RESEARCH PAPER

Nanofiber-Based Drug Delivery Systems: Current Trends, Applications, and Future Directions

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ABSTRACT

As a result of their special structural and physicochemical characteristics, nanofibers have emerged as attractive materials in cutting-edge drug delivery systems. Their porous structure, high surface-area-to-volume ratio, and adjustable morphology allow for effective drug loading and regulated therapeutic agent release. For the creation of nanofibers, numerous methods have been devised, including self-assembly, template synthesis, phase separation, freeze drying, drawing, and electrospinning. Because of its ease of use, adaptability, and capacity to create continuous nanofibers of nanoscale widths, electrospinning is the most popular technique among these. Drug delivery, tissue engineering, wound healing, cardiovascular treatment, and regenerative medicine are just a few of the biomedical applications in which nanofiber-based systems have shown great promise. In addition, their therapeutic potential have been further enhanced by recent developments including growth factor-loaded nanofibers, protein and peptide inclusion, and gene delivery. Despite their benefits, there are still issues with solvent management, high fabrication costs, large-scale production, and safety. It is anticipated that continual research and technical advancements will get over these restrictions and encourage the creation of effective drug delivery systems based on nanofibers for upcoming pharmaceutical and biomedical uses.

Keywords: Nanofibers; Electrospinning; Drug delivery; Tissue engineering; Controlled drug release; Biomedical applications; Nanotechnology.

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1. Introduction

Innovative drug-delivery systems that aim to provide targeted and regulated therapeutic results have been developed as a result of recent developments in biomedical research [1,2]. Developing solutions that enable medications to efficiently reach their intended site of action is one of the main difficulties in pharmaceutical research. Targeted delivery is the ultimate goal of medication therapy, but the effectiveness of this strategy is limited by a number of biological obstacles. These barriers limit the delivery of therapeutic agents to the necessary tissues while also shielding the body from dangerous chemicals [3,4].

Drug absorption and distribution are greatly influenced by a number of physiological barriers, including the epidermis, nasal epithelium, intestinal lining, oral mucosa, cell membrane, and blood-brain barrier. Furthermore, drug molecules may be altered by metabolic processes in the liver, kidneys, and gastrointestinal tract prior to reaching the target site, which could lead to decreased therapeutic efficacy or possible adverse consequences from accumulation in non-targeted organs [5, 6]. Hydrophilic medications are especially restricted by the cell membrane, but hydrophobic pharmaceuticals may have diffusion limits across mucus layers due to their hydrophilic nature. Drug absorption and bioavailability may be impacted by environmental conditions that further decrease drug solubility and stability, such as the stomach's acidic pH [7,8].

The stratum cornea's rich structure creates a powerful barrier that prevents drugs from penetrating the skin during transdermal medication delivery. Because the blood–brain barrier only permits passive diffusion of lipid-soluble chemicals within a limited molecular weight range and blocks almost 98% of tiny drug molecules, medication administration to the central nervous system is considerably more difficult [9,10]. The creation of effective drug delivery systems (DDS) has grown its importance in pharmaceutical research as a result of these constraints. In addition to delivering medications to the intended location, contemporary DDS improves drug stability, bioavailability, and therapeutic efficacy [11]. The creation of sophisticated drug delivery platforms has been made possible by the flexible materials made possible by breakthroughs in polymer science over the past century. Because polymeric materials may encapsulate medicinal substances and are biocompatible and biodegradable, they are widely used [12,13].

These polymers serve as protective carriers that enhance the solubility, controlled release, and stability of drugs. However, stringent safety rules frequently restrict the use of freshly synthesized polymers, thus researchers often use mixtures of FDA-approved polymers to create safe and efficient delivery systems [14,15].

Polymer-based medication delivery methods have been further enhanced by the development of nanotechnology. Nanostructured carriers such as nanoparticles, nanogels, micelles, microspheres, and nanofibers have attracted considerable attention due to their unique physicochemical properties and enhanced therapeutic performance. Because of their high surface-area-to-volume ratio, porous structure, and adjustable morphology, which enable effective drug loading and regulated drug release, nanofibers have attracted a lot of attention among these systems [16].

Electrospinning has emerged as the most popular fabrication technology for creating nanofibers. This method makes it possible to create continuous fibers with sizes on the nanoscale scale with an easy and affordable setup. Because of their high drug-loading capacity and regulated release of therapeutic drugs, electrospun nanofibers have demonstrated significant promise as drug delivery vehicles. Polymeric nanofibers can effectively include a variety of medications, including as proteins, nucleic acids, antibiotics, and anticancer medicines. As a result, electrospun nanofibers have shown promise in the creation of sophisticated drug delivery systems with increased therapeutic efficacy [16].

2. History

The first nanofibers were made by electrospinning more than 400 years ago. The electrospinning method was invented by William Gilbert in 1600. Gilbert's research is the first example of an electrostatic liquid attraction. In 1845, Louis Schwabe created a few techniques for making synthetic fibers and spinning silk. In 1889, Hughes and Chambers received the first patent for producing carbon nanofibers. American inventor John Francis Cooley patented the first electrospinning machine in 1902 under the name "Apparatus for electrically distributing fluids." In 1938, Rozenblum and Petryanov-Sokolov developed electrospun fibers, which they used to manufacture filter materials known as "Petryanov filters." In 1952, Radushkevich and Lukyanovich created hollow graphitic carbon fibers, and in 1966, Harold L. Simons developed a device that produced textiles with patterned fibers. Doshi and Reneker (1995) popularized the term "electrospinning" by producing fibers

from a variety of polymers with sizes ranging from 50 nm to 5 m microns and a range of cross-sectional morphologies [17]. Because electrospinning produces nanofibers with a high surface area to volume ratio and a greater number of inter/intra pores, it is chosen over other methods. Ongoing research in electrospinning has made laboratory-scale equipment more competitive. The market activity was revived with a variety of spinning and collecting electrode accessories. In an effort to combat low productivity, numerous companies have developed innovative production methods based on conventional electrospinning [18].

3. Methods for Producing Nanofibers

To produce nanofibers with regulated morphology and characteristics, a variety of fabrication processes have been devised. The functioning principles, benefits, and drawbacks of these methods vary. Self-assembly, template synthesis, phase separation, freeze drying, drawing, and electrospinning are a few of the often employed techniques.

3.1 Self-Assembling

Self-assembly is a top-down method of creating nanomaterials in which molecules use non-covalent interactions like hydrophobic, hydrogen bonding, and electrostatic forces to arrange themselves into ordered structures [19]. This method makes it possible to create nanofibers with lengths of several micrometers and diameters that are usually between a few nanometers and less than 100 nm. Small molecules are assembled into supramolecular hydrogels using weak intermolecular interactions including hydrophobic forces and hydrogen bonds [20] The molecular structure of the building blocks greatly influences the structure and shape of the final nanofibers. Nevertheless, this method has some drawbacks that restrict exact control over fiber parameters, such as intricate processes, lengthy processing times, and comparatively low production yield [21]. Furthermore, molecules that can spontaneously assemble or react to external stimuli are the only ones that can use self-assembly [22].

Self-assembly processes are frequently used by biological systems to create nanostructures like extracellular matrix (ECM) components [23]. In tissue engineering applications, artificial self-assembling systems are also extensively investigated. Creating amphiphilic peptide sequences that can self-assemble into nanofibrous structures is one popular tactic [24]. Hydrogen bonds and hydrophobic interactions control the formation of these peptide amphiphiles, which have hydrophilic head groups and hydrophobic tail groups [25-27]. Depending on the peptide design, hydrophobic tails have a tendency to cluster away from water during the self-assembly process, forming nanofibers with diameters ranging from 5 to 25 nm [28]. These nanofibrous materials have demonstrated encouraging uses in spinal cord regeneration, wound healing, and tissue engineering [29]. Figure 1 depicts the self-assembly technique schematically.

3.2 Synthesis of Templates

Another method for creating nanofibers from polymeric, metallic, semiconductor, or ceramic materials is template synthesis. This technique uses a porous template, like a metal oxide membrane, to regulate the fibers' diameter and form [30]. A polymer solution is typically passed through the membrane's pores, where the polymer solidifies to form nanofibers.

One drawback of this method is that it usually yields fibers that are just a few micrometers long, and the pore size of the template membrane determines the fiber diameter [31]. Nonetheless, a significant benefit of this technique is the capacity to create

nanofibers with consistent and regulated diameters by using templates with various pore sizes [32]. Figure 2 depicts the template synthesis scheme.

3.3 Separation of Phases

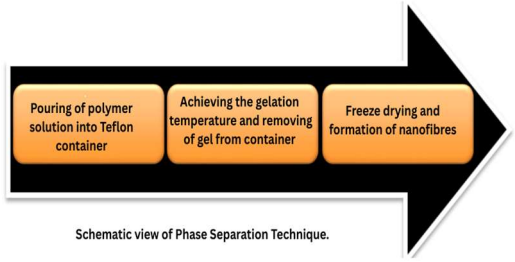

Fig 1: Phase separation technique [19]

The incompatibility of the solvent and polymer phases is the foundation of the phase separation process. The polymer is dissolved in a solvent, followed by gelation, solvent extraction, and freeze drying [33]. To create a homogenous solution, the polymer is first dissolved in an appropriate solvent. Phase separation and the formation of a nanofibrous matrix take place when the solution is chilled to cause gelation.

The characteristics of the nanofibers made with this technique are mostly dependent on the concentration of polymers. In general, increasing polymer concentration improves mechanical characteristics while reducing fiber porosity [34]. Nevertheless, this process is restricted to a small number of polymers, including polylactic acid (PLA) and polyglycolic acid (PGA), and it is unable to create long, continuous fibers [35]. Figure 3 depicts the phase separation approach schematically.

3.4 Drying with Freeze

Another technique for creating nanofibers is freeze drying, which is sometimes referred to as solid–liquid phase separation or ice segregation-induced self-assembly [36]. The three main stages of this process are freezing, primary drying, and secondary drying. To encourage the development of ice crystals, the polymer solution is first cooled to extremely low temperatures (−70 to −80°C). The frozen sample is subjected to lower pressure during primary drying in order to facilitate ice sublimation. Lastly, further drying is used to eliminate any leftover moisture [37].

When compared to alternative methods, freeze drying has a number of benefits. It makes it possible for porous structures to form without the need for harsh environments or chemicals that direct shape. Furthermore, the procedure is appropriate for biological applications since it doesn't call for high temperatures or organic solvents [38]. Nevertheless, applying this method to create hierarchical structures like vascularized scaffolds is still difficult. Figure 4 depicts the freeze drying process schematically.

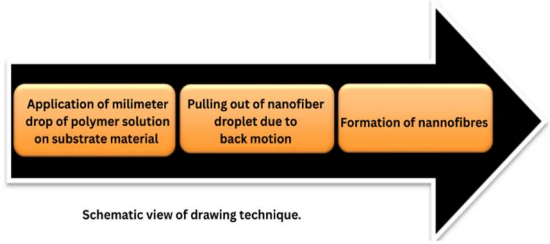

Fig 2: Drawing technique [19]

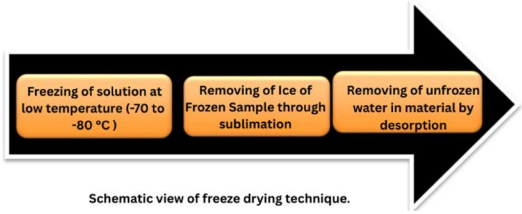

Fig 3: Freeze drying technique [19]

3.5 Sketching

Using a micropipette or sharp tip, drawing is a straightforward method for creating nanofibers.[39]. In this method, a droplet of polymer solution is stretched using a pointed tip to form thin fibers. The increased surface area causes the solvent to evaporate as the fiber is pulled, solidifying the fiber.

Fibers can be deposited onto a substrate and the drawing process controlled with a micropipette attached to a micromanipulator. By varying variables like drawing speed and solution viscosity, this method enables the creation of continuous nanofibers with regulated diameters [40]. However, the method is not appropriate for producing nanofibers on a wide scale and is somewhat slow.

3.6 Spinning electrodes

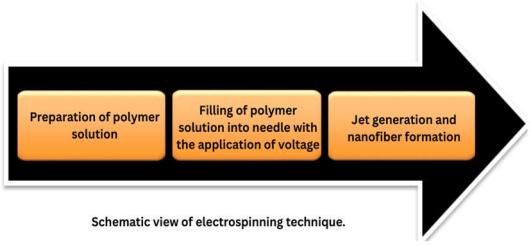

Fig 4: Electrospinning technique [19]

One of the most popular methods for creating ultrafine nanofibers with dimensions usually less than one micrometer is electrospinning [22]. The method, which is based on electrohydrodynamic principles, creates a charged jet by applying a high voltage to a polymer solution. Although electrospraying and electrospinning are closely related processes, electrospraying creates droplets while electrospinning creates continuous strands [41].

A syringe filled with polymer solution, a needle or spinneret, a syringe pump, a high-voltage power source, and a grounded collector make up the basic electrospinning setup [42].

A Taylor cone is created when a high voltage is supplied because electrostatic forces overcome the droplet's surface tension at the needle tip. After that, a charged polymer jet is released from the cone's tip and experiences whipping and stretching instabilities. The jet hardens and creates nanofibers that are deposited on the collecting surface when the solvent evaporates [43].

The development of the Taylor cone, extension of the charged jet, bending or whipping instability, and solidification of fibers on the collector surface are the four primary phases of the electrospinning process [42]. The diameter and shape of the generated nanofibers are influenced by variables like surface tension, conductivity, polymer viscosity, and applied voltage [43].

One of the most widely used methods for creating nanofibers for biomedical applications, especially in drug delivery and tissue engineering, is electrospinning because of its ease of use, scalability, and capacity to create continuous fibers with regulated morphology.

4. Advantages

1) Various materials and polymers are used to create nanofibers. Important physicochemical characteristics of materials and polymers include molecular weight, solution viscosity, electrical, mechanical, thermal, electrical conductivity, charge carrier mobility, tensile modulus and tensile strength, wettability, thermal stability, and degradation.
2) Various materials and polymers are used to create nanofibers.
3) Easy fiber functionalization: Surface functionalization can be carried out via core-shell electrospinning or by blending a straightforward polymer solution prior to spinning.
4) Combining materials is simple: Electrospinning allows for the easy use of a variety of materials with minimal requirements for producing fibers.
5) Reasonably low initial cost: The average cost of a simple electrospinning device is between $3,000 and $4,000. In a lab setting, a setup can be self-built with store-bought components.
6) Simple to understand the technique: A person can learn the principles of

electrospinning in a few weeks with the assistance of a mentor and some knowledge of electrostatics and polymers.
7) Fiber deposition onto different surfaces is simple.
8) A reduced static charge on the collecting surface is required for electrospun fiber deposition.
9) Electrospun fibers are commonly applied to water, glass, metal, and micro-fibrous mats.
10) Numerous nanofibrous structures have been built. Electrospinning setup and modification has enabled the production of tubular nanofibrous structures, yarns, and three-dimensional blocks of nanofibers.
11) Mass production capability: Large-scale nanofiber production is also possible with commercially available electrospinning technologies.
12) Commercial applications: The electrospinning process has been used to create a number of products that are available for purchase. [44,45].

5. Drawbacks

1) It can be difficult to achieve in situ nanofiber deposition on various surfaces.
2) The method necessitates high working voltages and frequently yields low results.
3) It is still difficult to produce nanofibers on a large scale with the appropriate characteristics.
4) Low material deposition thickness, high electrical dispersion with conductive mixes, and challenges with aqueous solutions and delicate biomaterials are among the limitations [46,47].
5)

6. Nanofiber Applications

Because of their adjustable shape, large surface area, and controlled release capabilities, nanofibers are becoming more and more useful platforms for drug delivery and biological applications.[90]. Tissue engineering, cardiovascular therapy, wound healing, contraception, and illness management are among the main uses [48].

6.1 Applications for the Heart

Using both natural and synthetic polymers, electrospun nanofiber scaffolds facilitate the introduction of stem cells and cardiac tissue engineering, promoting regeneration in diseases including atherosclerosis and myocardial injury [49,50].

6.2 Drug Administration

High drug encapsulation, enhanced therapeutic efficacy, and controlled release are all provided by nanofibers. Drug release kinetics are influenced by fiber composition, porosity, and polymer degradation [51].

6.3 Regeneration of Bone and Cartilage

Nanofiber scaffolds encourage osteogenesis and tissue healing by imitating the extracellular matrix of bone and cartilage. Adding bioactive substances like VEGF, BMPs, or silver nanoparticles promotes cell growth and mineralization [52-64].

6.4 Healing of Wounds

Drug-loaded nanofibers promote cell proliferation, speed up tissue repair, and offer antimicrobial protection. Scaffolds that are hybrid or composite enhance cell adhesion and mechanical stability [65-67].

6.5 Vaginal Delivery and Contraceptives

Flexible nanofiber mats increase the effectiveness of infection control and contraception by enabling localized distribution of hormones or medicinal substances [68,69].

6.6 Engineering Tissue

Electrospun nanofibers facilitate the regeneration of vascular, bone, skin, neuronal, and cartilage tissues by imitating the extracellular matrix. For functional tissue scaffolds, characteristics including fiber alignment, porosity, and mechanical strength are essential [69]. All things considered, nanofibers offer a flexible, high-performing platform for cutting-edge biomedical applications that combine tissue regeneration and regulated drug release.

7. New Developments in Nanofiber Technology

7.1 Gene Transfer

Electrospun nanofibers are useful scaffolds for targeted gene delivery that enable tissue engineering and regenerative therapy by imitating the extracellular matrix (ECM). They can use viral or non-viral vectors to transfer siRNA, plasmid DNA, and growth factor genes, increasing transfection efficiency and prolonging gene expression [70-79].

7.2 Delivery of Proteins and Peptides

Under controlled electrospinning conditions, proteins and peptides that are susceptible to degradation can be integrated into nanofibers utilizing appropriate polymers (PCL, PLA, chitosan, Eudragit®) and solvents (ethanol, DMF, HFIP, TFA). Proteins produced from plants, like gluten and soy protein, offer biocompatible scaffolding for tissue regeneration [72-77].

7.3 Delivery of Growth Factors

Growth factors can be released in a regulated and prolonged manner while maintaining their bioactivity thanks to coaxial electrospinning. Because growth factors like bFGF and NGF have brief in vivo half-lives, this is helpful in tissue engineering [76].

7.4 Applications in Medicine

Clinical trials for nanofiber-based devices for medication delivery, tissue repair, wound healing, and regenerative therapies have begun. Recent clinical applications are compiled in Table 1.

Table 1: Nanofibers in Clinical Trials [76-83]

Sr. No.	Study Title	Condition/ Disease	Intervention/Treatment	Sponsors	Reference
1	Rotator cuff healing using nanofiber scaffold	Rotator cuff tears	Nanofiber scaffold	Atreon Orthopedics	[76]
2	Modified antibiotic nanofibers' antimicrobial properties	Pulp and necrosis	TAP nanofibers that are electrospun	University of Cario	[77]
3	Hydroxyapatite nanofiber reinforced composite's marginal	Demineralized cracks and pits	Hydroxyapatite nanofiber reinforced flowable composite versus convent	University of Cario	[78]

	integrity		ional resin-based		
4	Hydroxyapatite nanofiber reinforced composite retention rate	Demineralized cracks and pits	Flowable composite reinforced with hydroxyapatite nanofiber	University of Cario	[79]
5	Urethral repair using a biomimetic PLLA nanofiber membrane	Urethral constriction	PLLA nanofiber membrane	Shanghai Sixth People's Hospital's	[80]
6	Tumor cells in circulation are captured by functional electrospunnanofibers	Cancer of the ovaries	CTC apparatus	Shanghai Jiaotong University's Xinhua Hospital	[81]
7	Transdermal medication delivery using	actinic keratosis	nanofiber patches	Shanghai University	[82]
	liposome nanofiber patches			of TCM's Shuguang Hospital	
8	Topical use of an acyclovir nanofiber patch	Herpes labialis	Nanofiber patch containing acyclovir	University of Medical Sciences in Esfahan	[83]

8. Difficulties in Producing Nanofibers

Despite their promising applications, the production of nanofibers faces several challenges. Compared to conventional fibers, nanofiber fabrication is relatively expensive due to low production rates and the high cost of specialized equipment and technology. Additionally, during electrospinning, solvent vapors are released as the polymer solution forms the nanofiber web. These vapors must be properly captured, recovered, or disposed of in an environmentally friendly manner, which requires additional equipment and increases operational costs.

Because workers may be at danger from inhaling fibers or volatile substances, the small diameter of nanofibers and the existence of airborne solvent vapors further offer possible health problems. Furthermore, the ultrafine size of nanofibers makes handling, shipping, storage, and packaging more difficult and necessitates specific

protocols to preserve fiber integrity and avoid contamination. The following are the primary obstacles to the development of nanofibers: • Exorbitant production expenses
• Possible health risks associated with fiber inhalation
• Control of vaporized solvents
• Safe handling, storage, and packaging
To enable the widespread, secure, and economical use of nanofibers in industrial and biological applications, these issues must be resolved [84].

9. Prospects for the Future

By permitting regulated release of therapeutic agents, constant dosing over long periods of time, cyclic administration, and customizable release of both hydrophilic and hydrophobic medicines, composite nanofiber architectures have greatly expanded drug delivery applications. Polymers customized for certain cargoes and anticipated biological functions are used in the creation of current medication delivery systems. For use in targeted drug delivery, tissue engineering, cancer treatment, and pharmaceutical formulations, composite electrospun nanofibers must be optimized as drug carriers.

In order to accomplish precise and localized medication release, future research is probably going to concentrate on creating smart drug delivery devices that react to external stimuli like light, pressure, electric fields, ultrasound, or magnetic signals. The development of multipurpose devices that can dynamically regulate drug release from nanofibrous membranes in response to physiological or environmental stimuli may be made possible by the use of cutting-edge responsive materials.

Furthermore, because of their large surface area, biocompatibility, and ability to improve drug-loading efficiency, secondary-phase nanomaterials, also known as filler materials, provide prospective benefits. Further investigation of these compounds in conjunction with natural polymers such as gum arabic, chitin, pectin, starch, dextran, honey, wool, and chitosan—may yield innovative approaches for creating highly efficient, regulated, and focused drug delivery systems. The next generation of nanofiber-based drug delivery platforms is anticipated to be driven by the convergence of sophisticated polymer composites, nanofiber production techniques, and responsive materials, providing accurate, effective, and patient-specific therapeutic solutions.

10. Conclusion

Because of their high surface-area-to-volume ratio, adjustable porosity, and capacity to give regulated drug release, nanofiber-based drug delivery systems have attracted a lot of interest. Electrospinning is the most popular production technology due to its ease of usage and capacity to create continuous nanofibers with regulated shape. Because they can replicate the natural extracellular matrix and promote cell growth and tissue repair, nanofibers have enormous potential in biomedical applications such medication delivery, tissue engineering, wound healing, and regenerative medicine. Their medicinal applications have been further increased by recent developments, such as gene and protein delivery systems. Large-scale production, expensive manufacturing, and safety issues are still issues, though.

Future clinical translation of nanofiber-based drug delivery systems is anticipated to be facilitated by ongoing research and technology developments.

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