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Review Article

Nanofiber In Wound Healing: A Comprehensive Review of Innovations and Application

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ABSTRACT

Nanofibers' distinct structural and functional characteristics have made them an innovative material in the field of wound healing. The potential of nanofibers to accelerate wound healing is examined in this paper, with particular focus paid to their capacity to replicate the extracellular matrix, encourage cell proliferation, and enable regulated medication administration. Different methods of manufacture, including as electrospinning, centrifugal spinning and many more are discussed. The integration of bioactive agents and growth factors within nanofiber scaffolds is examined, demonstrating significant improvements in healing rates and tissue regeneration. Furthermore, the article addresses current challenges and future perspectives in the clinical translation of nanofiber-based wound dressings. Through a comprehensive review of recent advancements, this study underscores the promise of nanofibers as a versatile and effective solution for advanced wound care.

INTRODUCTION

The process of a live creature replacing damaged or broken tissue with newly formed tissue is known as wound healing. The epidermis and dermis work together to form a barrier that shields healthy, normal skin from the outside world. A controlled sequence of biological reactions is about to start in order to repair the damage caused once the barrier is breached[1]. Hemostasis (blood clotting), inflammation, tissue growth (cell proliferation), and tissue remodelling (maturation and cell differentiation) are the predicted phases of this approach[2]. Rather than being a distinct stage, blood clotting may be viewed as a component of the inflammatory stage. Furthermore, inflammatory cells that produce cytokines and remove debris include neutrophils and macrophages that regulate the immune response and stimulate cell proliferation.[2] Types of wounds might also consist of abrasions, lacerations, burns, surgical incisions, stress injuries.

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Phases Of Wound Healing

Hemostasis, inflammation, proliferation, and remodelling are the four continuous, overlapping phases of the dynamic process of wound healing or repair.

1. Hemostasis: Blood vessels inside the wounded area constrict to reduce blood flow as soon as a wound may occur on the body. [3] They are referred to as vasoconstriction.[4] Simultaneously, clotting factors are introduced into the wound site, where they combine with fibrin to form a thrombus, which is commonly referred to as a blood clot. To prevent blood loss, the clot functions as a barrier between the injured blood vessels. Depending on how deep your incision is, this stage may extend for up to two days.[5]

2. Inflammation: The term "inflammatory phase" refers to the second stage of wound healing. White blood cells and a few enzymes enter the wound area during this phase to prevent contamination by removing microorganisms and particles and preparing the wound mattress for the growth of new tissue. It also includes phagocytic cells, which release reactive oxygen species.This segment's physical characteristics include pain, heat, edema, and inflammation or redness at the wound site.[4]This stage typically lasts four to six days and is characterized by discomfort, heat, erythema (skin reddening), and edema.

3. Proliferation: It aims to cover and fill the wound. Wound healing proceeds to the proliferation phase when inflammatory cells undergo apoptosis. This phase is marked by the creation of granulation tissue, angiogenesis (the production of blood vessels), wound contraction, and the epithelialization process.The presence of inflammatory chemicals causes the new tissue to appear purple or crimson.[4] This stage can vary in duration from four days to nearly a month, dependent upon the extent of your incision.[5]

4. Remodeling: The final Remodeling Phase, also known as Maturation, is characterized by the creation of scar tissue. The new tissue progressively gets more durable and adaptable throughout this stage. The synthesis of collagen protects the skin's elasticity and tensile strength.[4]

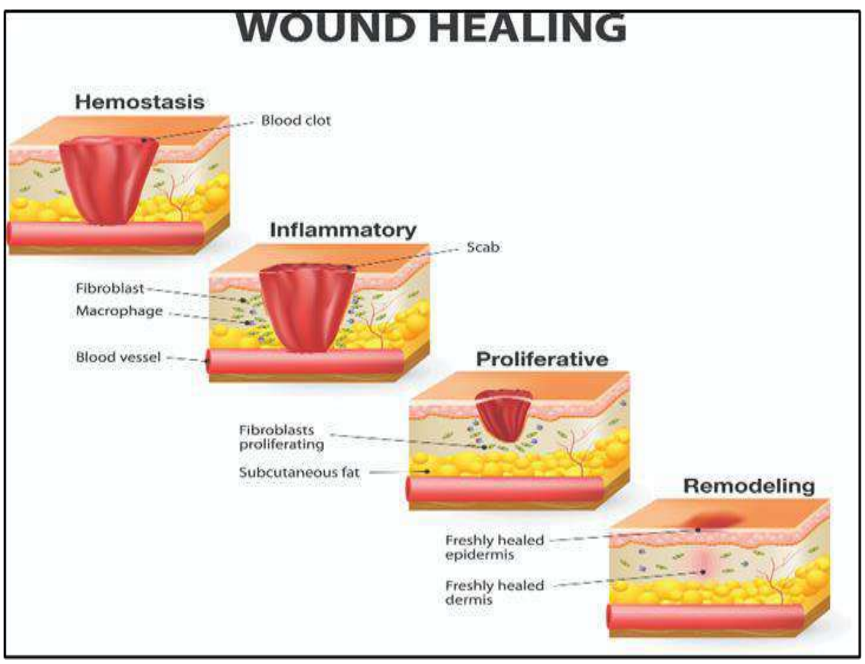


Fig 1: Process Of Wound Healing[6]

2.Nanofibers

Nanofibers represent a transformative class of materials with unique properties that hold great promise across diverse fields including biomedical engineering, environmental science, and advanced materials. Fibers with a diameter between 50 and 500 nanometers (typically, between 1 nm and 1 μm) are referred to as nanofibers.[7] They play an essential role for delivering the medication to the ideal location in the body because of their tiny sizes. They can be utilized to regulate the release of the medication by diffusion alone or diffusion in conjunction with scaffold degradation. They can be composed of biodegradable or non-biodegradable substances. Furthermore, a variety of medications, such as antibiotics, anticancer medications, proteins, and DNA, may be administered because of the flexibility in material selection. [8] Nanofibers are attracting a lot of interest in biomedical applications because of the ability they have to replicate the extracellular matrix (ECM) of natural tissues., promoting cellular adhesion, proliferation, and differentiation. Their structural similarities to ECM components facilitate enhanced bioactivity when functionalized with bioactive molecules or therapeutic agents, thereby supporting tissue regeneration and wound healing processes.[9]

Nanofibers exhibit remarkable properties that distinguish them from conventional fibers:

-High surface area-to-volume ratio: The surface area of nanofibers is very large in comparison to their volume. They are perfect for applications requiring for effective interactions with gasses, liquids, or living things because of this feature.

-High porosity: The permeability and gas or transfer of fluids made possible by nanofibrous materials are generally increased by their high porosity. Applications including medication delivery, tissue engineering, and filtration utilize this property.

-Tailorable mechanical properties: By modifying variables like fiber diameter, manufacturing conditions, and polymer composition, nanofibers' mechanical qualities may be accurately adjusted. Because of their adaptability, nanofiber materials may be designed to have certain mechanical properties that are appropriate for the uses for which they are intended. Hence in comparison to other dosage forms, nanofibers can provide enhanced bioavailability, targeted drug release, extended drug release profile, minimum toxicity, and reduced dosage frequency, which has indisputably improved patient adherence and compliance. Therefore, nanofiber can be used for the development formulations for oral, ocular, topical, transmucosal, and transdermal routes.

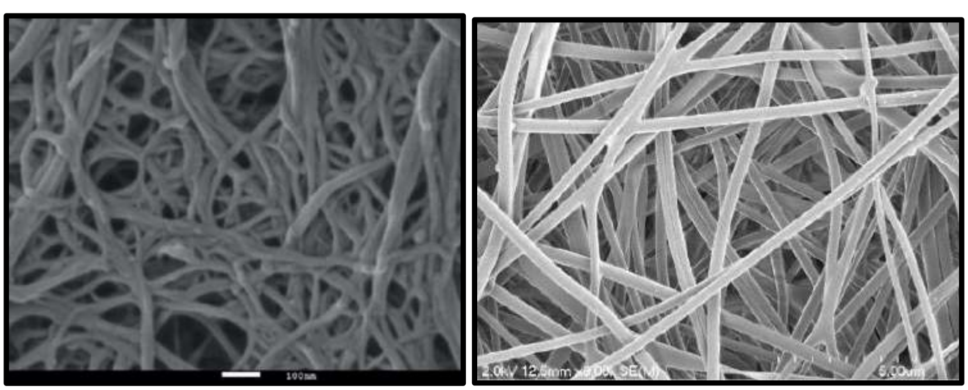


Fig 2: Microscopic image of Nanofibers

Advantage Of Nanofibers[10]

1. Nanofibers have a high surface area to volume ratio by nature due to their dimensions. Because of this feature, it is highly useful in applications like affinity membranes and sensors where a wide surface area is needed.
2. Polymeric, ceramic, and even metal nanofibers can be created using them and indirectly built by electrospinning their precursor material.
3. Electrospun nanofibers may be fully functionalized by using core-shell electrospinning configuration, post-spinning floor functionalization, or simple polymer mixing before spinning.
4.Ease of cloth mixing – Low requirements for electrospinning meant that different materials could be easily mixed together to spin into fibers.
5. Reasonably cheap initial outlay
6. A reduced static charge on the collecting surface is necessary for the deposition of electrospun fibers. Electrospun fibers were mechanically applied to a variety of surfaces, such as water, glass, metal, and microfibrous mats.
7. The creation of yarns, 3D blocks of nanofibers, and tubular nanofibrous structures have been made possible by improvements in the setup and technique of electrospinning.
8. Commercial applications: Electrospinning has been utilized in the production of a number of items that are sold commercially, including face masks, water filtration membranes, cell culture plates, air filtration membranes, and wound care patches.

Disadvantages Of Nanofibers[10]

1.It is a multi-step process.
2.Due to the pore size, there is limited control of the substance that can be selected or optimized for nanofiber formulation.
3.. There is use of organic solvent or any toxic substance.
4.The procedure for formation of nanofibers is a time consuming process as it is a multi-step process.
5..The formulation of fibers can be short or long due to which there can be uneven distribution of substance.

Material used

1.Natural Polymer

-Collagen- As it re the natural extracellular matrix, it promotes cell attachment and proliferation.
-Chitosan: It supports hemostasis and along with it, it has antimicrobial activities.
-Gelatin: Since it is biocompatible and biodegradable it is often used in combination with other materials.

2.Synthetic Polymer

-Polycaprolactone(PCL):It provides mechanical strength and prolonges degradation tims.
-Poly(lactic-co-glycolic acid)(PLGA):It has biodegradable properties and it is also suitable for controlled drug release.
-Polyethylene oxide(PEO):It enhances the electrospinning process and improves fiber uniformity.

3.Composite Materials

It is made by combining the natural and synthetic polymer to yield nanofibers with optimized properties, such as improved mechanical strength and enhanced bioactivity.

3.Method Of Preparation[11]

For the preparation of nanofibers there are various method used such a electrospinning, centrifugal method and many more.In which electrospinning is the most common method for preparation of nanofibers:

1. Electrospinning (ES): This is one of the most advanced and adaptable processes available currently for creating nanoscale fibers with regulated surface shape. A high electric field (between 5 and 30 kV) is supplied to the liquids during the electrospinning process, which causes fine-charged jets to form. These liquids typically consist of one or more active pharmacological components like suspensions, emulsions, polymer melts, or polymer solutions. Biomedical, tissue engineering, environmental, biochemical, medication delivery, protective apparel, and energy storage are just a few of the industrial uses for it.The syringe needle and collector will create an electric field as a result of feeding the spinning fluid into the syringe while high voltage is present. This causes the polymeric solution at the needle's tip to become electrostatically charged in the electric field, forming a Taylor cone. A charged polymer jet is expelled in the presence of an accelerating electric field and gets narrower when surface tension surpasses electrostatic force.[15] Additionally, solid nanofibers were formed on the collector wall as a result of the polymer chain stretching and quick solvent evaporation.[13,14]Electrospun Nanofibrous scaffolds utilize for wound healing process. They are a great alternative to or addition to current wound care therapies because of their structural and biological characteristics.[12]

Fig 3: -Image of electrospinning Machine[16]

2.Conventional electrospinning method: This particular setup consists of a precision syringe pump, a high-voltage source, a stainless-steel needle syringe, and a collector. The needle and collector wall are connected to the electric supply, which might have a positive or negative charge. A high voltage electricity is delivered to the polymer solution and a collector, allowing the solution to extrude from a nozzle and create a jet. The spinnable liquid inside the syringe contains a polymer solution with or without an active component known as the working solution. Fibers created by the jet will dry and land on the collector.[15]

3. Centrifugal spinning: It's also referred to as rotary spinning or rotary jet. This is one of the

methods for quickly and cheaply creating micro-to nanofibers with distinct shapes.[18] This method spins both conductive and nonconductive polymers in solution or melts by using centrifugal force rather than electrostatic force to expel polymer jets into fibers. To create fibers, emulsions and polymer solutions can be introduced during the centrifugal spinning process.The solution is injected into the spinning rotating head, which has several nozzles arranged around the walls, during the centrifugal spinning process. A liquid jet emerges from the orifice when the rotation speed increases to a critical point because centrifugal force is greater than the surface tension of the spinning fluid. In this phase, the solvent is extended by the liquid jet and concurrently evaporates, resulting in a substance that eventually stretches out in the form of fibers towards the collector wall.[17]

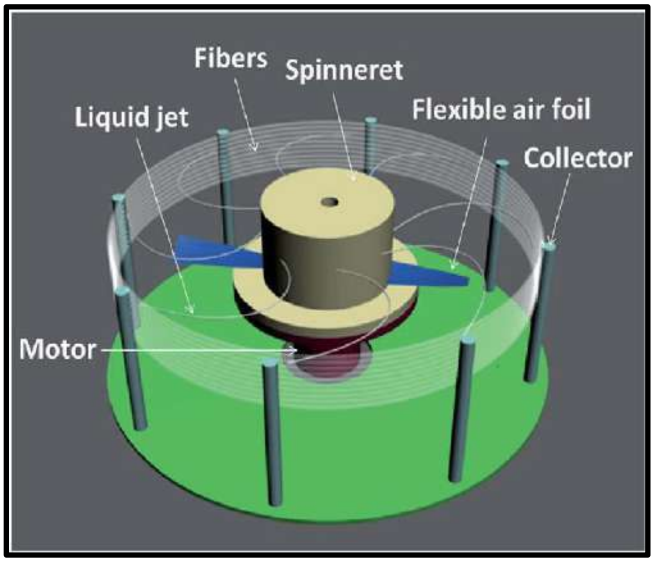


Fig 4: Image Of Centrifugal Spinning[19]

4.Solution and Blowing Melt Spinning is a novel method that combines the concepts of melt blowing and electrospinning to create polymeric nanofibers from a polymer solution. A simple device, a uniform polymer solution in a volatile solvent, and a fast-moving gas source are needed for solution-blowing spinning. A customized nozzle with an inner nozzle for pumping the polymer solution and an outside concentric nozzle for supplying pressured air is attached to the spinning device. During SBS, the outer nozzle's high gas velocity causes the solution streams to expand into ultrafine jets. Subsequently, the jet solidifies into nanofibers when the solvent evaporates.[20]

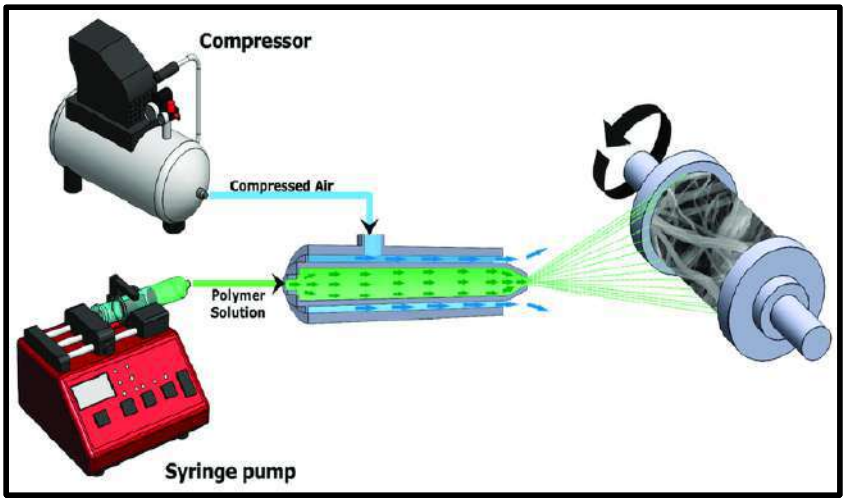


Fig 5: Solution and Melt Blowing Spinning[21]

Steps To Formulate Nanofibers

Formulating nanofibers involves several steps that are carried out through a process called electrospinning.

1.Preparation of Polymer Solution: - Choose a polymer suitable for nanofiber formation in which the most commonly used are choices include polyvinyl alcohol (PVA), polycaprolactone (PCL), and polylactic acid (PLA).Depending on the compatibility, dissolve the polymer in an appropriate solvent.Change the solvent composition and polymer content to modify the solution's surface tension, conductivity, and viscosity.

2. Electrospinning Setup: Assemble the grounded collector, high-voltage power supply, and syringe pump that make up the electrospinning equipment.Fill a syringe with the prepared polymer solution and insert the needle.

3. Electrospinning Process: It involves applying a high voltage between the needle and the collector, often between 10 and 40 kV. At the needle tip, the electrostatic force will overcome the solution's surface tension to produce a Taylor cone. The Taylor cone will release a narrow jet of solution in the direction of the collector.Solid nanofibers are created and left on the collector as the solvent evaporates during the jet trip.

4. Collecting Nanofibers: -Different types of collectors are used for e.g., stationary plate, rotating drum which can influence fiber alignment and morphology. Maintain appropriate environmental conditions e.g., humidity, temperature to control the fiber formation process.

5. **Post-Treatment: -** Ensure complete solvent evaporation for the formation of nanofibers.Perform thermal annealing if required to enhance fiber properties.

6.Characterization

- **Microscopy:** Use of scanning electron microscopy (SEM) or transmission electron microscopy (TEM)are made for analysing fibre morphology and diameter.
- **Mechanical Testing:** Assess mechanical properties such as tensile strength and elasticity.
- **Chemical Analysis:** Conduct Fourier-transform infrared spectroscopy (FTIR) or differential scanning calorimetry (DSC) to

study the chemical composition and thermal properties.

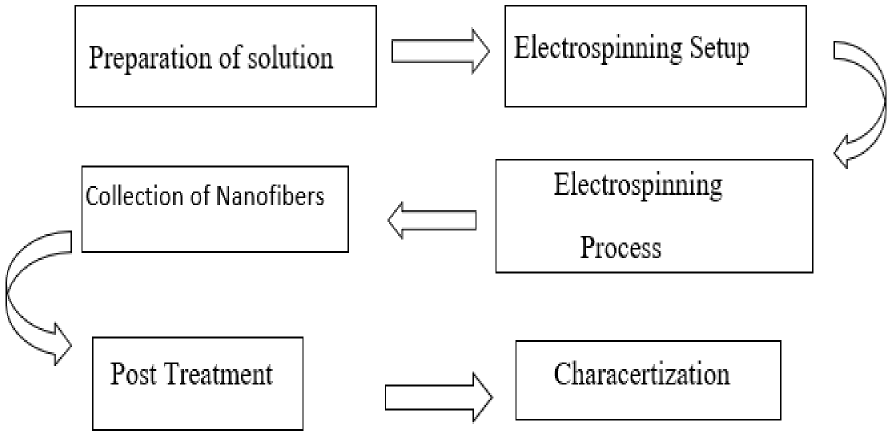


Fig 6: Flowchart for the formulation of Nanofibers

4.Application Of Nanofibers in Wound Healing:[22]

Nanofibers have emerged as a promising material for wound healing due to their unique properties. Here are some key applications and benefits of using nanofibers in wound care:

1. Enhanced Healing Environment [23]

- Extracellular Matrix (ECM) Mimicking: Nanofibers may imitate the ECM found in the body naturally, creating a scaffold that facilitates the adhesion, proliferation, and differentiation of cells—all of which are necessary for tissue regeneration.

-Moisture Balance: By allowing for ventilation and preserving a moist environment—which is essential for wound healing—they help keep the wound from being overly wet or dry.

2. Antimicrobial Properties [24]

- Antimicrobial Agent Incorporation: Antimicrobial agents such as antibiotics, silver nanoparticles, or naturally occurring antimicrobial substances or any antibacterial agent can be incorporated into nanofibers. This aids in avoiding infection, which is a frequent issue during the healing of wounds.

3. Controlled Drug Release[25]

-Sustained Release-They can be made to release therapeutic compounds in a controlled way, enabling the continuous supply of medications to the wound site, such as growth factors, anti-inflammatory medicines, and painkillers.

4. Enhanced Cell Proliferation and Migration[26]

-Cellular Interactions: The nanoscale structure of these fibers promotes better cell adhesion and migration, facilitating quicker tissue regeneration.

5. Reduced Scar Formation[27]

-Minimize Scarring: The conducive healing environment provided by nanofiber scaffolds can reduce excessive scar tissue formation by promoting orderly cell growth.

6. Biocompatibility and Biodegradability[28]

-Safe Materials: Many nanofibers are made from biocompatible and biodegradable materials such as polycaprolactone (PCL), polylactic acid (PLA), and natural polymers like collagen and chitosan. These materials do not induce adverse immune responses and degrade harmlessly in the body.

7. Ease of Application

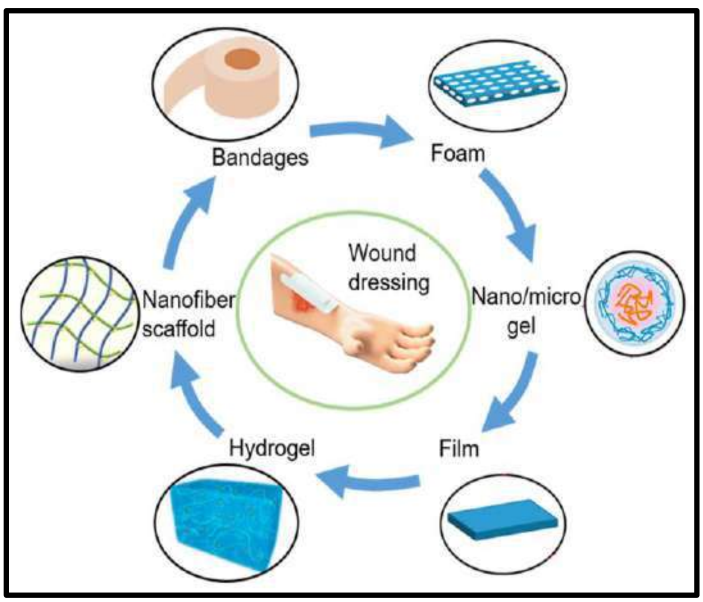
Flexible and Conformable: Nanofiber mats are often flexible and can conform to the wound shape, ensuring better coverage and adherence to irregular wound surfaces.

8. Real-Time Monitoring and Smart Wound Dressings

Integration with Sensors: Advances in technology allow for the integration of sensors within nanofiber dressings, enabling real-time monitoring of the wound environment, such as pH levels, temperature, and bacterial load, which can provide valuable information for timely medical intervention.

9.Vitamins- Electrospun Nanofibers can be used as carriers for delivery of some vitamins to the skin. Usually, vitamins are applied to the skin in the form of topical creams, lotions, or ointments. Therefore vitamins like vitamin E and vitamin-A, can be used for cosmetic purpose while Vitamin – A is naturally occurring, and lipid soluble substances, known to be used for the treatment of leukemia, acne, and other skin disorders. Vitamin-E is also lipid soluble vitamin, it shows potent antioxidant ability, owing to the presences of a hydroxyl group on its chromanol ring which can readily donates a proton to reduce free radicals.[29]

Table 1 shows marketed available product for nanofiber for various conditions



5.Evaluation[30]

Evaluating nanofibers for wound healing involves a comprehensive analysis of their structural properties, biocompatibility, and functional efficacy. This process is crucial for determining their potential and optimizing their use in clinical settings. The key parameters for evaluation include:

1.Morphological Characteristics:

- Fiber Diameter and Uniformity: Ensuring consistent fiber diameter is essential for reproducibility and predictable performance.

- Porosity: The inter-fiber spaces must support nutrient and gas exchange, as well as fluid drainage.

2. Mechanical Properties:

- Tensile Strength and Flexibility: The scaffold must be robust enough to withstand handling and application, while flexible enough to conform to wound contours.

3. Biocompatibility:

- Cytotoxicity: Nanofibers must be non-toxic to cells, promoting cellular viability and proliferation.

- Immunogenicity: The material should not provoke an adverse immune response.

4. Functional Performance:

- Cellular Interactions: Assessing how cells adhere, proliferate, and differentiate on the nanofiber matrix.

- Drug Delivery Efficiency: Evaluating the release kinetics of embedded therapeutic agents and their bioactivity.

- Antimicrobial Properties: Determining the effectiveness of incorporated antimicrobial agents in preventing infection.

5. Healing Efficacy:

- In Vitro Studies: Initial testing on cell cultures to observe cellular behaviors and interactions with the nanofibers.

- In Vivo Studies: Animal models to assess wound closure rates, tissue regeneration, and overall healing outcomes in a biological context.

6. Degradability:

- Controlled Degradation:Ensuring that the nanofibers degrade at a rate that complements the tissue regeneration process without leaving harmful residues. Evaluating nanofibers through these parameters provides critical insights into their practical applications in wound healing, facilitating the development of advanced, effective, and safe therapeutic solutions.

Table1:- Marketed Product Available For Nanofibers

Product	Uses
Integra Artificial Skin	Burn wound
Medtronic	Chronic wound
Carbon Nanofibers	Used as catalyst, lithium battery anodes, for drug delivery
CorMatrix Electrospun Cardiac Patch	Myocardial Regeneration
Axogen Electrospun	Peripheral Nerve Regeneration

6.CONCLUSION:

Nanofibers represent a promising platform for wound healing applications due to their unique properties and versatile fabrication methods. Continued research and development efforts are needed to overcome existing challenges and translate nanofiber-based wound dressings from the laboratory to clinical practice, ultimately improving patient outcomes in wound care. The use of nanofibers in wound healing represents a significant advancement in medical treatments, offering a multifunctional approach that addresses various challenges in wound management. By promoting faster and more effective healing, reducing infection risks, and potentially minimizing scarring, nanofiber-based dressings have the potential to improve patient outcomes significantly.

7.Challenges And Future Direction

Despite their potential, several challenges remain to be addressed in the field of nanofiber-based wound healing, including scalability of fabrication, optimization of mechanical and biological properties, and regulatory approval for clinical use. Future research efforts should focus on developing advanced nanofiber-based wound dressings with enhanced functionality, biocompatibility, and therapeutic efficacy.

1.Scalability and cost: Scaling up nanofiber production for commercial applications remains a challenge, requiring optimization of fabrication processes and cost-effective manufacturing techniques. The cost of raw materials and fabrication processes can be high, limiting their widespread use.

2.Regulatory approval: Standardization of nanofiber-based wound healing products and compliance with regulatory requirements are essential for clinical translation and market acceptance.

3.Enhanced functionality: Further research is needed to develop advanced nanofiber formulations with enhanced functionality, such as stimuli-responsive materials, bioactive coatings, and integrated sensing capabilities.

4.Clinical validation: Clinical studies evaluating the safety and efficacy of nanofiber-based wound healing therapies in human subjects are needed to validate their clinical utility and establish evidence-based guidelines for their use.

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