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Advances in Nanofiber Fabrication and Biomedical Applications: Emphasis on Cellulose-Based Porous Systems for Transdermal Drug Delivery - A Review

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ABSTRACT: Nanofibers have emerged as promising materials in biomedical applications due to their high surface area, porosity, and tunable structures. Among them, cellulose-based porous nanofibers offer excellent biocompatibility, biodegradability, and mechanical strength, making them ideal for advanced drug delivery systems. Recent advancements in fabrication techniques, particularly electrospinning and its variants, enable precise control over fiber morphology and pore architecture, enhancing drug loading and controlled release capabilities.

Transdermal drug delivery, favored for its non-invasiveness and ability to bypass first-pass metabolism, benefits significantly from nanofiber systems. Cellulose-based nanofibers provide effective skin adhesion, high encapsulation efficiency, and sustained release of both hydrophilic and lipophilic agents. This review highlights the latest advances in nanofiber fabrication, with a focus on cellulose-based porous systems for transdermal therapeutic delivery, and discusses current challenges and future perspectives in this evolving field.

KEYWORDS: Nanofibers , Cellulose-based nanofibers , Porous nanofibers , Transdermal drug delivery , Controlled release , Drug delivery systems , Skin permeation , Biocompatibility , Advanced therapeutics

I. INTRODUCTION

The creation and usage of materials at the nanoscale (0.1–100 nm) is the focus of nanotechnology, which has enormous potential in a number of scientific and industrial domains. Because of its special qualities, such as their high surface area-to-volume ratio, porosity, and adjustable structural elements, nanofibers have attracted special attention among nanomaterials. Because of these qualities, they show promise as biomedical applications, especially as transdermal drug delivery devices [1]. Nanofibers can be made from a variety of natural and synthetic polymers and are usually created using sophisticated fabrication processes like electro spinning, phase separation, and template-assisted methods. The biocompatibility, biodegradability, mechanical strength, and capacity to create linked porosity networks—all of which improve drug loading, controlled release, and adherence to biological surfaces— make cellulose-based porous nanofibers unique[2].

These nanofibers are especially effective for localized and sustained transdermal distribution because porosity is essential for fluid transfer, regulated drug release, and optimal biochemical exchange. Because of their superior mechanical qualities and high adherence to skin and mucosal surfaces, they can be used to deliver hydrophilic and lipophilic medications with fewer adverse effects and greater therapeutic efficacy [3].

In addition to transdermal delivery, cellulose-based nanofibers show promise in wound healing, tissue engineering, and as scaffolds for regenerative medicine. This review highlights recent advances in the fabrication, characterization, and biomedical applications of nanofibers, with a special emphasis on cellulose-based porous systems tailored for transdermal drug delivery [4].

➢ **Advantages of Nanofibers**

- **High Surface-to-Volume Ratio**: Nanofibers offer an extensive surface area due to their nanoscale dimensions, enhancing drug dissolution rates, cell attachment, and mass transfer, which is valuable in drug delivery and biomedical applications [5].
- **Material Versatility**: They can be fabricated from a wide range of polymers and materials, offering tunable physicochemical properties such as mechanical strength, thermal stability, wettability, and degradation rates [6].
- **Ease of Functionalization**: Nanofibers can be easily functionalized either by blending

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additives into the polymer solution before spinning or through surface modifications post-fabrication, including core-shell structures [7].

- **Simple Material Combination**: Different materials can be effortlessly combined during fabrication, with minimal technical requirements [8].
- **Low Startup and Operational Costs**: Basic electrospinning equipment is relatively inexpensive and can be assembled in a standard lab setting [9].
- **User-Friendly Fabrication Process**: Electrospinning is a straightforward and accessible technique, easy to learn and implement with basic training [10].
- **Flexible Fiber Deposition**: Nanofibers can be deposited onto various substrates such as metal, glass, microfibrous mats, or even water, requiring minimal static charge [11].
- **Structural Diversity**: A variety of nanofibrous architectures, including tubular structures, yarns, and 3D blocks, can be developed through process modifications [12].
- **Scalability**: Commercial electro spinning systems are available, enabling the mass production of nanofibers for industrial applications [13].
- **Established-Commercial Applications**: Electrospun nanofibers are already integrated into numerous commercial products across biomedical, filtration, and environmental sectors[13],[14].

➢ **Disadvantages of Nanofibers**

- **Limited In Situ Deposition**: Difficulty in directly depositing nanofibers onto various substrates in a controlled manner [15].
- **Low Production Yield**: Traditional electrospinning methods typically produce nanofibers in small quantities with limited scalability [16].
- **High Voltage Requirement**: The process demands a high working voltage, which increases energy consumption and operational complexity [17].
- **Scalability Issues**: Large-scale production of nanofibers with consistent quality and specific properties remains challenging [18].
- **Material Limitations**: Issues with the thickness of deposited layers, high electrical dispersion in conductive blends, and complications when using aqueous solutions or sensitive biomaterials [19].

❖ **Types of Nanofibers**

Over the past two decades, nanotechnology has advanced the development of various nanostructures such as nanorods, nanowires, nanosheets, and particularly nanofibers**,** classified as one-dimensional (1D) nanomaterials with diameters typically below 100 nm. Nanofibers are further categorized by size, shape, and material composition (e.g., metals, ceramics, carbon, polymers) into three primary types [20]:

➢ **Inorganic Nanofibers**

- Composed of metal oxides and sulfides such **as** CuO, ZnO, SnO_2 , $BaTiO_3$, and ZnS**,** and composites like TiO_2 /Bi_2 WO_6 **.**
- Typically produced through electrospinning followed by calcination**.**
- Widely used in photocatalysis, sensors, and biomedical products (e.g., sunscreens), offering reduced toxicity compared to nanoparticles.

➢ **Carbon Nanofibers (CNFs)**

- Consist mainly of sp^2 carbon layers, with structures like cones, cups, or plates**.**
- Possess high electrical conductivity, mechanical strength, and large surface areas**,** making them suitable for diagnostics and therapeutic delivery systems**.**
- Commonly fabricated by electrospinning or vapor growth [21]**.**

➢ **Polymer-Based Nanofibers**

- Fabricated from over 50 different polymers using electrospinning**,** with diameters ranging from 3 nm to 1 µm.
- Applications include medical textiles, filters, scaffolds, wound dressings**,** and drug delivery systems, owing to their biocompatibility, flexibility, and ability to form porous structures ideal for transdermal drug delivery**.**

➢ **Composite Nanofibers**

Composite nanofibers consist of multiple phases with different chemical compositions, offering enhanced surface area**,** small pore sizes**,** thermal resistance**,** high conductivity, and cycle stability. These properties make them suitable for various applications**,** including biomedicine, energy storage, and environmental remediation**.**

They are typically fabricated by electrospinning polymer solutions containing nanoparticles or through polymer template

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methods, followed by thermal or chemical processing. Despite their advantages, challenges include long processing times and limited control over material incorporation within the fiber structure [22].

❖ **Role of Polymers in Nanofiber Technology**

Polymers play a pivotal role in nanofiber fabrication, influencing their mechanical strength, biodegradability, biocompatibility, and hydrophilicity, all critical for biomedical applications. Nanofibers can be produced from natural polymers, synthetic polymers, polymer blends, and composites, each offering unique advantages.

The choice of polymer dictates the functional properties of nanofibers, including porosity, surface area, and mechanical integrity, which are essential for applications such as tissue engineering scaffolds, wound dressings, vascular grafts, and controlled drug delivery systems. Polyblend nanofibers, combining different polymers, allow fine-tuning of mechanical and biological properties, providing high pore volumes and varied pore diameters suitable for cell attachment, proliferation, and localized therapeutic delivery [23].

❖ **Polymers**

While many of the polymers utilized in nanofiber technology, such as nylon, polystyrene, and polyethylene, can only be produced synthetically, proteins, cellulose, and silk are found in nature. High extension properties of polymers in ambient circumstances often generate elastomers.

Synthetic fibers, such as polyester and nylon, can successfully replace natural fibers like cotton, wool, and silk. Commercial plastic resins may contain a variety of fillers and additives in addition to two or more monomers. These improve mechanical qualities, processability, and thermal or environmental stability [24].

❖ **Types of Polymers Used in Nanofiber Fabrication**

➢ **Natural Polymers**

Natural polymers are preferred in nanofiber technology for transdermal drug delivery due to their biocompatibility, biodegradability, and low toxicity. Commonly used polysaccharides include cellulose, alginate, and chitosan. These materials offer structural advantages and are widely explored for drug delivery systems, tissue engineering scaffolds, and wound dressings.

- Cellulose: A robust, porous polymer from plant cell walls; often blended with PVA and cellulose acetate for hybrid nanofiber applications.
- Hyaluronic Acid (HA): Used in tissue engineering and drug delivery, electrospun HA derivatives (e.g., HA-DTPH) mimic extracellular matrices and support cell encapsulation and tissue regeneration.
- Chitosan/Gelatin Blends: Improved hydrophilicity and biodegradability; optimized for mechanical strength and cell attachment in scaffolds [25].

➢ **Semi-Synthetic Polymers**

Semi-synthetic polymers are derived from natural polymers via chemical modification. Examples include cellulose acetate (produced by acetylation of cellulose), gun cotton, and cellulose nitrate.

- PVA/Hydroxyethylcellulose (HEC) Scaffolds: Developed for transdermal drug delivery, incorporating ethosome-loaded FITC. Studies showed enhanced drug permeability and cellular uptake due to the lipid-rich ethosome structure, facilitating membrane fusion and endocytosis [26].

➢ **Synthetic Polymers**

Synthetic polymers offer precise control over nanofiber properties and are widely used in biomedical applications. Common examples include PEO, PVA, PCL, PLA, and polyvinylpyrrolidone, many of which are FDA-approved.

- Polycaprolactone (PCL) and Polylactic Acid (PLA): Frequently used for tissue scaffolds and drug delivery, offering biodegradability and mechanical strength.
- Surface Optimization: For example, PLLA nanofibers treated with extracellular matrix (ECM) coatings significantly enhance cell adhesion and osteogenic differentiation, showing promise in bone tissue engineering [27].

II. FABRICATION METHODS OF NANOFIBERS

Few methods can effectively create nanofibrous structures for systemic gene transport and inclusion phenomena, despite the fact that there are numerous ways to create nanofibers, such as phase separation and self-assembly. Electrospinning and coaxial electrospinning are

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used to provide an efficient delivery technology for targeted gene delivery based on nanofiber composites. Along with

1-Electro-spinning

The method most commonly employed to create nanofibers is electrospinning. The invention of electrospinning as a workable technique for producing nanofibers can be traced back to a 1934 patent on a formula for artificial suits that used a powerful electromagnetic Yield [28].

Electrospinning uses electrostatic forces to create nanofibers from liquid droplets in capillaries. When an electrically charged cone forms at the droplet's tip, high charge densities can produce fine jets. These fibers are collected on a grounded collector, which dissipates most charges, though some residual charge remains due to low solution conductivity [29].

Electrospinning techniques are classified into solution electrospinning and melt electrospinning, with solution electrospinning being more popular due to its simplicity, scalability, and cost-effectiveness. Electrospun fibers form porous networks, allowing high gene loading and sustained release. Both natural polymers (e.g., zein, collagen) and synthetic polymers (e.g., PCL, PLGA) have been successfully electrospun for gene delivery [30].

The characteristics of nanofibers are influenced by three key factors:

1. **Process parameters** – voltage, flow rate, and distance from the Taylor cone to the collector.
2. **Material parameters** – polymer concentration, molecular weight, surface tension, conductivity, and solvent volatility.
3. **Environmental parameters** – temperature and humidity.

Higher polymer concentration and molecular weight increase solution viscosity, impacting fiber formation. Nozzle size is also crucial: too small a nozzle can block the viscous polymer solution. Surface tension, influenced by solvent composition, affects fiber morphology. Lowering surface tension can transform beaded (pearl) fibers into smooth fibers [31].

Solvents play a critical role in nanofiber properties. Their boiling point and polymer solubility determine processing efficiency, while solvent vapor treatments can enhance the mechanical strength of nanofiber mats without altering their structure [32].

2-Coaxial Electrospinning Coaxial electrospinning is a technique used to produce nanofibers with a core-sheath (core-shell) structure, ideal for sustained and controlled drug release. This method allows drugs, proteins, growth hormones, antibiotics, and other bioactive molecules to be encapsulated in the core, protected by the outer polymer sheath. This structure maintains the biological activity of sensitive molecules, prevents direct contact of biomolecules with the external environment, and prolongs drug release while preserving functionality [33].

The unique core-shell architecture enhances the stability and bioactivity of encapsulated agents. It also enables multilayer nanofiber structures that are effective for gene delivery, offering controlled and localized gene release. Coaxial nanofibers help protect genes during delivery and prevent unwanted systemic viral transduction.

An example includes PCL/PEG coaxial nanofibers, used for gene transduction into RAW 264.7 cells in vitro, showcasing their potential in tissue-engineered frameworks and gene therapy [34].

3-Multi-jet electrospinning

Multi-nozzle electrospinning systems were designed for manufacturing large quantities of nanofibers to boost output and coverage. Multi-needle electrospinning has reportedly been utilized to develop skin-core structures. It comprises two steps for creating nanofiber filaments: spinning and drawing together. When an auxiliary electrode is inserted during the formation of spun nanofiber filaments, the electrostatic field interference between needles decreases, leading to either a reduction in beam offsets or an enhancement in Taylor cone and beam stability. An electrospinning apparatus with several or fewer nozzles can produce electrospun nanofiber jets [35].

Using a multi-jet electrospinning apparatus, multicomponent polymers can be electrospun to create an amalgamation of nanofiber mats with a consistent thickness and sufficient dispersibility. This method also allows for the creation of mixed nanofiber mats that comprise multiple polymers. CNR-ISMAC has created an electrospinning system with many nozzles that are bottom-up. It has a 50 cm wide metal collector with 31 to 62 nozzles. The configurations create overlapping deposition zones to achieve a uniform deposition of nanofibers on the collector [36].

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4-Emulsion electrospinning

Emulsion electrospinning is a quick, cost-effective, and potential method for fabricating electrospun core-shell nanofibers. It is a versatile and prospective technology for encapsulating diverse pharmaceuticals in nanofibers. Metformin hydrochloride (MH) or metoprolol tartrate (MPT) were added to the fibers of poly (ϵ-caprolactone) (PCL) and poly (3-hydroxybutyric-co-3-hydroxy valeric acid) (PHBV) using emulsion electrospinning. Emulsion electrospinning was a more effective method in this study than mixed electrospinning, particularly for modifying the pace at which drugs are released by controlling the water and oil phases of the emulsions to achieve the desired drug release. PCL demonstrated superior drug transport capabilities compared to PHBV [37].

The biomolecule-laden stage can be disseminated throughout the fiber for low molecular-weight drugs. A core-shell fibrous architecture may be formed if macromolecules combine with an aqueous phase [38].

5-Physical Fabrication Techniques

The manufacturing of nanofibers has been researched using a variety of physical, chemical, and biological procedures, such as milling, physical vapor deposition (PVD), laser ablation, and spin fabrication methods. In addition, mechanical processing, refining cellulosic-based materials like wood or tunicates, produces parts with 50 nm to 3 μm with 5–50 nm diameters [39].

6-Physical Vapor Deposition (PVD) techniques

Vapor or bottom gas phase deposition are the two most used processes for producing carbon and metal oxide nanoparticles. Recently, vapor-phase deposition methods, including chemical vapor deposition (CVD) and PVD, have been used to build highly structured metal oxide and carbon nanofibers [40].

1. The two most popular PVD techniques are plasma sputtering and electron beam evaporation.
2. Plasma sputtering involves bombarding the material with electrons to heat and create a vapor that can be used to deposit nanofibers.
3. Vacuum arc deposition, in which the arc vaporizes the target material in a vacuum before re-depositing it to produce nanofibers.
4. Pulsed laser deposition involves the formation of nanofibers on a solid substrate following high-power laser ablation of the material.

Recently, the possibility of creating polymeric materials with nanostructures resembling fibers has been investigated using PVD. Typically, CVD is used to create carbon nanofibers. Carbon nanofibers are produced by mixing a carbon feed (such as CO or a hydrocarbon gas) with catalyst particles of transition metals like Fe, Ni, Co, Pt, and Cu at temperatures between 500 and 1200 °C [41].

7-Laser Ablation Method

The laser ablation technique is a simple, one-step process used to create densely packed and randomly arranged nanofibers. By directing a femtosecond laser at silica glass, nanofibers of various shapes and sizes—ranging from tens to hundreds of nanometers in diameter—can be produced. This method results in interwoven structures that require minimal preparation and allow for fast processing. The fibers typically range from millimeters in length to thicknesses between 10 nm and several hundred nanometers [42].

Pulsed laser ablation applied to dielectric materials has demonstrated the ability to create fibers as small as 150 nm and as large as 100 micrometers.Additionally,polyvinylpyrrolidone (PVP) nanofibers with embedded gold nanoparticles have been developed using a combination of laser ablation and electrospinning. Compared to chemical and thermal techniques, laser ablation offers advantages such as lower cost, process cleanliness, flexibility, and faster production times, making it a promising approach for fabricating various types of nanomaterials [43].

8- Mechanical Fabrication Method

Mechanical methods, including grinding, ball milling, cryo-crushing, and high-pressure homogenization, are commonly used top-down approaches to produce cellulose nanofibers (CNFs) from natural sources like pulp. Process parameters such as milling media, speed, state (dry/wet), duration, and energy input directly influence the size and morphology of the resulting nanofibers [44].

However, mechanically derived CNFs often exhibit low crystallinity, aspect ratio, and polymerization degree, limiting their mechanical strength—crucial for biomedical applications like transdermal drug delivery. To overcome these challenges, chemical pretreatments (acid hydrolysis, alkaline, or oxidative treatments) are applied prior to mechanical processing. These modifications enhance fiber breakdown, reduce energy consumption, and improve nanofibril yield

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and quality, resulting in cellulose-based porous systems suitable for advanced drug delivery applications [45].

9- Vapor Deposition Of Chemicals (CVD)

Reactive gas-phase molecules are broken down into film-forming or particle-growing reactive species during the flexible chemical vapor deposition (CVD) process. A variety of conductors, semiconductors, and insulators can be deposited using the CVD process. regulated production of The CVD approach has recently focused on nanomaterials in porous hosts, like zeolite nanochannels. The ability of CVD processes to reliably form thin material films, even on irregular geometries, is one of their advantages. Enhancing the commercial synthesis of carbon nanofibers using catalytic chemical vapor deposition is of interest. A MnO/carbon nanofiber (MnO/CNFs@G) membrane was made by Wang et al. using a straightforward electrospinning method, and it was subsequently put through an ambient pressure chemical vapor deposition (APCVD) process [46].

10- Microwave-Assisted Synthesis of Carbon Nanofibers for Biomedical Applications

Microwave-assisted synthesis offers a rapid and energy-efficient method for producing carbon nanofiber (CNF) coatings on various substrates. This technique enables CNF formation within seconds of microwave irradiation, often completing the process in under a minute with minimal thermal impact on the environment. Optimizing key parameters is essential for controlling nanofiber quality during these fast synthesis processes [47].

For example, Drunka et al. demonstrated the microwave synthesis of TiO_2 nanoparticles, later modified with platinum, using 10 M KOH and anatase nanopowder. This approach yielded nanostructures with diameters around 10 nm and surface areas ranging from 70–150 m^2/g, highlighting the potential of microwave methods for fabricating nanofibers and nanowires [48].

While microwave synthesis is effective, electrospinning remains the preferred technique for producing nanofibers with high surface area-to-volume ratios and extensive inter/intra porosity—critical attributes for transdermal drug delivery systems. Advances in scalable electrospinning technologies have expanded laboratory capabilities, with new spinning and collection devices addressing the challenge of low productivity and enhancing commercial viability for biomedical applications [49].

III. APPLICATIONS OF NANOFIBERS

For the administration of pharmacological compounds with a wide range of biomedical applications, nanofibers provide a substantial advantage. It may be easy to create nanofibers with various forms and release properties because to recent advancements in nanotechnology.

Tissue engineering, cardiovascular conditions, infectious diseases, and other biological applications are among the most promising. Pain management, contraception, dentistry, neuro-degenerative diseases, GIT-related disorders, and other biological conditions [50].

1-**Cardiovascular-Diseases**

According to a WHO report, the world's top cause of death is cardiovascular disease. An estimated 17.9 million deaths, or 32% of all fatalities, are predicted to occur globally in 2019. Mortality from heart attacks and strokes accounted for 85 percent of these fatalities. Using a range of synthetic and natural biomaterials, electrospinning has been utilized to create nanofiber scaffolds for cardiac ventricular tissue engineering applications. A new era of tissue regeneration that is immune-suppressed has begun because of nanofiber scaffolds that contain stem cells. To improve their effectiveness as stem cell transporters, nanofibers have undergone a number of alterations, such as coaxial electrospinning, layer-by-layer manufacturing, and a phase separation technique. Additionally, the potential of stem cell-containing nanofibers to treat cardiovascular conditions like atherosclerosis and cardiomyocyte regeneration has been demonstrated [51].

2-Drug-Delivery

Due to the porous nanostructure's many unique characteristics, such as its high encapsulation efficiency (EE%), high drug loading, enhanced therapeutic index, significantly fewer side effects, ability to integrate drug release, and control over the conditions of the solution and processing. As a result, the use of nanofiber in drug delivery systems in biomedicine is growing quickly. Drug release is influenced by the composition, swelling, diameter, porosity, shape, geometry, and thickness of electrospun fiber. Drug release from fibers is thought to be caused by a confluence of factors, including drug solubility,

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polymer breakdown, drug partitioning in polymers, and diffusion [52].

3- Bone Regeneration

Bone tissue engineering combines biomaterials and cells to create biosynthetic grafts that support mineralization and repair of fractured or damaged bone. The natural bone matrix derives its stiffness and strength from the alignment of collagen fibers and hydroxyapatite crystals, providing both mechanical integrity and resilience [53].

Electrospinning has emerged as a versatile technique for fabricating scaffolds that mimic the structural and functional properties of native bone. To promote osteogenesis, the scaffold material must be bioactive, biocompatible, and capable of supporting osteoblast proliferation and mineralization. Electrospun nanofiber scaffolds, often enhanced with bioactive agents, have demonstrated the ability to accelerate bone regeneration. For effective bone repair, these scaffolds should be biodegradable and possess mechanical properties that match the bone environment [54].

4- Wound Healing

Wound healing is a complex process involving hemostasis, inflammation, proliferation, and remodeling. Acute wounds typically heal faster than chronic wounds, which are more susceptible to bacterial infections and delayed recovery. Recently, drug-loaded nanofiber scaffolds have gained attention in skin tissue engineering due to their flexibility, controlled drug release, and biocompatibility, facilitating tissue regeneration [55].

Various fabrication techniques—such as melt blowing, rotary jet spinning, hand spinning, pressurized gyration, and electrospinning—are employed to create these nanofibrous scaffolds. Incorporating therapeutic agents like antibiotics, anti-bacterials, and anti-inflammatories into the nanofibers enhances their ability to prevent infection and promote healing processes, including vasodilation [56].

Electrospun collagen nanofiber scaffolds closely mimic the extracellular matrix, supporting cell attachment, proliferation, and penetration. Additionally, hybrid polymer scaffolds, such as chitosan-graft-polymer nanofibers, overcome limitations like the “fishnet effect” seen in single-polymer systems, offering improved mechanical integrity and enhanced performance in skin tissue engineering [57].

IV. RECENT ADVANCEMENTS IN NANOFIBER TECHNOLOGY

1- **Electrospun Nanofiber Scaffolds for Gene Delivery**

Gene delivery facilitates targeted genetic modification to achieve therapeutic outcomes, such as inducing cell differentiation, promoting apoptosis in tumors, and enabling cellular therapies. Electrospun nanofiber scaffolds have emerged as promising platforms for gene delivery, closely mimicking the extracellular matrix (ECM) to support cell adhesion, proliferation, and morphology.

Techniques like electrospinning and coaxial electrospinning are commonly used to fabricate nanofiber composites from polymers and ceramics. These scaffolds can deliver genetic material by immobilizing plasmid DNA (pDNA) or incorporating it into fiber-forming solutions prior to spinning. For example, siRNA adsorbed onto polycaprolactone (PCL) nanofibers successfully transfected mesenchymal stem cells (MSCs) to promote neural differentiation. Similarly, electrospun poly(L-lactic acid) (PLLA)/collagen nanocomposites loaded with rhBMP-2 plasmid DNA have demonstrated ectopic bone formation through localized gene expression [58].

Non-viral vectors, such as DNA/polyplexes or naked pDNA, are increasingly incorporated into nanofiber scaffolds for safe and targeted gene delivery. Hybrid systems combining electrospun fibers with viral vectors can further enhance gene transfer efficiency and prolong gene expression. These advances highlight the potential of electrospun nanofiber composites as spatiotemporally controlled delivery systems for regenerative medicine and tissue engineering applications [59].

2- **Protein and Peptide Delivery via Electrospun Nanofibers**

Proteins and peptides are prone to degradation, requiring careful control of electrospinning conditions (pH, temperature) to maintain their stability. Organic solvents like ethanol, DMF, and HFIP enhance solubility but must be used cautiously to prevent structural damage.

Blending proteins with polymers such as PLA, PCL, and chitosan improves fiber stability and mechanical properties. Soy protein, due to its biocompatibility and biodegradability, has been electrospun with PEO to create scaffolds supporting stem cell growth. Similarly,

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vancomycin-loaded soy protein nanofibers show promise in wound healing. Plant proteins like gluten and zein are also explored for cost-effective, sustainable biomedical applications [60].

V. CELLULOSE-BASED POROUS SYSTEMS FOR TRANSDERMAL DRUG DELIVERY

Electrospun porous nanofibers, with their high surface area and interconnected pores, have gained significant attention across various fields. In environmental applications, they enhance filtration efficiency and provide superhydrophobic surfaces. For energy storage, their porosity maximizes active site utilization and improves mass transfer during redox reactions. In biomedicine, porous structures promote controlled drug release, enhance cell adhesion, and support tissue engineering, particularly in vascular regeneration. By combining electrospinning with surface modifications and functional additives, these nanofibers are widely used in air and water purification, energy devices, sensors, and biomedical applications [61].

Cellulose and its derivatives have gained significant attention in transdermal drug delivery (TDD) systems due to their biocompatibility, biodegradability, and non-toxic nature. As a natural polysaccharide, cellulose offers excellent film-forming abilities and mechanical strength, making it an ideal matrix for porous structures that enhance skin permeability and controlled drug release.

1- Advantages of Cellulose-Based Porous Systems

Cellulose-based porous materials, particularly in nanofiber form, present several benefits:

- **High Surface Area**: Facilitates efficient drug loading.
- **Porosity and Pore Connectivity**: Enhance drug diffusion and promote sustained release.
- **Mechanical Flexibility**: Ensures better adhesion to the skin, improving patient compliance.
- **Moisture Retention**: Maintains a moist wound environment, accelerating healing [62].

2- Fabrication Techniques

Electrospinning is the most common method used to fabricate cellulose-based porous nanofibers for TDD. Blending cellulose derivatives like cellulose acetate (CA), hydroxypropyl methylcellulose (HPMC), and carboxymethyl cellulose (CMC) with biodegradable polymers (e.g., PCL, PLA) enhances fiber spinnability and functionality. Post-treatment methods, such as surface modification or crosslinking, can further optimize drug release profiles.

3- Drug Loading and Release

Cellulose porous systems can encapsulate both hydrophilic and hydrophobic drugs. The porous structure allows for:

- **Controlled and Sustained Release**: Reducing dosing frequency.
- **Enhanced Skin Penetration**: Through the creation of micro-reservoirs within the porous matrix. Examples include systems delivering anti-inflammatory agents, antibiotics, and pain relievers transdermally with improved bioavailability [63].

4- Applications and Future Perspectives

Cellulose-based porous transdermal systems have been successfully applied in wound dressings, hormone therapy, and localized pain management. Future research is focusing on smart drug delivery systems incorporating stimuli-responsive polymers and nanocarriers to enable on-demand drug release, further expanding the potential of cellulose-based TDD [64].

VI. CONCLUSION

In recent years, significant advances in nanofiber fabrication technologies have revolutionized the field of biomedical applications, particularly in transdermal drug delivery (TDD). Among various biomaterials explored, cellulose and its derivatives have emerged as highly promising candidates due to their inherent biocompatibility, biodegradability, mechanical robustness, and ease of chemical modification. Cellulose-based porous nanofiber systems, fabricated predominantly through electrospinning and other innovative techniques, offer unique advantages, including high surface area, interconnected porous structures, and tunable physicochemical properties. These characteristics enable efficient drug loading, controlled and sustained release, and enhanced skin permeability—addressing key challenges in conventional TDD systems.

Furthermore, the ability to functionalize cellulose nanofibers with bioactive molecules, polymers, and nanoparticles broadens their potential in regenerative medicine, wound healing, and targeted therapeutics. While current research demonstrates promising in vitro and in vivo outcomes, further investigation is required to

ensure clinical translation, including large-scale production, long-term safety evaluation, and regulatory approval.

In conclusion, cellulose-based porous nanofiber systems represent a transformative approach in the design of next-generation transdermal drug delivery platforms. Continued interdisciplinary research and technological innovation will pave the way for their successful integration into clinical practice, ultimately enhancing patient care and therapeutic outcomes.

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