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Nanofibers: Transforming Drug Delivery with Innovation

Harminder Pal Singh[1], Geetanjali Saini[1]*, Daljeet Kaur[2], Maninder Pal Singh[3]

[1]School of Pharmaceutical Sciences, CT University Ferozepur Road, Sidhwan Khurd-142024, India.

[2] S.S. College of Pharmacy, Hayat Nagar, Gurdaspur, Punjab-143521, India.

[3] Rayat Bahra Institute of Pharmacy, Hoshiarpur, Punjab-146101, India.

Corresponding Author: viceprincipal@ctuniversity.in,

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Abstract:

Polymer have garnered significant interest owing to their exceptional properties, including a large surface area, high porosity, small pore size, robust mechanical strength and the ability to incorporate surface functionalities. Among the techniques for producing nanofibers, electro spinning stands out due to its simplicity, versatility, and cost-effectiveness. Electrospun polymer nanofibers particularly significant in biomedical applications, acting as carriers for the controlled delivery of bioactive molecules like cytokines, growth factors, anticancer drugs, enzymes and vitamins. The ability to fine-tune the physical and chemical properties of nanofibers enables precise control over drug release profiles, enhancing therapeutic outcomes while minimizing side effects. Their high porosity and large surface area enhance drug loading capacity and ensure effective diffusion. Applications of polymer nanofibers extend beyond drug delivery to include tissue engineering, wound dressings, filtration membranes and energy storage devices. Their versatility and potential for innovation make polymer nanofibers a cornerstone of advanced material science. The fabrication of nanofibers employs techniques such as, electro spinning, phase separation, template synthesis and self-assembly. Electro spinning, the most prevalent method, uses an electric field to draw polymer solutions into continuous nanofibers. Critical parameters influencing this process include polymer concentration, solution viscosity, applied voltage, flow rate and environmental factors like humidity and temperature. These parameters directly impact fiber morphology, diameter and uniformity. This article provides an overview of nanofibers, highlighting the various fabrication techniques, methods for their characterization, the key parameters influencing the electro spinning process and their diverse applications.

Keywords: Drug delivery, electro spinning, nanofiber, sensor devices.

Introduction

Nanofibers are defined as fibers having at least one dimen-sion of 100 nm or less.Nanofibers are a new class ofmaterial used for several value-added applications asmedical, filtration, barrier, personal care, wipes, garments,composite, energy storage, and insulation. The nanofibers possess unique properties thatmake them a suitable carrier for drug delivery. Owing to thesmaller size possessed by nanofibers, drug can be deliveredto the appropriate site in the body. Major advantages of nanofibers scaffold formulations are excellent stability, better targeting, minimum toxicity, high drug-loading

capacity, exceptional mechanical properties, encapsulation of various ranges of drugs, and suitabilityfor thermoliable drugs. Delivery of drugs to patients in amost physiologically acceptable manner has always beena matter of concern. A wide variety of polymeric materialseither biodegradable or nonbiodegradable but compatiblecan be used as delivery matrices. The biodegradable or non-degradable polymers can be used to control fordrug release either via diffusion alone or via diffusion and scaffold degradation. The ultimate goal of drug delivery is to deliver a definedamount of drug in a precise, efficient, and controlled release manner. The nanofibers produced by electrospinning canbe used as carriers for various types of drugs, genes, growthfactors, proteins, antibiotics, and DNA. As an essential and key element of the nanomaterialsrevolution, organic and inorganic nanofibers persist in anincreasingly adaptable class of nanomaterials that assureto touch upon and improve different facets of humanailments, from improving human health to playing a key role in driving energy production.

Characteristics of nanofibers

- The unique characteristics of nanofibers, such as biocom-patibility, biodegradability, excellent mechanical property, sterility, and controlled release pattern, make it an idealcandidate for drug as well as cell delivery.Nanofibers scaffold formulations exhibit excellent biocompatibility with incorporated substances as well as body tissues.
- Nanofibers possess acceptable biodegradability profile and their degradation products are nontoxic andare eliminated easily from the implantation site of thebody or are integrated with surrounding tissues.
- Nanofibers formulations have open and interconnected pore structure, which allow for optimal interaction with bioactive molecules.
- Nanofibers formulations have excellent ability to deliver their encapsulated substances to the target siteand avoid their side effects.
- Nanofibers have maximum entrapment as well as loading capacity so the drug is released continuouslyfor longer duration upon insertion into the body.
- Owing to biocompatibility, nanofibers or its degradation products do not show toxicity in the body.
- Nanofibers scaffold formulations have sufficient binding affinity to allow release of the encapsulatedsubstance continuously for longer duration after inser-tion into the body or to allow retaining cells in their pore structures.

Production method of nanofibers

Various techniques have been successfully used for the fab-rication of nanofibers:

Drawing of nanofibers

In the drawing process, contact is made with the sharp tipof a micropipette or a glass rod with a previously depositedpolymer solution droplet. The micropipette or glass rodis then withdrawn slowly, thus producing nano fibers. While drawing the micropipette or glass rod, thesolvent evaporates from the liquid fibers and ultimatelysolid nanofibers are formed. There is a specific time at whichthe fibers can be pulled. In the drawing process, a polymer solution should have proper

viscoelastic properties. Owingto solvent evaporation from the deposited droplet, theviscosity of the droplet continuously increases, thus leading to shrinkage of the droplet. This affects the diameter ofthe fiber drawn and limits the continuous drawing of fibers.

Template synthesis

Template synthesis involves the use of membranes ortemplates to obtain a desired structure. Nanoporous metaloxide membranes (e.g., aluminum oxide membrane) are commonly used, where a polymer solution is allowed topass with a certain force through to a nonsolvent bathto produce nanofibers depending on the pore diameter.

Phase separation

It is a method frequently used to prepare three-dimensionaltissue engineering scaffolds. Phase separation of a polymersolution can be induced either by changing the temperature (thermally induced) or by adding a no solvent (no solvent induced) to the polymer solution to produce a polymer-richphase and a solvent-rich phase. The morphology of the polymer-rich phase can be fixed by quenching under low temperature. Solvent canbe removed by either freeze-drying or extraction, therebyproducing porous polymer scaffolds. Polymer scaffoldsobtained by the phase separation method generally have a sponge-like porous morphology with micro-scale spherical pores. It is a simple technique that does not require much specialized equip-ment. It is easy to achieve batch-to-batch consistency andthe mechanical properties of the scaffolds can be easilychanged. However, this method has some drawbacks; thatis, only a selected number of polymers can be used and isstrictly a laboratory-scale technique.

Self-assembly

It is a promising technology for controlled build-up of definednanostructured geometries from small units. It involvesthe organization of individual components spontaneouslyinto an ordered and stable structure through non covalent bond interaction. Self-organization of molecules into a defined structurewithout any human intervention is common through out technology and nature. Self-assembly of synthetic or natural macromolecules produces nano sized supra molecular structures, sometimes nanofibers. Self-assembly can produce much. Thinner nanofibers—only several nanometers in diameterin comparison with electrospinning. Another problem isthat mass production is not easy because of a complicated manufacturing process and low productivity.

Electrospinning

Electrospinning is a versatile and simple process meantfor the production of nanofibers by exposing a polymersolution/melt to a high voltage (30–50 KV). Electrospun nanofibers show great promise for develop-ing many types of novel drug delivery systems (DDSs) dueto their special characteristics and the simple but useful fabricating process.

An electrospinning unit consists of three essentialcomponents: a capillary tube with a pipette or needle of asmall diameter, metal collecting screen, and a high-voltagesource. In this process, one electrode is placed into thespinning solution/melt and the other attached to thecollector. High voltage is applied to the end of a capillarytube containing polymer solution/melt held by its sur-face tension. This leads to the induction of charges on thesurface of polymer solution/melt. When the applied

electricfield approaches a certain critical value, the repulsive electrical forces overcome the surface tension forces. As a result, a charged jet of the fluid is ejected from the tip of the Taylorcone. Finally, the solvent evaporates from the dischargedpolymer solution, leaving behind a charged polymer fiber.In the case of the melt, the discharged jet solidifies when it travels in the air stream [1].

Drug loading strategies of the polymernanofibers based DDS

Drug loading technology is a crucial stage in achieving theoptimal release mechanism, and it is influenced by a varietyof element such as the drug's solubility, the combination with the material, and so on. According to data, hydro-phobic compounds account for around 60% of all drugs onthe market, and organic solvents are frequently used for the dissolution of them [2].

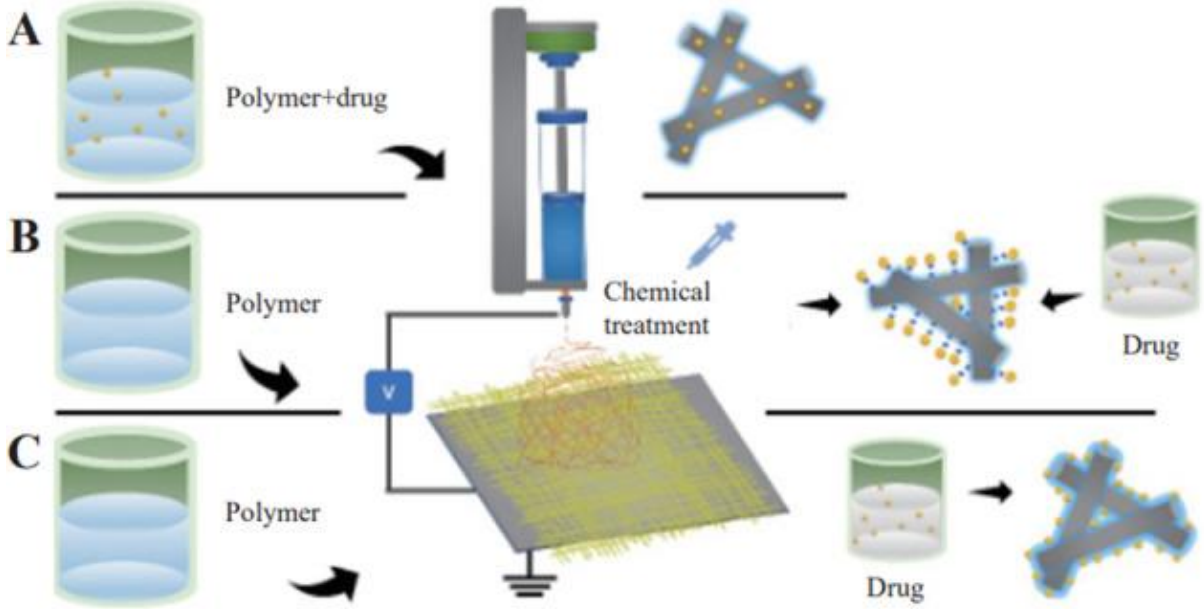

Figure 1: Drug Loading Strategies

Encapsulation

Encapsulation is a method of encapsulating a drug in apolymer, and the encapsulation process can load morehydrophilic or hydrophobic drugs due to the high specificsurface area and volume ratio of nanofibers, and the entiredrug delivery system can avoid degradation of the activedrug component and deliver the drug in a directed or con-tinuous manner, thus offering advantages such as increaseddrug solubility, reduced drug degradation and improved drug bioavailability [3]. However, the diffusion limitationsimposed by the nature of the carrier that encapsulates thedrug in a polymer, which in some cases may reduce the biocatalytic rate [4], is a drawback of the current polymerencapsulation of drugs. Currently, drug encapsulation ispossible only with biodegradable and biocompatible poly-mers such as some natural polymers (chitosan, cellulose, etc.) [5, 6] and synthetic polymers (polycaprolactone, polyvinyl acetate, etc.) [7,8].Cao et al. [9] achieved the controlled release of siRNAby encapsulating siRNA in polycaprolactone nanofibers. siRNA encapsulated in polycaprolactonenanofibers by electrostatic spinning technique and subjectedto morphological characterization, in vitro release assays, and other tests[10].

Chemical immobilization

Another method of immobilizing the drug is through covalent bonding. Covalent bonding between drug andcarrier is a method to enhance the performance of slow andcontrolled release of drug by covalent bonding between drug and carrier [11]. The advantage of covalent bonding isthat it can improve the binding and stability betweencomposite nanofibers, and also the method of immobiliza-tion by covalent bonding facilitates better observation ofdrug loading and plays a quantitative role. Mateo et al. [12] also found that for multi-point binding of bioactive sub-stances to the carrier surface, the method of covalentbonding immobilization may be the best. However chemical modifications such as the use of cross-linkingagents during the preparation process may lead to changesin the functional conformation of the drug and the carrier, causing certain effects. Choi et al. [13] electrospun amine-terminated poly-ethylene glycol with polycaprolactone to expose the aminegroup, and acted nerve growth factor (NGF) on mesench-ymal stem cells at the same time to complete investigationson NGF release. In another study, tyrosinase is extremelyversatile in the market and is often used to catalyze varietyof reactions; Dagli et al. [14] prepared polyacrylonitrile/polyurethane/m-aminobenzoic acid nanofibers by electro-static spinning and immobilized tyrosinase by EDC-NHSactivation. Figure 4 shows the process of tyrosinaseimmobilization in nanofiber mats by EDC/NHS activation.The results showed the average diameters of PAN/PU andPAN/PU/P3ANA nanofibers containing 0.075, 0.150, and0.300 mg P3ANA, respectively, were 103 ± 11, 144 ± 24,111 ± 17, and 119 ± 22 nm. The amount of immobilizedtyrosinase determined by the BCA method showed thatabout 87% of the tyrosinase was covalently bound to the nanofibers.

Physical adsorption

In addition to using encapsulation and covalent bonding methods, researchers often use physisorption to achieve binding between the drug and the carrier. Many factors influence physisorption, including the interaction of hydrophobic and hydrophilic forces, Vander Waals forces, etc. Currently, physisorption immobilization using vander Waals forces is one of the simplest immobilization methods and the advantage of a high specific surface area to volume ration of polymeric nanofibers can increase the drug loading capacity [15]. However, the weak binding of the drug to thecarrier in physisorption may cause drug shedding. Siqueiraet al. [16] studied the design of PLA/chitosan nanofibers forthe adsorptive immobilization of lipase and after twoapplications, the immobilized enzyme activity was sig-nificantly reduced. Thus physical adsorption methods areless frequently applied for drug delivery in cancer therapy.Chen et al. [17] investigated the production of nanofiber materials from polylactic acid (PLA) as a starting material.

Drug release methods of the polymer nanofibers-based DDS

Researchers can choose the best drug delivery route basedon factors including the drug’s site of action, mode of action, and bodily degradation, for example, the use ofenteric solvents to overcome the impairment of drugs in the stomach and the use of extended-release agents to overcomethe higher number of doses administered.

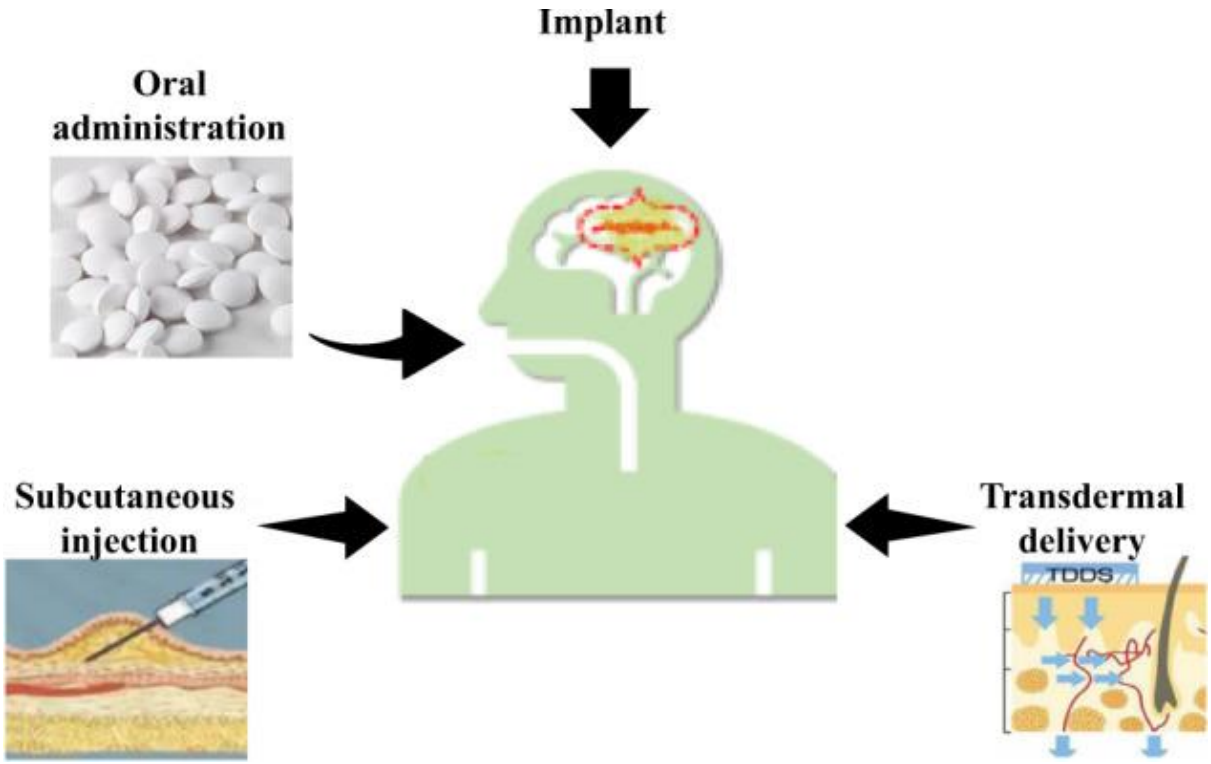

Figure 2: Drug release methods of the polymer nanofibers-based DDS

Oral administration

Oral administration is currently the clinically main techni-que of administration, with oral pharmaceuticals accountingfor more than half of all FDA-approved drugs [18]. The medicine is absorbed into the body through the digestivesystem, disseminated into the blood circulation by the drugmolecule, and carried to the target tissue/organ to exert itsmedical action following oral delivery [19]. Oral administration contains the advantages of low price, convenience, easy and stable transportation, portability, and no directdamage to the skin. However, oral administration is to beabsorbed through the mucous membrane of the gastro-intestinal tract, drugs that are easily degraded by the gas-trointestinal tract are not suitable, such as penicillin, insulin,etc., and are easily destroyed by oral administration and canonly be used by injection.For smart oral medication administration, Liang et al.[20,21] developed a self-ablative nanoparticle. They insertedthe hemagglutinin-2 peptide into polylactic-glycolic acid nanoparticles modified with zwitterionic di-lauroyl phos-phatidylcholine. In addition, Limoee et al. [22] used electrospinning technology to create polyvinyl alcohol (PVA)/carboxymethyl cellulose (CMC) nanofibers thatwere then loaded with the drug pramipexole to create anew oral drug delivery system for the treatment of Parkinson's disease. In another study, Akhgari et al. [23] prepared folic acid enteric microfibers containing the pH-sensitive polymer Eudragit®S 100 by electrostatic spin-ning to overcome the sensitive environment caused bygastric acid and enzymes and to prepare suitable enteric reagent systems.

Subcutaneous injection

Subcutaneous injection is usually a slow absorption of thedrug through the subcutaneous extracellular matrix and intothe bloodstream through the permeation of the endothelium [24]. Subcutaneous injections are generally indicated fordrugs that cannot be administered via the gastrointestinaltract. It can also be used for local anesthesia or preoperativedrug supply. The bioavailability of drugs delivered sub-cutaneously is said to be higher than that of drugs administered orally [25]. Furthermore, compared to oraldelivery, subcutaneous injection results in faster, betterabsorption and higher blood drug levels [26]. However,subcutaneous administration is generally not an optionwhen administered at high concentrations and may reduceserum levels [27]. Neuberg et al. [28] used photopolymerization to prepare poly diacetylene nanofibers, loaded siRNA cells, inhibitedthe oncogene Lim-1 in renal cancer cells, and confirmed thedelivery of siRNA into subcutaneous tumors via poly-diacetylene nanofibers via intraperitoneal injection, result-ing in a novel system for delivering siRNA. In addition, Johnson et al. [29] successfully prepared various porous nanofibers made of poly (ε-caprolactone), poly (lactic-ethanolic acid), gelatin, gelatin methacrylate, bioglass, and magnetically responsive polymer composites. Compared tononporous nanofibers, porous nanofibers are easier to growhuman nerve cells because more neurons and a largernumber of cells can be grown. In addition, after sub-cutaneous injection into rats, porous nanofibers have better biocompatibility than nonporous nanofibers.

Implant

The implant is a drug formulation with a controlled release that is implanted subcutaneously or in other specific areasusing a particular cannula or surgical process. Subcutaneous implants, as opposed to transdermal and oral controlled release formulations, penetrate the skin barrier and enable long-term drug release under the skin, avoiding first-pass effects and gastrointestinal enzymatic degradation while enhancing drug bioavailability. Implant applications rangefrom contraceptive treatment to long-term or targeted drugdelivery in multiple therapeutic areas, such as the cosmeticindustry, but implant delivery systems may require sec-ondary surgery to remove the implant. Elshazly et al. [30] used a low-temperature sol-gel process to make bioactive glass, and then combined it with apolymer solution and electrospun the glass sol to make nanofibers. The nanocomposites were implanted into the buccal folds of the maxillary mucosa of New Zealand malerabbits with type I diabetes to see if they might be employedas bioscaffolds for diabetics with weakened immune sys-tems. In addition, the biocompatibility of titanium implantsis not ideal in biomedicine, and the addition of polymericnanofibers remedy this deficiency. Nhlapo et al. [31] summarized this year's narrative of polymeric nanofibers loaded with titanium implants, in which Jahanmard et al. [32] electrostatically spun polycaprolactone and poly (lactic acid-ethanolic acid) nanofibers loaded with vanco-mycin and rifampicin onto titanium implants to study theircontrolled independent drug delivery systems and bactericidal effects.

Transdermal delivery

The transdermal drug delivery is to coat the drug on the skin's surface and penetrate the subcutaneous tissue viastructures like hair follicles, conduits, or microchannels inthe skin so that the drug can be absorbed by the capillariesin the subcutaneous tissue and transported to the entire body

via blood systemic circulation. Transdermal delivery, asopposed to typical oral and subcutaneous injections, avoids the liver's first-pass action and is less invasive, painless, and cost-effective [33]. Drug encapsulation and release affect transdermal drug delivery, which is currently used in the treatment of numerous skin illnesses such as psoriasis, contact dermatitis, and skin cancer [34].Transdermal nanocarrier systems can be divided into twomodes of release: sustained release and activated modulatedrelease. Shekh et al. [35] synthesized polymer nanofibers from polyacrylonitrile, which were then chemically mod-ified with oxidized chitosan and loaded with acyclovir fordrug release tests. Activated modulated release, unlikesustained release, necessitates a specific physical or che-mical response, as well as a specified reaction state. For theactivated modulated release, at present, there have beenstudies on temperature-responsive nanofibers [36, 37], and photothermal nanofibers [38, 39]. Zheng et al. [39] released the drug in response to temperature changes. Theymade temperature-responsive polymer nanofibers with oliveoil as the core and Nisopropylacrylamide and N-methylolacrylamide (5:1) as raw ingredients using the coaxial elec-trospinning method. Meanwhile, the nanofiber carriertechnology has a lot of promise for precise delivery. Thetransdermal method, unlike intravenous treatment, avoidsthe circulatory system, resulting in a lack of substantialpermeability and retention effects. As a result, advances innanofiber carriers are still required

Applications of polymer nanofibers-based DDS

Polymeric nanofibers are gaining more and more attention inmany fields, especially in drug delivery, which can be used in several applications [40].

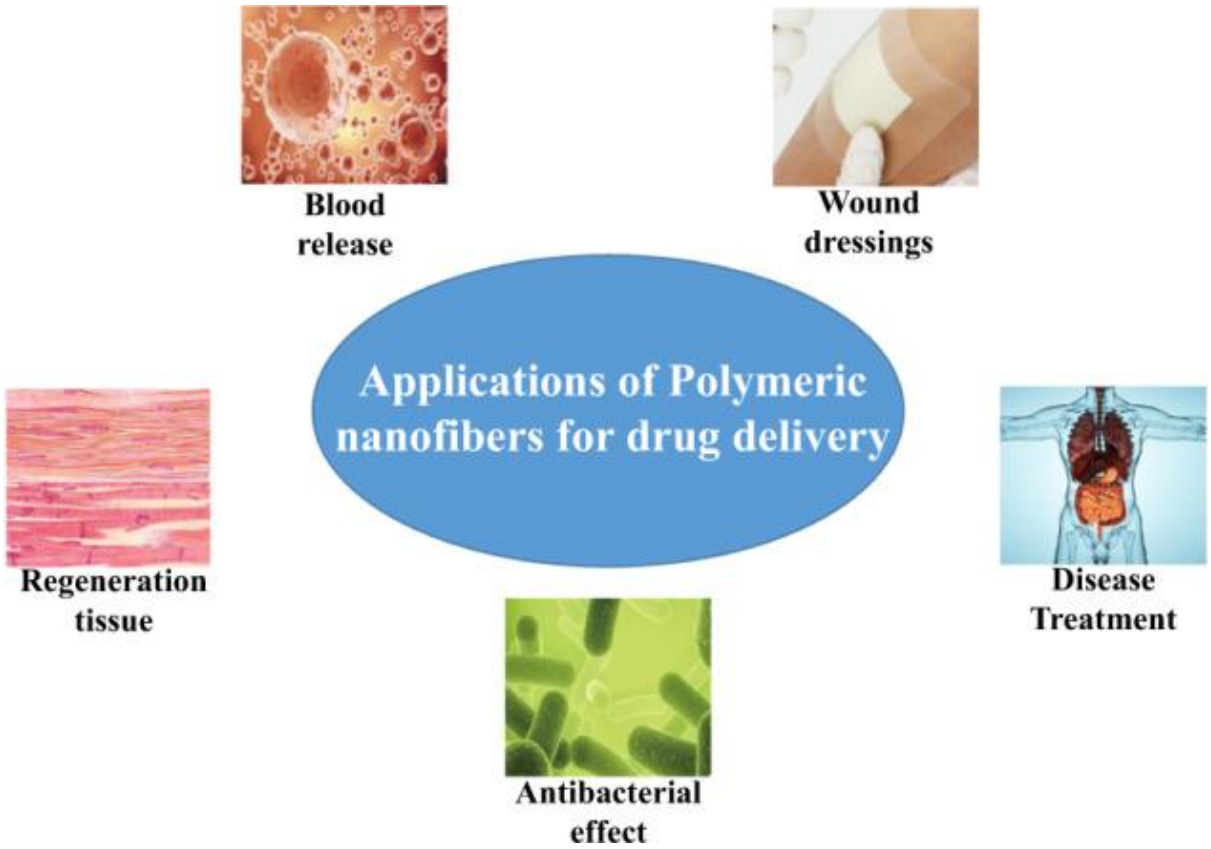

Figure 3: Applications of polymer nanofibers-based DDS

Regeneration tissue

The natural extracellular matrix (ECM) consists of various protein protofibrils and fibers interwoven in glycosami-noglycans (GAG) [40], and the fibrous scaffold formed by ECM protectively supports cells at all times. Mean while, nanofibers with ECM-like structures generated from naturaland synthetic polymers are investigated for use in a varietyof applications. For example, Niu et al. [41] used hyaluronic acid functionalized collagen nanofibers in mod-ulating macrophages to promote healing in urothelialregeneration. At present, nanofibrous structures have beenfound to significantly improve the use of tissue scaffoldmaterials for bone, cartilage, cardiovascular, nerve, and bladder regeneration and reduce scar formation [42,43,44], and the preparation of more complex intracorporeal scaf-folds using composite nanofibers materials is becoming areality, but the construction of scaffolds at the cell-matrixlevel has not yet been observed. Rezk et al. [45] employed composite nanofibers madeof polycaprolactone (PCL) and polyglycerol sebacate (PGS) as well as loaded hydroxyapatite nanoparticles (HANPs)and simvastatin (SIM) to mimic the bone extracellular matrix (ECM) to improve bone cell proliferation andregeneration processes. At the same time, the morphology, drug release, and cytocompatibility of the fiber mat werestudied. The results showed that the average fiber diametersof PCL-PGS, PCL-PGS-HA, and PCL-PGS-HA-SIMreached 0.86 ± 0.34, 0.87 ± 0.35, and 0.88 ± 0.25 μm, respectively. The initial release of the PCL-PGS-HA-SIMnanofiber mat was around 20%, and it was gradually released slowly and virtually linearly until 24 h and released79.5% within 7 days, according to the in vitro release study.The drug release data were consistent with the Korsmeyer–Peppas model and the Kopcha models. Thegrowth of MC3T3E1 osteoblasts sown on various compo-site nanofiber mats was used to perform a cytocompatibilitytest. After day 2, different nanofibers samples showedsimilar cell adhesion and spreading results, while after day 6, the morphology of MC3T3E1 cells seeded on PCL-PGS-HA-SIM composite nanofibers confirmed that there aremore associated fully extended cell layers and an increasedrate of cell proliferation. Thus, this experiment provides thebasis for bone tissue regeneration.

In another study, to enhance the fibroblast lineage dif-ferentiation of bone marrow mesenchymal stem cells, Xuet al. [46] used coaxial electrospinning technology toprepare silk fibroin/polylactic acid-caprolactone-polyethylene oxide into core-shell fibers for delivery ofFibroblast growth factor 2 and connective tissue growthfactor. The test conditions were optimized, and the optimalconcentration in the preparation process was determined tobe 7.2 wv.% of silk fibroin in the core solution and 19.2wv.% in the shell solution of PLA-caprolactone and poly-ethylene oxide at a concentration of 4.8 wv.%. The SEMimage shows that the diameter of the prepared nanofibers isabout 1.19 ± 0.34 μm. The in vitro release test shows thatthe initial burst release is 37.6 ± 1.8% within the first 8 h, and the cumulative release reaches 81.7 ± 1.8% on the 7thday. After day 7, the release profile showed a deceleratingrelease of less than 1% per day, and on day 14 the cumu-lative release from the shell reached 91.6 ± 1.8%. In addi-tion, to confirm that the composite nanoclay polymer fiberscan be fabricated as scaffolds for bone tissue engineering application. The results show that the polymeric fiber scaffold has good biocompatibility and can raise alkalinephosphatase levels in the body, thereby promoting the dif-ferentiation of bone marrow mesenchymal stem cells. Itmay also be utilized to make non-healing scaffolds for bone tissue regeneration.

Wound dressings

With a total thickness of 1.5–4.0 mm, the skin is the greatestorgan required for life and functions as a barrier between theinside and outside of the body [47]. Although the skin hasa natural ability to heal itself, open wounds are frequentlyinfected by microorganisms that cause infection at thewound site and spread to nearby healthy tissues, delaying wound healing [47]. Wound dressing is one of the clinicaltherapeutic materials, but there is no ideal wound dressingthat can meet all of the requirements of wound dressing.The requirements that a functional wound dressing shouldmeet in clinical practice are

(1) Good breathability;

(2) Absorption of excess tissue exudate;

(3) Efficient protection of wounds from microbial infection;

(4) Promotion of tissue regeneration;

(5) Stronger hemostasis;

(6) Non-adherence to wounds;

(7) Provision of a moist environment;

(8) Non-toxic, biocompatible and easily degradable. Inrecent years, polymeric nanofibers have gotten a lot ofinterest because of their high porosity and specific area tovolume ratio, among other things. High porosity can pro-mote cellular respiration and a large specific surface area tovolume ratio can activate cellular signaling pathways quickly. Most importantly, polymer nanofibers have astructural shape that is remarkably similar to that of thenatural extracellular matrix, allowing them to protect sup-porting cells and encourage cell proliferation while also healing damaged tissues [48-54]. Electrospun a mixture of PCL–PEG andPCL block copolymers into nanofibers sheets, submergedthem in an aqueous solution, exposed functional aminegroups on the nanofiber surface, and immobilized recom-binant human epidermal growth factor (EGF) on electro-spun nanofibers. EGF nanofibers increased keratinocytesexpression and stimulated epidermal growth in human pri-mary keratinocytes, according to the findings. In addition, Jafari et al. [55] made a bilayer nanofibrous scaffold with a top layer loaded with amoxicillin (AMX) and a bottomlayer loaded with ZnO nanoparticles using polycaprolactone (PCL) and gelatin as raw ingredients. The average diameterof the constructed nanofibrous scaffolds was576.36 ± 197.77 nm, according to SEM images. In vitrorelease assays showed that the materials had a rapid releasetime of 24 h and a slow release time of 144 h for amox-icillin, and paper diffusion and cytotoxicity testing validatedthe inhibition of bacterial growth and promotion of cellproliferation. Finally, in vivo tests on twelve male Spra-guedawley rats (200–250 g) showed that the preparednanofibers accelerated wound contraction and increasedcollagen deposition and angiogenesis, A shows the optical images (scale bar =5 mm) of the woundsites of the control and experimental groups (containing 4%ZnO and 15% AMX) at different time points, and B showstheir corresponding wound contraction rate images. Theimages show that on day 3, the wound shrinkage was36.73 ± 4.93 and 46.58 ± 3.66% in the control and experi-mental groups, respectively, but on day 6, the woundshrinkage was 64.77 ± 3.35 and 69.44 ± 3.65% in the con-trol and experimental groups, respectively, and on day 10, the wound shrinkage was 95.07 ±

1.51, 95.60 ± 2.99%, andboth reached healing levels on day 13, and the experimentalgroup demonstrated a considerable healing effect in the first three days.

Blood release

The advantages of polymeric nanofibers, such as large surface area and high porosity, have attracted much atten-tion, and this advantage can enhance the interaction between cells and nano fibers, facilitating the preparation of novel materials for cell and blood release [56]. Bloodrelease requires materials with anticoagulant properties, andpolymeric nanofibers can be used for loading antith-rombotic drugs to capture erythrocytes and complete bloodrelease, such as heparin, natto kinase, and aspirin [57]. It is alsopossible to prepare nanofibers with hydrophilic surface and other routes [58]. However, they currently exist only in thelaboratory, and relevant animal experiments still need to be perfected. Shi et al. [59] prepared polycaprolactone/poly(N-iso-propyl acrylamide) (PCL/PNIPAAm) nanofibers by elec-trostatic spinning with a single spinneret to capture andrelease erythrocytes by coupling bovine serum albumin topoly (N-isopropyl acryl amide) nanofibers, and then gener-ated chemically cross-linked nanofiber platforms by thienereactions. The prepared nanofiber platform was experi-mentally confirmed to be thermally responsive andhydrophilic-hydrophobic interchangeable, and capable of directly capturing red blood cells. At the same time, thecaptured erythrocytes were easily released in response totemperature stimulation, achieving a capture and releaseefficiency of up to 100%. In another experiment, Shi et al. [60] mixed poly-N-isopropyl acrylamide (PNIPAAm), polycaprolactone (PCL) and nattokinase (NK) solutions inthe ratio of 5/5/1 and 5/5/2, respectively, and preparednanofibers with PCL/PNIPAAm core-shell layer by elec-trostatic spinning, They showed that the smart PCL/PNIPAA micro composite nanofibers loaded with NK Fig. 9A shows theschematic diagram of the preparation of NK-loaded smartPCL/PNIPAAm composite nanofiber. The *in vitro* NK release test through figures showed higher cumulative NK release at a temperature of 37 °C, and curves a and b indicated that the higher NK loading result higher release, and both composites could release NK formore than 180 min. After the measurement of water contactangle, it was found that PCL/PNIPAAm nanofibers could switch between hydrophobic and hydrophilic by temperature adjustment were all 37 °C and all werehydrophobic (water contact angle >120°), and when thetemperature was lowered to 25°, C, d-f all showed hydrophilic (water contact angle <24°), and, as thehigher NK loading, more tends to be hydrophilic, whichmay be due to the predominant hydrogen bonding betweenPNIPAAm and water molecules at a temperature of 25 °C. Upon heating, the intra-molecular hydrogen bonding of PNIPAAm replaces the intermolecular hydrogen bonding, which leads to the hydrophobicity of the nanofibers. Insummary, when the nanofibers come in contact with blood, NK is released from the nanofibers to facilitate the captureof red blood cells (RBCs) from the blood, and the capturedRBCs are released in a nondestructive manner due to tem-perature changes, obtaining a release efficiency of up to100%. When the temperature is about 32 °C, NK is releasedfrom the nanofibers to facilitate the capture of RBCs asindicated by the nanofibers, and when the temperature is below 32 °C, the nanofibers complete the hydrophobic-hydrophilic switch to facilitate the release of RBCs without damage.

Antibacterial effect

Nanofibers have a high specific surface area and volumeratio, allowing oxygen to pass through, while submicron-sized pores have been found to “filter” bacteria [61]. At thesame time, in order to better improve the antibacterial per-formance, there are several ways. Firstly, the nanofibersthemselves are supplemented with other antimicrobialmaterials, for example, supramolecular assembly’s usingpolyethylene glycol-b-polylysine (PEG-b-PLL) and ethylenediaminetetraacetic acid (EDTA) to effectively inhibit the proliferation of E. coli [62]. Secondly, the antibacterialeffect can be improved by adding antibacterial metal par-ticles to the material, such as Ag, Cu, and Zn [63,64].Finally, researchers can improve the antimicrobial effect ofmaterials by adding antimicrobial drugs or natural anti-microbial reagents, and can adjust the antimicrobial effectaccording to the dosage of drugs or reagents. Antibacterial drugs include gentamicin, moxifloxacin, ciprofloxacin, etc., and natural antibacterial agents include Centella asiatica, propolis, hinokitiol, etc. created antibacterial silver nanoparticles/chitosan (AgNP/CS) nanocomposites with effective anti-bacterial activities against Escherichia coli and Staphylo-coccus aureus strains using in situ synthesis. And thesupramolecular assembly of polyethylene glycol-b-polylysine (PEG-b-PLL) and ethylenediaminetetraaceticacid (EDTA) is used to effectively inhibit the proliferationof E. coli [65]. In another study, He et al. [66] also used melt electrospinning to create fiber mats containing variousamounts of polyethylene glycol (PEG) polycaprolactone(PCL), and the antibacterial drug ciprofloxacin(Cip), wherethe ratios of PEG and PCL were 0:100, 5:95, 10:90, and15:85, respectively, and evaluated the release of cipro-floxacin in experiments. The results showed that the dia-meter of nanofibers increased and then decreased withincreasing PEG content, and the diameters of PCL/Cip,5PEG/95PCL/Cip, 10PEG/90PCL/Cip, and 15PEG/85PCL/Cip were 123.41 ± 27.92, 41.99 ± 9.06, 136.10 ± 23.82, and78.72 ± 17.24 μm. In the drug release test, the Cip release ofthe four composite nanofibers was about 16, 48, 36, and63% in the first 12 h, respectively. After 168 h of immer-sion, the Cip release of the four composite nanofibers wasabout 60, 72, 75, and 90%, respectively. The inhibition wasjudged by the measurement of the bacterial zone of inhi-bition, and the mean diameters of the zones of inhibition ofthe four composite fiber mats for E. coli were 2.49 ± 0.14, 2.18 ± 0.18, 2.64 ± 0.21, and 2.91 ± 0.17 mm, respectively, while for S. aureus, the zones of inhibition of the fourcomposite fibers were 1.92 ± 0.22, 1.86 ± 0.13, 2.32 ± 0.18and 2.65 ± 0.15 mm. Figure 10 shows the inhibition of Escherichia coli and Staphylococcus aureus by differentratios of nanofibers. However, this method was found to be difficult to avoid the initial burst release of the drug, which leads to short-term antimicrobial effects [67].

Disease treatment

Traditional disease treatments have drawbacks such as lack of controlled drug release, insufficient drug accumulation in target organs/tissues, or uneven drug distribution in theorganism, which can lead to drug toxicity in healthy tissues/cells, resulting in drug side effects, and so on, and limiting theiruse. Polymeric nanofibers are ideal for the delivery ofdrugs, DNA, and proteins for therapeutic applicationsbecause of their high specific surface area/volume ratio,high porosity, and high flexibility, at the same time,the development of new polymers, along with other tech-nologies, will result in even better drug-carrying nanofibersthat are excellent for drug delivery and provide moreeffective disease treatment solutions.Altun et al. [67] used a single-nozzle electrostaticspinning

method to prepare hollow particles that couldcontain amoxicillin; in the meantime, they usedpolymethylsesimiloxane/chitosan/bovine hydroxyapatite/hexagonal boron nitride blends as raw materials and studiedtheir drug delivery capacity according to the treatment method of osteomyelitis. Sharma et al. [68] developed a composite nanofiber prepared by electrospinning ofpolyvinyl alcohol and sodium alginate and loaded with insulin, an antidiabetic drug for the treatment of diabetes.Experiments have verified that the sustained delivery andcontrolled release of drugs can be achieved by controllingthe morphology of the composite nanomaterials[69]. In anotherstudy, linalool can be used in biomedicine, cosmetics, antibacterial products, and other industries as naturalvegetable oil. Linalool can be used for tumor suppressionand treatment of anxiety disorders [70], therefore its application has gotten a lot of attention. Souza et al. [71] investigated the release properties of 10, 15, and 20 wt. %linalool in PLA nanofibrous films prepared by electrospin-ning and solution blow molding. SEM images showed thatthe prepared fibers were smooth, with an average diameterof about 200 nm. Drug release experiments showed that thetime required to release half of the linalool in solution-jettednanofibers was 1645 s for 10 wt.% linalool, 411 s for 15wt.% linalool, 291 s for 20 wt.% linalool, Under the sameconcentration of linalool, the corresponding times of elec-trospinning fibers respectively were 575s, 329s, and 76s.Therefore, compared with the PLA nanofibers prepared by electrospinning, the PLA nanofibers prepared by the solu-tion jet method have more durable drug release, whichprovides a basis for designing a preparation method thatbetter controls the drug release rate.

Some challenges in nanofibers

Although electrospinning is the most widely used technique for the fabrication of nanofibers, there are some challenges associated with this process, particularly while fabricating electrospun nanofiber–based drug delivery system. The manufacturing process of nanofibers is quite expensive as compared to that of conventional fibers because of high cost of technology and low production rate. To keep control on properties and mass production of nanofibers, one needs to understand how electrospinning process transforms a polymers liquid system into solid nanofibers, which are ultrafine in diameter, through a millimeter-diameter capillary tube. The vapors emitted during the electrospinning process pose a health threat. Therefore, the vapors emitted need to be disposed of in an environmental-friendly manner.

Conclusions and future perspectives

The development of a promising DDS is essential toenhancing drug safety, bioavailability, and minimizingnegative side effects due to advancements in all biomedicalfields as well as the increasing complexity of diagnostic andtherapeutic procedures. This review presents a timely andcomprehensive summary of polymeric nanofibers for DDS.We first describe the common methods for polymer nano-fiber fabrication and then introduce controlled techniquesfor drug loading into and release from polymer nanofibers.The applications of polymer nanofibers in drug delivery aresummarized. In particular, we focus on the relation betweenthe physiochemical properties of polymeric nanofibers andtheir DDS performance. Overall, this review aims to sum-marize and discuss the recent advances in polymernanofibers-based DDS, providing information and guidancefor researchers who are interested in the research field.Although polymer nanofibrous

materials have obtainedexciting research results in DDS, there are still some pro-blems to overcome before their practical applications. first one is about the toxic problem because most solventsfor fabrication of polymer nanofibers materials are toxic.There has been researching on non-toxic solvent systems.For example, Seon-lutz et al. [148] prepared biocompatibleinsoluble hyaluronic acid nanofibers by using pure watersolvent and naproxen, a non-steroidal anti-inflammatorydrug, and electrostatic spinning technology. Therefore, suitable materials should be selected and can be naturallydegraded after use to promote the development of safenanofibers. The second concern is about critical factorsincluding air permeability, antibacterial properties, anti-oxidant effects, sensitivity, and nanofibers recovery ratewhen to obtain the optimizing conditions. It should be notedthat the use of apparatus for large-scale and efficient pro-duction of nanofibers membranes is also a difficult problem.Moreover, most studies about polymer nanofibers for DDSare still at the laboratory level. More clinical trials areneeded to validate, etc. When the issues discussed above areovercomed, polymer nanofibers for DDS can be applied inwide ranges of applications in biomedical drug delivery, tissue engineering, environmental monitoring, food safety and disease diagnostics.

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