenicity
Fibrin	Facilitates cells migration during wound healing. Contributes to cease bleeding. Act as substrate for endothelial cells, platelets, fibroblasts, and macrophages	Biocompatible Minimal adverse effects on the immune system High mechanical strength
Cellulose	Stimulates PDGF, FGF and EGF, which increase granulation tissue formation and vascularization	Biocompatible
Dextran	Stimulates the structure of the fibrin clot Stimulates macrophages	Inert in biological systems Hardly affects the cell viability. Hydrophilic
Hyaluronic acid and chitosan	Promote blood clotting and possess antibacterial properties Enhances the granulation of wound	Biocompatible Biodegradable Nonantigenic Nontoxic Oxygen permeability
Collagen	Facilitate Cell adhesion properties Act as support in connective tissue.	Biocompatibility High mechanical strength Good cell recognition

2) Synthetic Polymers

Synthetic polymers can be adjusted in a controlled mode, in order to acquire a constant physico-chemical properties and stability. They are biologically inert, and also biocompatible. But they do not employ much therapeutic actions like natural polymers. They are mechanically stable too. Synthetic polymers are of hydrophobic and hydrophilic[31]. The most used synthetic polymers in wound healing process are shown in Table 2[32,33,34].

Table II: Synthetic Polymers in Wound Healing

Polymer	Role in Wound Healing	Advantages
Polyethylene glycol (PEG)	It can be targeted to the wound site Initiating skin cells growth and their proliferation	Biocompatible Nonbiodegradable Bioinert Hydrophilic
Polyurethane (PU)	Acts as a semi-permeable membrane protecting the wound from its surrounding environment and bacterial entry.	Biocompatible Degradation rate can be adapted. Tough and durable
Poly(lactide-*co*-glycolide) (PLGA)	Degradation results in completion of wound repairing process.	Biocompatibility Good mechanical strength Can be manipulated to desirable shapes and sizes.
Polycaprolactone (PCL)	Regulate growth of microbes and initiates wound healing	Hydrophobic Semicrystalline Good elastic properties Biocompatible Biodegradable

1.5 Complications of Diabetes Mellitus and Nanotechnology

The increasing prevalence of diabetes-related complications is largely attributed to advancements in living standards, changes in dietary habits, and evolving lifestyles. These complications pose significant health risks and continue to impact individuals worldwide[33,35,36].

Diabetic foot ulcers (DFUs) are a serious complication of diabetes, often leading to significant morbidity and mortality. Recent studies have highlighted several key complications associated with DFUs:

1) High Mortality Rates

Individuals with DFUs face alarmingly high mortality rates. A study published in *Diabetologia* reported a 14.4% mortality rate within 52 weeks for patients presenting with new DFUs, with higher rates observed in older individuals and those with cardiovascular or renal comorbidities.

2) Increased Risk of Amputation

DFUs significantly elevate the risk of lower limb amputations. Approximately 50–60% of DFUs are infected at the time of clinical presentation, and about 20% of these infections may lead to limb or foot amputation.

3) Recurrence and Reinfection

The recurrence of DFUs is a notable concern. A study indicated that patients with wounds taking three months or longer to heal were three times more likely to experience reinfection. Additionally, those with bone infections had more than twice the likelihood of reinfection compared to patients with only soft tissue infections.

4) Association with Other Complications

DFUs are closely linked with other diabetes-related complications. For instance, individuals with a history of DFUs or amputations are more prone to microvascular complications such as diabetic neuropathy and ischemia, which can further exacerbate the risk of subsequent ulcers.

These findings underscore the critical need for proactive management and preventive strategies to mitigate the severe complications associated with diabetic foot ulcers.

Some of the most critical complications are outlined in Table III.

Table III: Complications of Diabetes

Complication	Application of Nanotechnology	Route	Advantage
Diabetic retinopathy	Gold nanoparticles	Activation and suppresses VEGFR-2 signaling pathway	Effective inhibition of retinal neovascularization, nontoxic
Diabetic retinopathy	Silver nanoparticles	Targeting the activation of PI3K/Akt signaling pathways	Inhibition of VEGF induced angiogenesis
Diabetic foot	AuEA	Anti-inflammation and angiogenesis modulation	Promote wound healing by reducing RAGE expression in fibroblasts
Diabetic retinopathy	Titanium dioxide (TiO2) nanoparticles	not affecting PI3K/Akt pathway	Intravitreal injection can effectively inhibit retinal neovascularization

2. Safety of Nanoparticles

A comprehensive discussion can be conducted regarding the potential toxicity of nanoparticles. According to several studies, a limited number of potential toxic effects have been identified. Research indicates that silver nanoparticles (Ag-NPs) exhibit concentration-dependent toxicity[36]. However, a study by Wu J. et al. demonstrated that Ag-NPs do not exhibit toxicity toward keratinocytes[37]. These nanoparticles facilitate a sustained release of silver ions, thereby preventing cellular

toxicity. Various scientific methods are employed to evaluate nanoparticle toxicity, ensuring their safe application in wound treatment.

Nanoparticles (NPs) are increasingly utilized across various industries, including medicine, electronics, and environmental applications, due to their unique properties. However, recent studies have raised concerns regarding their potential toxicity and environmental impact.

The small size of NPs allows them to cross biological membranes, leading to potential accumulation in tissues and organs. This accumulation can result in adverse health effects, such as lung toxicity, inflammation, and oxidative stress. A comprehensive review highlighted that increased human exposure to NPs, especially in daily life, makes individuals more vulnerable to NP toxicity.

Metal-based nanoparticles, widely used in various industries, have been scrutinized for their ecological toxicity. Recent advancements in research have focused on understanding the exposure pathways, toxic effects, and mechanisms of toxicity of these nanoparticles in the environment.

In the medical field, lipid nanoparticles (LNPs) are prominent for drug delivery systems. However, as synthetic entities, LNPs face challenges related to therapeutic efficacy and safety concerns, including toxicity, reactogenicity, and immunogenicity. A recent review provided a comprehensive overview of advancements in LNP research, emphasizing preclinical safety assessments.

The rapid development of nanotechnology has outpaced the establishment of comprehensive safety guidelines. Enhanced safety standards and improved risk assessment tools are necessary to evaluate potential exposures and risks associated with NPs. Recent findings aim to inform the development of more precise safety guidelines for industries working with nanoparticles.

To address these safety concerns, researchers are exploring ways to mitigate the toxicity of nanoparticles. For instance, studies on silver nanoparticles have focused on understanding their toxicity mechanisms and developing strategies to reduce their environmental impact.

In conclusion, while nanoparticles offer significant benefits across various sectors, recent findings underscore the importance of thorough safety assessments and the development of regulatory frameworks to mitigate potential health and environmental risks.

3. Challenges and Future Perspectives

The transition of nanoparticle-based therapies from bench to bedside faces several significant challenges. One of the foremost barriers is the scalability of nanoparticle production. Achieving consistent, reproducible, and cost-effective manufacturing processes without compromising nanoparticle quality and functionality remains a considerable hurdle.

Furthermore, there is a pressing need to better understand the interaction of nanoparticles with the biological microenvironment. Factors such as protein corona formation, off-target accumulation, and clearance mechanisms must be meticulously studied to optimize nanoparticle design for therapeutic efficacy and safety. Clinical translation is hampered by limited large-scale, randomized controlled trials evaluating the efficacy of nanoparticle-based therapies in diabetic foot ulcers. Most studies remain at the preclinical stage, and existing clinical trials often suffer from small sample sizes and short follow-up periods.

Future research should focus on the development of multifunctional and stimuli-responsive nanoparticles capable of delivering a combination of therapeutic agents, including antimicrobial peptides, growth factors, and gene therapies. Advances in biomimetic nanoparticles, such as cell membrane-coated systems, hold promise for enhancing biocompatibility and targeting specificity.

Emerging areas like 3D bioprinting of nanoparticle-laden scaffolds and the integration of nanoparticles with wearable wound monitoring devices are also expected to revolutionize chronic wound management. Finally, the establishment of interdisciplinary collaborations between material scientists, clinicians, regulatory authorities, and industry stakeholders will be essential to accelerate the clinical adoption of nanoparticle-based therapies for diabetic foot ulcers.

4. Conclusion

A significant challenge in managing diabetic foot ulcers is the persistence of non-healing wounds. Research findings indicate that the application of nanoparticles in combination with biocompatible polymers can effectively promote wound healing in diabetic foot ulcers. The exceptional targeting efficiency, biocompatibility, and ability to facilitate skin regeneration establish nanoparticles as indispensable agents in the treatment of diabetic foot ulcers. The integration of nanomaterials with suitable, non-toxic scaffolds presents a promising advancement in nanotechnology for wound healing. Further research on nanoparticles will undoubtedly provide deeper insights into mitigating the severe complications associated with diabetic foot ulcers.

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