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Nanomedicine In Healing Chronic Wound: Opportunities and Challenges

Jyoti Jwala[1], Kumari Himanshi[2], Rajesh Kumar Sharma[3]

[1]Pharm.D (PB), Department of Pharmacy Practice, NIMS Institute of Pharmacy, NIMS University, Rajasthan, Jaipur
Corresponding Author Email: *jyotijwala2018[at]gmail.com*

[2]Pharm.D (PB), Department of Pharmacy Practice, NIMS Institute of Pharmacy, NIMS University, Rajasthan, Jaipur
Email: *himanshichak193[at]gmail.com*

[3]Department of Pharmacy Practice, NIMS Institute of Pharmacy, NIMS University, Rajasthan, Jaipur, India

Abstract: ***Wounds occur when the skin is harmed and its protective barrier is compromised. Over time, the number of acute wounds caused by physical injuries has decreased due to changes in the types of illnesses people experience. Meanwhile, there has been an increase in the prevalence of chronic wounds among individuals due to factors such as aging, diabetes, and infection. There are currently over six million individuals in the United States who are dealing with chronic wounds. These wounds collectively lead to annual expenses of ten billion dollars. Treating chronic wounds can be quite challenging due to various factors. Traditional treatments for chronic wounds include dermatological procedures like skin grafting, flap transplantation, negative-pressure wound therapy, and gauze dressing. On the other hand, these procedures can potentially harm the tissues or limit activities. In the field of biomedicine, nanobiotechnology is now being utilized. This field encompasses diverse technologies derived from engineering, chemistry, and biology. This article aims to explore the development, execution, and testing of nanotechnology-based treatments for chronic wound healing in a way that is accessible and relatable to readers. We also highlight the potential therapeutic applications of nanomedicine in treating specific conditions. In this study, we present a concise overview of previous nanobiotechnology research, laying the foundation for future advancements in wound care using a multifunctional smart system based on nanotechnology***

Keywords: Healing, Chronic, Wound, Nanomedicine, Biotechnology

1. Introduction

Chronic wounds often experience a disrupted repair process, which can prevent them from healing within three months [1] Three of the most frequently encountered types of ulcers are nonhealing ulcers caused by pressure, ulcers of the veins, and ulcers in diabetic feet. Varicose ulcers result from blood valves that aren't working properly or veins that are blocked, typically occurring in the legs [2]. On the other hand, NHPUs are injuries to the skin and underlying tissues that occur when individuals are bedridden or have limited mobility for extended periods. Diabetes-related foot ulcers can arise from various complications associated with diabetes, including foot deformities, outside blood vessel conditions, and peripheral neuropathy [3]. Diabetic neuropathy occurs when nerve damage is caused by high levels of glucose in the blood, leading to a decrease in skin sensitivity. When the foot undergoes deformation, it can cause the development of acne and callus, which can further worsen wounds and potentially lead to gangrene [4]. Patients with diabetes also experience changes in their capillary system, such as thickening of the basement membrane and a reduction in capillary size. As time goes on, changes in glucose levels can lead to narrowed blood vessels and increased blood clotting, which can result in blocked arteries, reduced blood flow, and the formation of ulcers (known as peripheral arterial disease). The application of nanotechnology in persistent wound management signifies a significant change in how we approach treatment, offering improved accuracy and effectiveness. As we begin this journey, we dive into the essential elements of incorporating nanotechnology into wound care [5]. Although conventional methods for treating wounds work well for sudden injuries, they are not sufficient for dealing with the intricacies of long-lasting wounds. There has been a shift in therapeutic strategies that acknowledges the importance of precise and specific approaches in managing chronic wounds [6]. A chronic wound fails to heal and regain its normal structure and function because the healing processes, such as blood vessel formation, movement of skin cells, and cell growth, are severely impaired. This is further complicated by continual irritation and an existence of microorganisms [7-10]. Despite extensive efforts in developing strategies and promoting different therapeutic products, achieving efficacy in clinical trials in repairing chronic wounds has been challenging. This is primarily due to the intricate nature of the recovery process and our limited knowledge of the chemical, biological, immune-related, and natural mechanisms involved in skin regrowth [11-14]. Several factors can contribute to the delay in wound healing, such as diabetes, infections, and prolonged inflammation. Diabetes mellitus has a detrimental effect on the microcosm of the epidermis, which plays a crucial role in the healing of wounds. This leads to higher levels of reactive oxygen species and inadequate collagen deposition [15-17]. High blood sugar levels can hurt the performance of various cells that play a crucial role in the healing of wounds [18]. Microbial infections can have a detrimental effect on tissue regeneration by depleting the necessary energy and cells. Additionally, bacteria can form biofilms that exhibit antimicrobial resistance, immune escape, and injury adherence [19, 20]. In the case of unhealed skin, excessive inflammation can further prolong the healing process due to its harmful effects on cells and the resulting tissue damage, both of which hinder the wound from healing [21-23]. The present arsenal of therapies for chronic wounds focuses on wound management techniques, including debridement and the application of different types of dressings like hydrocolloids, hydrogels, and foams. Additionally, efforts are made to address underlying conditions that contribute to the development of wounds, such as using off-loading devices or employing negative pressure wound therapy. In more serious injuries, it may be necessary to utilize advanced treatments like bioengineered pores replacement, growth factors, and even autologous skin grafts [24, 25]. Recent developments in nanomedicine have revolutionized the way we diagnose and treat a wide range of diseases. These include cardiovascular disease, diabetes, connective tissue trauma, transplantation, tissue regeneration, autoimmune disorders, and wound repair [26-28]. Various inorganic and organic tiny substances have been extensively studied for their special properties in reducing inflammation, managing microbial infections, and promoting faster wound healing.

Skin wounds are a very common form of tissue damage, which can happen for various reasons such as trauma, surgery, blisters, persistent illnesses, or malignancies [29, 30]. In challenging circumstances, wounds frequently become long-lasting. Enhancing the healing process and promoting faster wound repair are the main goals for long-term treatment for wounds. The field of nanobiotechnology brings together various scientific disciplines, such as biology, physics, chemistry, optical science, mechanics, and nanotechnology science and technology. It focuses on utilizing tiny particles in biological systems. Tools and technologies from the field of nanobiotechnology can be used to study and manipulate biological systems [31,32]. Through the application of nanotechnology in the realm of biomedicine, numerous innovative biological materials, biological sensors, and bio-therapies are being developed and extensively researched. There is a growing understanding that the integration of biotechnology and biology has the potential to greatly assist in handling, monitoring, and repair of wounds [33,34]. The advancements in wound care through nanotechnology are made possible by the remarkable characteristics of nanoparticles. These tiny particles enable precise actions at the atomic and cellular stages, leading to customized treatments. By gaining a deep understanding of the unique traits of persistent wounds and recognizing the constraints of traditional methods, we are now poised to delve into the revolutionary potential of nanotechnology [35].

Chronic wounds show increased levels of ROS, which in turn lead to the breakdown of the extracellular matrix and damage to cells. These cellular abnormalities prevent the growth of tissues with granulation and ECM deposition, leading to the development of wounds that do not heal [36]. Chronic wounds also have a notable characteristic - their ability to form new blood vessels, known as angiogenesis, is impaired. Angiogenesis is a natural process that plays a crucial role in the healing of wounds [37]. In the typical process of wound healing, the equilibrium between the development and growth of veins and their development and rest is crucial. This equilibrium is disrupted in diabetic patients. Exposure to high levels of glucose has been found to cause endothelial cells to age and lose their integrity, ultimately resulting in cell death [38]. In these wounds, the decreased angiogenesis can be attributed to a deficiency in macrophages. These cells are responsible for producing a great deal of VEGF, as well as other proangiogenic mediators. Using small particles as transporters can enhance the effectiveness of wound-healing drugs like antimicrobial agents, growth hormones, or anti-inflammatory agents. This is achieved by improving their solubility, stability, and bioavailability, while also preventing degradation and reducing potential toxicity [39].

The treatment of persistent wounds is determined by the cause of the wound. It is essential to properly clean and remove any debris from the wound, prevent infections, and apply appropriate dressings. NHPU treatments involve the use of specialised dressings that help speed up the healing process of wounds and provide relief from tissue pressure. Yet, diabetic foot ulcers and venous ulcers prioritize dressing that creates a moist environment to promote wound healing and also focuses on compression [40]. Conventional approaches to treating chronic wounds with delayed healing often involve the use of drugs, either applied directly to the wound or taken internally. Nevertheless, the effectiveness of these medications is not ideal due to certain constraints, including their limited solubility and bioactivity [41]. Innovations in nanobiotechnology have paved the way for the creation of medication, genetic material, and exosome transport mechanisms that can address these limitations [42]. Cell therapy, particularly therapy with stem cells, is currently a prominent area of interest in the field of regenerative medicine and the treatment of diabetic wounds. In certain fundamental healthcare and preliminary investigations, the use of stem cells in treating chronic wounds has yielded highly promising results [43]. However, even though stem cell therapy holds immense promise, the clinical application for treating chronic wounds is facing obstacles due to the absence of suitable techniques for encapsulating and transplanting cells. Therefore, the advancement of nanobiotechnology in cell-carrying systems has the potential to enhance therapeutic outcomes. In this brief overview, we delve into the intricate workings of biological processes and pathology related to typical and persistent wounds. In addition, we delve into the significance of nanomedicine in tackling the primary concerns linked to chronic wounds, providing a concise overview of the obstacles involved.

Nanoparticle varieties and wound regeneration responses

It is crucial to have a comprehensive understanding of the various types of tiny particles and how they contribute to the healing of wounds to fully utilize the capabilities of nanotechnology for treating chronic wounds [44]. Inorganic nanoparticles, like metal-based or metallic oxide nanoparticles, have some really interesting properties. They have a high surface area and can be adjusted to react in different ways [45]. These characteristics allow for customized interactions inside the wound microcosm, affecting how cells respond and creating an environment that promotes healing. Using polymeric nanoparticles, scientists have developed a method to release drugs in a controlled manner, which leads to long-lasting therapeutic effects [46]. Through the utilization of polymers' distinctive properties, these nanoparticles facilitate the gradual dissolution of medications, enhancing their effectiveness at the site of the wound as time progresses. It is crucial to have a comprehensive understanding of the various types of tiny particles and how they contribute to the process of wound healing. This knowledge is essential to fully utilize the capabilities of nanotechnology. Utilizing nanoparticles made from lipids can be a game-changer in enhancing the dissolution and stability of therapeutic agents for chronic wounds. This is essential for ensuring long-lasting and efficient healing of wounds [47]. These tiny particles, sometimes using liposomes or carriers made of lipids, help to package and slowly release healing substances within the wound's surroundings.

It is essential to give thorough consideration to infections that hinder the healing of tissues when treating chronic wounds. For many years now, silver nanoparticles, which are created through nanobiotechnology, have been successfully utilized in clinical settings to treat microbial infections. In addition, there have been several recent studies that have delved into the realm of nanoplatform-based anti-infection therapies. These studies have looked into the potential of using nanoparticles as a means to combat infections [48-50]. To address tissue defects in the region of wounds, it is crucial to create a platform that promotes cell attachment, migration, and proliferation. This platform, often referred to as a scaffold, plays a vital role in supporting and guiding the cells. This scaffold can also be used as a foundation for multi-functional modification. Due to their excellent compatibility with the human body, ability to promote blood vessel growth, and ability to mimic human biological skin, nano-scaffold systems have become extensively utilized in biological engineering [51].

Approaches in Nanotechnology for tackling microbial infections

There is still much to learn about how nanoparticles (NPs) harm different types of bacteria, as the exact processes involved are not fully understood. However, scientists have put forth several theories to explain these mechanisms. The direct contact with the cell wall of bacteria and the consequent discharge of harmful ions or the production of reactive oxygen species could potentially lead to a bactericidal effect [52]. The interaction between tiny particles and bacterial cell walls is influenced by various forces and receptor-ligand interactions, which can impact the membrane's permeability and integrity [53]. Additionally, NPs can penetrate the outer layer of the cell and can potentially cause negative effects on different parts of the cell, such as proteins and DNA. The oxidative and nitrosative stress caused by NP exposure can result in protein deactivation and changes in gene expression and protein synthesis. These effects ultimately lead to the inhibition or death of bacterial growth. It is not uncommon for chronic wounds to become infected. Although the host defense system is effective in initially controlling the emergence and propagation of microbes, it is important to note that pathogens, like bacteria, can quickly change, evolve, or cultivate biofilms. As a consequence, these microbial infections can hurt the healing process of wounds. It has been shown that nanomedicine has great potential in effectively eradicating infections [54]. Scientists have discovered that nanomaterials have remarkable antimicrobial properties. These tiny materials can directly combat microbes and also serve as carriers for antimicrobial agents or other antibiotics.

Currently, nanomaterials are being utilized as direct antimicrobial agents. This is not only because of their unique "nano" characteristics, but also because of their inherent ability to combat microbes. Additionally, they are being employed as carriers for antimicrobial agents or other antibiotics (Table 1). Photothermal therapy involves the precise application of heat to eliminate bacteria when exposed to radiation. It is highly improbable for drug resistance to occur and it does not have any widespread effects on the body. However, to get rid of microbes in the injury, it is necessary to expose it to high levels of irradiation or local heat. Unfortunately, this can potentially cause damage to the surrounding area.

Table 1: Analysis of Wound Healing with Antimicrobial Nanocomposites

Bacterial species	Bactericidal effects mechanism	Therapeutic effects	NPs properties	NP composition	Comments	References
S. aureus	Release of silver ions, impairment of biofilm, and bacterial destruction of membranes	Disinfection	The size is between 200 and 500 nanometers, while its thickness measures 1.3 nanometers. Additionally, it has a charge of -22 millivolts.	MoS_2@PDA-Ag nanosheets	Photothermal therapy effectively halted the biofilm and microbial membrane, leading to significant changes in their structure	[55]
S. aureus, E.coli	ROS production and microbial rupture of membranes	Disinfection, tissue regeneration, angiogenesis, and proliferation	The size is 25 nanometers.	A unique combination of materials was used to create a hybrid hydrogel, which included 3-(tri-methoxy silyl)propyl methacrylate and mesoporous silica modified CuS NP Ag/AgBr/MSNs.	When exposed to the near-infrared radiation, it exhibited photo-thermal/photodynamic properties.	[56]
S. aureus, E.coli	Release of silver ions when subjected to rays	Promoting cleanliness, encouraging the regrowth of skin cells, and enhancing the production of collagen	The size is approximately 190 nanometers.	A nanocomposite was formed with a core made of gold and silver, and a shell made of CuO_2.	Responsive to light	[57]

S. aureus, E.coli	The antimicrobial property of hydrogel is influenced by the presence of iron – copper No investigation was conducted into the mechanism of toxicity.	Inflammation prevention, disinfection	The size is approximately 14.4 ± 5.8 nanometers.	Bimetallic Iron-Copper nanocomposite	Safe and biocompatible	[58]
Bacillus subtilis, E. coli	Deterring the growth of biofilms and reducing the generation of active oxygen species (O2).	Disinfection	The size is approximately 85 ± 37 nanometers.	Membrane composed of hydrogel nanofibers	Excellent compatibility with living cells	[59]

Exploring the limitations and challenges of Integrating Nanotechnology

Although the use of nanotechnology shows great potential in the field of chronic wound care, certain obstacles and limitations need to be addressed for its successful implementation. This section explores the intricacies, of understanding and tackling challenges related to biocompatibility and regulatory considerations. This section emphasizes the importance of a thorough and careful approach to address challenges, to responsibly harness the possibilities of the technique of nanotechnology in the ongoing treatment of wounds. In the following section, we will delve into the exciting possibilities and advancements that could enhance the use of nanotechnology in the realm of wound healing.

It is of the utmost importance for investigators, regulatory agencies, and industry individuals to work together to make regulatory pathways more efficient and to make it easier to incorporate nanoparticle-based therapies into regular clinical practice. Specialized regulatory considerations are necessary for nanoparticles due to their unique characteristics, which differ from those of traditional drugs [60]. It is crucial to navigate through these regulatory hurdles to guarantee the safe and efficient transition of quantum technology from studies to everyday clinical practice. Ensuring the efficacy and lasting impacts of nanoparticle-based treatments before clinical translation is of utmost importance. The most important challenge is to ensure that tiny particles proposed into the site of the injury microenvironment are compatible with the human body [61]. The complex interaction among tiny particles and biological structures requires a thorough examination to minimize any potential negative impact on cellular processes and the overall process of wound healing.

Opportunities in Nanotechnology for Persistent Wounds

Delving into the wide range of possibilities in nanotechnology for chronic wounds uncovers two interconnected paths: improving how cells absorb treatment and delivering drugs directly to the affected areas. By taking advantage of all these opportunities, nanotechnology not only provides precise beneficial oversight but also understands the complex workings of chronic wounds at a cellular level. In the following sections, we will explore the difficulties that arise when incorporating nanotechnology into the treatment of chronic wounds. Additionally, we will suggest potential ways to overcome these challenges in the future. This improved cellular uptake focuses on an important aspect of persistent wounds, encouraging the start of cellular functions needed for a faster healing response. Chronic wounds frequently show reduced cellular functions, which can impede the body's healing process [62]. By harnessing the power of nanoparticles, we can improve the way we deliver therapeutic agents to the cells responsible for wound repair. These tiny particles have a small size and large surface area, which allows for better cellular uptake and ultimately more effective treatment. This focused approach shows great potential, especially in conditions such as ulcers in diabetic feet where localized treatment is crucial. Nanoparticles offer an accurate platform for delivering drugs directly to the site of chronic wounds, effectively tackling the unique challenges they present [63]. Through the clever manipulation of nanoparticles, we can ensure that therapeutic agents are directed exactly where they are needed, reducing the risk of unwanted side effects and maximizing their effectiveness.

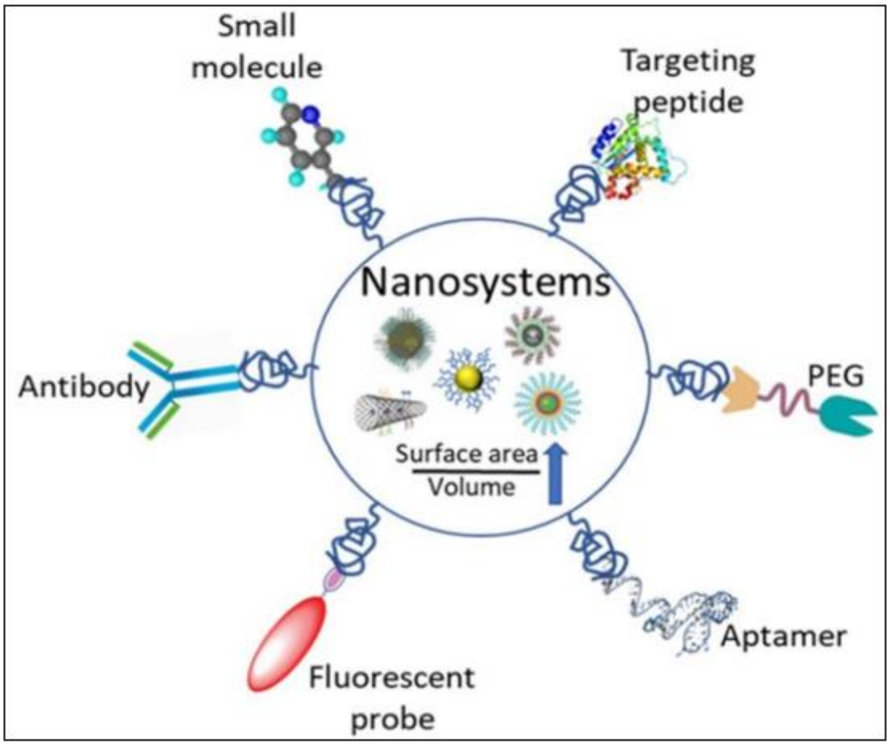

Figure 1: Challenges in the integration of nanotechnology [64].

2. Discussion

Tiny diagnostic devices can be used right at the point of care to assess and treat wounds in the future. These devices, equipped with nanosensors, have the potential to completely transform wound monitoring by giving us real-time information about the wound microenvironment. As we consider those potential paths and innovations, it becomes crucial to foster collaboration among teams from different disciplines. Collaboration between engineers, chemists, scientists, doctors, and legislative professionals is essential to tackle the obstacles and unlock the vast potential of nano-medicine in the field of long-term wound treatment [65].

The combination of nanotechnologies with other advanced disciplines like machine learning and personalized medicine has the potential to lead to groundbreaking discoveries [66]. By utilizing AI algorithms, vast amounts of data can be analyzed to accurately predict personalized responses to therapies involving nanoparticles. This approach allows for a more customized and efficient method of managing chronic wounds [67].

There are two main groups when it comes to nanotechnology methods for chronic healing of wounds. In a more conventional approach, nanomaterials are utilized as carriers to efficiently transport substances that promote blood vessel growth, such as VEGF, FGF, or chemical angiogenic agents, to specific areas [68]. On the other hand, mimicking the tiny surface characteristics of cells in veins and using nanotechnologies to send chemical signals can also help promote the growth of new arteries in persistent wounds. These wounds often have poor blood flow and lack the necessary blood vessels. In broad terms, nanotechnology stimulates vascular development through various mechanisms, such as encouraging the movement of cells that line the vessels, triggering oxidative signaling pathways, controlling the reorganization of the cellular structure, or developing concentrated adhesions [69]. The production of ROS is also believed to play a role in redox signaling pathways during vascular development.

To address the dynamic nature of the epidermis during the recuperation phase of chronic wounds, scientists have created a range of biomaterials that can monitor and respond to various stimuli [70]. To further advance the field of nano-biomaterials, it is crucial to explore their unique properties, including the photothermal impact, chemo-dynamic impact, luminescence, and thermosensitivity. These properties hold great potential for the development of advanced wound treatment methods that can respond to stimulus and provide dynamic surveillance. Many studies have primarily focused on the effects of encouraging movement, activity against bacteria, and delivering substances in the context of wound healing. Nevertheless, there are limited advancements in the field of nanotech-based versatile intelligent systems, including the creation of intelligent coverings that exhibit targeted reactions to various stimuli. Scientists in this field ought to concentrate on creating intelligent systems that mimic the natural healing process for long-term injuries. These systems have the potential to showcase the benefits of nanobiotechnology in enhancing wound healing.

Several studies have shown that certain nanomaterials can enhance the growth of new blood vessels in different tissue regeneration situations, including bone repair, nerve impulse restoration, recovery following ischemia-reperfusion, and healing from wounds [71]. Using nanomaterials instead of growth factors like VEGF-A or PDGF could offer a more favorable option for promoting angiogenesis. This approach may help avoid potential issues like harmful vascular development, blood clots, and inflammation [72]. In addition, many physiological angiogenic agents, like growth hormones, are often expensive, necessitate intricate processing methods, and either have short lifespans or become unsteady in the challenging conditions of chronic wounds [73]. For instance, even though the second phase of the clinical investigation of the fibroblast growth factor 7 demonstrated promise in treating ulcers of the venous system, it did not lead to a significant increase in the general rate of wound repair within the twenty-week study period. The primary explanation for the treatment's ineffectiveness has been identified as the inadequate accumulation of expansion variables within the injury [74]. Utilizing nanotechnology as a delivery vehicle could potentially overcome this issue.

Exciting advancements in nanotechnologies have expanded the possibilities for drug delivery, enabling the transportation of important biomolecules like RNA and DNA or growth factors for use in the rehabilitation of persistent wounds [75]. Due to their compact size and unique characteristics, biomolecules or substances can easily enter cells, safeguarding them from deterioration and improving their ability to reach the affected area. Overall, it enables the delivery of these medications directly to the affected area and extends their effectiveness, reducing the need for frequent applications and expenses. Furthermore, by incorporating drugs and biomolecules into nanocarriers, it becomes possible to create profiles of drug release that are tailored to meet the specific needs of wound healing.

The injury-healing processes observed in monkeys, including human beings, might not be as effective compared to those in mice and rats [76]. Additionally, the expense associated with nanotechnology and the manufacturing platforms needed for widespread production also poses a challenge to the practical application of nanotechnologies in the medical field. In recent years, there has been a significant amount of research focused on utilizing nano-materials and methods to effectively treat wounds that persist. This review provides an overview of various nanobiotechnology-based structures and nanoplatform concepts that have shown promise in the treatment of chronic wounds. It emphasizes the potential of developing a cutting-edge getting for persistent wounds that combines continuous tracking and stimuli-responsive capabilities, pointing towards an exciting future for nano-wound-repairing systems.

3. Conclusion

Through a comprehensive exploration of processes, uses, difficulties, and potential futures, this study paves the way for an exciting new era in the management of wounds with utmost precision. Interaction between teams from different disciplines is crucial as we get around the complexities, making sure that nanotechnology is integrated responsibly and effectively into everyday medical procedures. This exploration provides valuable insights for clinicians, scientists, and elected officials, offering guidance in their ongoing endeavors to utilize nanotechnology to tackle the enduring obstacles presented by chronic wounds. As we peer into the future, we can see the exciting possibilities that lie ahead in the field of nanotechnology. With advancements like nanoengineered scaffolding and the incorporation of AI, we are entering a new era where personalized approaches and cutting-edge technologies come together to revolutionize the way we manage chronic wounds. This in-depth review highlights the crucial impact of nanotechnology in revolutionizing the treatment of chronic wounds. By studying different types of nanoparticles, we can gain a better understanding of how they contribute to the healing of wounds. This research highlights the wide range of applications for lipid-based, crystalline, and inorganic particles. Investigations and research studies have shown the practical effectiveness of nanotechnology in encouraging healing from wounds, highlighting its real-world applications. Ultimately, the investigation into nanotechnology in the realm of chronic wound care uncovers a vast array of possibilities, obstacles, and promising advancements. The unveiling emphasized the urgent requirement for more advanced therapeutic approaches in the treatment of long-term wounds, creating a foundation for further investigation. Promising possibilities in nanotechnology for persistent wounds have surfaced, with a focus on specific drug delivery and improved cellular absorption. These advancements offer precise interventions for better treatment outcomes. Nevertheless, there were recognized obstacles such as concerns about how well the technology would work with the human body and the need to navigate through complex regulations. This highlights the significance of conducting thorough assessments and finding efficient ways to navigate the regulatory process.

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