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Design And Development Of Nanofiber Formulation For Wound Healing

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Abstract

Nanofibers have gained significant attention in pharmaceutical sciences due to their unique properties such as high surface area-to-volume ratio, controlled drug release, and enhanced drug stability. Among the various drug delivery systems, electrospun nanofibers stand out for their ability to provide localized and sustained drug release, particularly in wound healing applications. This study focuses on the design and development of nanofiber formulations to improve wound healing outcomes. Fluconazole, a potent antifungal agent, was incorporated into electrospun Eudragit nanofibers to address fungal infections commonly associated with chronic wounds. The study aimed to overcome challenges related to topical nanofiber application, including vehicle deployment, spreading, and retention. Electrospun nanofibers provide a biomimetic structure resembling the extracellular matrix, promoting cell proliferation and tissue regeneration. Furthermore, the integration of bioactive agents like fluconazole enhances antifungal efficacy while reducing systemic side effects. Controlled drug release over 24 hours was observed, demonstrating the potential of nanofiber-loaded topical gels for efficient drug delivery. The developed formulation exhibited significant antibacterial and antifungal activity, facilitating faster wound healing. This research highlights the promising role of electrospun nanofibers as an advanced platform for localized drug delivery, providing a multifunctional approach for addressing complex wound care challenges. Future work will explore optimizing the composition and incorporating additional bioactive agents to enhance therapeutic efficacy and patient compliance.

Keywords: Nanofibers, Electrospinning, Wound Healing, Drug Delivery, Fluconazole, Antifungal, Controlled Release, Biomimetic Structure, Topical Gel, Tissue Regeneration.

Introduction

Nanofibers have attracted a lot of pharmaceutical interest in drug delivery, because of their benefits, which include increased drug entrapment, a bigger surface area, reduced formulation ingredient waste, improved drug stability, and ease of manufacture. In order to achieve the maximal bioavailability of the medicine at the target location in any drug delivery method, electrospun nanofibers have assisted in obtaining a controlled release of the drug systemically. 4. The core sheath structure of nanofibers, which may be helpful for pulsatile drug delivery and encapsulating numerous medicines, is another significant factor that has attracted the attention of researchers. 5–7 Nanofibers can be easily used to treat various dermatological diseases and as a dressing for topical wounds.

The application of nanofibers for the treatment of skin infections and regeneration has been discussed in various reviews. 8–10 Azarbayjani et al., has developed a smart polymeric nanofiber for the topical delivery of levothyroxine which helps to reduce the deposition of adipose tissue on skin. 11 Papain loaded poly vinyl alcohol nanofibers have been developed with an aim to enhance the wound debridement to hasten the process of wound healing. 12 However, adherence and application of nanofibers topically to skin has certain challenges such as vehicle deployment, spreading, retention and hence may have poor patient compliance. 13

Due to their high patient compliance, localised drug activity at the target site, and decreased risk of systemic side effects, topical delivery systems have become more significant in the contemporary drug delivery landscape. 14 In contrast to alternative semisolid dosage forms, topical gels were chosen for the current study because of their improved stability, non-greasiness, and simplicity of application. 15. Carbopol 940, a polymer produced from anionic acrylic acid, was chosen because of its superior rheological behaviour and gelling qualities. Since it is an anionic polymer, neutralising chemicals such as tri-ethanol amine can be used to jellify it. The benefits of carbopol include higher viscosity at lower concentrations, superior flow characteristics, improved heat stability, and good adhesion properties. 16

Infections in wounds are the most destructive type of trauma in the world and a serious health concern. 17 Numerous fungal species are responsible for these illnesses in addition to bacteria. Due to a lack of clinical awareness, a longer growth period, and inadequate mycology labs, the majority of fungal infections go unnoticed. 18 Body surface area, full thickness burns, extended hospital stays, open dressings, central venous catheters, antibiotics, steroid treatment, long-term artificial ventilation, fungal wound colonisation (FWC), hyperglycaemic episodes, and other immunosuppressive conditions are major risk factors for developing fungal infections in wounds. 19–21 In addition, persistent wounds are more likely to become infected with fungi.

Therefore, development of materials that enhance the wound healing process along with the antifungal therapeutics would reduce the complication of wounds as well as trauma.

In humans, most of the topical fungal diseases were caused by *Candida* species.²² Fungal infection arises due to the fungal infestation through the topical layers of the skin and damage to the superficial stratum corneum layer.²³ In this study, effective fungi static drug fluconazole was selected as a model drug to evaluate the efficiency of the delivery system. Fluconazole has gained interest in the treatment of topical fungal diseases due to its advantages of longer half-life, lower molecular weight, poor protein binding and high level of penetration ability.

The design and development of nanofiber formulations have emerged as a promising approach in wound healing applications. Electrospinning is a widely used technique to fabricate nanofibrous scaffolds that mimic the extracellular matrix, providing an ideal environment for cell proliferation and tissue regeneration. These nanofibers can be engineered to possess mechanical properties similar to human skin by carefully selecting their composition, thereby enhancing their suitability for wound healing applications. Incorporating bioactive agents into nanofiber matrices has been shown to accelerate the wound healing process. For instance, neomycin-loaded chitosan/gelatin/polyvinyl alcohol/polyacrylonitrile (CG/PVA/PAN) nanofibers have demonstrated improved healing in burn wound models. Similarly, electrospun nanofibers containing natural compounds like curcumin and rutin have exhibited enhanced antibacterial and antioxidant properties, contributing to more effective wound management. Advancements in nanofiber technology have also led to the development of multifunctional wound dressings. For example, electrospun nanodiamond-silk fibroin membranes have been designed to provide both biosensing capabilities and support for tissue regeneration. These membranes can monitor wound conditions and promote healing simultaneously.

Moreover, the integration of stimuli-responsive elements into nanofiber dressings has opened new avenues for dynamic wound care. Researchers have developed two-layer electrospun systems capable of managing wound exudate and providing visual infection responses, thereby enabling real-time monitoring and tailored treatment strategies. At last, the strategic design and development of nanofiber formulations offer significant potential in enhancing wound healing outcomes. By tailoring the composition, incorporating bioactive agents, and integrating multifunctional features, these nanofibrous scaffolds can effectively address various challenges in wound management.

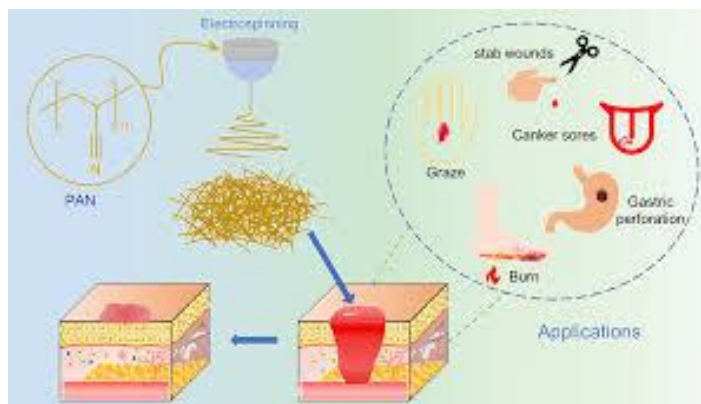


Figure 1: Electrospun Polyacrylonitrile Nanofiber



Figure 2: Diabetic Wound Healing

Literature Review

Because of its high porosity, huge surface area-to-volume ratio, and programmable properties, electrospun nanofibers have been extensively explored in the biomedical field, including tissue engineering, haemostasis, wound healing, cell scaffolds, bionics, and controlled drug release. To vary their use, researchers have been expanding the structural design of electrospun nanofibers in recent years. These nanofibers have progressed from one-dimensional to three-dimensional forms. Because of their enhanced blood coagulation and concentration, these characteristics allow nanofibers to physically and functionally replicate the natural extracellular matrix (ECM), creating a physiological milieu that is conducive to wound healing and haemostasis. However, there isn't a thorough analysis that highlights the latest developments in the structural and functional design of electrospun nanofibers for wound healing and haemostasis. This review summarizes electrospun nanofibers used for hemostasis and wound healing, with a focus on structural design and modification strategies. The wide application of electrospun nanofibers in hemostasis and wound healing is clarified using a special structural and innovative design for electrospinning. The advantages and limitations of electrospun nanofibers with various structural forms are also discussed, as are the main challenges and future development directions for the development of structurally specific electrospun nanofibers for hemostasis and wound healing (1).

With the programmable release of several angiogenic growth factors (vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), and endothelial growth factor (EGF), either directly embedded in the nanofibers or encapsulated in the gelatin nanoparticles (GNs) by electrospinning technology, the goal of this research study is to create a collagen (Col) and hyaluronic acid (HA) inter-stacking nanofibrous skin equivalent substitute. While the release of PDGF and VEGF in the late stage is intended to induce blood vessel maturation, the early distribution of EGF and bFGF is anticipated to speed up epithelialisation and vasculature sprouting. The Col–HA–GN nanofibrous membrane has mechanical characteristics that are comparable to those of human skin, according to the physiochemical characterisations. Growth factors can be released gradually and under control for up to one

month because to the particle-in-fiber structure. Endothelial cells grown on biodegradable Col–HA membrane with four different growth factors (Col–HA w/4GF) not only grow faster but also improve the network with a tubular structure that resembles threads. As demonstrated by Masson's trichrome stain and immunohistochemical analysis, respectively, the therapeutic effect of Col–HA w/4GF membrane on streptozotocin (STZ)-induced diabetic rats results in an accelerated rate of wound closure, increased collagen deposition, and improved vessel maturation. According to the aforementioned, a promising bioengineered construct for chronic wound healing in skin tissue regeneration might be the electrospun Col–HA–GN composite nanofibrous skin substitute with a stage-wise release pattern of numerous angiogenic agents (2).

Infection, oxidative stress, and inflammation are nearly always present in the chronic consequences of diabetes mellitus, one of the most worrisome diseases. During the acute inflammatory stage of diabetic wound healing, it is essential to treat the wound by lowering excessive reactive oxygen species and the inflammatory response. For this study, neomycin sulphate (NS) nanofibers containing *Malva sylvestris* extract (MS) were created, and their effect on the healing of diabetic wounds was evaluated. To achieve the required entrapment efficacy [EE] and average nanofiber diameter (ND), the electrospinning procedure for creating NS nanofibers (NS-NF) was modified using Design Expert for applied voltage (X1), the distance between the needle tip and the collector (X2), and the feed rate (X3).

Using the desirability approach, an ideal formulation may be created with a voltage of 19.11 kV, a distance of 20 cm, and a flow rate of 0.502 mL/h. Drug delivery from nanofibers is impacted by all of the chosen parameters and reactions. Furthermore, *M. sylvestris* extracts have been included into the ideal formulation [MS-NS-NF] and evaluated for their in vitro drug release studies, surface shape, tensile strength, and water absorption capacity. Delivery of NS and MS from MS-NS-NF has been prolonged for over 60 hours. When compared to plain NS nanofibers, *M. sylvestris*-loaded nanofibers showed better antibacterial activity. Scaffolds have a wide aspect and a porous fibrous network structure with many links. The formulation's effectiveness in treating diabetic wound healing is demonstrated by the histomorphometry study and the in vitro scratch assay. The cells treated with MS-NS-NF in vivo demonstrated that wound dressings successfully reduced both acute and chronic inflammations. To improve the healing of diabetic wounds, MS-NS-NF may be regarded as an appropriate candidate for wound dressing (03).

The primary barrier to healing processes is infection brought on by microorganisms such as bacteria, fungus, etc. Oral, intravenous/intramuscular, topical, and inhalation are the traditional methods of administering antibacterials. These types of drug administration's face important problems include faster than planned drug delivery, which can lead to bacterial resistance, systemic toxicity from dose, tissue irritation, and ultimately a delayed healing process that needs to be addressed. New drug delivery methods, overcoming toxicological issues and resistance, and ultimately localising the molecules at the site of action in the right dosage have been the focus of recent research. To address the aforementioned issues, numerous nanotechnological strategies, including nanoparticulate medicinal systems, have been created.

The primary benefits of drug-loaded electrospun nanofibers for pharmaceutical and biomedical applications include regulated drug delivery, high drug loading capacity, high encapsulation efficiency, simultaneous administration of numerous medications, ease of production, and cost effectiveness. Thus, the design of electrospun nanofibers as potential antibacterial drug delivery systems has received special attention. Numerous antibacterial substances, including triclosan, biocides, antibiotics, quaternary ammonium salts, metallic nanoparticles (such as silver, titanium dioxide, and zinc oxide), and antibacterial polymers (such as chitosan and polyethyleneimine) have been impregnated into nanofibers using a range of techniques. These nanofibers demonstrate potent antibacterial activity in conventional tests. This review highlights the design and delivery of antibacterial drug loaded nanofibers with particular focus on their function in the fields of drug delivery, wound healing, tissue engineering, cosmetics and other biomedical applications (04).

Delivery systems based on nanofibers have become increasingly significant in the biomedical industry in recent years. However, one of the biggest challenges facing formulation scientists is the development of a dosage form and the practical administration of nanofibers. Nanofiber topical treatment has drawbacks of its own, including vehicle deployment, spreading, and retention at the targeted location of action. Therefore, we have tried to create a topical gel in this work to apply and administer fluconazole-loaded eudragit nanofibers in an efficient manner. The medication content, rheological characteristics, penetration effectiveness, and antifungal efficacy of the electrospun nanofiber-loaded topical gel were assessed. Controlled release of the drug up to 24 h was observed in the in vitro diffusion studies and a better drug release was obtained in the nanofiber loaded gel based delivery system when compared to the release profile of nanofibers alone. Antifungal study confirmed the efficiency of the developed system in controlling fungal growth. Thus, an efficient dosage form for the delivery of drug loaded nanofibers has been developed and it opens up new avenues for the treatment of topical infections using nanofiber based therapeutics (05).

Electrospun Nanofibrous Wound Dressings with Enhanced Efficiency

This study explores the potential of electrospun nanofibers in wound healing, highlighting their ability to deliver active agents, retain moisture, and promote tissue regeneration (06).

Recent Advances in Electrospun Nanofibers for Wound Healing

A comprehensive review discussing the unique features of electrospun nanofibers critical for wound healing applications, including their structural similarity to the extracellular matrix and their role in drug delivery (07).

Antibacterial and Wound Healing Stimulant Nanofibrous Dressing This article presents a novel nanofiber-based wound dressing that accelerates the healing of severe skin wounds with a risk of infection, demonstrating both antibacterial properties and enhanced healing rates (08).

Electrospun Nanofibers Synthesized from Polymers Incorporated with Nanoparticles for Wound Healing
The review discusses the effects of nanofibrous scaffolds loaded with nanoparticles on wound healing, emphasizing the enhanced antibacterial and regenerative properties of these composite materials (09).

Advances in the Preparation of Nanofiber Dressings by Electrospinning for Diabetic Wound Healing
This article summarizes the advantages and research progress of electrospun nanofibrous membranes in treating diabetic wounds, highlighting their potential in promoting faster and more effective healing (10).

Electrospun Nanofibers Promote Wound Healing
A systematic review on how electrospun nanofiber scaffolds promote wound healing, focusing on their fabrication and multifunctional properties that contribute to improved healing outcomes (11).

Recent Progress of Electrospun Nanofiber Dressing in the Treatment of Wound Healing
This review provides a detailed overview of current research on electrospun nanomaterials for wound healing, addressing challenges and suggesting future research directions to advance the field (12).

Electrospun Nanodiamond-Silk Fibroin Membranes: A Multifunctional Platform for Biosensing and Wound Healing Applications
The study reports on hybrid electrospun membranes combining nanodiamonds and silk fibroin, designed to provide both biosensing capabilities and support for tissue regeneration in wound healing applications (13).

Advancing Biomedical Applications: Antioxidant and Biocompatible Cerium Oxide Nanoparticle-Integrated Poly- ϵ -caprolactone Fibers
This research focuses on the development of electrospun poly- ϵ -caprolactone fibers integrated with cerium oxide nanoparticles, aiming to reduce reactive oxygen species and improve cell viability for potential wound healing applications (14).

Nanomaterials Decoration on Commercial Cotton Bandages for Pain and Infection Management
The study explores the modification of commercial cotton gauze bandages with nanomaterials to provide sustained drug release and antibacterial properties, enhancing their effectiveness in wound dressing applications (15).

Khalid et. al studied about hybrid electrospun membranes. This study reports on hybrid electrospun membranes combining nanodiamonds and silk fibroin, designed to provide both biosensing capabilities and support for tissue regeneration in wound healing applications (16).

Jahan UM et. al. studied about Advancing biomedical applications: antioxidant and biocompatible cerium oxide nanoparticle-integrated poly- ϵ -caprolactone fibers. This research focuses on the development of electrospun poly- ϵ -caprolactone fibers integrated with cerium oxide nanoparticles, aiming to reduce reactive oxygen species and improve cell viability for potential wound healing applications (17).

Parkale R. et. al. studied about Nanomaterials decoration on commercial cotton bandages for pain and infection management. The study explores the modification of commercial cotton gauze bandages with nanomaterials to provide sustained drug release and antibacterial properties, enhancing their effectiveness in wound dressing applications (18).

Kuddushi M. et. al. studied about Recent advances in novel materials and techniques for developing transparent wound dressings. This review provides a comprehensive overview of transparent wound dressings, focusing on novel materials and fabrication techniques, including transparent electrospun nanofibers, which allow for real-time monitoring of the healing process (19).

Conclusion

The design and development of nanofiber-based formulations present a significant advancement in the field of wound healing. This study successfully demonstrated that electrospun nanofibers loaded with fluconazole offer a promising approach to address the limitations of conventional topical treatments. The unique structural properties of electrospun nanofibers, including their high porosity and surface area, facilitate effective drug loading and sustained release, ensuring prolonged therapeutic action at the wound site. This controlled release profile not only enhances drug bioavailability but also minimizes systemic absorption and associated side effects, improving patient safety. The study also highlighted the ability of nanofibers to mimic the extracellular matrix, creating a favorable environment for cellular adhesion, proliferation, and tissue regeneration. The incorporation of fluconazole into the nanofiber matrix proved effective in combating fungal infections, a major complication in chronic wounds. The *in vitro* studies confirmed the controlled drug release for up to 24 hours and demonstrated superior antifungal activity compared to conventional formulations. Additionally, the nanofiber-loaded gel formulation addressed the common challenges of topical application, including better adherence, spreading, and retention on the skin.

Nanofiber-based delivery systems open new avenues for personalized and targeted therapy. By tailoring the composition and integrating multifunctional agents, these systems can address diverse wound types and stages. Moreover, the use of advanced polymers such as Carbopol 940 enhances the mechanical properties and bioavailability of the drug, further supporting the clinical translation of these formulations. Future research should focus on optimizing the electrospinning process to achieve consistent fiber morphology and drug distribution. Expanding the scope of bioactive agents, including anti-inflammatory and growth-promoting compounds, could further enhance the therapeutic potential of nanofiber formulations. Additionally, *in vivo* studies and clinical trials are essential to validate the efficacy and safety of these advanced systems for human use.

In conclusion, the integration of nanotechnology in wound care represents a transformative approach to managing complex wounds. The findings from this study underscore the potential of electrospun nanofibers as an innovative and effective platform for drug delivery, providing improved therapeutic outcomes, reduced

side effects, and enhanced patient compliance. With ongoing advancements, nanofiber-based systems are poised to revolutionize the future of wound healing and broader biomedical applications.

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