Recent Advances in Nanocarrier Delivery Systems for the Treatment of Gangrene

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Abstract
Introduction: Gangrene is a horrible disease that kills tissue. Since its pathophysiology is so intricate, with ischemia, infection, and inflammation all playing a role, it is particularly hard to cure. Standard treatments are vital for preserving lives and limbs, but they can be intrusive, create a lot of problems, and don't always work effectively since medications don't penetrate into damaged tissues very well, they might be bad for the whole body, and antimicrobial resistance is on the rise. Methods and materials: Nanocarrier delivery systems are a new technique to address these needs that have never been met before. This study gives a full picture of the most recent developments in several nanocarrier platforms, such as liposomes, polymeric nanoparticles, micelles, dendrimers, nanosuspensions, and solid lipid nanoparticles. It explains their basic principles, structural benefits, and wide range of uses. Result: These uses including as improving the distribution of antibiotics, encouraging tissue regeneration through gene and growth factor treatment, and allowing for several therapeutic methods for gangrene. The talk also talks about problems with toxicity, stability, and clinical translation that are happening right now, as well as where personalized medicine and smart wound care are headed in the future. Conclusion: The use of nanocarrier technologies together has a lot of potential to change the way gangrene is treated by providing tailored, long-lasting, and very effective treatments that reduce tissue loss and enhance patient outcomes.

Keywords
Gangrene, liposome, nanocarrier, micelles, dendrimer
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1. Gangrene

Gangrene is a very bad medical illness that happens when body tissue dies, usually because there isn't enough blood flow (ischemia) or because of a bad bacterial infection. This painful illness often affects the arms, legs, toes, and fingers, but it can also affect internal organs like the gallbladder or intestines [1]. The quick progression and risk of systemic problems, such as sepsis and limb loss, make it clear that immediate action is needed.

Gangrene can be of several types with vivid symptoms and etiology. Dry gangrene is usually caused by ischemic tissue that has dried up. This is prevalent in advanced peripheral artery disease or atherosclerosis [2].

Wet gangrene, occurs when ischemic tissue gets infected with bacteria, or it might happen right after a bad injury, a deep burn, or an existing infection. Wet gangrene is fatal and can be caused by Staphylococcus, and, in rare cases, Gram-negative sea organisms like *Vibrio vulnificus* [3].

Gas gangrene, or Clostridium myonecrosis, is a quickly spreading necrotizing illness that mostly attacks deep muscle tissue. *Clostridium perfringens* and other Clostridium species are the most prevalent causes. *Staphylococcus aureus*, and *Vibrio vulnificus* can also cause it [4].

Fournier's gangrene is an uncommon but deadly kind of necrotizing fasciitis that affects the genitals or perineum and is caused by both aerobic and anaerobic bacteria [5].

Some of the most important risk factors for gangrene are diabetes mellitus, which can damage blood vessels and make it harder for blood to flow; blood vessel diseases like atherosclerosis and blood clots; severe traumatic injuries or surgical wounds that let bacteria in; smoking; overweight; and a weakened immune system.

The complex pathophysiology of gangrene, resulting from a combination of ischemia, bacterial infection, and inflammation, necessitates combined therapeutic approaches. Hence there is need of multi-modal medicines that can fight infection, improve blood flow, get rid of toxins, lessen inflammation, and help tissues heal all at the same time.

1.2. Standard treatment methods

The standard approach to treating gangrene is using a lot of different methods that are meant to stop the infection, restore normal blood flow, and remove dead tissue. In certain situations biosurgery, may be employed as an alternative to conventional debridement [6].

Antibiotic treatment is a key part of treating bacterial infections. It is sometimes given through an IV to make sure that strong doses reach the affected area. Penicillin and clindamycin are two drugs that are often used together to treat gas gangrene.

Vascular surgeries like bypass surgery and angioplasty are done to get blood flowing again to places that aren't getting enough blood.

Hyperbaric Oxygen Therapy (HBOT) is a non-surgical treatment that involves breathing 100% oxygen in a room that is pressurized. This treatment raises the amount of oxygen in tissues by a lot, which helps them heal, lowers the chance of infection, encourages the creation of new tissue and blood vessels (neovascularization), and is especially good at killing anaerobic bacteria like Clostridium through hyperoxia [7].

Although these common practices can save lives, they can also lead to numerous issues and are frequently highly invasive. Patients' quality of life is significantly impacted and they are often hospitalized for an extended period of time due to the necessity of extensive surgical debridement, repeated procedures, and amputation.

1.3. Challenges in Gangrene Management

Many issues still make it difficult to effectively control gangrene, even though traditional treatments have improved. One major issue with high-dose antibiotics is their systemic toxicity. Regular antibiotics must frequently be administered systemically at doses that may result in adverse effects, such as organ damage, in order to achieve therapeutic levels at the infection site. Due to frequent exposure to low concentrations of antibiotics, this broad distribution also aids in the evolution of resistant strains of bacteria [1].

Additionally, conventional antibiotics and other medications are less effective when they are unable to penetrate tissues that are necrotic, ischemia-infected, or biofilm-infected. Because of their altered bacterial physiology and protective extracellular matrix, biofilms are notoriously difficult to destroy. This renders them impervious to both the host's immune system and conventional antimicrobial therapies. This penetration issue is exacerbated by the blood flow issues in gangrenous tissue, which leads to a vicious cycle of tissue destruction and infection.

Another significant issue is the short half-life and rapid degradation of therapeutic macromolecules, such as growth factors (GFs), which are essential for angiogenesis and tissue regeneration.

Numerous illnesses and exorbitant medical expenses result from the combined impact of these connected issues. The inability of current methods to successfully break the cycle of infection, ischemia, and tissue damage demonstrates the urgent need for novel, focused, and regenerative therapeutic approaches. Delivery technologies for nanocarriers are emerging as a practical solution to these significant issues.

2. Nanocarrier based Delivery Systems

The field of nanomedicine is undergoing rapid change. It employs materials with sizes ranging from 1 to 1000 nanometers for both therapeutic and diagnostic applications. Because it circumvents many of the issues associated with conventional drug delivery systems, particularly in complex situations like gangrene, this approach has the potential to revolutionize the game [8].

2.1. Advantages of nanotechnology in Drug Delivery

Drug delivery using nanoparticles is based on their special physicochemical characteristics, which can be precisely engineered to produce the best therapeutic outcomes. It offers several advantages over the conventional delivery systems [8].

- High Surface Area to Volume Ratio
- Ease of modification
- Improved Solubility and Stability
- Increased Bioavailability and Efficacy
- Reduced Toxicity/Side Effects
- Permeating the Biological Barriers

2.2. Mechanisms involved in Targeted Delivery

Advanced targeting techniques are used in nanoparticle-based drug delivery to ensure that therapeutic drugs are delivered to the appropriate locations with high specificity. This minimizes off-target effects and increases their efficacy. These mechanisms can be divided into two primary categories: passive and active.

Passive Targeting: This technique encourages the accumulation of nanoparticles in specific regions by utilizing the physiological and pathological characteristics of diseased tissues. The most well-known method of passively targeting something is the Enhanced Permeability and Retention (EPR) effect. Nanoparticles, which are typically 20–200 nm in size, may seep out of these vessels and accumulate in the diseased tissue's interstitial space. The lymphatic system's inability to remove them keeps them there. The EPR effect might not always be sufficient to reach therapeutic levels or penetrate deep tissue, and it might only marginally enhance drug delivery when compared to normal organs [9].

Active Targeting: The modification of nanocarrier surface with specific ligands makes them more specific and overcome the problems with passive

targeting. These ligands bind to specific receptors or antigens that are overexpressed on the target cell. They can be antibodies, peptides, aptamers, or small molecules. This reduces the possibility of damaging healthy tissues, increases the selectivity of drug delivery, and facilitates cell uptake of the drug (usually through receptor-mediated endocytosis) [9].

It is possible to design nanocarriers as systems that react to stimuli. When these "smart" nanoparticles sense changes in the pathological microenvironment, such as changes in pH (infected or inflammatory tissues have an acidic pH), redox potential (in cells, glutathione levels are higher), enzyme activity (in necrotic tissue, there are more proteases), or reactive oxygen species (ROS), they are made to release their therapeutic agents [10]. Other external factors that can also cause medication release include heat, light, ultrasound, and magnetic fields. By ensuring that the medication is released precisely when and where it is required, this optimizes the therapeutic benefit and further reduces off-target effects [11].

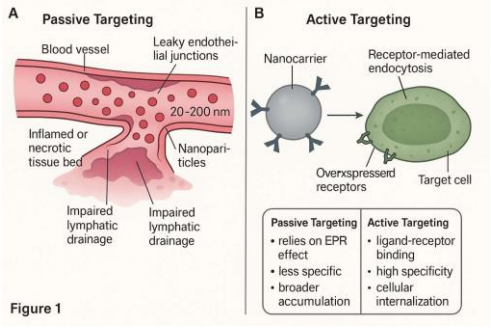

Figure 1: Schematic of Nanocarrier Targeting Mechanisms (Passive vs. Active)

3. Types of Nanocarrier systems

Numerous nanocarrier platforms have been developed in nanomedicine, each with unique structural characteristics and therapeutic advantages. By circumventing the issues with conventional treatments, researchers are investigating these platforms to see if they could alter the way gangrene is treated.

3.1. Liposomes

Typically ranging in diameter from 50 to 450 nanometers, liposomes are spherical vesicles with one or more concentric phospholipid bilayers encasing distinct water spaces. They can hold hydrophilic (water-soluble) materials in their watery core and hydrophobic (fat-soluble) drugs in their lipid bilayers thanks to this unique structure [12].

Liposome-entrapped aminoglycosides have demonstrated a significantly stronger antibacterial action against resistant strains of Pseudomonas aeruginosa when used to administer antibiotics for the treatment of gangrene. Furthermore, novel toxin-triggered liposomal antibiotic delivery systems are being developed. These systems break down liposomes and release antibiotics only at the infection site by using bacterial leukotoxins, such as LtxA. Localized bacterial infections in gangrenous tissue can be effectively treated with this customized release system. Prostaglandin E1 integrated into lipid microspheres, or lipo-PGE1, demonstrated a notable improvement in ulcer healing and peripheral vascular disease in a clinical study. This implies that it might increase blood flow and prevent gangrene from worsening, which is crucial for both preventing and treating gangrene and diabetic wound healing. Additionally, in diabetic mice, liposomes containing microRNA-132 have accelerated wound healing, reduced inflammation, and promoted keratinocyte growth. Epidermal growth factor (EGF), insulin-like growth factor-1 (IGF-1), and platelet-derived growth factor-A (PDGF-A)-containing cationic elastic liposomes have also been shown to aid in wound healing, dermal tissue reconstruction, and re-epithelialization in diabetic mice with ulcers [13].

Because liposomes can hold a variety of substances and mimic biological systems, they are an excellent treatment for both the infectious and ischemic aspects of gangrene. They can directly interact with cellular structures and are biocompatible due to their phospholipid nature, which is similar to that of biological membranes. Since gangrene requires a variety of treatments, it's critical that this can contain a variety of medications, including growth hormones, nucleic acids, and antibiotics. The development of "toxin-triggered" release mechanisms is a significant advancement. They release medications that react to the environment where the bacteria are active, going beyond simple passive accumulation. This provides extremely focused and localized care for the gangrene's infectious areas [12,14].

3.2. Polymeric Nanoparticles

Another novel kind of nanocarrier is polymeric nanoparticles (PNPs), which are typically 10–1000 nanometers in size. They are very helpful for delivering drugs because of their small size, flexibility, and ability to move and preserve drugs. The ability to create "smart" PNPs that respond to specific internal stimuli present in diseased microenvironments, such as variations in pH, temperature, or enzyme activity, has been made possible by recent advancements. PNPs are widely used in gene delivery, cancer treatment, and the administration of drugs that are difficult to absorb or dissolve [15].

PNPs provide numerous beneficial gangrene treatment options. Additionally, polymeric nanoparticles are effective at delivering growth factors to non-healing wounds, such as vascular endothelial growth factor (VEGF), keratinocyte growth factor (KGF), and epidermal growth factor (EGF). They facilitate the

gradual release of these fragile biomolecules, accelerating tissue regeneration and wound healing. With a controlled release profile and minimal cytotoxicity, chitosan nanoparticles loaded with metronidazole have demonstrated potent antibacterial activity against *Clostridium perfringens*, a primary cause of gas gangrene. Additionally, it has been demonstrated that poly(lactide-co-glycolide) (PLGA) nanoparticles release lactate, which promotes the formation of new blood vessels and the healing of wounds [16].

The ability to modify the responsiveness and composition of polymeric nanoparticles is crucial for tailoring therapies to the dynamic and diverse gangrene microenvironment. Different types of bacteria, varying degrees of tissue damage, and variations in oxygen, pH, and enzyme activity are all present in gangrenous tissue. Drug delivery is incredibly precise and targeted thanks to the ability to create "smart" PNPs that react to these particular physiological cues, such as releasing medications in acidic diseased areas or at necrosis sites [17].

3.3. Polymeric Micelles

Polymeric micelles (PMs) are tiny drug delivery devices with a unique core-shell structure that is generated when amphiphilic block copolymers come together in water. The hydrophobic parts of the copolymers come together to make the core during this self-assembly process. The core is where non-polar medicinal chemicals are stored, which makes them far more soluble and bioavailable. The hydrophilic parts make up the outer shell, which keeps the micelles stable in the blood and makes them last longer by stopping the mononuclear phagocytic system from quickly clearing them away [18].

Receptor-mediated endocytosis is the main way that PMs get into cells. This is a process that lets them get over efflux pumps like P-glycoprotein (P-gp), which frequently make it harder for many common drugs to get into cells. You can also change the surfaces of these things by adding targeting ligands or PEGylating them to make them more specific for targeting and keep them in the body longer. Polymeric micelles are great for delivering medications that don't mix well with water, such paclitaxel and docetaxel, which are hard to make because they don't dissolve well in water. They are also being looked into for use in gene therapy, cancer treatment, and delivering drugs by mouth [19].

Polymeric micelles have showed promise in the treatment of gangrene, notably in cases of lower limb ischemia. Researchers have produced ultrasound-responsive micelles that hold mesenchymalstem cell-derived extracellular vesicles (MSCs-EVs) to treat ischemic lesions in the microcirculation. This new technology makes it possible to release therapeutic EVs in a specific area at the site of injury [19].

A new method for delivering hydrophobic medications and biologics to ischemic tissues is offered by polymeric micelles. This broadens the spectrum of gangrene treatments beyond standard antibiotics. Hydrophobic drugs, such as tiny substances that promote angiogenesis or anti-inflammatory therapies, are excellently dissolved and delivered by polymeric micelles. Delivering complex biologics like MSCs-EVs for lower limb ischemia via ultrasound-responsive micelles is a significant advancement.

3.4. Dendrimers

Dendrimers are a class of artificial macromolecules that typically range in size from 1 to 10 nanometers and have a distinctive hyperbranched, tree-like shape. They have a central core unit from which branching macromolecules proliferate in successive generations, culminating in a highly functionalized terminal surface. Dendrimers are monodisperse and globular, and they can be made simply with perfect control over their structure. They have internal chambers for encapsulation and several surface groups for chemical conjugation [20].

Dendrimers look like they could be useful in treating gangrene because they kill bacteria and help wounds recover. For example, phosphorus dendrimers have been shown to kill both Gram-negative and Gram-positive bacteria by changing how easily bacteria can get through their cell membranes. This method is very important for getting around bacterial resistance, which is becoming more and more of a problem in treating gangrene. Researchers have also found that dendrimers can help wounds recover by fighting infection, lowering too much inflammation in burn wounds, and lowering oxidative stress [21].

3.5. Nanosuspensions

Surfactants and polymers in water stabilize nanosuspensions (NS), which are colloidal mixtures of pure medicine particles that are very small (typically 200–600 nm, with particles that are typically smaller than 1 micrometre).

The primary advantage of NS is its ability to significantly increase the solubility, rate of dissolution, and bioavailability of drugs that are poorly soluble in water, particularly those classified as class II and IV in the Biopharmaceutics Classification System (BCS).

The poor aqueous solubility problem with a number of potentially useful drugs used to treat gangrene is resolved by nanosuspensions. Drug particles are reduced by nanosuspensions to the nanometer range. This improves solubility and bioavailability by significantly increasing the surface area and rate of dissolution. This capability is a significant

advancement that will enable the use of a broader range of therapeutic compounds, such as the natural substance berberine, in clinical settings for gangrene, which may not have been feasible due to formulation issues [22]. Additionally, boron nitride nanosuspensions are lowly harmful to cells and have antibacterial qualities. In addition to their antimicrobial qualities, selenium nanoparticles in nanosuspensions can prevent the formation of biofilms, which may aid in the management of infections in gangrenous wounds [23].

3.6. Solid Lipid Nanoparticles (SLNs)

Lipids make up Solid Lipid Nanoparticles (SLNs), a kind of colloidal drug carrier. They typically range in size from 50 to 1000 nanometers. They consist of spherical particles encasing drug molecules in a solid lipid matrix. They remain stable in water thanks to a layer of surfactants. The second generation of SLNs are called nanostructured lipid carriers, or NLCs [24]. Because of their demonstrated safety record, ability to deliver antibiotics, and ability to heal wounds over time, SLNs and NLCs are clinically transferable nanocarrier platforms for the treatment of gangrene. In both laboratory and real-world settings, studies have shown that SLNs loaded with ciprofloxacin (Cip-SLN) and ampicillin and vancomycin (Amp-Van-SLN) are highly effective in treating wound infections brought on by Pseudomonas aeruginosa and Staphylococcus aureus. By gradually releasing antibiotics over time, SLNs aid in their accumulation at the infection site. This promotes wound healing and inhibits the growth of bacteria. For the treatment of gangrene, this capacity to both combat infection and promote tissue healing is crucial. In rat models, SLNs containing Obeidi grape seed extract (GSE) nanoparticles have also accelerated tissue regeneration, controlled inflammation and infections, and aided in wound healing. Optimized M-CO-SLNs added to a collagen sponge demonstrated improved wound healing and antibacterial activity in a diabetic mouth ulcer model [25].

4. Nanocarrier linked therapeutic strategies for Gangrene

Nanocarrier systems have unique abilities that are allowing new ways to treat the many different forms of gangrene, going beyond what traditional treatments can do.

4.1. Enhanced Antibiotic Delivery

Bacterial infection is a major cause of gangrene progression, however standard antibiotic treatments have a lot of problems. Some of these problems are that many effective antibiotics don't dissolve well, aren't very stable (so they break down quickly), don't penetrate tissues well (particularly necrotic or ischemic areas and bacterial biofilms), are toxic to the whole body at large doses, and antibiotic resistance is becoming a bigger problem [26].

Nanocarriers offer a multi-pronged approach to overcome these challenges:

- Increased Solubility and Stability
- Improved Permeability and Bioavailability
- Prolonged Half-Life and Controlled Release
- Targeted Delivery
- Biofilm Disruption

By addressing bacterial infections in gangrene from multiple perspectives, nanocarriers circumvent issues with drug delivery while simultaneously combating antibiotic resistance. The main problem with using antibiotics to treat gangrene is not just that they don't work well against the bacteria, but also that they can't get to the bacteria well because of poor blood flow and the fact that biofilm formation protects them. Resistance frequently results from this. By increasing the solubility and stability of hydrophobic antibiotics, nanocarriers enable more medication to reach the target and overcome these biological and physical barriers. They facilitate access to difficult-to-treat tissues that are dead, not receiving enough blood, or covered in biofilm. By enabling localized and sustained release, nanocarriers also reduce systemic toxicity while maintaining therapeutic concentrations high where they are required [27].

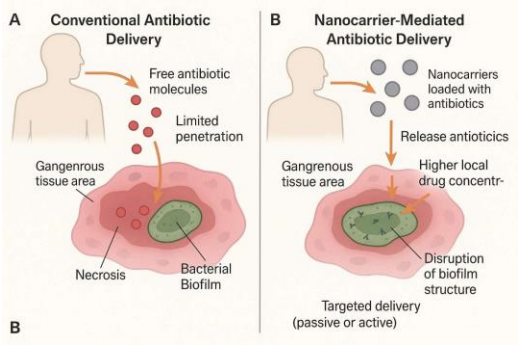

Figure 2 Nanocarrier Mediated Antibiotic Delivery

4.2. Growth Factor Delivery

Angiogenesis and tissue regeneration are important for healing gangrenous wounds, although it is still very hard to promote them effectively. Growth factors (GFs) are important for healing wounds, but they have certain problems. For example, they don't last long in the body, break down quickly, are expensive, and can cause negative effects when given in large amounts [28].

Nanocarrier systems provide effective remedy by:

- Protection and Controlled Release
- Enhanced Loading and Targeted Delivery
- Promotion of Angiogenesis
- Improved Collagen Alignment and Tissue Regeneration

Nanomaterials can be used as GF carriers in a number of ways, such as scaffolds, hydrogels, nanofibers, and nanoparticles (for example, mesoporous silica nanoparticles, polymer nanocapsules, lipid-based nanoparticles, and albumin-based nanoparticles) [27,29].

By avoiding pharmacokinetic issues and actively coordinating the numerous stages of tissue regeneration, nanocarrier-mediated growth factor administration is revolutionizing the healing process of gangrene wounds. Due to their "rapid degradation" and "short half-life," GFs have proven difficult to use in medicine. By protecting GFs and allowing them to "sustain release" over several days or weeks, nanocarriers solve this issue. Growth factors must remain at the wound site for an extended period of time in order for the intricate and sequential phases of wound healing—hemostasis, inflammation, proliferation, and remodelling—to function properly. Additionally, by influencing the immune system or activating signal pathways, nanomaterials can both stimulate endogenous GFs and provide exogenous GFs. Beyond simply removing dead tissue, this active coordination of angiogenesis, re-epithelialization, and collagen alignment actively rebuilds healthy, functional tissue. This significantly enhances patients' long-term functional results and limb salvage [29].

4.3. Gene Therapy

Since gene therapy targets the genetic causes of diseases and employs techniques like gene editing, overexpression, and suppression, it is a revolutionary approach to disease treatment. This implies that treating the symptoms alone is not enough for gangrene.

Non-viral nanocarriers are especially promising for gene delivery because they have a number of advantages over traditional viral vectors. For example, they are less likely to cause an immune response, are easier to make, and can deliver a wide range of genetic materials, such as plasmid DNA, messenger RNA (mRNA), small interfering RNA (siRNA), and gene-editing tools like CRISPR-Cas9 [30].

- Lipid Nanoparticles (LNPs)
- Polymer-Based Vectors
- Dendrimers
- Inorganic Materials
- Exosomes and DNA Nanostructures

Gene therapy supplied by nanocarriers has a lot of potential for repairing and regrowing tissue in the case of gangrene [31,32]:

- Bone Regeneration
- Cartilage Regeneration
- Blood Vessel Regeneration (Angiogenesis)
- Neuroregeneration
- Cancer-Resected Tissue Repair

4.4. Multifunctional Nanocarriers and Combination Therapies

Comprehensive treatment options are necessary due to the complex and multifactorial pathogenesis of gangrene, which includes tissue necrosis, inflammation, ischemia, and infection. To maximize their effectiveness, these cutting-edge systems integrate multiple therapeutic substances or diagnostic instruments into a single nanocarrier system [33].

- Antibiotic plus Anti-inflammatory/Analgesic
- Antibiotic plus Wound Healing Promotion
- Growth Factor plus Antimicrobial
- Growth Factor plus Stem Cell/Exosome Delivery
- Gene Therapy plus Other Agents
- Theranostics [34]

The creation of "cocktail formulations" within a single nanocarrier or the synergistic mixing of different nano-agents lets manage infection, reduce inflammation, promote angiogenesis, and stimulate tissue regeneration all at the same time, which directly addresses the linked problems of gangrene.

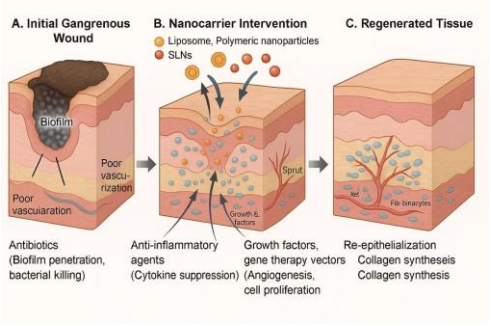

Figure 3. Nanocarrier enhanced Wound Healing and Tissue Regeneration

5. Challenges and Future Directions

Nanocarrier delivery methods for treating gangrene have come a long way, but there are still several problems that need to be solved before they can be widely used in the clinic.

5.1. Toxicity, Stability, and Scalability Issue

Some nanoparticles, like certain polymeric nanoparticles when they break down, cationic dendrimers, and different metal nanoparticles, can have negative consequences even if they are said to be biocompatible. These can show up as skin irritation, oxidative stress, DNA damage, hemolysis, or unplanned systemic distribution that hurts organs [35].

It is important to maintain the physical and chemical integrity of nanocarriers during manufacturing, storage, and administration *in vivo*. Interactions with bodily fluids, like plasma proteins, can change how nanocarriers are distributed, how quickly they leave the body, and how drugs are released.

For clinical and commercial success, it is important to be able to turn small-scale laboratory production into

large-scale, cost-effective, and reproducible manufacturing processes.

5.2. Regulatory and Clinical Translation

It is very important to do a lot of preclinical characterization, but it is hard since the physicochemical properties of nanocarriers are very dependent on the physiological environment, which makes it hard to compare in vitro and in vivo results. Even though there has been a lot of success in preclinical trials, many polymeric nanoparticles still haven't been tested in people.

5.3. Emerging Trends and Future Aspects

There are a lot of new trends that make the future of nanocarrier delivery methods for treating gangrene promising [36].

- Personalized Medicine [37]
- AI based Design
- Intelligent and Responsive Systems
- Multifunctional and Hybrid Systems
- Intelligent Wound Dressings [38]
- Bacterial Carriers

6. Conclusions

Gangrene is still a very difficult therapeutic problem because it has a complicated pathophysiology that includes ischemia, infection, inflammation, and tissue necrosis, which can lead to severe morbidity and limb loss. A revolutionary solution to these issues is offered by recent advancements in nanocarrier delivery techniques. Liposomes, polymeric nanoparticles, solid lipid nanoparticles, dendrimers, micelles, nanosuspensions, and other nanocarriers are transforming drug delivery. Additionally, by developing stimuli-responsive nanocarriers, medications can be released in response to the unique pathological milieu of gangrene, such as pH or enzyme activity changes, ensuring that the treatment is effective.

Large-scale manufacturing, long-term stability, and toxicity remain issues despite these positive advancements. Nanomedicine is expected to become even more precise and successful in treating gangrene thanks to new developments like AI-driven design, smart wound dressings that can track wounds in real time, and innovative bacterial carrier systems. These cutting-edge nanocarrier delivery technologies could significantly improve limb salvage rates, reduce patient morbidity, and alter the treatment of gangrene if they are further investigated and clinically integrated.

Conflict of Interest

None to declare

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Not Applicable

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