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The Role of Lipid-Based, Polymeric and Metallic Targeted Nanoparticles Delivery for the Treatment of Burn Wound Repair

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Abstract

Burn injuries present key medical issues because of their complexity, alongside long healing periods, and with the higher likelihood of infection. Typical burn care, such as ointments and wraps, features some cons like poor drug permeation, spotty drug dispersal, and promoting antimicrobial resistance. Thus, nano-drug delivery systems arose as a new way to better treat burn wound. Nanoparticles (NPs) offer many advantages, such as targeted drug delivery into cells, greatly improved bioavailability, relatively sustained drug release, and enhanced protection of therapeutic agents against degradation. This review explores the role of lipid-based, polymeric, and metallic NPs in burn wound repair. Lipid-based NPs, such as liposomes along with nanostructured lipid carriers, greatly improve drug retention via controlled release. Certain polymeric NPs, including dendrimers and chitosan-based systems, improve wound healing by controlled drug delivery and biocompatibility. Metallic NPs particular silver and gold NPs, exhibit strong antimicrobial properties significantly reducing the risk of burn wound infections. Thus, this lessens the chance of getting burn wound infections. Also, some specific nanocarriers, such as with stimuli-responsive and biomimetic NPs, show added gains in accurate drug transport and for faster wound repair. Despite their promising applications, problems are present, such as potential toxicity. Definite regulatory concerns, along with the highly optimized penetration need throughout damaged skin, remain real barriers against routine clinical implementation. Additional future research should focus intently on improving of nanoparticle safety profiles along with on refining of delivery mechanisms, besides conducting of wide-ranging clinical trials for generally validating their efficacy. Nanotechnology driven approaches definitely hold great potential for transforming burn care by addressing existing limitations and improving therapeutic outcomes.

Keywords: Nanoparticles, Solid lipid nanoparticles, Nanostructured lipid carriers

Introduction

Burns are complex injuries that are classified based on their depth as superficial (first-degree), partial-thickness (second-degree), or full-thickness (third-degree). Due to their complexity, burn severity results from an intricate healing process that necessitates careful balance between several phases, including hemostasis, inflammation, proliferation, and remodeling (1).

The inflammation phase involves protective responses initiated by the body characterized by increased vascular permeability and infiltration of immune cells. The proliferative phase is characterized by the extensive development of granulation tissue, angiogenesis and re-epithelialization, while the remodeling phase includes the overall reconfiguration of the extracellular matrix and progressive formation of scars. In severe cases, burn care must address each phase equally. Standard care focuses on various stages of the recovery process.

One major obstacle to effective burn care is the heightened risk of infection from compromised skin integrity. Typical treatments like antibacterial drugs or wound care aim to mitigate these issues. However, these treatments often do not address all aspects of burn treatment (2). Despite the use of traditional burn treatments, there are limitations to topical antibiotic application, such as the development of antibiotic resistance and substandard drug delivery to the site. Burn injuries which involve inflammation, oxidative stress, and impaired angiogenesis require a more advanced and targeted therapeutic approach.

Traditional burn treatments face challenges such as poor tissue penetration, inconsistent drug release, and limited efficacy. To address these issues, scientists have looked at specific treatments. Nanoparticle-based systems offer attractive solutions to these issues due to their small size (1-100 nm). They can target specific cell types or healing-related tissues, release therapeutic compounds over an extended period of time, and penetrate damaged skin barriers. They may target specific cell types or healing-related tissues, release therapeutic compounds over an extended period of time, and penetrate damaged skin barriers. With their innovative approaches to tissue repair and wound healing, nanoparticles (NPs) have become a viable medication delivery method (3,4). By targeting local areas, even in burn wounds where cells are suffering, they

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increase drug solubility, improve bioavailability, provide sustained drug release, and reduce systemic toxicity (3). NPs systems not only preserve medicinal chemicals but also protect them from deterioration, increase their retention time, and promote deeper penetration through compromised skin barriers. Additionally, by functionalizing NPs with the proper ligands, they can bind to specific receptors expressed at burn sites, allowing accurate drug delivery to the targeted site of action.

NPs possess unique physicochemical characteristics that allow them to encapsulate and release various therapeutic agents. They have emerged as an effective strategy for treating injuries caused by blunt or penetrating trauma. Strategies to enhance drug solubility, target specificity, and therapeutic delivery over time can be incorporated into these nanoscale carriers (5). Among various nanotechnology-based approaches, dendrimer-based hydrogels have been shown to effectively enhance the bioavailability and efficacy of healing drugs that are applied after injury to tissue such as hesperidin in full-thickness wounds. (6). Nanotherapeutics, including metallic and polymeric nanoformulations, are being extensively developed to manage various types of burns.

This review provides data beyond the limitations of traditional burn treatments and emphasize the advantages of nanoparticle-based medication delivery systems. Additionally, it presents the significance of lipid-based and polymeric nanocarriers, their unique properties, and their applications in the healing of burn wounds. Finally, the challenges and possible future directions of burn wound healing in this rapidly evolving field, with a focus on the development of safe, effective, and clinically useful nanotherapeutics for burn injuries are discussed.

Traditional Burn Wound Treatments

A key aspect in the care of burn wounds is the severity of the burns, including mild, severe, and clinical burns. In 76 children, minor burns are defined as burns that involve less than 10% of TBSA, and in adults, less than 15%. As opposed to critical burns, which are also referred to as life-threatening burns, major burns are defined as burns that involve up to 30% TBSA in children and 35% in adults. A crucial part of burn care is pain management. Opioids and non-steroidal anti-inflammatory medicines are two examples of painkillers that are frequently used to treat burn burns. Conventional methods of treating burn injuries depend on these therapies.

Pathology of Burn Wounds

Burn wound healing can be divided into three different phases. Inflammation, an initial step, by means of immune cell activation sets the basis for repair to eliminate waste and pathogens (7). During the second step, damaged tissues get replaced through new tissues. This stage is characterized by the proliferation of several cell types, to include fibroblasts, keratinocytes, as well as endothelial cells (8). The final stage within burn wound healing is remodeling. This lengthy process can last for months to years. Throughout this entire stage, the new tissue steadily matures and changes, supporting increased strength and functionality (9).

Burn injuries create an inflammatory environment marked by elevated pro-inflammatory cytokines brought on by oxidative stress that presents special opportunities for personalized nanoparticle treatments. Anti-inflammatory medications can be delivered exactly to the spot with NPs for response, as required, to inflammatory markers. Via the precise distribution of anti-inflammatory drugs as well as the employment of particular inflammatory markers, NPs tackle pathological hyper inflammation, which can sometimes make burn recovery more challenging. NPs can fully encapsulate multiple growth factors along with several bioactive substances. They specifically promote tissue regeneration, in addition to cell proliferation throughout the proliferative phase, and also prevent fragile molecules from rapidly degrading inside the harsh wound environment.

Patient health considerably affects burn healing. Certain conditions such as diabetes, malnutrition, and immunosuppression delay healing (10,11). Malnutrition prevents complete cellular repair, diabetes impairs blood flow as well as sensibility, in addition to immunosuppression increases the infection risk. Successful wound closure needs treatment that is specialized for these diseases. Malnutrition prevents cellular repair, diabetes impairs blood flow and sensibility, and immunosuppression increases the infection risk. These conditions require specialized treatment for successful wound closure.

General Use of NPs in Burn Treatment

A key advantage of NPs delivery systems is that they may help avoid existing drawbacks associated with traditional topical treatments. They can improve drug permeation through the stratum corneum, the outermost layer of the skin that often serves as a barrier to drug absorption, and thus increase drug bioavailability and extend the effective treatment life of agents that are prescribed to help patients with a wide variety of diseases caused by bacteria, viruses or parasites.

For hydrophobic drugs, NPs offer improved dissolving conditions. The placement of specific medications is improved due to these nanoparticle' ideal tumoral transport and enhanced macrophagic drug solubility (12). Nanocarriers for topical delivery of drugs encompass several categories based on their material, including polymers, lipids, metals, and vesicles. Among these, lipid-based NPs have gained the most attention due to their versatility and biocompatibility with human tissues (12).

Type of NPs for Burn Wound Management

Lipid Based NPs

Lipid based NPs include liposomes, nanostructured lipid

carriers (NLCs), and solid lipid nanoparticles (SLNs). These carriers enhance target-specific drug delivery by increasing drug loading capacity and efficacy. These lipid-based nanocarriers offer prolonged and controlled drug release, thus enhancing the therapeutic outcomes and the distribution of drugs (13).

For the most particular, the greater drug loading capacity, 125 improved drug release patterns, and improved physical stability of NLCs make them a significant improvement over SLNs. Their matrix structure, which blends liquid and solid lipids, has these benefits because it creates a more imperfect 128 crystal arrangement that increases medication accommodation and reduces expulsion while being stored. According to comparative studies, NLCs frequently perform better than SLNs in terms of stability, drug release control, and encapsulation efficiency—especially at higher drug concentrations. However, it is crucial to remember that both NLCs and SLNs have formulation issues, such as potential cytotoxicity based on the lipid composition and troubles scaling up for commercial manufacturing (14).

Polymeric Nanoparticles

Polymeric NPs are conjugated from suitable biocompatible polymers like PLGA, chitosan, and PEG. They can be specifically engineered to optimize burn wound treatment through enhanced delivery, enabling controlled stepwise release of medicines, and improving their interaction with damaged tissues (15). Dendrimers, a subtype of polymeric NPs, are designed for burn site delivery due to their ability to transport various drugs (16). Polymeric nanomaterials are biocompatible and biodegradable, they are frequently used to create nanotherapeutics, including liposomes, NPs, nanoemulsions, nanogels, nanofibres, and nanosheets, that are used to treat burn injuries. Hydrophilic and hydrophobic medications can be included in these materials (17). With the natural ability to promote wound healing, polysaccharides (such as chitosan-based NPs) aid in accelerating epithelialization and reducing scarring. Silver and gold metallic NPs have demonstrated encouraging outcomes in the treatment of burn injuries.

Metallic Nanoparticles

Metallic NPs such as silver and gold, have shown promising results in burn wound management. To prevent infection and promote fast healing metal are incorporated on nanogels (18). The management of burn wounds frequently involves the use of metal and metal oxide nanotherapeutics, especially silver nanoparticles (Ag NPs), which have shown potent antibacterial activity. Because Ag NPs have better penetration and retention than ionic silver, they have better antibacterial properties (19).

Ag NPs are frequently placed onto biological or polymer materials to increase their duration and efficacy. Porcine small intestinal submucosa (PSIS) loaded with Ag NP, for example, considerably enhanced healing in rat models by lowering inflammation and encouraging neovascularization and re-epithelialization. Safer formulations, such as Ag/AgCl NPs coated with graphite, have been developed because Ag+ ion release can be hazardous to people (e.g., argyria) (20). With less Ag+ toxicity, these composites demonstrated improved tissue regeneration and antibacterial activity in animal models. However, new evidence suggests that using Ag NPs for a long time or too much can give rise to bacterial resistance, which could restrict their value in the long term. This increasing concern shows how important it is to use resistance mechanisms alongside additional techniques carefully and do additional studies on them.

Nanofibres

Nanofibres (1–100 nm), produced from different polymers such as polydimethylsiloxane, polyethylene terephthalate, polyethersulfone, poly (acrylic acid) (PLA) and poly (methyl methacrylate) have been incorporated to fabricate nanofibres. They can be loaded with polyethylata terephthalate, poly (acrylic acid) (PLA) or peptides to promote healing and fight infection (21). Particularly, heparin-mimetic peptide nanofibres help full-thickness burn recovery by imitating the extracellular matrix, increasing growth factor expression (e.g., VEGF, bFGF), promoting angiogenesis, accelerating wound closure, and minimizing scar formation (22). Nanofibres also serve as a physical barrier to pathogens, hold moisture, allow gas exchange, absorb exudate, and can be loaded with medicinal compounds to hasten healing and enhance cosmetic results (23).

Titanium Dioxide Nanoparticles

Titanium dioxide nanoparticles (TiO_2 NPs) emerged as attractive applicants in burn wound therapy because of its multifunctional properties. They are used in chitosan-cellulose membranes by freeze gelation, they improve swelling, biodegradability, and angiogenesis stimulation—important for tissue regeneration. Particularly when combined with laser-assisted treatment, polycaprolactone yolk-shell particles comprising TiO_2-Ag NPs and Ganoderma lucidum polysaccharides provide antioxidant, antibacterial, and photothermal effects. Strong ROS scavenging, mechanical strength, and wet adherence have been demonstrated by a hybrid sponge dressing made of TiO_2 NPs, hyaluronic acid, gelatin, and antibacterial agents. In vivo, it increases re-epithelialization, angiogenesis, collagen accumulation and reduces inflammation. Overall, TiO_2 NPs support wound healing by promoting angiogenesis, improving cell metabolism, and reducing inflammation (1).

Specialized and Composite Nanoparticle Systems

Over the past five years, ever more advanced nanoparticle systems have been developed especially to meet the

complex needs of burn to repair. These consist of hybrid NPs incorporating the characteristics of multiple substances, core-shell architectures for sustained release of multiple therapeutics, and functionalized NPs that mediate delivery to certain cell types or molecular pathways pivotal to repair. One such innovation is luminol-conjugated cyclodextrin (LCD) nanoparticle therapy recently developed by researchers at the Army Medical University, in China (24). This system is designed to target burn-induced damage to the intestinal barrier, an acute systemic complication of severe burns that can lead to sepsis and organ failure. The disturbance of the intestinal barrier, which causes systemic health issues in addition to inflammation, is a serious concern in burn patients with severity. LCD NPs target the increased oxidative stress. Neutrophil hyperactivation causes barrier dysfunction as well. In preclinical studies, these NPs observably reduced intestinal permeability, also decreased systemic inflammatory markers, further improved survival rates following severe burns. This tailored strategy shows how certain nanoparticle therapies can address the major systemic consequences of severe burn injuries as well as local wound healing.

Mechanisms of Action

Occlusive Effect

Increased hydration and improved medication penetration result from an occlusive layer formed on the skin by SLNs and nanolipid carriers (25). Burn wounds benefit especially from this process since it can preserve a moist environment conductive to healing.

Vesicular Penetration

Entrapped medications can be more effectively penetrating into deeper layers of the skin via vesicular carriers like liposomes, niosomes, and ultradeformable vesicles (25). By delivering therapeutic drugs more precisely to the burn site, these carriers might improve therapy results.

Stimuli Responsive Delivery Systems

pH Responsive Systems

pH Responsive Systems are designed to release therapeutics according to fluctuations in the wound microenvironment**.** The pH-sensitive vancomycin loaded silk fibroin-sodium alginate NPs embedded in poly(N-isopropylacrylamide) (PNIPAM) hydrogel containing epidermal growth factor (EGF) for the treatment of chronic burn wound infections (26).

Temperature-Responsive Systems

Temperature-responsive NPs, such as those incorporated into hydrogels, can release drugs in response to body temperature and minimize systemic side effects. An inventive hydrogel dressing, named PHDNN6 combines remote Bluetooth temperature checking and light-triggered nitric oxide (NO) discharge to improve wound healing and administration (27).

Targeted Delivery Mechanisms

Ligand Targeted Delivery

The precise distribution of therapeutic drugs intended to bind specific molecules at the wound site is ensured using ligand-targeted NPs. This technique improves therapy's effectiveness and lessens off-target effects (28).

Direct Therapeutic Effects

Antimicrobial Properties

Strong antibacterial activity is exhibited by NPs, which is crucial for the treatment of burn wound infections. The reactive oxygen species produced by silver (Ag) and zinc oxide (ZnO) NPs degrade bacterial membranes, proteins and DNA thereby eliminating pathogens including antibiotic resistant strains such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii.* Additionally, silver ions released by Ag NPs disrupt the respiration of microorganisms.

Biomimetic Nanoparticles

These are used to produce a local effect and enhance treatment efficacy (29). They serve as drug delivery systems that increase therapeutic efficacy and safety. Examples include platelet-mimicking NPs that target particular regions of vascular injury in burn wounds and cell membrane-coated NPs that may prevent immune clearance (30).

Advantages

NPs offer several advantages in wound healing applications. Globally, wound treatment is difficult and expensive (31). Current wound dressings frequently don't adjust to the conditions of the wound and might hurt to remove, especially when applied on uneven skin. Bioadhesive nanocomposite hydrogels are being investigated as a solution to these problems because of their strong mechanical, elastic, and antibacterial qualities (32). Too much oxidative stress hinders healing, particularly in diseases like diabetes. In diabetic patients, antioxidant-based hydrogels (such as those containing quercetin and oleic acid) have demonstrated enhanced healing. Using tea tree oil and antioxidants (quercetin and α-tocopherol). Costa-Fernandez et al created NLCs, which were then supplemented with chitosan or alginate for bioadhesion (33). Fibroblast migration was facilitated by these, indicating the possibility of successful wound healing.

The L-DOPA-based proteins found in mussels and gallic acid, a polyphenol with antibacterial and metal-binding properties, serve as inspiration for bioadhesives that show promise for use in wound care. In numerous investigations, the potent immunosuppressant rapamycin showed only mild adverse effects (34). Because it suppresses the immune system and has anti-inflammatory properties in

some immune cell subsets, it has been shown to prevent allograft rejection in obese graft recipients. Furthermore, rapamycin and programmed death-ligand 1 co-delivery in nanovesicles can result in allograft acceptance (35).

ZnO NPs have been used as potential antimicrobial agents. The production of reactive oxygen species and electrostatic contact between the microbial cell-surface and ZnO NPs ascribed to their antibacterial activity finally causes photodestruction by oxidative stress. In fact, even at extremely low concentrations ZnO NPs can inhibit pathogenic microbial growth, which is beneficial in comparison to other kinds of NPs (36). ZnO NPs were incorporated into the gelatin-catechol matrix as antimicrobials. It was seen that the nanocomposites showed increased antimicrobial properties, especially when 3% weight of ZnO NP was included (37).

Challenges and Limitations

Combating various restrictions of current topical treatments, including poor drug solubility, limited penetration across the stratum corneum, and low bioavailability, nanoparticle-based drug delivery methods have showed promise (38). However there are still challenges to overcome. Ensuring efficient penetration of NPs across damaged skin barriers in burn wounds while preserving specific delivery to particular locations of action offers a significant difficulty (25).

Nanotechnology has a lot of benefits, but it also has a lot of problems and obstacles. Some NPs have shown that they could be harmful to both people and the environment. They often have biological effects that are different from those of larger NPs. Also, we are still unaware of how NPs interact with living things, so it's hard to properly forecast how they will affect human health and the environment in the 267 long run. There remain not many clinical uses for nanotechnology. Liposomal doxorubicin is a 268 NP-based formulation that has been approved by regulators. However, most nanomedicine applicants have not gone previous early-phase trials. Limited long-term safety evidence, variations in how 270NPs behave in different biological systems and a lack of knowledge about their pharmacokinetics and 280 biodistribution are some of the problems that make it hard for clinical adoption.

Despite the numerous benefits offered by nanotechnology, they exhibit several drawbacks and challenges. Several NPs possess potential toxicity to humans and to the environment, due to their biological effects, when compared to their large sized counterparts (39). Additionally, the details of interactions existing between the biological systems and NPs are not completely elaborated. Hence, the consequences of their use on human health and ecosystems are not fully estimated (40).

Despite being the gold standard treatment for burn wounds, SSD has been shown to have detrimental effects on the healing process in a number of researches conducted in the past ten years. SSD's inability to dissolve limits its therapeutic potential, and antibacterial activity cannot be observed until SSD separates into silver ions (Ag+) and sulfadiazine (SD) (41).

Generally, by reducing inflammation, the nano-delivery technology improves compatibility and modifies the bioactive compound's efficacy on burn wounds. Their investigation is still lacking, though, thus clinical models must be used to determine potential paths and mechanisms of action (42).

Future Directions

To this extent, nanotherapeutics, such as metallic and polymeric nanoformulations, have been designed to treat different types of burns however, targeted NPs delivery has been making rapid strides in the realm of plastic surgery research and development.

The emphasis has been on the development of nanocarriers that are biodegradable and non-toxic and can provide controlled drug release, which would permit therapeutic effects to occur only at the site of application (4).

Traditional burn management techniques, which can have drawbacks such donor site morbidity, scarring, and protracted healing times, are being replaced by more modern approaches, as the editor document emphasizes. Improved medicine delivery, tissue regeneration, and more effective infection control are all made possible by nanotechnology. In the burn wound microenvironment, NPs can be designed to target particular cells and tissues.

The use of silver NPs in contemporary dressings is one area of special interest, as it is being investigated for its effects on tissue morphology and clinical healing after skin burns (43).

Novel materials like zinc oxide nanoparticle TiO_2, and cerium oxide (CeO_2) are under investigation for their antioxidant, antimicrobial, and pro-regenerative properties. To promote healing and reduce cytotoxicity, composite dressings that combine Ag NPs with additional substances like growth factors or curcumin are being explored.

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Assessment of Burn Wounds Treated With Nanotherapeutics

Both in vitro and in vivo models have been extensively used to assess the therapeutic efficacies of nanotherapeutics. Nanotherapeutics' in vitro therapeutic efficacies have primarily been evaluated using antibacterial, anti-inflammatory, and cell proliferation tests. Nonetheless, a lot of research has examined the in vivo therapeutic effectiveness of nanotherapeutics using animal models. The therapeutic benefits of nanotherapeutics on burn wounds, whether or not they are bacterially infected, have

been assessed in a variety of studies using animals with burn wounds, including mice, rats, rabbits, dogs, and piglets (44). Researchers also looked at the clinical use of nanotherapeutics in people who had partial-thickness thermal burns that ranged from 15% to 40%. Burn wounds are still mostly treated with nanotherapeutics using antibacterials, anti-inflammatory drugs, and GF expression mediation.

Conclusions

Due to the shortcomings of conventional topical treatments, drug delivery systems based on NPs provide a revolutionary approach to the management of burn wounds. By facilitating targeted therapeutic delivery, increasing drug penetration, and improving bioavailability, these systems hasten healing and lower the risk of infection. Metallic NPs provide strong antimicrobial activity, polymeric NPs allow for controlled drug release, and lipid NPs create an occlusive effect that retains moisture, promoting an optimal healing environment. However, issues like possible toxicity, regulatory hurdles, and the need for improved tissue penetration continue to be barriers to clinical use. The optimization of nanoparticle formulations, human application safety, and extensive clinical trials to confirm efficacy should be the top priorities of future research. With continued advancements, NPs have the potential to revolutionize burn treatment, offering safer, more precise, and highly effective therapies for improved patient recovery. With ongoing advancements, nanotechnology is set to revolutionize burn care, providing safer, more effective, and highly targeted therapeutic solutions for improved patient recovery.

But despite their promise, a number of obstacles still exist. The need for more efficient penetration into deep tissue, regulatory obstacles, cytotoxicity, and a lack of clinical evidence are all issues that need to be addressed. Preclinical to clinical stage advancement, long-term safety assessment, and nanoparticle formulation improvement should be the top priorities of future research. Nanotechnology could completely change the way burn wounds are managed with further research and meticulous validation, leading to safer, more effective, and patient-specific solutions.

Conflict of Interests

Authors have no conflict of interest.

Ethical Issues

Not applicable.

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