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Mini-review of the bi-component nanofibrous scaffolds and drug delivery applications

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ABSTRACT

Drug delivery systems perform to improve the drug's efficacy and heal the affected region. Electrospun nanofibers are strong drug carriers as a scaffold due to their high specific surface area, easy processing, lightweight material. Fibrous scaffolds encapsulating functional bioactive agents are important for drug delivery applications, and they show higher encapsulation efficiency and higher drug loading capacity than various types of carrier materials such as hydrogels, micro/nanobeads, films, conventional fibers, and sponges. In comparison to conventional electrospinning, bi-component electrospinning where drug loading does not occur largely on the surface of the polymer matrix, core-shell nanofibers showed delayed release and a decrease in burst release because the drug was loaded into the core layer. The purpose of this mini-review is to investigate the production and applications of the drug-loaded bi-component nanofibers in structure core-shell, side-by-side, hollow nanofibers, and also emulsion nanofibers using co-axial nozzles. Further, the parameters which influence of these electrospinning process, such as working conditions and polymer properties, as well as drug delivery profile of the resulting nanofibers, have been outlined briefly. The limited clinical studies on the nanofibers have been discussed. Eventually, perspectives on the problems, possibilities, and new approaches for electrospinning advancements have been presented, as well.

I. INTRODUCTION

Nanofabrication is a rapidly growing topic for the production of all kinds of functional nanomaterials. Many chemical and physical techniques have been developed for nanofabrication with the advancements in nanoscience and nanoengineering over the last three decades [1]. The progress of novel concepts and theories is necessary for nanofabrication. These can be the top three potential routes for nanofabrication: (1) decreasing in size to picotechnology; (2) more sophisticated nanodevice structures; (3) more organized nanoproducts such arrays of different inorganic nanotubes and aligned nanofibers [1-3].

Electrospinning enables the production of nanofibers with adjustable fiber diameters, homogenous fiber distributions, greater wound exudate absorptions, and improved encapsulation efficiencies, among other benefits. Furthermore, adopting an appropriate drug delivery system with a high surface-to-volume ratio and a high drug loading capacity of fibers improves wound healing [4-6]. In this regard, polymer materials have been considered to be potentially effective drug delivery carriers due to their excellent pharmacokinetic properties. A formulation or technique that permits a therapeutic drug to be incorporated into the body is referred to as polymeric drug delivery [7, 8]. Bi-component nanofibers containing different drugs are used as scaffolds fabricated by different approaches such as core-shell, side-by-side, and also emulsion electrospinning methods (Figure 1). In this chapter, it has been given a comprehensive explanation of core-shell nanofibers, including the design of the fibers, production procedures, functions, and applications of biomolecule release behavior.

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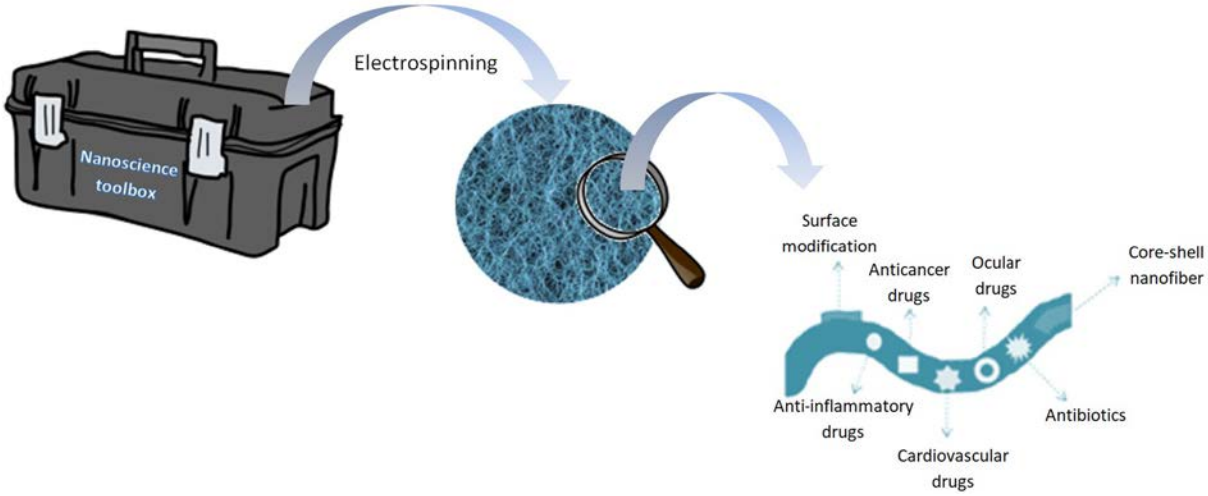

Figure 1. Nanofibers for drug delivery [9]

II. BI-COMPONENT NANOFIBROUS SCAFFOLDS

Co-axial electrospinning and side-by-side electrospinning are both types of double-fluid electrospinning. The shell fluid must be spinnable for classic co-axial electrospinning to proceed smoothly. When the shell fluid concentration and flow rate are only a little bit higher than those of the core fluid, the shell layer effectively encloses the core layer. Conventional co-axial electrospinning can be altered to create smooth nanofibers with a monolithic structure using a non-spinnable solvent as the shell fluid to encapsulate the core fluid. Figure 2 shows different kinds of bi-component structured nanofibers.

Figure 2. Different bi-component nanofiber types [10]

2.1 Side-by-side electrospinning

Dual-phase composite nanofibers are created by side-by-side electrospinning [11]. It is possible to create appropriate nanofibers following the requirements of particular situations by preparing two semi-circles in parallel that contain various phases. It can be accomplished double-drug controlled release by electrospinning beads-on-the-string nanofibers as side by side, and medication delivery at the same time [12]. Different nanofiber architectures in co-axial and side-by-side electrospinning result in changes in the management of drug delivery properties [13-16].

Side-by-side electrospinning is an improved version of single-nozzle electrospinning. Figure 3 depicts the side-by-side electrospinning method, which uses two parallel needles to generate fibers with the Janus structure. It is disadvantage both solutions are subjected to the same voltage, and the fiber usually divides due to repulsion between the two solutions. In side by side electrospinning, separate polymer solutions are given through a spinneret that is split into two cavities by a thin polymer or metal film. Controlling the electric field strength is crucial in side by side electrospinning compared to typical electrospinning. Side by side nanofiber is known as an anisotropic system. Polymers with diverse physical properties are mixed in one fiber in an anisotropic yet uniform manner, resulting in some attractive mechanical properties like bending and crimping [17, 18]. This is due to differential shrinking inside the fibers, which causes one of the components to compress. One benefit of side by side fibers is that each component can exhibit its own characteristics in a single fiber [19].

2.2 Co-axial electrospinning

Co-electrospinning is the best method for producing continuous fibers that encapsulate components inside of polymer sleeves, however it demands the use of coannular nozzles that are quite complicated. Core-shell nano- and/or microfibers were first produced in a two-step procedure that began with the core polymer being electrospun normally (with a single nozzle) in step 1 and completed with the shell polymer being encapsulate in step 2 [20-22]. For co-electrospinning, the inner core must be filled with either a polymer solution, a non-polymeric Newtonian liquid, or even a powder [23, 24]. A compound droplet continues to flow at the edge of a core-shell nozzle in the co-electrospinning physical arrangement, which develops into a compound Taylor cone with a core-shell jet emerging from its tip [20, 25]. The jet is instantly stretched, extended, and winded up by the electric forces just like in a typical electrospinning process [20]. The core-shell nano/micro fibers are produced as the solvent fast evaporates, forcing the shell jet to solidify. After co-electrospinning, the core component should be removed selectively to remove the inner core and create hollow tubes [20, 26]. In nanofibers, increasing the thickness of the shell layer causes an increase in fiber diameter. Whereas in hollow nanofibers made using oil as the core and titanium isopropoxide /polyvinylpyrrolidone (PVP) as the shell layer, increasing the PVP concentration led to a rise in fiber diameter from the nano- to microscale [27].

There are several issues with co-annular nozzles used in co-electrospinning studies. Initially, it might be challenging to get the core and shell components to be evenly distributed inside the as-spun fibers; as a result, a long fragment of the core material could pull out from the shell. It follows that removing the co-annular nozzle characteristic from co-electrospinning would speed up advancement in this field [20]. Furthermore, the objective of controlling the core-shell structure may be attained by modifying the solution characteristics and process settings [28]. The core-shell structure can significantly increase the flexibility of electrospinning in the wide range of drug delivery, tissue engineering, filtration, sensing, and energy storage [29-32].

A typical electrospinning system includes a high-voltage power source linked to the spinneret. The charged polymer solution exits the spinneret, and the solvent evaporates during this process. Then the fibers formed on the collector surface begin to form. The solvent evaporates during this process, followed by the fibers formed on the collector surface. Co-axial electrospinning, which uses the same operating technique as traditional electrospinning, may be utilized to create the core-shell arranged nanowebs by electrospinning two different types of polymer solution via a single spinneret.everal factors, including processing parameters (flow rate, voltage, operating

distance), solution parameters (solvent's volatility, solution's conductivity, and surface tension) and environmental parameters (e.g., humidity, temperature), could be used to manufacture core-shell fiber with varied morphologies and architectures. Amongst them, solution conditions have a significant impact on the shape and architecture of the as-prepared core-shell fiber. Recently, a great number of scientists have investigated the connection between the production of the core-shell structure and the polymer solution [28]. In the case of a low concentration of shell polymer solution, beaded beads-on-a-string morphology is formed in resulting nanofibers owing to starting Rayleigh instability. On the other hand, increasing the sheath polymer concentration/viscosity inhibits instabilities and forms smooth fibers. According to Moghe and Gupta (2008), low interfacial tension between the core and sheath is a need for co-axial electrospinning [33]. When the core and sheath solutions are miscible, the interfacial tension between them is insignificant. Many studies showed that co-axial electrospinning of miscible solutions led to smaller diameter core-sheath fibers with separate surfaces due to the low interfacial tension between the solutions [34].

The choice of solvents for the specified polymers is a critical and difficult issue in achieving core-shell fibers. Figure 3 depicts the impact of solvent inter-miscibility throughout the co-axial spinning. There is no adverse interaction between the solvent and solute in solutions (Figure 3a and Figure 3b). Once the solvents are miscible, but the solutes are not dissolved in the solvent of the other layer (Figure 3c), the core/sheath solutes might precipitate out of solution at the end of the nozzle, resulting in an unstable co-axial electrospinning process [34].

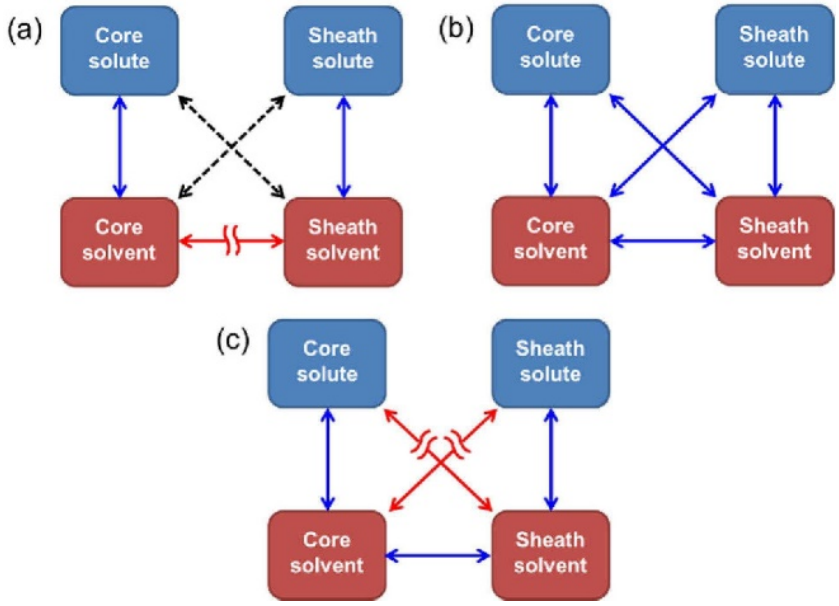

Figure 3. Miscibility of core and sheath solutions used in co-axial electrospinning: (a) totally immiscible solutions (solute and solvent); (b) totally miscible solutions (solute and solvent); (c) partially miscible solutions (solvent-only miscible) [35]

The electrical conductivity of the core solution can be controlled to product core-shell nanofibers. In the process, different conductivity of the solution can be obtained by adding ionic salts to polymer solutions or changing conductive solvents [28]. The induced charges are localized at the sheath-air contact if the sheath polymer solution is more conductive. In this regard, the sheath is the driving polymer solution, and core also drifts through

Coloumbic forces in the sheath. The more conductive core component is, the more it functions as the driving component by dragging the sheath along with it [34]. Earlier studies have given little consideration to optimize the conductivity of the shell and core solutions during co-axial electrospinning. Actually, it is more vital to investigate whether the core or shell solution influences the amount of current delivered by co-axial jets and the size of the resulting droplets [28]. In this scope, to obtain successful co-axial electrospinning depends on the characteristics of component solutions and other process parameters jets and the size of the resulting droplets. In this scope, to obtain successful co-axial electrospinning depends on the characteristics of component solutions and other process parameters [34]

It is very critical to adjust the flow rate of each precursor solution while co-axial electrospinning. When evaluating the sheath precursor flow rate, faster rate tend to raise the total fiber diameter until a maximum is reached, causing the core to segment. Once the sheath flow rate is too low, the core will not be totally encapsulated. The flow rate of core is not effect so much thickness of shell polymer [34].

The visibility of the burst release behavior often observed in blending nanofibers can be reduced via core-shell nanofibers produced by co-axial electrospinning. The polymeric core is often drug-embedded, whereas the shell serves as a physical barrier between the core and the solution. The existence of the barrier in co-axial fibers enables extended release, protecting the medicine from environmental deterioration more effectively. The existence of the barrier in co-axial fibers enables extended release, protecting the drug or active ingredients from environmental degradation more effectively [9, 37]. However, co-axial electrospinning is more complicated than mono-axial electrospinning and needs the use of specialized equipment, such as a co-axial needle and two syringe pumps. The choice of suitable polymers and process conditions may take more time than other methods. Emulsion electrospinning is another method to produce core-shell nanofibers [38]. Polymer and micelles help achieve a slower and more long-term release in this situation [9, 39]. As the applied voltage is increased (above the critical voltage) in single-nozzle spinning, stronger Columbic repulsion between charges can stretch the jet, which causes the fiber diameter to decrease. Only a narrow range of applied voltages produces core-sheath fibers in the case of co-axial electrospinning. The jet fails to exist when the voltage is too low, and liquid drops from the spinneret. If the voltage rises, a jet escapes from the sheath but does not entrain the core component. When the voltage is raised further, a stable jet made up of both the core and the shell is formed. However, at higher voltages, the electrical field pulls more solution, causing the core and sheath solutions to withdraw into the spinneret, break up, and result in many jets. The production of fibers with various morphologies is controlled by spinneret or nozzle geometry. The nozzle is the part that ensures the polymer flows and the voltage is carried out in practice [9]. The single-axial arrangement is the simplest for electrospinning. Co-axial or multi-axial equipments are used in a more advanced arrangement. Figure 4 represents the nozzle configurations [9, 40].

The academic research has given core-shell fibers a great deal of attention, both their potential use in the fields of tissue engineering and drug delivery, and for non-biomedical applications like, supercapacitors, adsorbents, and desalination, and energy-harvesting properties. However, the majority of core-shell fiber applications have been focused on tissue engineering and drug delivery because of their distinctive and innovative properties that are perfect for these applications [41].

The charged polymer solution exits the spinneret, and the solvent evaporates during this process. Then the fibers formed on the collector surface begin to form. The solvent evaporates during this process, followed by the fibers formed on the collector surface [11].

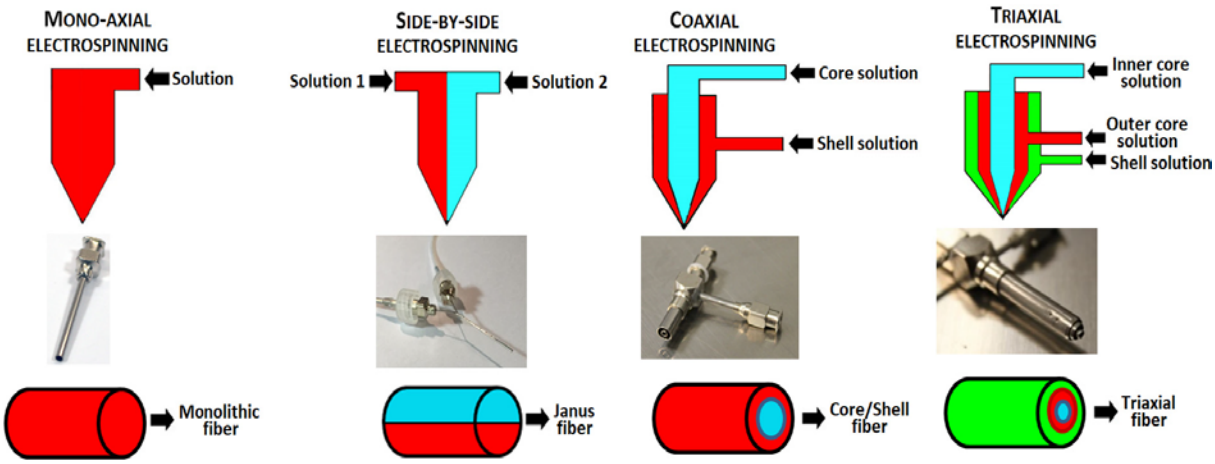

Figure 4. Nozzle configurations [9]

In the co-axial electrospinning process, it can be used non-polymeric liquid or powder (as core) as well as polymer solutions. It is also possible to create systems with inconsistent drop-shaped inclusions inside a continuous shell. Moreover, production of hollow and non-spinnable material nanofibers by the selective removal of the core or shell of nanofibers are performed via this process. Hollow nanofibers are produced when the inner component in the core shell fibers is eliminated using selected solvents or heat treatment procedure [42, 43]. Thus, non- spinnable solutions are extruded via the inner capillary, whereas spinnable solutions are extruded through the outer capillary [19, 26, 42].

The choose to core and shell materials is important to define preferred physicochemical, biological and mechanical properties of the core–shell fibers, and also it effects the release behavior of bioactive agents. Many core/shell polymer combinations have been studied, such as synthetic/synthetic, synthetic/natural, and also natural/synthetic layer combinations. Two alternative core-shell fiber fabrication methods and their significance in releasing numerous bioactive compounds with adjustable release patterns for tissue engineering and drug delivery applications (Figure 5).

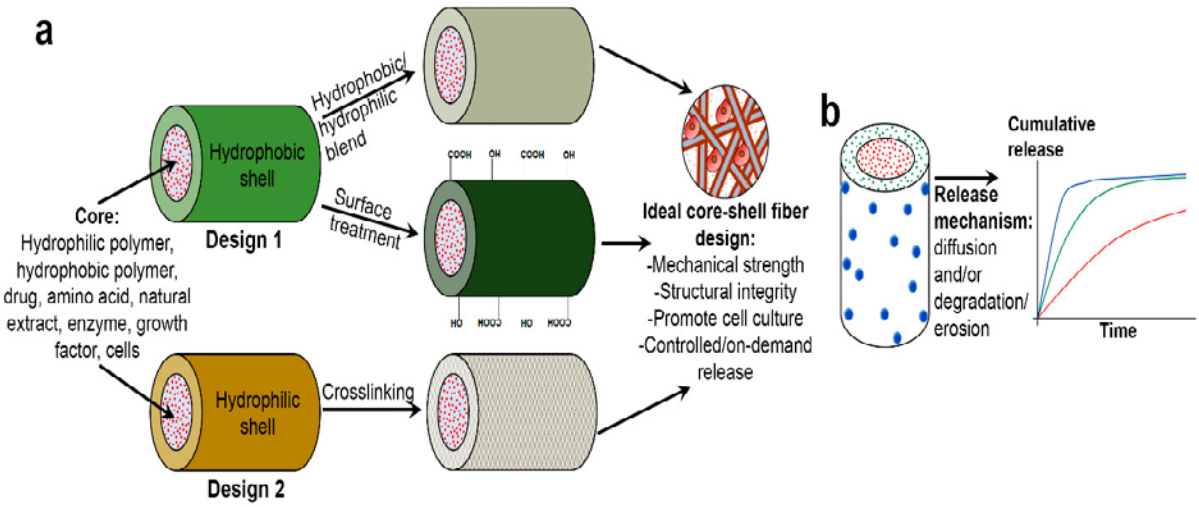

Figure 5. (**a**) Scheme illustrating two different design approaches of core–shell fibers and (**b**) their role in multiple biomolecules delivery with controllable release profiles [41]

2.3 Fabrication of Hollow Fibers via Co-axial Electrospinning

Hollow nanofibers are becoming increasingly popular in a variety of study fields due to their high length-to-diameter ratios, small diameters, hydrophilic architectures, and big topmost layer-to-unit mass benefits [44]. Hollow fibers have been investigated for many applications such as photocatalysis, biosensing, tissue engineering, and antimicrobial treatment. To make hollow nanofibers, a variety of approaches such as template synthesis, self-assembly, emulsion electrospinning, and co-axial electrospinning can be employed. Co-axial electrospinning is a simple process for producing hollow fibers. Firstly, electrospinning of core/shell nanofibers and then removing the core (inner) layer. Generally, mineral oil, olive oil, and silicon oil can be used as non-polymeric based core part, while PVP, PMMA, PEO, PEG, PS, and PAN can be used as core polymer part [34]. Considering literature, co-axial nanofiber studies are observed as the production of the drug-loaded hollow fiber. Wei et al. (2014) produced curcumin-loaded PVA/Polyethersulfone (PES) hollow nanofibers. They have studied the effects of different solvents used in the process on the release amount. Figure 6 shows the SEM images of the resulting hollow fibers in the study [45].

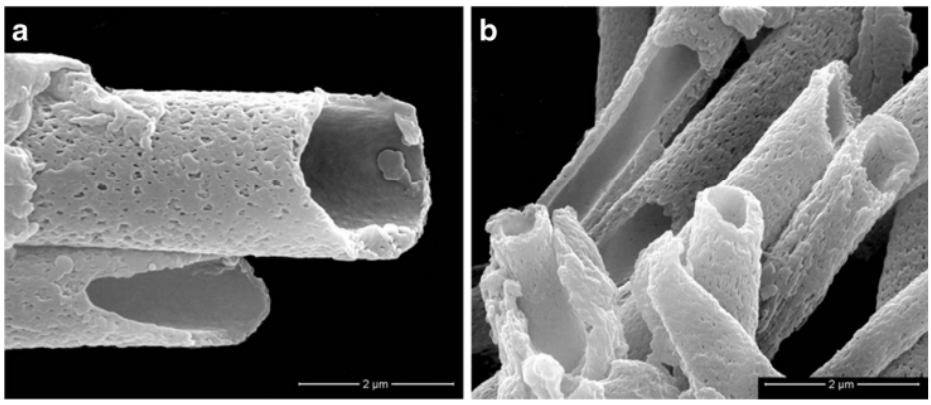

Figure 6. SEM images of cross-section of hollow ultrafine fibers prepared by the core solutions of PVA/DMSO (a) and of PEG/ DMSO (b), respectively [43]

III. DRUG DELIVERY SYSTEMS

Novel drug delivery methods have been designed to improve drugs' effectiveness, pharmacokinetics, and toxicity. There are many approaches to delivery suitable for drug delivery to the human body [46]. Over the past several decades, the drug delivery administration has become attractive. There are four primary categories of current drug delivery system research: delivery routes, carriers for cargo, and targeting approaches. [47, 48]. In line with this, as drug delivery techniques, nanomaterials such as nanofibers, Pickering emulsions, nanoemulsions, liposomes, micro/nanoparticles, micelles, and dendrimers have received considerable interest [34, 49-54]. Polymeric nanofibers (NFs) have the potential to encapsulate many drugs. Electrospinning is a novel nanotechnology-based drug delivery technology which enables to fabricate nanofibers with high porosity and specific surface area, low density, and controllable morphology. Electrospinning allows for more flexibility in selecting materials and pharmaceuticals for drug delivery applications in comparison with alternative formulations [47].

3.1. Drug Loading Approaches

Pharmaceutical study of novel drugs is one of the most difficult issues in both academia and business. The pharmaceutical industry invested an estimated 83 billion dollars in research and development of new drugs in 2019. Most drug concepts fail in clinical studies owing to unforeseen toxicity or ineffectiveness in treating the intended medical ailment. As scientists have learned in recent decades, the route of distribution has a substantial influence on a drug's therapeutic efficacy [47].

Different strategies are used to integrate drugs into electrospun fibers. Drug loading has a significant impact on drug release profile, therefore selecting the appropriate loading strategy for the particular application is critical. The most basic method is direct combining of the polymer and the drug by dissolving the two ingredients in an appropriate solvent. In comparison to other methods, blending has particularly high drug loading rate. The strength of the polymer-drug interaction, as well as the drug solubility characteristics will influence the release profile. However, this approach has some disadvantages such as the possibility of biooactive components/drugs to decompose due to the existence of organic solvents [55]. Further, a burst release mechanism of drugs is commonly reported [9, 56].

Emulsion electrospinning offers a potential alternative, allowing the drug to be encapsulated inside micelles and formed into core-shell nanofibers. It is known that drug-containing micelles are formed by adding a supernatant to a drug-containing water solution. A strong combination of the generated micelles with a polymer oil solution produces a good emulsion stability is suitable for electrospinning. Thus, the interaction between the bioactive molecule and the organic solvents is decreased, and different combinations of hydrophilic drugs and hydrophobic polymers can be used. Moreover, no effort, such as the usage of co-axial device, is required during the production of core-shell nanofibers [56].

Co-axial electrospinning is a loading process as well as a technology for the production of core-shell nanofibers. As previously stated, the co-axial approach requires a particular equipment and optimizing time. It provides an endless arrangement of polymers for the core and shell, as well as a modular framework for the loading of various drugs in various fragments of the fiber. The co-axial loading of a single drug has the significant benefit of allowing the drug to be introduced into the core polymer while the shell acts as a physical barrier restricting burst release,

as well [9]. Further, different profiles can be observed while obtaining a wide range of drug release kinetic (Figure 7).

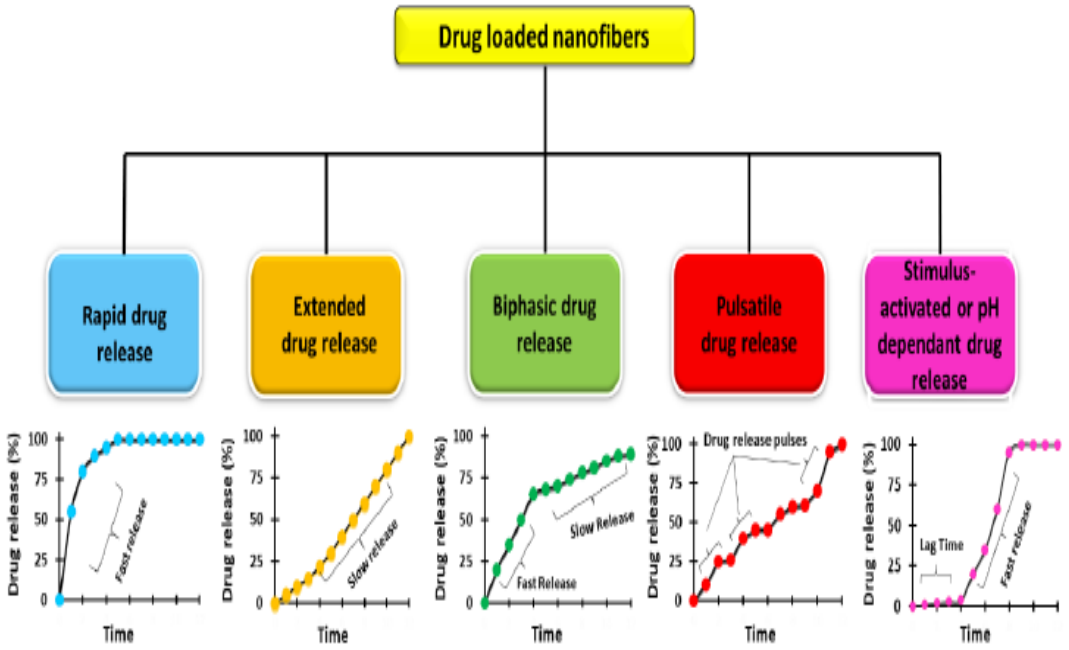

Figure 7. Drug release profiles of various nanofiber-based drug delivery systems [57]

3.2 Tissue Engineering Applications of the Scaffolds

Electrospinning is the most widely utilized technology for producing drug-loaded nanofibers in drug delivery applications because of the following reasons:

- It has a large loading capacity.

- Encapsulation effectiveness is high.

- Operation is simple.

- Inexpensive [58]

The aim of tissue engineering is to develop technologies for cells, structures, or living systems to restore injured or diseased tissue structures and functions. Scaffolds are used in tissue engineering applications that assist in the repair or regeneration of injured tissue. Numerous tissue scaffolds are composed of various materials, most of which have already been confirmed for use in medical applications by regulations [59].

Electrospun fiber scaffolds in tissue engineering for skin regeneration have been studied by many researchers. Because they basically resemble native tissue architecture, oriented nanofibers have been become a preferred substrate for in vitro tissue engineering efforts [60]. Therefore, biomimetic structural signals for guiding cell attachment and activity are available. On the other hand, typical electrospun scaffolds should possess some requirements for good therapeutic outcomes. To solve the problem, cells, drugs with low molecular weight, and other bioactive molecules integrated into nanofiber structures. Thus, the nanofiber scaffolds can be customized to convey a wide range of substances [61]. Nanofibrous scaffolds with larger surface area for adhering proteins and

providing many more binding sites to receptors found in cell membranes would be extra biomimetic and aid in improved cell-matrix connections [62].

It is reported that hydroxyapatite (HAp) containing nanofiber scaffolds have good bone regeneration due to the osteoconductivity, effective bone-binding capability, and excellent biodegradability properties of HAp [63-65]. Li et al. (2018) developed ascorbic acid (AA) and β-glycerophosphate disodium salt hydrate (β-GP) loaded electrospun gelatin/hydroxyapatite (GH) scaffolds and *in vivo* studies demonstrated almost bone defects with 5 mm completely closed within 6 weeks thanks to the nanofibrous scaffolds [66]. In a similar study, hydroxyapatite/gelatin-chitosan core-shell nanofibers showed increment of osteoblast cells proliferation by to mimicking the microenvironment and chemical structure of natural bone [67]. Further, *in vitro* studies of the obtained scaffolds indicated any cyctotoxic effect for 24 h and 48 h.

Cellulose acetate (CA)/polyvinylpyrrolidone (PVP) nanofibers have been fabricated by co-axial electrospinning method [68]. The mineral crystal nucleation and growth have been found based on SEM images of the core-shell scaffolds.

Yılmaz et al. (2023) created polylactic acid (PLA) and polyurethane (PU) core-shell nanofibers. In their study, silver NPs used as an antibacterial agent, and it was investigated zone inhibition to Gram (-) and Gram (+) analysis, and in-vitro cytocompatibility test [69]. PLA is a biopolymer widely used in medical practices. It was selected because of its biodegradable and biocompatible properties. However, to overcome some restricted properties of PLA, PU with superior elasticity and mechanical properties has also been used. It has been found that biological results can change with the change of core and shell material. Once bicomponent nanofibers with pure PU in the core and pure PLA in the shell were utilized, or when PLA-Ag NPs in the core and pure PU in the shell were used it was underlined that promote ~~to~~ fibroblast proliferation within 24 hours.

Many drugs and bioactive substances like growth factors, antibiotics, DNA, and proteins, could be introduced effectively into the core, which was enclosed by the shell fragment, and a prolonged release of these substances from the structure of core/shell nanofibers might result over time [70]. Chen et al. (2023) produced core-shell nanofiber membranes include hyaluronic acid (HA) and platelet-rich plasma (PRP) [71]. In the study, PLA was used as shell part and changes in the release studies and other properties of the nanofibers were noticed in the core part on varied HA and PRP ratios. Regarding controlled drug release, the NFM may allow for site-specific administration of therapeutic agents to solve the obstacles associated with systemic delivery of treatment to a damaged site. It was revealed that HA release values were not affected by the PRP concentration. Further, HA release rate was stable during the first 7 days, and the cumulative HA release amount reached almost 90% in this period. The sustained release profile may be due to the attraction between PCL and HA. Generally, these core-shell NFs showed minimizing peritendinous adhesion and promoting tendon healing.

3.3 Anticancer Drugs Containing Nanofibrous Scaffolds

Today, cancer is a serious public health issue to cure and one of the world's most lethal illnesses [72, 73]. For the past three decades, targeted anticancer medicines have been increasingly developed to kill cancer cells. Some efforts were performed on cancer diagnosis and therapy [7, 74-78]. A folate-conjugated PCL-PEG copolymer was synthesized to produce hydrophobic doxorubicin (DOX)-encapsulated active targeting micelles, which they then

mixed with PVA [79]. The electrospun core-shell fibers were created by the co-axial electrospinning process, with the core layer from PVA and the synthesized micelles and also the shell layer from crosslinked gelatin.

Overexposure to ultraviolet (UV) radiation, alcohol intake, family history, and also immunological suppression are all risk factors for melanoma. Transdermal drug delivery has been disadvantaged by low penetration in the deeper skin layers. Therefore, several strategies have been proposed to achieve the stratum corneum barrier and enhance drug absorption at the target site. In many studies, microneedles and nanoparticles were widely used compared to conventional drug delivery techniques [79]. Nevertheless, using solid-lipid nanoparticles or the development of encapsulating drugs via core-shell nanofibers is required for controlled drug delivery phenomena. Zhu et al. (2019) have reported that the core-shell nanofibers they have fabricated may provide a synergistic effect for skin cancer [80]. In the study, chitosan (CS)-loaded PCL was used as a shell part, while the core part ~~was~~ consisted of poly(N-vinyl-2-pyrrolidone) (PVP) with 5-fluorouracil (5-FU). According to in vitro drug delivery results, the burst release of 5-FU initially suppressed the growth of cutaneous melanoma cells. 78% of CS and 91% of 5-FU were released from the nanofibers in 24 h period, respectively. Moreover, over 87% of 5-FU and 40% of CS was released from the core-shell nanofibers with a max of 5-FU for 120 min. This showed a desired anticancer property with the lowest side effects. The nanofibers had an average fiber diameter of around 500 nm and demonstrated strong drug-encapsulating efficiency as well as good mechanical properties.

Solar UV radiation is the principal cause of skin damage owing to the production of reactive oxygen species (ROS), that results to skin defects and imperfections, skin cancer, and eventually, early aging [81]. The most common risk factor for all forms of skin cancers is repeated long-term exposure to UV radiation on the skin. The deadliest kind of skin cancers, melanoma, frequently presents as an asymmetrical, irregularly shaped lesion with random boundaries and a range of colors typically black or brown [82]. In a study conducted by Yuan et al. (2021), it was reported that the produced poly (lactic-co-glycolic acid) (PLGA)/PVP nanofibers with 5-fluorouracil drug for skin tumors showed good cell growth [83]. In another study, different amounts of imiquimod loaded PCL nanofibers indicated drug release between 43.5 - 83.9 % for 244 h (~10 days) [84]. Moreover, it was notified that the melanoma cells grown on imiquimod-containing fibers showed a $\geq$ 50 % reduction in cell viability and a 10% drop in cell counts between 6 and 48 h.

In recent decades, the main concern of drug delivery systems has been on effective transmission and minimal harmful side effects, and hence ecologically sensitive drug delivery systems have attracted increased attention. The drug delivery system both targets the intended site and improves drug absorption, and can quantitative release the drug at time to create an effective as well as reliable therapeutic effect. In this scope, the pH-sensitive drug delivery system, which is known as one of the most extensively researched environmentally sensitive drug delivery methods, modulates drug delivery by variations in the pH of the area of damage. There is a pH range in which each drug can work effectively. Therefore, it is essential to create a drug carrier with pH sensitivity for tumor treatment and wound healing in the clinical research [85]. The pH-sensitive PVA/PCL core-shell nanofibers with PVA and PCL forming the core and shell layers were fabricated by Yan et al. (2020). It was appointed that these PVA/PCL nanofibers containing DOX anticancer agent degraded under acidic and neutral media [86]. In acidic media, the DOX in PVA core layer was exposed to burst release due to the PVA core leaking into the PCL shell layer. The burst release behavior/mechanism of drug was decreased as the thickness of the shell layer. That means hydrophobic PCL shell layer showed the barrier property between the drug and release media. The total DOX

release from the fibers was found to be 83%, 69%, and 66% depending on the changed PVA/PCL ratios (0.5:0.5, 0.5:0.6, and 0.5: 0.7, v/v, respectively). Although the release under neutral media was similar to the acidic release profile, the slower drug release mechanism was observed in this media. As a result, the obtained PVA/PCL core-shell nanofibers can be used as a carrier for the anticancer agent DOX, which demonstrated long-term and pH-responsive drug release for cervical cancer.

3.4 Anti-inflammatory Drugs Containing Nanofibrous Scaffolds

Centrifugal spinning is a new method for producing core-shell nanofibers with excellent performance and lower cost than electrospinning [87]. In this method, high rotational speed is required to design 3D formed nanofibers. Unlike electrospinning, centrifugal spinning generates centrifugal force to overcome the surface tension of the polymer solution and thus the solution evaporates by air owing to high rotating speed in the method [88]. Li et al. (2021) created core-shell nanofibers from carboxylated chitosan (CCS) and polyethylene oxide (PEO). Two different model drug anti-inflammatory drug (ibuprofen) and human epidermal growth factors (hEGF) were used and these drugs loaded into both core PEO layer and shell CCS/PEO layers, respectively. It was found that the fibers show controlled hEGF release rate in PBS condition. It could be due to the hEGF being incorporated in the core layer, which was contained by the shell layer, and the hEGF release rate being controlled by the encapsulation. Besides, thickness of nanofibers effect the release rate due to changing the polymer erosion rate. In the study, the polymer erosion rate of core-shell CCS/PEO nanofibers were lower compared to monoaxial CCS/PEO nanofiber one. Considering the release rate of ibuprofen, ibuprofen released from core-shell nanofibers were higher than monoaxial ones owing to the loading of this drug into the shell CCS/PEO layer.

Emulsion electrospinning originated as a technique for developing core/shell nano microfibers without the use of a complicated co-axial nozzle syringe, as is done with conventional co-electrospinning, and it also removed the demand for a common solvent for natural and synthetic polymers. Core-shell structured polycaprolactone-chitosan nanofibers were produced by emulsion electrospinning approach for wound healing applications [89]. It is claimed that core chitosan layer cause fibroblasts to release interleukin, which is required for migration and growth, hence speeding up wound healing by increasing proliferation of tissues and angiogenesis.

The local delivery of biological signals such as nerve growth factor (NGF) and glial cell line derived growth factor (GDNF) may stimulate nerve tissue regeneration. In a study, poly (D, L-lactic acid) (PDLLA)/(PLGA) nanofibrous bicomponent scaffolds were developed for controlled NGF and GDNF release [90]. When compared to the control nanofibers, all of the nanofibers containing NGF and GDNF produced by varying the active substance/polymer ratios showed significant cell proliferation. Further, the 2:1 ratio of NGF/PDLLA to GDNF/PLGA in bicomponent nanofibers led in a synergistic effect of NGF and GDNF on cell differentiation.

Chitosan (CS) is one of the best prospects biological molecules for wound dressing due to biocompatibility, biodegradability, and antibacterial efficiency [91, 92]. However, almost none of the natural polymers can be spinnability by themselves in the electrospinning process. Compared to synthetic polymers, natural polymers have lacking mechanical properties and processing problems, while being biocompatible and biodegradable [93]. Thus, natural polymers are blended with synthetic polymers have the potential to enhance stiff and weak properties properties of natural polymers [81]. To overcome this problem, non-cytotoxic but biocompatible polymers such as

PVA can be mixed to produce bicomponent fibers. Although hydrophilic-based nanofibers are usually preferred in tissue engineering applications, they are negatively affected by fast hydrolysis. Thus, they can be chemically crosslinked using chemical crosslinker such as glutaraldehyde (GA). But often-utilized GA is cytotoxic. On the other hand, thermal crosslinking approach is damage to incorporated bioactive agents and also cells in the nanofibers. Photocrosslinked maleilated chitosan/methacrylated poly (vinyl alcohol) (MCS/MPVA) bicomponent nanofibrous scaffolds were perfectly produced by electrospinning and subsequent photopolymerization to increase water stability of hydrophilic-based nanofibers [94]. The study indicated that the samples have suitable *in vitro* cellular compatibility.

Temperature responsive hydrogels, which may change their physicochemical characteristics in response to changes in ambient temperature, are particularly important and have received lots of research. They were utilized drug delivery applications owing to fast response property. Zheng et al. (2021) studied on the temperature-responsive polymer nanofibers with olive oil as the core and N-isopropylacrylamide/N-methylol acrylamide as shell components [95]. Fluorescein isothiocyanate (FITC)-dextran as a model biomacromolecular drug. After six or seven temperature alternation cycles for FDLH-3 or the drug-laden SNFH, almost all of the loaded FITC-dextran was released.

Core-shell fibers from silk fibroin/polylactic acid-caprolactone polyethylene oxide including fibroblast growth factor 2 were created by Xu et al. (2017) [96]. According to the drug release test results, 37.6 ± 1.8 % of burst release was found during the first 8 h, and also 81.7 ± 1.8% of total release was attained at 7th day. In another study, thermos-responsive core-sheath PCL/PNIPAAm nanofibers containing nattokinase (NK) with one-step electrospinning were fabricated by Shi et al. (2016). These smart PNIPAAm/PCL/NK nanofibers demonstrated more than 55% of NK release for both 20 °C and 37 °C temperatures [97]. Figure 8 illustrates fabrication of core-shell nanofibers by inside a UV-cured hydrogel shell structures.

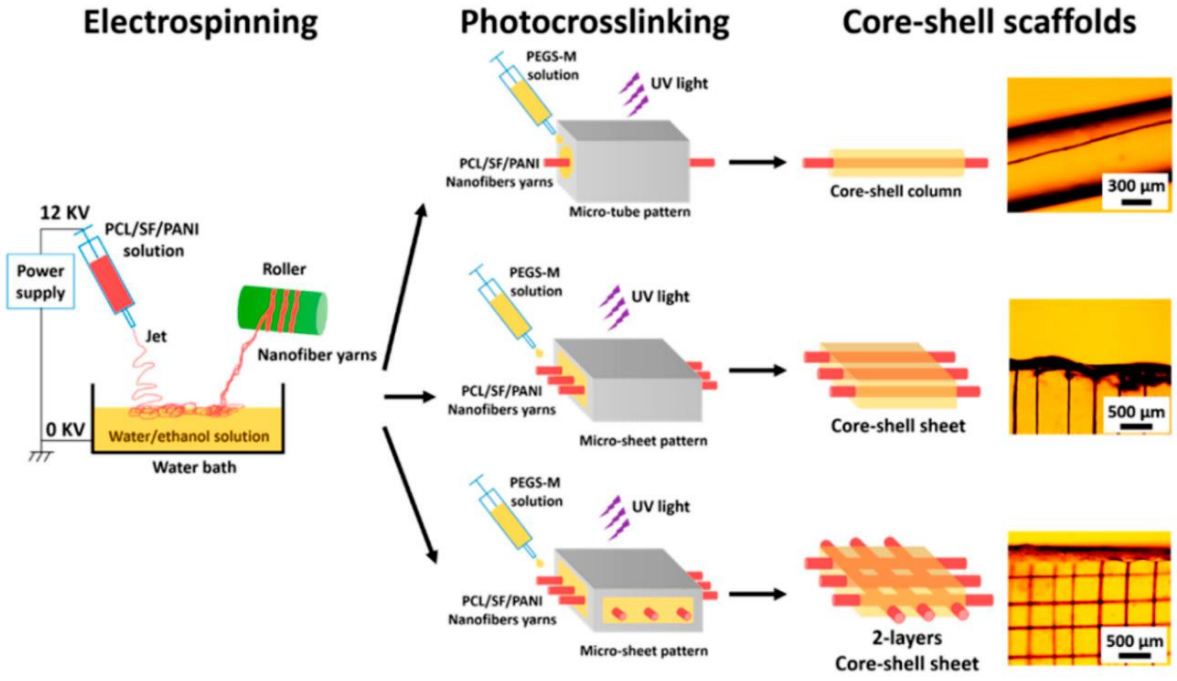

Figure 8. Schematic illustration of core–shell fibers preparation via single electrospinning plus UV photocross-linking. Reprinted from the work in [68]. Copyright 2015 with permission from [42].

The core-shell drug-loaded polyvinyl pyrrolidone (PVP)/polylactic acid (PLA) nanofibers are produced by emulsion electrospinning using a single nozzle. A kind of natural antioxidant which is known procyanidin, were loaded into these fibers. The core layer consisted of hydrophilic PVP solution, while the shell layer consists of hydrophobic PLA solution. Procyanidin was added into the core layer and the antioxidant activity of resultant nanofibers were measured as 88.62 % by the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay [98].

Polycaprolactone (PCL) is a polymer synthesized via the ring-opening polymerization of "€-caprolactone," an FDA-approved substance. PCL has been prevalent in scientific literature concentrate on scaffolds for tissue engineering for a few years. It is commonly used as wound dressing due to its excellent spinnability and tensile strength [99, 100]. PCL/gelatin co-axial scaffolds including an antibiotic minocycline were fabricated by Ramalingam et al. (2021) for healing of burns. Further, these nanofibers showed good antibacterial efficiency [101].

Core-shell nanofibers are attractive materials over single structure ones because they provide to release multiple bioactive molecules with various release kinetics, without degradation by incorporating drug in core [102-104]. Among the numerous biomaterials for wound care, hyaluronic acid (HA) has received the most interest since it is the most abundant component of the extracellular matrix (ECM) and acts a significant role in wound healing and tissue regeneration. Hadisi et al. (2020) developed co-axial nanofibers consisting core layer as SF-ZO and shell layer as HA to use in burn healing. Various concentrations of ZO were loaded into fibers. These HA-SF nanofibers displayed excellent cell adhesion, proliferation, in case of 3% ZO loading. [102].

3.5 Nanofibrous Scaffolds for Ocular Drug Delivery

Corneal abrasion is described as a scrape on the outer layer of the eye produced by a foreign body, which can cause discomfort, redness, itching, and obscured sight in a short time. Even if it is not treated in time, the wound can cause infection and which may result to substantial sight loss [105]. It is known that Gram (-) bacteria *Pseudomonas aeruginosa* (*P. aeruginosa*) can cause corneal abrasion. Antibiotics and antibacterial agents have been among the most often encapsulated therapeutic compounds in recent years, with various polymers and their combined form serving as carriers [106]. Pirfenidone-PLGA/moxifloxacin-PVP core-shell nanofibers were fabricated to treat corneal disease [105]. The presence of the drugs was proved that DSC and XRD analysis. Further, encapsulation efficiencies of moxifloxacin and pirfenidone were calculated as 87.5 % and 80.2 %, respectively. However, moxifloxacin showed a 60 % fast release within 30 minutes, followed by a 10% increase (70% total release). This was caused by the existence of moxifloxacin in the core layer of nanofiber. Similarly, Martin et al. (2022) developed an antimicrobial core-shell microfiber for using wound dressing [107]. In the study, tetracycline hydrochloride was used as the model drug, while zein was used as the core layer and shell layer was composed of polyethylene oxide (PEO), either alone or mixed with PCL. The core-shell microfibers produced at different drug concentrations and in different combinations have all shown antimicrobial activity both *E.coli* and *S.aureus.* Tetracycline hydrochloride-loaded zein/PCL fibers showed increased sustain release behavior compared to zein/PEO fibers for 48 h period. In general, mechanical properties of fiber should be suitable for wound dressings. The resulting zein-PCL core-shell fibers without PEO displayed the required mechanical strength, and ductility, as well.

A detailed study of the controlled release mechanism of core-shell nanofibers containing anti-inflammatory and antibacterial agents (Wen et al., 2019). Flurbiprofen and vancomycin were utilized ~~in~~ as anti-inflammatory and anti-bacterial agents in the study [108]. Flurbiprofen was added to the shell PEO layer, while vancomycin was added to the core polymer mixture consisting of silk/type I collagen. The cross-sectional TEM and SEM micrographs confirmed the two different layers. In brief, the release of flurbiprofen from the nanofibers was performed by a fast-release mechanism whereas a slower release of vancomycin was obtained due to the extra protective effect of the core layer.

Alginate is a natural polymer that is commonly utilized in biological applications. It can improve the efficacy of wound dressings and hence accelerate wound healing. Li et al. (2018) produced calcium alginate/Rana chensinensis skin peptides (RCSPs) core-shell nanofibers and these nanofibers increased epidermal regeneration and collagen deposition in-vitro release study indicated that the total release amount of RCSPs reached 100% for 10 sec [109]. Table 1 summarizes some studies on drug delivery applications.

Table 1. Summarized studies on core-shell nanofibers for drug delivery applications

Core layer	Shell layer	Drug(s)	Properties	Release time	Reference
PCL and Pluronic ® F-127	Silver and PCL	Gentamicin	Burst release and sustain release	2.35 ± 0.13 µg/mg for 5 weeks	Chen et al. (2017) [110]
PEG-PLGA with Ag or Au	Fe_2O_3 in PVA	Silibinin	Sustained drug release	70 % almost 200 h	Fazio et al. (2019) [111]
PVA	PCL	Doxorubicin	pH-responsive drug release	< 60 % almost 50 h in alkaline condition	Yan et al. (2020) [112]
PCL	Chitosan	Rosuvastatin	pH-responsive release	84 % for 48 h in pH 4	Yousefi et al. (2022) [113]
PCL	Zein with Titanium dioxide nanoparticles	Erythromycin	Sustained release	98.1% for 72 h	Baghali et al. (2022) [114]
PVP	PLGA	Moxifloxacin	Initial burst and sustained drug release	87.5 ± 3% almost 24 h	Tawfik et al. (2020) [105]
na	PCL	Platelet lyophylisates	Emulsion centrigufal spinning	> 60 % for 14 day	Buzgo et al. (2017) [115]
PVP	PLGA	Naringin, metronidazole	MC3T3-E1 cells	> 90% for 24 h	He et al. (2018) [116]

3.6 Bi-component Nanofibrous Scaffolds in Clinical Trials

Biocompatibility can be described that the ability of any foreign substance to interact with an organism or tissue without creating toxic adverse effects, immunologic response as well as biological reaction. A material's biocompatibility is often crucial owing to differences in intended usage, body type, time, and endurance [117]. In this context, the performance of the obtained or to be obtained bicomponent nanofibers in pre-clinical *in vivo* studies compared with the standard surgical treatment method evaluation is important. The biological evaluation of a material (for example; nanofiber, sponge, film, hydrogel, nanoparticles etc.) for human use is handled according to the International Organization for Standardization (ISO) ISO 14971:2007 and ISO (10993-1:2010)

standard. Although a large number of in vitro studies on studying the security of nanofibers have been performed, security of *in vivo* security studies is considerably lower.

Wijeyaratne and Kannangara (2011) studied clinical evaluation of electrospun polycarbonate-urethane fibers to use as vascular graft [118]. In the study, nanofibers were implanted in 17 patients from different age groups and their clinical studies were followed for about 1 year. The study's overall findings has shown that the novel multilayered polycarbonate-urethane which name is AVflo™ graft has been secure with no undesirable device-related problems. The fabricated electrospun chitosan / polyethylene oxide (PEO) fibers as a wound dressing and investigated clinical studies on some patients having second and third degree burns [119]. In comparison with typical healing therapies for second and third degree burns and donor wounds, a newly created fibers promotes faster self-regeneration of the wounded skin layer (Figure 9).

As explained before, although many efforts are being made for in vitro and in vivo studies of nanofibers, studies for their clinical research are limited. Few studies are listed the studied on clinical researches of nanofiber materials [120].

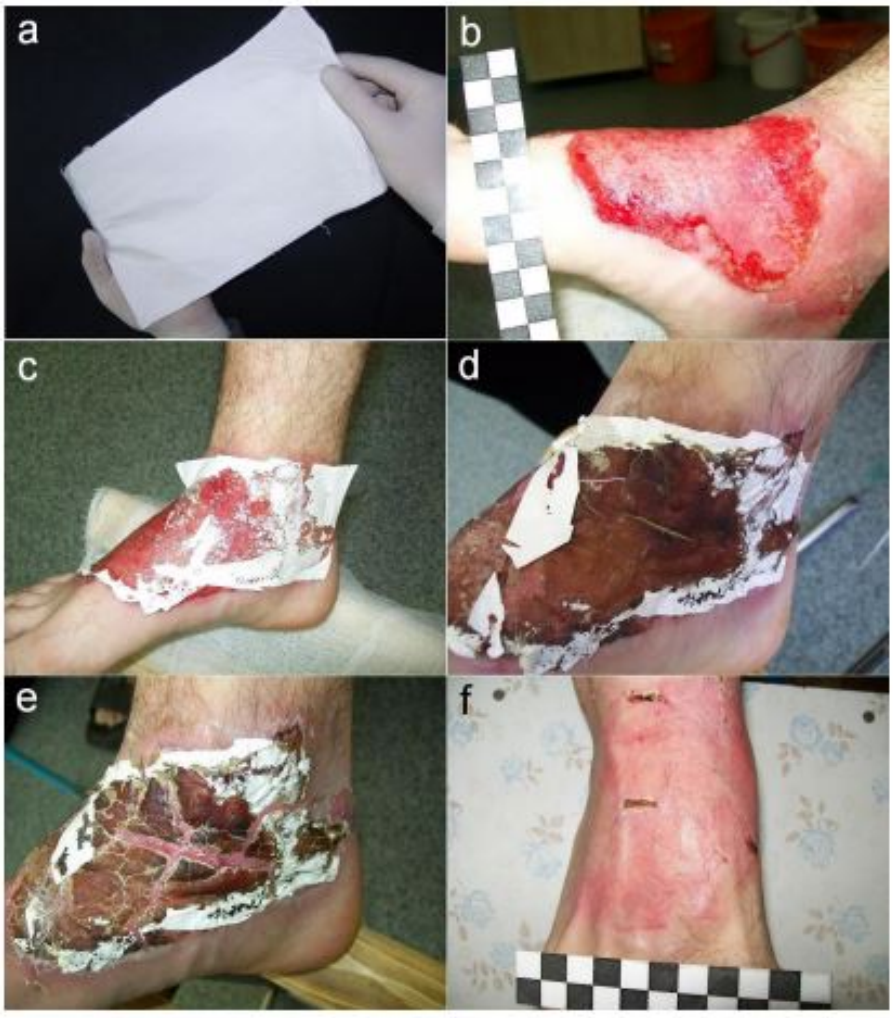

Figure 9. Example of healing of IIIa burn: a)sample of chitosan nanofiber dressing, b) IIIa burn before covering, c) after covering, d) 5 days after covering, e) 10 days after covering, f) 14 days after covering. Copyright 2010 with permission from [119] Springer

Consequently, if the drug-loaded bicomponent fibers planned to be developed with the studies achieve successful *in vivo* results, it will be important from the standpoint of medicine to present a potential treatment approach for many applications, particularly cancer studies and tissue scaffolds for wound healing in the clinic.

IV. CHALLENGES, FUTURE DIRECTIONS, AND CONCLUSION

Conventional electrospinning, melt blowing, centrifugal spinning, and bicomponent electrospinning approaches have been seriously studied for the purpose of producing nanofibers, with different levels of commercial success. The worldwide nanofibers market is predicted to be worth USD 785 million in 2021 and USD 3350 million by 2030, growing at an 18% CAGR during the estimated time frame (2022-2030) [120]. Nanofibers have a significant role in the pharmaceutical applications as a drug delivery mechanism for a variety of illnesses. They are a good drug carrier due to its tiny size for drug delivery to an appreciate location in the body.

Compared to blend electrospinning, where drug loading occurs mostly on the surface of the polymer matrix, core-shell nanofibers displayed delayed release and a decrease in burst release because the drug was loaded into the core layer. Nonetheless, the co-axial electrospinning approach include some disadvantages including high production costs, the development of fibers with different characteristics during the shell layer, and also some defects between both core and shell layers. The emulsion electrospinning technology was designed for drug release applications to solve the drawbacks of both blend and co-axial electrospinning. Emulsion electrospinning is preferable than co-axial electrospinning in that it is a simpler, less expensive, and more efficient way of producing core-shell nanofibers.

The advancement of co-axial electrospinning, side-by-side electrospinning, and triaxial electrospinning has resulted in superior-quality products. Extra sophisticated and complicated multi-fluid electrospinning technology can be used in the future to create nanofibers with novel forms. The rise in popularity of controlled drug delivery system still confronts several obstacles that should be addressed, and many researchers have expressed different opinions. The shortcomings of system include its expensive cost, which makes productivity difficult, and its limited capacity to change doses. To improve regeneration procedures, targeted drug delivery systems have been created. But, the most intelligent scaffolds produced from nanofibers used in drug delivery systems must be assessed in a significant number of clinical studies before it can be used in the clinic. These core-shell, emulsion, side by side and triaxial electrospinning is gradually progressing toward large-scale production, with certain systems currently in operation at the commercial level (for example, NanoSpinner416n, FibeRio® Technology).

Even though these approaches provides to obtain scaffolds as drug delivery systems with various polymer ranges, the favored chemical, mechanical, and morphological features, particularly during large-scale production. Further, to control of working environment and solutions is critical. Further challenges are always associated with drug delivery adjustment. In many situations, improving the drug delivery profile due to polymer-drug combination might easily lead to an enhancement of the overall approach. So, the making of a database containing data such as scaffold characteristics, composition, and ultimate output in terms of drug delivery might provide an easy summary of what the subsequent tuning stage could be. Therefore, the unique properties and ease of use of customized nanofibers may serve as a major step toward personalized treatment. Lastly, an increase in both government and

private sector investment on illness treatment will stimulate interest in nanofibers, which are utilized as tools for drug delivery systems to particular organs in the body.

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