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NANOFIBERS - A NOVEL CARRIER FOR DRUG DELIVERY: A REVIEW

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ABSTRACT

The drawbacks of traditional therapeutic medications succeed in making the development of innovative therapies to treat a variety of medical conditions. Polymeric nanofibers, which are interesting prospects for a variety of functionalities comprising drug delivery, biomedical engineering, enzyme immobilization, personal protective equipment, textiles, packaging, wound care, purification process and sensors have seen a significant increase in demand in recent years. Researchers have developed a variety of methods, including many non-electrospinning approaches and several electrospinning approaches, to meet this demand for the creation of nanofibers. Electrospinning approach is most widely used for the creation of nanofibers. Due to their high surface area to volume ratio and porosity, nanofibers have unique characteristics that have drawn for the development of controlled drug delivery systems. This review describes the numerous process innovations for the creation of nanofibers as well as various pharmacological applications of polymeric nanofibers.

Keywords: Nanofibers, Non-Electrospinning, Electrospinning, Mechanism, Controlled release, Drug delivery

INTRODUCTION

Several decades ago, It soon became clear that a drug's therapeutic potency depends on the route of distribution, altering a variety of aspects such as pharmacokinetics, distribution, pharmacodynamics, metabolism and toxicity **[1]**. In tandem with the development of novel drug delivery strategies, such as microspheres, nanogels,

nanoparticles, micelles and nanofibers the pharmaceutical industry gained a new promising tool **[2]**. Nanocarriers can be used to wrap and distribute drugs that are too poisonous, intractable, quickly eliminated, or unstable when molecules are free by adopting active or passive targeted approach depending on the resulting formulation **[3,4]**. One newly established technique as medication delivery is utilisation of a delivery system relies on cell and even sometimes it's derived byproducts which including stem cells, RBCs, extracellular vesicles, and thrombocytes as nanocarriers. These carriers have recently been used to various industries **[5]**.

Nanofibers made from biodegradable and biocompatible polymers have drawn the most interest among all of these substitutes because of their extensive flexibility, efficiency, and distinctive physiochemical characteristics, such as a large surface area, small diameter, and high aspect ratio **[6,7]**. Additionally, the use of electrospun nanofibrous scaffolds in situ potentially reduce the drawbacks of systemic transfusion with free drugs or alternative delivery methods and by contrast, a controlled and sustained release of the drug at the site of action will maximise its pharmaceutical effects **[8]**. As an illustration, By enabling the dose-specific, site-specific as well as scheduled release of various drugs, a nanofibers can diminish the risk of multi-drug tolerance in cancer therapy and antibiotic-resistant microorganisms **[9-11]**.

Several methods exist for preparation of nanofibers, including thermal-induced phase separation **[12]**, self-assembly **[13]**, template synthesis **[14]**, and electrospinning. However, among these, the electrospinning technology is the most appealing because to its ability to produce nanofibers into 2D and 3D structures and it is easy, continuous, basic, quick, and economical manufacturing procedure **[15]**. By combining various polymers with different functionalities in the solution phase, electrospinning is the most effective method for creating composite fibres with synergistic properties for new applications **[16]**.

A. Non-electrospinning Methods

Interfacial Polymerization

This approach uses two distinct monomeric units that may further dissolve in two separate phases, such as the oil and water phases. The two monomers will dissolve and then polymerize at the emulsion droplet contact. For instance, after the diamine has been dissolved in the water phase, The solution is supplemented with the oil-soluble diacid chloride, which interacts with such original precursor at the contact to create the wall material. This method makes it possible to create nanofibers because of uniformly nucleated development. By

choosing dissimilar monomers, several types of polymers can be made, but most papers mention polyamide membrane **[17, 18]**.

Drawing

Another technique used to create fibres is drawing. It's like dry spinning. The fundamental benefit of this technique is that all that is needed is a sharp tip or a micropipette. In this technique, a droplet an already placed polymeric solution is drawn as wet fibres using a pointed tip. Following that, the solvent evaporates as a result of the large surface area causing the wet fibres to solidify. Cylindrical shaped capillary tubes can be utilized in place of tip of sharp end with continuous polymer administration to prevent the mass shrinkage issue, that restricts the steady pulling of the fibres and influences their dimension **[18]**. With the aid of a micromanipulator, the droplet is incorporated into the micropipette, which is then gently (about 10^{-4} m/s) drawn out of the liquid. By pinching the micropipette's end, nanofibers are subsequently drawn and fallen onto the ground. To create nanofiber, this technique was done numerous times on each droplet **[19]**. Using this technique, continuous nanofibers of any configuration can be created. In addition, it is possible to acquire accurate regulation of drawing's essential variables, such as viscosity and drawing speed, allowing for control and repeatability over the size or shape of the fibres produced **[20]**. This method is straightforward although restricted to the lab size since nanofibers being produced one at a time, making it an interrupted technique with low yield (single nanofibers can be produced one at a time) and it is also feasible to regulate the diameters of such fibres using this technique. Solely viscoelastic materials may be utilised in such approach to resist the stress generated by squeezing, as well as depending on the size of the orifice, only fibres with dimensions more than 100 nm can be generated.

Phase Separation

A polymer is treated with a solvent in the phase separation technique prior it goes through the gelation process. Phases separate as a consequence of physical interference. After extracting the solution from one phase, the other phase is then eliminated. This approach achieves unique benefits such as low equipment requirements and bulk uniformity. The mechanical characteristics of nanofibers are determined by the polymer content, which also influences fibre diameter as well as thickness **[21]**. Three-dimensional tissue engineering nanocomposites are often made using this technique. Furthermore, such approach has certain limitations, including considerable range of polymers may be utilised and that it is solely a experimental procedure **[22]**. Phase separation techniques could be utilised to create numerous

chemically synthesised polymeric nanocomposite in tissue engineering considerations **[23]**.

Template Synthesis

This technique creates nanofibers in tubular passages of spongy ceramics or polymeric substrates. The initial step is to fill the spongy template with monomers. The monomers are subsequently converted into polymer nanofibers chemically or electrochemically in the narrow passages of the spongy template. After etching or dissolving the template, separated nanofibers are obtained. As a result of the synthesised polymer's propensity to deposit it onto internal wall of the void passages, nanofibers made via this approach frequently have a hollow structure. Nanofibers can also be created without the use of monomers by feeding polymer solutions directly into the hollow channels, where they solidify into nanofibers when the solvent is removed. This method uses polymer solutions rather than monomers to create the nanofibers. Since the higher viscosity of polymeric solutions renders it challenging to employ completely tubular passages having low diameters, nanofibers made via polymeric solutions typically have bigger diameters than monomer made ones **[24, 25]**.

Self-Assembly

Numerous nanofibers have been created via the self-assembly technique, which is described as the spontaneous grouping of materials into shapes or shapes without human interference **[26, 27]**. It is an excellent method for making relatively thin nanofibers (generally less than 100 nm to few nm) having a dimension approximately a few micrometres through generating supramolecular hydrogels by the self-assembly of smaller chemical compounds by non - covalent interactions including hydrophobic interactions and hydrogen bonding. The primary mechanism relies upon such an inter molecular interactions which bind smaller units (molecules); a macromolecular nanofiber's overall shape is determined by the configuration of the smaller units of molecules. The main drawback this procedure is that it is a labour-intensive, drawn-out process that produces little and has poor control over fibre diameters. Additionally, the creation of nanofibers using this technique is restricted to smaller bioactive components that could self-assemble on their own or in response to a stimuli from outside **[25, 28]**.

Freeze Drying

This method of fibre synthesis is sometimes referred to as solid-liquid phase separation or ice segregation-induced self assembly. There are three main steps in it: The mixture is initially freeze at extremely low temperatures (-70 to -80 ^{0}C) to promote the development and nucleation of ice crystals, After the frozen sample is placed in an

assembly and its pressures is decreased to a few mm-hg using partially vacuum, a water can be directly sublimated without undergoing any chemical reactions or producing any unwanted byproducts. This process is known as primary drying and finally, in a secondary drying step, desorption removes the majority of the unfrozen water in the material. Over other methods, freeze drying (FD) provides a number of significant advantages. As a result, it has attracted growing interest in the creation of nanofibers. In contrast to other methods like self-assembly and electrospinning, it may directly build nanocomposites with adjustable dimensions from polymeric materials like chitin without the requirement for structure-directing chemicals or pretreatments. Additionally, the freeze-drying procedure does not require a high temperature or additional leaching phase, and the scaffold building procedure uses water and ice crystals rather than an organic solvent, making it more appropriate for biomedical applications. The freeze-drying technique has a number of benefits, but it is still difficult to use it to create composites with hierarchy structures, such as perfused systems. The resulting nanofiber mats can be used to create macroporous carbon nanocomposite, drug delivery devices, or templates for the manufacture of synthetic fibres. The construction of three-dimensional nanofibrous scaffolds in tissue reconstruction has received much research into the freeze-drying technique **[29]**. A freeze-drying approach has received a lot of attention for making three-dimensional nanofibrous scaffolds for tissue regeneration **[30, 31]**.

B. Electrospinning Methods

In order to produce fibres via electrospinning, high voltage is applied to a polymer solution that is passing across a tip of the needle. By examining the solvent source as well as the type of tip of the needle, several electrospinning techniques can be categorised **[32]**

Monoaxial Electrospinning

The complete procedure in this electrospinning method is done by using polymeric solution. Pumping the polymeric solution across a tip of the needle with a high voltage. The polymer liquid can expand to take on the shape of the suspended drop when a voltage is applied, whereas surface tension typically forms a sphere. A cone shape known as Taylor's cone is generated when a charged polymer liquid's electrostatic repulsion is above the interfacial tension. The jet originates at the tip of the needle and fibres deposit across a grounded metallic collector. It is useful for the synthesis of nanofibers containing single drug **[33]**.

Side-by-side Electrospinning

Side by side spinnerets generally represented by two or sometimes more

capillaries, the one parallel with another while one beneath it. To create the Janus beads-on-a-string products, a side-by-side electrospinning technique characterised by a home-made eccentric spinneret was devised. A side-by-side electrospinning procedure with a homemade eccentric spinneret was used to create Janus beads-on-a-string. In order to construct nanofibers and carry a first model drug, one side of the Janus beads on a string utilised the hydrophilic polymer polyvinylpyrrolidone K90 (PVP K90), while the opposite side used the hydrophobic polymer ethyl cellulose (EC) to form particles and carry a second model drug. Because Janus nanocomposite's various polymer matrices and architectures have varied effects on two drug release characteristics **[34]**. Rui Li *et al* prepared antibacterial PCL/PVP-AgNP janus nanofibers by uniaxial electrospinning **[35]**.

Coaxial Electrospinning

When it comes to electrospun core-sheath nanofibers, coaxial or triaxial electrospinning is thought to become the most efficient method for achieving prolonged drug release. To create a fibre, it entails the synchronous flow of a core solution and a sheath solution through different capillaries **[36]**. In order to create a fibre with varied inner and exterior portions, such as a hollow fibre and functional fibres that might contain coatings, coaxial electrospinning has the ability to make core-sheath structural fibres using a variety of core as well as sheath solutions **[37]**. In coaxial electrospinning, the spinneret is altered to create a co-axial shape by adding a smaller capillary that fits concentrically inside the larger capillary. The inner needle has a core solution, whereas the outside needle has a sheath solution. A core-shell droplet is created at the nozzle's output as a result of the simultaneous pumping of two separate spinning solutions by the inner and outer nozzles. Once the polymer solutions being charged with a high voltage level, the majority of the charge accumulates in the sheath solution that emerges from the coaxial capillary. Due to the charge-charge repulsion, the suspended droplet of the sheath solution elongates and expands, producing a cone shape. Once the charge buildup exceeds a certain threshold, a jet erupts from the distorted droplet's tip and is aimed over the counter electrode. Afterward, on the substrate, a core-shell fibre being collected **[38]**. Hai *et al*. recently revealed the Taylor cone creation process in normal one-fluid electrospinning and coaxial electrospinning methods **[39]**. To offer a long-lasting action against the S. aureus resistant bacterial strains, Peiwen *et al*. (2020) created electrospun nanofibers via this technique in which the antibiotic emodin within a hydrophilic PVP core and encasing it in a sheath of hygroscopic cellulose acetate **[40]**.

Triaxial Electrospinning

Controlled release of molecules trapped in coaxial fibre cores is often solitary conceivable when the fibre sheath material is nonhygroscopic. Water molecules develop passages among the fibre core and the surrounding atmosphere when the sheath layer is hygroscopic, either due to the use of hygroscopic polymers or the incorporation of water-soluble chemicals. As a result, release from the core happens rather quickly and resembles burst release more than regulated release. Due to their good biocompatibility and frequent hygroscopicity, various materials (such as gelatine, collagen, peptides, etc.) are selected for the sheath layer in many in vivo applications, which presents a difficulty. Triaxial electrospinning is used to create three-layer (core, intermediate, and sheath) structured fibres to address this problem. Between the innermost core and the external sheath, the intermediate layer serves as a buffer zone. In order to achieve great biocompatibility when employing hygroscopic material for the sheath, the triaxial fibre method is crucial. Instead of being released quickly by dissolution in this instance, the bioactive components from the core are forced to permeate via intermediate layer by the hydrophobic intermediate layer **[41]**. Nagiah *et al*. (2020) created triaxial fibres with a core layer of PCL, a sheath layer of 50:50 PLGA, and an intermediate layer of gelatine **[42]**.

MECHANISM OF DRUG RELEASE

Drug release mechanisms of biodegradable polymers are commonly recognised as erosion and diffusion. The mechanism of release and polymer breakdown will be influenced by the drug used and its concentration **[43]**. Both of these mechanisms work together to release drugs from biodegradable polymers in vivo and the ratio of erosion to diffusion rate is a key factor in this process. Enzymatic and hydrolytic degradation are responsible for the breakdown of the majority of biodegradable polymers utilised in drug delivery. An interaction among both water molecules and the linkages across the polymer network, which frequently contain ester bonds that continuously shorten the polymer chain until it reaches the monomers, is known as hydrolysis. Once water molecules disrupt chemical bonds with polymer chains during enzymatic breakdown, the structural consistency of polymeric materials is weakened, allowing the release of drugs from biodegradable polymers **[44]**.

PHARMACOLOGICAL APPLICATIONS OF NANOFIBERS

The primary and most common usage of nanofibers for drug delivery that has been documented in the literature, as well as the

method employed for their production is the main topics of this section.

A. Antibiotics

The invention of new, highly adjustable, and versatile antibiotic delivery strategies may reduce the risks of overdosage and the growth of bacterial resistance by acting selectively at the site of infection. Due to their distinctive qualities, electrospun nanofibers might make an appealing foundation for the development of a novel antibiotic drug delivery system **[45, 46]**. Electrospun nanofibers created by Pisani *et al*. (2019) which are made of polylactic acid and polycaprolactone (PLA-PCL) and loaded with gentamicin sulphate. They may be used to stop the growth of bacteria biofilms following surgical procedure. Gentamicin sulphate is an aminoglycoside antibiotic that has a low oral bioavailability and a significant incidence of side effects when given intravenously or intramuscularly, including ototoxicity and kidney toxicity. The creation of a targeted drug delivery system may be able to minimise the negative side effects while maximising the antibacterial activity **[47]**. Vancomycin, a glycopeptide antibiotic, was loaded into blended fibres of chitosan and gelatine by Behbood *et al*. (2017) to construct the bio mucoadhesive oral administration mechanism **[48]**. Those kinds of inserts' increased absorption and bioavailability, consistent release as well as elimination of first-pass metabolism are their three key benefits.

B. Anti-cancer drugs

Chemotherapy for cancer uses cytotoxic medications like doxorubicin, which can disrupt the cell cycle and cause apoptosis, to slow the growth of the tumour **[49]**. Due to the tumour's rapid growth, healthy tissue must receive more nutrients, which causes a high level of vascularization. Because of this, the drug's primary site of biodistribution is the tumour, where it must act **[50]**. However, the serious adverse effects of cancer chemotherapy are widely documented. Therefore, the development of localised administration of chemotherapeutics medications could retain the drug's cytotoxic effect while lowering the patient's systemic toxicity. Electrospun scaffolds are well suited for use as chemotherapeutic delivery systems due to their high biocompatibility and strong tunability toward drug release **[51]**. A scaffold with a regulated release of doxorubicin was created by Kuang *et al*. (2018) **[52]**. The authors used the mix electrospinning method with polyethylene oxide) (PEO) and PLLA, two hydrophilic and hydrophobic polymers, respectively. The release was tweaked twice to maximise the therapeutic impact. A portion of the medicine can be quickly released in the first stage to suppress the tumour in its early stages. On the other hand, the second stage

displays a prolonged release profile to extend a duration of treatment.

C. Ocular diseases

Eye drops, which are saline solutions containing active pharmacological ingredients, are typically used to treat eye diseases. Due to the system's limited volume, the tear film's rapid turnover, and the presence of multiple physiological barriers that medications must get past, it has a poor bioavailability. Solid delivery methods for eye diseases are drawing more attention since they may have higher bioavailability than liquid ones due to the system's potential for less clearance **[53, 54]**. Coaxial electrospun nanofibers were created by Tawfik *et al*. in 2020 and included two distinct medications in separate regions to cure corneal irritation and stop the spread of microbial infection **[55]**. The shell was made of PLGA and loaded with pirfenidone, an anti-fibrotic medication that is prescribed in clinics to cure eye conditions. In contrast hand, the core was made of hydrophilic PVP and contained moxifloxacin as an antibiotic. For the treatment of topical eye disorders, Gottel *et al*. (2020) employed a solid in situ gelling approach premised on Phytagel/pullulan electrospun nanocomposites **[56]**. The authors created a technique that can twist the scaffold into a specific shape because the eye's configuration makes the administration of solid medication quite difficult than administering of eye drops. Additionally, such method increases the contact between the fibre and the eye, enhancing the device's capacity for drug administration.

D. Anti-fungal drugs

Additionally investigated for transdermal administration of several antifungal medications are polymeric electrospun nanofibers. In order to cure cutaneous fungal infections, Harini *et al*. **[57]** looked into the antifungal potential of polycaprolactone (PCL)/egg lecithin-based nanofibers. Confocal microscopy revealed that developed nanofibers with a diameter of 127.7±43.7 nm was not toxic to human dermal fibroblasts. They also demonstrated excellent in-vitro antifungal activity against a variety of fungi, including Trichophyton mentagrophytes and Epidermophyton, which cause topical fungal infections.

E. Anti-inflammatory drugs

Pharmaceutical researchers have also looked into electrospun nanofibers for the transdermal administration of several anti-inflammatory medicines. Ibuprofen-impregnated nanofibers with a cellulose acetate/poly (vinyl pyrrolidone) base were studied by Shi *et al*. for transdermal administration. Ibuprofen was distributed uniformly and in amorphous form across the nanofibrous network in the optimised nanofibers, which had a diameter of 167±88 nm. When compared to a traditional transdermal patch of the same medicine, the

developed nanofibers demonstrated superior in-vitro skin penetration followed by higher water vapour permeability, demonstrating their great thermodynamic stability **[58]**.

F. Wound care management

The three primary roles of the skin which is the biggest important organ and also the outermost layer of a body are defence, homeostasis, as well as sensibility. Skin is extremely susceptible to damages because it serves as a shield in the body's protection against microorganisms and injury between both external and internal environment **[59, 60]**. The focus of research is shifting more and more toward developing nanofiber-based dressings that can mimic the dermal extracellular matrix as well as have a high surface area to volume ratio, and exhibit high porosity. In contrast to their typical mechanisms, such nanofibrous dressings were designed to encourage wound healing by generating a pleasant condition **[61]**. Utilizing the ability to incorporate active ingredients including medications might enhance healing or supply antimicrobial medicines to decrease wound inflammation **[62]**. pH responsive nanofibrous scaffold produced by Guo *et al* (2020) for consecutive delivery of two drugs in wound care management. The fibres were made out of a chitosan/Polyethylene oxide mixture incorporated with such a shell of lidocaine hydrochloride, which is employed to relieve inflammation, and PCL incorporated curcumin, which is an anti-inflammatory drug, into the core. Chitosan as well as sodium bicarbonate were both present in the core of the object, which resulted in the pH-responsive behaviour **[63]**. Chitosan (CS) has excellent haemostasis **[64]** as well as wound healing characteristics, making it an excellent candidate for wound care management **[65, 66]**. Because of the rigidity of the polymeric chains, CS has low spinability; hence, spinning agents such as polyethylene oxide are frequently used to boost spinnability **[67]**.

CONCLUSION

Due to their many benefits, including high porosity and a high surface area to volume ratio that make them appropriate for a wide range of applications, nanofibers have recently grown in prominence, especially in controlled drug delivery systems. Electrospinning approach is most widely used for the creation of nanofibers. For more uses, there are number of concerns that must be resolved including the stability of active ingredients, the residual organic solvent, the initial burst effect, the combined use of new biocompatible polymers and drug entrapment. Recent advancements and patent rights will facilitate nanofibers in the succeeding years, and scientific investigations will shortly be anticipated corresponding to rising advancements.

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