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Electrospun polymeric micro/nanofibrous scaffolds for long-term drug release and their biomedical applications

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Abstract

Electrospun polymeric micro/nanofibrous scaffolds have been investigated extensively as drug delivery platforms capable of controlled and sustained release of therapeutic agents *in situ*. Such scaffolds exhibit excellent physicochemical and biological properties and can encapsulate and release various drugs in a controlled fashion. This article reviews recent advances in the design and manufacture of these scaffolds for long-term drug release using electrospinning, placing particular emphasis on polymer selection, types of incorporated drugs and latest drug-loading techniques. Finally, applications of such devices in traumatic or disease states requiring effective and sustained drug action are discussed and critically appraised in their biomedical context.

1. Introduction

Current means of maintaining therapeutic levels of medications within the bloodstream are limited to repeated administration of the drugs either via the oral or parenteral route. This is inconvenient and, more importantly, puts the patients at risks of accidental or intentional overdoses [1,2]. For example, opioid analgesics are commonly used to treat patients suffering from severe pain (e.g., post-operative or chronic cancer-related pain) by daily administration for continuously several weeks or even longer [3,4]. Whilst the use of opioid analgesics for severe pain is justified, frequent administration poses a potential risk of overdose, abuse or addiction, which can significantly limit its therapeutic efficiency. To improve the drugs' therapeutic efficacy, it is therefore crucial to develop a delivery system that is administered once and can continue to release drugs in a controlled and sustained manner to achieve safe delivery and maintenance of therapeutically appropriate drug levels for a long term.

Polymeric micro/nanoparticle or micro/nanofibrous scaffolds have been investigated extensively as carrier vehicles for delivery of therapeutic agents. These scaffolds can deliver drugs specifically to a predetermined site whilst avoiding systemic distribution of their cargo. This renders such systems highly efficient and enables the use of lower drug doses with subsequently lower adverse side effects [1,2]. Compared with their micro/nanoparticulate counterparts, micro/nanosized fibrous scaffolds display several advantages: (1) their physical structure mimics naturally occurring extracellular matrix (ECM), thus supporting cell adhesion, proliferation, migration, and differentiation better than particulate scaffolds do; (2) they exhibit a higher surface area to volume ratio and higher interconnected porosity with tunable pore sizes, enabling them to release biofactors such as proteins or genes and to facilitate nutrient and oxygen diffusion and waste removal [5-9]. These unique characteristics have made the micro/nanofibers superior for both drug delivery and tissue regeneration applications.

To manufacture these micro/nanofibers, electrospinning, self-assembly or phase separation can be employed, among which electrospinning is most popular due to its simplicity, cost-effectivity, scalability and versatility [10]. Most importantly, the ability to electrospin a variety of materials enables the fabrication of scaffolds with controllable drug release profiles. Polymers of natural, synthetic or composite origin are commonly used in electrospinning due to their different degradation kinetics and remarkable ability to encapsulate hydrophobic as well as hydrophilic drugs and biomacromolecules [10]. By (a) selecting an appropriate

polymer-drug-solvent system and (b) optimizing electrospinning techniques and processing parameters, factors influencing drug delivery including fiber chemistry and diameter, surface charge, drug diffusion coefficient, and degradation rate can be finely tuned to obtain long-term drug-eluting scaffolds. Moreover, the limitless creativity of drug-loading designs endows such systems with even tighter control over sustained drug release. For instance, drug-loaded nanoparticles (NPs) dispersed in the polymer solutions can be electrospun to form composite nanofibers. The extended drug diffusion route for drug particles encapsulated within the NPs results in a prolonged release period up to 90 days [11,12]. Details on drug loading and release profiles will be discussed in Section 3.

Being an incredibly versatile technique, electrospinning of polymeric micro/nanofibrous scaffolds has the potential for widespread applications in traumatic or disease states requiring effective and sustained drug action such as in skin regeneration or treatment of cancer [10]. In this paper, we critically appraise the status quo of electrospun drug-eluting polymeric materials and their potential for clinical applications. First, we summarize the classification of polymers into natural, synthetic and composite polymers and their respective benefits and disadvantages. We then critically appraise the current literature pertaining to drugs loaded onto micro/nanofibers and discuss in detail commonly used drug-loading protocols for long-term drug release. These include surface modification of micro/nanofibrous scaffolds, blending of drug particles with scaffolds, as well as coaxial and emulsion spinning of solutions containing drugs and polymers. We subsequently discuss the mechanisms of drug release from the micro/nanofibrous scaffolds to explain how the rate and extent of drug release is customizable according to needs. Finally, we highlight the potential applications of drug-loaded systems in the biomedical arena including the regeneration of bone, skin and neural tissues as well as the treatment of cancer. We focus our attention on drug-eluting fibers which can release drugs at minimum effective concentrations for periods longer than 20 days to satisfy clinical needs. The aim of this paper is to provide the readers with a broad understanding of our current knowledge of electrospun polymeric micro/nanofibrous scaffolds used for long-term drug release and their biomedical applications upon which they shall be better able to base their research on in the future.

2. Polymers used for fiber fabrication

Electrospinning offers great flexibility in the choice of polymers used for drug delivery applications. Polymers make for an ideal carrier material for long-term controlled drug

release considering their compatibility with a wide range of drugs, and capacity to be modified to suit a variety of delivery routes. When designing an effective polymer micro/nanofibrous system for drug release, various properties of polymers should be considered, including biocompatibility, biodegradability, hydrophilicity and mechanical properties [13]. Polymers used for electrospinning are broadly classified into three categories: (1) natural polymers, (2) synthetic polymers and (3) blends of the two. The biological, physicochemical, mechanical and degradation properties of the most commonly used natural and synthetic polymers are shown in Table 1.

2.1 Natural polymers

Natural polymers are amongst the most popular base materials used for tissue engineering scaffolds due to their similarity to many macromolecular substances found in the human body. With the advantages of low toxicity, favorable biocompatibility, and remarkable physicochemical properties, many natural polymers, such as collagen, gelatin, silk fibroin, chitosan and hyaluronic acid (HA) have been extensively studied as drug delivery systems [14].

Collagen, the basic building block of ECM, is the most prevalent and intensely studied natural biomaterial [15,16]. Gelatin, a hydrolyzed form of collagen, maintains the properties of biocompatibility and biodegradability, in addition to being more readily modifiable compared to collagen [1]. They both display excellent biocompatibility with various cell types and are considered as ideal scaffold materials for drug delivery in tissue engineering. Another natural polymer, silk fibroin, is considered a favorable scaffold material for the incorporation and delivery of a range of therapeutic agents in tissue regeneration applications, owing to its biocompatibility, relatively slow biodegradability, facile processability and better mechanical properties [17,18]. In addition, chitosan and HA which can be found in large quantities in mammals are the most extensively studied polysaccharides for micro/nanofibrous scaffold production. In particular, their excellent biocompatibility, biodegradability and many other characteristics contribute to their broad range of biomedical applications [19]. However, despite these important advantages of natural polymers, some characteristics remain suboptimal: their limited mechanical strength and relatively rapid degradation profile as well as a potential for immunogenicity, batch to batch variation, their limited supply, high cost of production, and susceptibility to cross-contamination limit their

clinical applications [14,20]. In addition, as they are generally hydrophilic and rapidly degradable, the use of natural polymers for long-term drug delivery is restricted.

2.2 Synthetic polymers

Synthetic polymers, compared with natural polymers, have tunable biodegradability and are abundantly available as they can be manufactured easily and at low cost. They are classified into non-degradable and biodegradable polymers. Polyurethanes (PU), for example, are non-degradable and have excellent chemical stability, abrasion resistance and high mechanical strength, rendering them a widely used material as drug delivery devices and artificial organ systems [21,22]. In comparison, biodegradable polymers such as polyvinyl alcohol (PVA), polylactic acid (PLA), polyglycolic acid (PGA), polylactic-*co*-glycolic acid (PLGA) and poly-ε-caprolactone (PCL) broken down by enzymolysis or hydrolysis, have attracted significant attention for drug delivery as they offer tunable degradation rates which can match the new tissue formation [23]. Moreover, the ability to self-absorb over time renders a second operation to remove the implant obsolete, widening their range of clinical applications.

Specifically, PVA, a linear water-soluble polymer that possesses satisfactory spinnability, biocompatibility and excellent physical properties, has diverse biomedical applications such as in rapid drug delivery systems or as temporary tissue engineering scaffolds [24,25]. PLA and PGA are both biodegradable materials with desirable biocompatibility and configurable physical properties that allow facile incorporation of various medications. Both PLA and PGA have been approved by the Food and Drug Administration (FDA) as scaffolds for application in drug delivery [26]. PLGA, a synthetic copolymer made of PLA and PGA possesses tunable biodegradability by adjusting the PLA/PGA ratios, rendering *in vivo* degradation and drug release from PLGA carriers highly controllable [24]. PCL is another biodegradable synthetic polymer. It is superior not only due to its slow biodegradation rate but also due to its excellent spinnability and good mechanical properties, which makes it an ideal long-term delivery system for drugs that require extended body retention times [24].

Although synthetic polymers possess advantages such as durability, relative inexpensiveness and tunable degradation time, they lack cell-specific recognition and attachment affinities. This has urged the development of composite polymers, which can maximize the advantages of both natural and synthetic materials and minimize their disadvantages.

2.3 Composite polymers

Composite polymers are made of two or more polymers including natural and synthetic polymers, which combine advantages of natural polymers such as their resemblance to the extracellular microenvironment and those of synthetic polymers such as excellent mechanical properties and tunable biodegradability. For instance, PLGA/gelatin nanofibers were prepared by blending electrospinning for the delivery of fenbufen (FBF) [27]. Such scaffolds were found to have suitable mechanical and degradation properties as well as bioactivity. Moreover, the release rate of FBF from this nanofibrous scaffold could be tailored by altering the ratio of PLGA and gelatin, with increased PLGA content enhancing scaffold hydrophobicity, resulting in slower FBF release. In another study, PCL/gelatin composite nanofibrous scaffolds were fabricated such that the PCL component conferred tunable hydrophobicity and degradation properties, whilst the gelatin component provided a favorable extracellular environment for adhesion and proliferation of bone marrow-derived human mesenchymal stem cells (hMSCs). Such controllable physicochemical properties have made this nanofibrous scaffold a promising drug delivery system for tissue engineering applications [28].

When designing electrospun polymeric micro/nanofibrous scaffolds, the type of polymers is of crucial importance as it affects the scaffolds' wettability and degradation rates. These are key factors controlling the drug release profile. In addition to the properties of polymers, other factors including the types of drugs and drug loading techniques are equally important for designing long-term drug delivery vehicles. In the following sections, we will review these in detail.

3. Drug loading and release from electrospun polymeric micro/nanofibrous scaffolds

In addition to the polymer properties, the types of drugs and the drug loading techniques play a vital role in fabrication of polymeric micro/nanofibrous scaffolds with long-term drug release profile.

3.1 Types of drugs incorporated

Electrospun polymeric micro/nanofibrous scaffolds are capable of encapsulating and releasing a wide variety of therapeutic reagents including chemicals (e.g., hydrophobic and hydrophilic drugs) and biologicals (e.g., proteins, nucleic acids). In general, drugs exhibiting

similar physicochemical properties as their carrier polymers dissolve better than those showing opposing properties. Hydrophilic drugs like doxorubicin and chloroquine are effectively encapsulated within hydrophilic polymers including gelatin [29] and PVA [30,31], while hydrophobic drugs such as paracetamol and ibuprofen (IBU) are better incorporated into and released from hydrophobic polymers like PCL [32], PLGA [33], and PLA [34]. The long-term release of hydrophilic drugs is, however, more challenging compared to that of hydrophobic drugs. This is because the hydrophilic drugs exhibit poor dispersion within the hydrophobic polymers and are highly soluble in the release media (usually water based), leading to a higher risk of burst release. These issues may be counteracted by using low loading doses, which decreases the localization of drugs to the surface of fibers and thus avoids burst release. Also, improvement in drug-loading designs with the aim of establishing a barrier to isolate drugs from the incompatible polymers has been explored, such as core-shell fibers of which drugs locate in the core. Such designs have demonstrated their capability to achieve sustained release of hydrophilic drugs. Compared to hydrophilic drugs, hydrophobic drugs are relatively easy to load and release over a longer period due to their poor solubility in the release media and good dispersion within hydrophobic polymers.

Apart from chemicals, biologicals have also been incorporated into electrospun polymeric micro/nanofibrous scaffolds for different purposes. Growth factors (GFs) are a group of bioactive proteins capable of regulating proliferation, migration, and differentiation of cells by transferring signals between cells and their ECM [35]. Thus, the incorporation of GFs into ECM-mimicking micro/nanofibers is advantageous in tissue engineering applications. However, retaining the bioactivity of GFs is still challenging as they can quickly become inactive during the electrospinning process. Previous studies have suggested that GFs, such as nerve GFs (NGF), fibroblast GFs (FGF) and vascular endothelial GFs (VEGF) are suitable for incorporation into different polymers for steady release using various techniques [36-38]. Nucleic acids, another group of biomacromolecules with the ability to interfere with biological process by integrating into the cellular genome, can modulate the secretion of signaling molecules on a long-term basis to enhance or prevent specific biological functions. For instance, sustained release of DNA from the electrospun scaffolds can expedite cell transfection or increase transfection efficiency to promote secretion of bioactive molecules, resulting in improved therapeutic efficacy [39]. In addition, siRNA, a type of bioactive macromolecule, which can suppress the expression of certain proteins, has been used in cancer treatment for inhibition of tumor-inducing genes to reduce the secretion of specific

factors to reduce tumor size [40].

As regeneration of damaged or diseased tissues (e.g., bone fracture, skin burns) may take several weeks or even months, it is important to synthesize scaffolds which are capable of releasing drugs over an extended period to achieve effective therapeutic efficacy. To attain a sustained release profile of the above-mentioned therapeutic reagents, various drug-loading strategies have been developed.

3.2 Drug-loading techniques

Different drug-loading techniques including surface modification, blending, emulsion and coaxial electrospinning have been employed to encapsulate therapeutic molecules into various electrospun structures (e.g., single fiber, core-shell structured fibers). Different drug-loading techniques will produce fibers with different structures and different drug release kinetics (Figure 1) [10].

3.2.1 Surface modification

The surfaces of electrospun micro/nanofibers can be chemically and physically modified with a variety of bioactive molecules including anti-cancer drugs, GFs, nucleic acids, and carbohydrates (Figure 1 (a)). Modification of polymer fiber surface with drugs can avoid the process of drug dispersion within the bulk phase of the polymer fibers, so that the drugs, particularly the fragile reagents (e.g., proteins and nucleic acids) do not need to pass through the harsh electrospinning conditions. Additional benefit of surface modification includes the capability to deliver charged macromolecules (e.g., heparin) which normally are extremely difficult to be homogeneously dissolved within the polymer matrix during electrospinning [41,42]. With bio-functionalization of the surfaces, the micro/nanofibers are capable of enhancing cell adhesion, proliferation, and differentiation by mimicking morphology and biological functions of ECM. Moreover, these functional scaffolds provide a robust delivery platform due to an extremely high surface area to volume ratio, leading to higher drug loading capacity. Furthermore, immobilization of biomolecules onto the fiber surfaces via chemical bonds can attenuate the initial burst release, thus releasing drugs for over 15 days [43,44]. However, as the drugs are located on the surfaces of the micro/nanofibers, the drug release time lasts usually less than 45 days. To achieve long-term release of therapeutic agents for optimal therapeutic efficacy which usually requires a prolonged drug release route, other techniques including blending, coaxial and emulsion electrospinning have been

developed.

3.2.2 Blending electrospinning

In blending electrospinning, drugs are encapsulated by direct dissolution within the polymer solution before electrospinning (Figure 1 (b)). Drug encapsulation efficiency, drug distribution inside the micro/nanofibers and drug release kinetics are dictated by the polymer-drug interaction and physicochemical properties of the polymer. Poor solubility of the drugs can result in non-uniform drug distribution throughout the polymer solution as well as drug migration towards the fiber surface, which may ultimately lead to an undesirable initial burst release [45]. Therefore, when selecting blending electrospinning, it is essential for the drug and polymer to have similar physical properties with respect to wettability for a better drug solubility and distribution in the polymer solution. When incorporation of drugs into polymers of different properties is necessary, either surfactants can be introduced or the drugs can be incorporated into NPs or microspheres prior to electrospinning to create a physical barrier between the drug and the polymer [11,46].

Blending electrospinning creates only single-layered micro/nanofibers, and drugs blended into such fibers are shown to be released for up to 48 hours only [47]. In order to fabricate micro/nanofibers with a core-shell structure in which fragile biological reagents are protected and drugs can be released for a prolonged period [48,49], coaxial and emulsion electrospinning are possible options (see sections below) [50].

3.2.3 Coaxial process

When incorporating biomolecules into micro/nanofibers using coaxial electrospinning, the biomolecule is located in the inner portion (the core) and the polymer solution in the outer portion (the shell) of the solution jet (Figure 1 (c)) [51]. In this way, the polymeric shell can effectively protect the biomolecule core against exposure to environmental insults, which preserves the bioactivity of the incorporated biomolecules. Other types of pharmaceutics like antibiotic or antioxidant drugs, can also be loaded inside polymer fibers using this technique [52]. Moreover, compared to blending electrospinning, coaxial electrospinning can prolong the drug release period as it can create fibers with core-shell structure which has been shown to extend the drug diffusion route by modulating the thickness and composition of the shell [39].

3.2.4 Emulsion electrospinning

In emulsion electrospinning, droplets composed of drug molecules are dispersed in the polymer solution prior to electrospinning [46]. A core-shell fibrous structure is configured as macromolecules aggregate in the aqueous phase forming the core (Figure 1.4) and the polymers form the shell (Figure 1 (d)) [53-55]. The core-shell structure formed by emulsion and coaxial electrospinning has a drug release time of up to 60 days as the outer shell layer can act as a barrier for diffusion of the drug encapsulated [56,57]. Furthermore, emulsion electrospinning does not require a common solvent for the drug and the polymer in comparison to blending electrospinning. Therefore, a solution containing therapeutic reagents and polymers with drastically different hydrophilic-hydrophobic property can be easily electrospun without significant contact of the drug with the organic solvent [58].

3.2.5 Other drug-loading techniques

Another technique to achieve long-term drug release is via incorporation of nano- or micro-sized drug delivery devices, such as NPs, nanotubes, micelles, microspheres, and liposomes into electrospun fibers [59]. For instance, electrospun polymeric micro/nanofibers hybridized with NPs have been developed to improve drug-loading efficiency, release manner and drug stability. In addition, modification of NPs with multi-functional ligands can not only achieve active target recognition, but enhance therapeutic efficacy as well and reduce side effects [60]. Similar to the above-mentioned drug-loading techniques, NPs can be integrated into micro/nanofibers by assembly onto their surface or within the micro/nanofibers as they can maintain the drug stability in organic solvents to which they are exposed during the fabrication process. Moreover, due to the existence of the two barriers provided by NPs and miocro/nanofibers, the drug diffusion route and release time from scaffolds are relatively extended compared with naked electrospun micro/nanofibers. At present, the use of NPs such as silver NPs [61-63], mesoporous silica nanoparticles (MSNs) [1,12,64,65], biopolymer-based NPs (e.g., albumin NPs [66], HA NPs [56]) has brought about tremendous progress in long-term controllable drug release in electrospun polymeric micro/nanofibers.

Another advanced design is to fabricate layer-by-layer micro/nanofibers via stacking the fibrous sheets. Similar to coaxial micro/nanofibers, this structure can control the drug release by forming sheet barriers. In a study by Okuda et al., tetra-layered nanofibrous mesh was fabricated via a sequential electrospinning process of different solutions to achieve

time-programmed dual-drug delivery (Figure 2 (a-c)) [67]. Poly (l-lactide-*co*-ε-caprolactone) (PLCL) solutions containing two different model drugs were prepared and sequentially electrospun to fabricate the first drug-loaded mesh (top side) and then the second drug-loaded mesh. The electrospun PLCL meshes without drugs were layered between the meshes containing different drugs so as to form barrier mesh to control the drug release. It was found that the drug release rate could be controlled by varying the fiber diameter and the mesh thickness. This tetra-layered system not only prolonged the drug release time of the second drug-loaded mesh but also provided timed release of the respective drugs. These features render this tetra-layered system a useful scaffold for advanced multidrug combination therapy requiring respective administration of different drugs at different times.

Triaxial electrospinning is another novel strategy to create functional trilayer micro/nanofibers for drug release. For example, different concentrations of ketoprofen (KET) were dissolved into the same polymer solution (ethyl cellulose) to form the outer, middle, and inner laminar fluids throughout the electrospinning process, with the KET concentration in each layer being gradually increased from the outer to the inner layer (Figure 2 (d-f)) [68]. This method successfully eliminated the initial burst release of KET. Also, it was found that the KET released from these layered fibers exhibited a linear release pattern, which could be widely exploited in clinical settings, such as oral administration to treat gastrointestinal diseases.

These basic drug-loading techniques mentioned above can be integrated with each other to obtain novel polymeric micro/nanofibrous scaffolds with controllable release profiles. To better design and control the drug release from electrospun polymeric micro/nanofibrous scaffolds, the drug release mechanisms should be understood. Details of these are presented in section 3.3.

3.3 Mechanism of drug release

The drug release from micro/nanofibers can be described mainly through the desorption of fiber surface, channel and pore diffusion, as well as micro/nanofiber degradation [6]. The release process of drugs from fibers is showed in Figure 1, of which the fiber degradation process existed only in degradable polymers is not exhibited. All three release mechanisms almost exist in the whole period of release (except the non-biodegradable polymeric matrix) and can significantly impact the drug release kinetics. When the nanofibers containing

various drugs are surrounded by the aqueous phase, the drugs attached to the fiber surfaces are released firstly by desorption and followed by fast diffusion into the aqueous phase. The desorption mechanism is not limited to the outer surface of the nanofibers but also includes drugs on the surfaces of the nanopores inside the nanofibers [24]. Among the three mechanisms described, desorption of the drug from the fiber surface results in a relatively quick burst release pattern of the drug due to the close contact between drugs on the nanofiber surface and the surrounding medium, weak association between the drug and the surface. This mechanism of drug release plays a significant contribution to burst release, and is not generally thought useful as a controlled means of sustained-release bioactive agents. Hence, surface modifications, especially physical modification, must be considered carefully when designing carrier scaffolds to achieve a controlled and sustained drug release profile. To tackle this issues, a variety of techniques mentioned above such as coaxial and emulsion electrospunning have been showed the ability of further controlling the release rate by reduced amount of drugs on the surface. Channel and pore diffusion manners, for example, represent a predominant mechanism for drug transfer as they are dependent on the concentration gradients along which the drug may diffuse, the diffusivity of the drug inside the polymer matrix and on the diffusion route. For example, in the drug delivery system formed by blending electrospinning, the concentration gradients is the main influence factor of drug diffusion, thus leading to an initially remarkable burst release unfavorable for long-term drug release. For attenuating this increased drug release, researchers created a barrier (e.g., the incorporation of drug-loaded NPs into electrospun fibers, coaxial and emulsion electrospinning) between the drug and the aqueous phase to prolong the release time by extending the diffusion routes relatively. In such a system with or without the barrier, however, micro/nanofiber degradation has a great effect on release profile, which must be taken into account during the process of diffusion of drugs through the solid polymer matrix prior to diffusing into the solution. For most non-biodegradable polymeric matrices, drug release rates only correlate with the diffusion distance through the polymer or through the formed aqueous pores caused by water sorption [21]. However, when using a biodegradable carrier system, drugs can be released both through diffusion and via spaces created by degradation of the micro/nanofibers. Through fiber degradation, drugs entrapped inside the polymer materials are released into the surrounding medium. This is more pronounced in rapidly degrading polymers such as chitosan, PVA, and PLA due to the more rapid breakdown of these polymers and the subsequently shorter release route, which can increase the complexity and difficulty in controlling the drug release. Thus, both the drug release

routes and material degradation manners warrant careful consideration when selecting biodegradable materials for a drug carrier scaffold. More details about drug release mechanisms can be found in a review prepared by Leung et al [24] and Szentivanyi et al [69]. In summary, a satisfactory drug release profile over the whole period of release is eventually determined by a certain balance among the three release mechanisms, which in turn correlate with the drug-loading techniques. Thus, these factors affecting the release mechanisms, such as drug-loading design and polymer selection, can be thought over to fabricate the drug delivery platform for a long-term release.

4. Biomedical applications of electrospun polymeric micro/nanofibrous scaffolds for long-term drug release

Increasing efforts have been made to fabricate electrospun polymeric micro/nanofibrous scaffolds for long-term drug release. Such scaffolds have been applied in the field of regeneration of damaged tissues like bone, skin, neural tissues, and disease treatments such as cancer and adhesion formation (a frequent complication following surgery). In the following paragraphs, we introduce the latest applications of electrospun polymeric micro/nanofibrous scaffolds as long-term drug release carriers in the field of tissue engineering and disease treatment.

4.1 Tissue engineering

4.1.1 Bone tissue engineering

Being a rigid organ, bone tissue makes up our skeleton which serves multiple functions including supporting and protecting our vital organs, enabling mobility, producing red and white blood cells, as well as storing minerals [70]. Collagen and hydroxyapatite (HAp) are the main organic and inorganic components of bone ECM, respectively. Electrospun fibers incorporating HAp, tricalcium phosphate and dicalcium silicate are promising scaffolds for bone tissue engineering due to their similarity to the structure and composition of naturally mineralized collagen fibers found in bone ECM [71-73]. To further facilitate the regeneration of fractured bones, a variety of GFs like bone morphogenetic protein-2 (BMP-2) and VEGF have been encapsulated into the electrospun fibers. For example, Chiu et al. covalently conjugated heparan sulfate-decorated recombinant domain I of perlecan/HSPG2 onto an electrospun PCL scaffold for binding and controlled release of recombinant human BMP-2 (rhBMP-2) [74]. This PCL scaffold provided sustained release of rhBMP-2 over 23 days *in vitro*. Additionally, rhBMP-2 released from the modified scaffolds enhanced alkaline

phosphatase (ALP) activity in W20-17 mouse bone marrow stromal cells, suggesting its osteogenesis potential. This novel platform has been considered conducive for rhBMP-2 delivery and for enhancement of bioactivity of the PCL scaffold for bone tissue regeneration [74].

Although previous studies have shown that direct delivery of GFs showed great therapeutic potential *in vitro* or *in vivo*, few studies have successfully completed clinical trials due to the requirement of high amounts of therapeutic reagents and insufficient local retention [75]. Maintaining a localized high concentration of different GFs is crucial as during natural bone healing, varying GFs and cytokines are excreted from different functional cells in a temporo-spatially predetermined way. Thus, a novel scaffold capable of efficient and long-lasting delivery of multiple therapeutic agents to mimic and accelerate natural healing is needed [75]. For instance, incorporation of BMP-2 and dexamethasone (DEX) into PLCL/collagen nanofibers by coaxial electrospinning has demonstrated excellent control over their drug release profile, thereby promoting osteogenic expression of hMSCs [76]. This scaffold with the shell layer loaded with DEX and the core layer loaded with BMP-2 exhibited an initial fast release of DEX and a subsequent steady long-term release of BMP-2 for over 22 days. This dual GF-loaded scaffold combined the biological functions of both drugs, synergistically inducing the differentiation of hMSCs into osteogenic cells and improving osteogenic efficacy.

Compared to GF delivery, gene delivery is a more fundamental approach to achieving controlled long-term release for bone regeneration through the transfer of local nucleic acids into somatic cells for sustained therapeutic expression of osteoinductive factors [77]. In a study, Xie et al. [78] designed a core-shell electrospun fibrous scaffold made of PLGA (shell) and polyethylenimine (PEI) (core) incorporating BMP-2 plasmids (pBMP-2) to protect pBMP-2 from direct exposure to organic solvents and to control its release. Compared to the single axial scaffolds, this scaffold showed higher transfection efficiency and stable BMP-2 expression for over 28 days in human periodontal ligament stem cells (hPDLSCs). To date, there have been many achievements in bone tissue engineering, and electrospun polymeric micro/nanofibrous scaffolds count amongst the most versatile and promising scaffolds capable of controlled and sustained delivery of different bioactive factors for a programmed time period to mimic natural bone healing and accelerate bone repair.

4.1.2 Skin tissue engineering

Skin is the largest organ of our body. Loss of integrity of our skin may lead to disability and even death. Most superficial skin wounds can heal by themselves. This is not the case, however, in wounds involving the deep dermis or wounds affecting large areas of the body (greater than 20% of the total body surface area [79]), caused by, e.g., burns, trauma and chronic skin ulcers in patients with diabetes mellitus, etc. Such wounds are difficult to heal because of the lack of cellular and molecular signals necessary for normal wound repair and the existent of inflammation and infection delaying the healing process. To promote healing, they require the external administration of therapeutic agents at a controlled concentration over a period of weeks or months, as well as a three-dimensional supporting structure such as ECM [80,81]. Therefore, artificial matrices such as electronspun polymeric fibrous membranes containing various therapeutic drugs (e.g., anti-inflammatory and antimicrobial drugs) or GFs have been trialed in skin repair strategies. In the early healing phase of this skin wound, especially in burn injury, the rapid and effective neovascularization of biomaterials plays a significant role after implantation. Sun et al. constructed 3D electrospun hydrogel fibrous scaffolds for accelerated vascularization using a synthetic photocrosslinkable GelMA [82]. With excellent mechanical and degradable properties, such scaffolds not only supported endothelial cells and dermal fibroblasts adhesion, proliferation, and migration into the scaffolds *in vitro*, but also displayed higher flap survival rate and more microvascular formation *in vivo* as skin flap implantation than control group. This scaffold capable of promoting neovascularization has the potential to be further designed to improve the skin regeneration by incorporating various therapeutic agents. The incorporation of angiogenic factors has been showed to be a direct and efficient way to further increase the formation of blood vessels [83], whereas the scaffold with only one type of angiogenic factor may not be enough to induce a mature, stable vascular structure which usually require a stimulation of different stages of angiogenesis [84]. For this reason, Lai et al. designed a Col-HA-GNs (collagen-hyaluronic acid-gelatin nanoparticles) composite electrospun scaffold with the ability of stage-wise delivery of multiple angiogenic growth factors for full-thickness skin regeneration with vascularization function [85]. In this delivery system, multiple growth factors including VEGF, basic fibroblast growth factor (bFGF), endothelial growth factor (EGF) and platelet-derived growth factor-BB (PDGF-BB) were encapsulated either in nanofibers or in nanoparticles and showed a stage-wise release pattern lasting for 1 month. Most interestingly, the initial delivery of bFGF and EGF mimicked the early stage of the wound healing process, whereas slow controlled release of VEGF and PDGF-BB imitated the

late stage of skin reconstruction, and thus this delivery platform could promote the re-epithelialization, dermal reconstruction and the formation of mature vasculature on the diabetic rats. In addition to neovascularization, the anti-inflammation and anti-infection in chronic wounds also play critical roles in the wound healing process and must be considered carefully. For instance, ibuprofen, a frequently used nonsteroidal anti-inflammatory drug, could be loaded into PLA nanofibrous scaffold via blending electrospinning for skin regeneration [34]. Such a scaffold with a controlled ibuprofen release (about 14 days) could reduce wound contraction and promote healing of full thickness incision wounds. In another study performed by Chen et al., mupirocin was incorporated into PU fibers via blending electrospinning for preventing wound infection [86]. The release amount of mupirocin from this blending fibers exceeded 90% at the third day, which were critical to the long-term integrity of wound dressing. Moreover, this drug delivery scaffold displayed an excellent antibacterial burn wound dressing specialized against *S. aureus*, which had the potential of infection control at the early phase of burn injury and accelerating wound healing process. Because the wounding healing is a complex multicellular process, the combination of medicaments *in vivo* is suggested as a promising treatment to achieve active wound healing [87]. Xie et al. developed the composite nanofibrous delivery system containing chitosan, poly(ethylene oxide), VEGF and PDGF-BB-loaded nanoparticles for wound healing applications [88]. This dual growth factor-releasing nanoparticle-in-nanofiber system was capable of anti-infection due to the antibacterial action of chitosan, whilst it showed a short-term release of VEGF to enhance angiogenesis and displayed a sustained release of PDGF-BB throughout the whole process to accelerate tissue regeneration and remodeling. In this unique delivery device, the several key factors affecting the healing process was integrated with each other, and thus this system could synergistically improve the chronic complex wound healing.

It is known that skin injuries extending deep into the reticular layers of the dermis usually take up to 20 days to heal. Throughout this period there is a greater than 70% risk of developing a hypertrophic scar [89]. Consequently, it would be desirable to develop a wound dressing which can facilitate wound healing at the early stage and suppress scar formation later on. For example, Cui et al. [90] have successfully developed Ginsenoside Rg3 (G-Rg3)-coated electrospun poly(l-lactide) (PLLA) fibrous scaffolds to reduce scar formation in a rabbit ear model. The G-Rg3/PLLA electrospun fibrous scaffolds exhibited an initial burst release of G-Rg3 during the first 2 days and then continued to gradually release of the

drug for up to 40 days (Figure 3). The long-term release of G-Rg3 significantly inhibited proliferation of human hypertrophic scar fibroblasts (HSFs) *in vitro*, and the *in vivo* results showed significant prevention of hypertrophic scar formation by decreasing the thickness of neodermis and number of proliferative cells as well as collagen fibers. Overall, scar-free skin regeneration can be achieved using electrospun fibrous membranes which can release drugs for a long term, thus re-establishing lost functions of skin. In another study, the silk fibroin/gelatin nanofibrous scaffold encapsulated with astragaloside IV by blending electrospinning also exhibited the ability of improved wound healing and inhibited scar formation, which had the promising potential application in partial-thickness burn wound [91]. In order to achieve efficient wound repair which aims to eliminate complications like chronicity or fibrosis and improve the each phase of wound healing, Chouhan et al. developed non-mulberry silk fibroin based electrospun mats with EGF and PVA blended, and ciprofloxacin coated [92]. This novel mats showing sustained drug delivery and antibacterial activity were capable of modulating ECM behavior by the function of PVA, and achieving scar-less healing by combined properties of EGF and non-mulberry silk fibroin. Overall, although there has been great achievements in skin regeneration applications by using electrospining nanofibers as drug delivery vehicles in recent years, various delivery platforms, especially the multidrug treatments, can be further investigated to enhance wound healing.

4.1.3 Neural tissue engineering

The nervous system (NS) is a complex collection of specialized excitable cells known as neurons which receive, process, store and transmit information gathered from within and outside of an cell body [93]. Nerve injuries including peripheral nerve injury (PNI), spinal cord injury (SCI) and traumatic brain injury (TBI) are very common and are a leading cause of morbidity and mortality due to resultant neurological deficits and gliosis [94-96]. The subsequent burden on the individuals, their families as well as society is understandably grave [97]. Due to the advantages of ECM-like structure, feasibility in control over the diameters of fibers and porosity of fibrous meshes, scaffolds fabricated by electrospinning have been applied in the investigation of treatment for these neurological injuries. Thus far, many reports have already demonstrated the effects of elctrospun fiber topography and density, surface coating and supporting substrate on nerve regeneration [98-100], and here we only emphasize those drug-loading electrospun scaffolds for improved nerve regeneration. Take the treatment of PNIs for example, this disease involving the loss of long segments between the proximal and distal nerve ends have been shown to respond favorably to an

electrospun polymeric micro/nanofibrous scaffold containing therapeutic reagents [101]. Hu, et al. [102] developed electrospun PCL scaffolds loaded with NGF and bovine serum albumin (BSA, used as stabilizer to avoid initial burst release) by emulsion electrospinning technique. NGF and BSA were encapsulated within the core, while PCL formed the shell (Figure 4). It was found that the presence of the stabilizer prolonged the release of NGF for over 28 days, which was beneficial for both axonal regeneration and neurite outgrowth. Moreover, these scaffolds can be successfully applied to situations where cell apoptosis as opposed to cell growth was required such as in the management of glioblastoma [103]. By coaxial electrospinning technique, another study also showed the NGF encapsulated into the core of aligned silk fibroin /P(LLA-CL) nanofibers exhibited a sustained release over 60 days and remained biological activity, which was favorable for promoting peripheral nerve regeneration [104]. In addition to GFs, the electrospun fibers can provide a long-term delivery of other therapeutic agents for nerve injury treatment. For instance, methylcobalamin (MeCbl), one of the active forms of vitamin B12 homologues, is benificial to promote nerve regeneration and neuronal cell survival [105]. However, it is difficult to achieve prolonged administration and effective drug concentrations because of the short half-life of MeCbl. Just for this reason, Suzuki et al. developed a novel electrospun nanofiber sheet incorporating MeCbl to locally deliver a high concentration of the compound to the peripheral nerve injury site [106]. This sheet showed a sustained release of MeCbl for at least 8 weeks *in vitro* and the promotion of functional recovery and nerve regeneration *in vivo* without adverse effect on nervous system. Furthermore, it is an alluring method of nerve injure treatment via the sustained non-viral delivery of nucleic acid by using electrospun fibers. For example, Nguyen et al. incorporated miR-222 into an aligned poly (ε-caprolactone-co-ethyl ethylene phosphate) (PCLEEP)-collagen hybrid scaffold showing a controlled release pattern, which was rapidly released within the first month and then was steadily released for at least 2 months [107]. Such a scaffold provided not only biochemical signals to enhance axon regeneration and remyelination, but also topographical signals to effectively direct neurite extensions and support remyelination. Thus, It is envisioned that electrospun micro/nanofibrous drug delivery systems with favorable characteristics of fiber/meshes, have great potential to synergistically guiding nerve tissue growth and promoting nerve regeneration as well as preventing the propagation of undesirable cell types.

4.1.4 Other tissues

In addition to bone, skin and neural tissues, electrospun polymeric micro/nanofibrous

scaffolds can find broad applications in regeneration of blood vessels [108], cartilage [109] and cardiac tissue [110]. For example, Zhou, et al. [111] developed an efficient intracellular delivery system for miRNA-126 (miR-126), a regulator of vascular integrity, by encapsulating it within a bilayered electrospun fibrous structure resembling a blood vessel (encapsulation efficiency of 68%). This entrapment method enabled the direct intra-cellular delivery of miR-126 to vascular endothelial cells seeded onto the luminal surface of the scaffolds for a period of 56 days, resulting in significantly improved proliferation of vascular endothelial cells and enhanced endothelialization *in vivo*. In another study, Wang et al. [109] developed a bioactive PLCL/collagen nanofibrous scaffold via coaxial electrospinning technique for cartilage regeneration. The scaffold was loaded with transforming growth factor β3 (TGF-β3) (encapsulation efficiency of 45%) which was released from the scaffolds in a sustained and stable manner for over 57 days whilst retaining bioactivity throughout. The slow release pattern was mainly attributed to the slow degradation of PLCL, which was the shell layer of the scaffold. This study indicated that PLCL/collagen scaffolds containing TGF-β3 could promote the chondrogenic differentiation of human umbilical cord stem cells (WMSCs) for cartilage regeneration in trachea repair. For restoring cardiac function after ischemia, Lakshmanan et al. [112] fabricated a dual GFs-loaded (VEGF and bFGF) PLCL/ poly(2-ethyl-2-oxazoline) (PEOz) composite nanofibrous scaffold through blending electrospinning, which mimic the topographical and chemical cues of the natural cardiac tissue. This scaffold loaded with angiogenic GFs not only showed a sustained release of dual GFs for up to 10 days compared to the PLCL scaffold, but improved the biological response of ischemic tissue and facilitated neovascularization without adhesions and edema formation.

Electrospun polymeric micro/nanofibrous scaffolds are ideal candidates for tissue regeneration due to their structural similarity to natural ECM, adequate drug loading capacity and controllable release kinetics. The following sections will further discuss their suitability as drug delivery systems with sustained and controlled release of GFs/proteins/other drugs for treatment of diseases such as cancer.

4.2 Therapeutic delivery

4.2.1 Cancer Therapy

Cancer recurrence is a recognized complication of inadequate medical and/or surgical treatment and can happen at any time point (weeks, months, or even many years) after treatment [11]. The mechanism of recurrence is either by *de novo* transformation of

dysplastic cells, or the multiplication of malignant cells, which have somehow remained in the body after treatment. It is therefore important to develop implantable scaffolds capable of releasing drugs long after primary cancer treatment/resection.

Recently, electrospun PLLA scaffolds containing MSNs capable of releasing drugs for up to 90 days have been developed (Figure 5 (a)) [113]. The long-term drug release is due to the extended drug diffusion route provided by the MSNs: the entrapped drugs must first be released from the MSNs, and then diffuse through the polymeric fibers to be released into the medium. In this way, therapeutic agents can be continuously delivered at a controlled rate over a period of weeks and months. Not only is this beneficial for the sustained fight against cancerous cells, but it also improves patient compliance and comfort, reduces fluctuations in drug blood levels, decreases adverse effects at the doses required for clinical efficacy, and overall improves upon existing pharmacotherapies.

A major drawback of conventional drug release systems involves the nonspecific release of drugs upon encountering a cellular environment, which is not necessary for the cancerous tissue. Thus, it is desirable to develop a drug-eluting strategy responsive to the tumor microenvironment to improve treatment. As tumor cells secrete acids, it would be more sensible if the electrospun fibers were sensitive to acids and thus released their cargo in response to an acidic environment only. To develop a tumor-triggered drug delivery system, Zhao et al. constructed electrospun PLLA fibers incorporating drug-loaded MSNs caped using $CaCO_3$ (Figure 5 (b)) [11]. The inorganic caps $CaCO_3$ could control the opening of pore entrances of MSNs encapsulated inside the PLLA fibers. This is because $CaCO_3$ being stable at the physiological pH of 7.45 is readily dissolved into biocompatible Ca^{2+} (cations) and CO_2 gas in response to an acidic environment ($pH < 6.8$) which is frequently encountered in and around cancer tissues. This system was not responsive at normal pH ranges, thus reducing the risk of damage to healthy cells. Furthermore, this system released the drug over a period of 40 days due to the existence of MSNs which could extend the drug diffusion route, demonstrating effective anti-tumor efficacy.

4.2.2 Adhesion prevention

Adhesion is a physiologically important part of wound healing. However, adhesion formation after surgery can result in serious complications, pain and functional obstruction, which may require subsequent operations. It is therefore essential to inhibit adhesion formation on a

long-term basis during the healing process [114]. Some studies have induced fibroblast apoptosis and inhibited collagen secretion using drug-eluting electrospun polymer fibers, thereby preventing adhesion formation [114]. In one study, Zhao et al. [56] developed PLLA fibers encapsulating Mitomycin-C (MMC)-loaded HA hydrosols by micro-sol electrospinning for accelerated healing and prevention of adhesion formation in a tendon wound model. In this system, drug-loaded electrospun fibers achieved continuous and controlled release of MMC over several months to inhibit fibroblast proliferation via up-regulation of the apoptotic protein Bax and down-regulation of proteins Bcl2, collagen I, collagen III and α-SMA. The HA hydrosols provided nutrients required for tendon healing and acted as a lubricant for tendon gliding. The relatively slow burst release of MMC during the early stage combined with its long-term sustained release over 40 days resulted in faster tendon regeneration compared with other carrier systems whilst preventing significant adhesion formation. In another study, Jiang et al. [114] incorporated celecoxib (a drug to suppress fibroblast proliferation and collagen expression) into PELA diblock copolymer fibrous membranes via blending electrospinning (Figure 6). The results of *in vitro* studies showed celecoxib-loaded PELA membranes effectively sustained the drug release over 20 days and inhibited the proliferation and adhesion of rabbit fibroblasts and tenocytes. *In vivo* studies demonstrated that celecoxib released from this PELA membrane down-regulated ERK1/2 and SMAD2/3 phosphorylation, leading to reduced collagen I and collagen III expression, reduced inflammation and fibroblast proliferation and thus successfully preventing tissue adhesion. This research has demonstrated that the celecoxib-loaded PELA membranes which could release celecoxib for a long term could effectively prevent tendon adhesion formation.

4.2.3 Other diseases

Apart from treating cancer and inhibiting adhesion formation with sustained and long-term drug release, electrospun polymeric micro/nanofibers have also served as drug delivery vehicles in other disease states, such as periodontal disease [115], rheumatism [116], and esophageal stenosis [117]. For example, Zamani et al. [115] constructed electrospun PCL nanofibers containing metronidazole benzoate (MET) and evaluated their therapeutic efficacy in the treatment of periodontal disease. Sustained release of MET from the nanofibers was achieved for about 20 days *in vitro* with low initial burst release. This could be a desirable treatment period for periodontal diseases due to more prolonged drug availability and sustained drug action. Siafaka et al. [116] encapsulated teriflunomide (the active

pharmaceutical ingredient of leflunomide, which is used for the treatment of rheumatoid arthritis) into a series of novel electrospun fibrous mats using PLA and poly (butylene adipate) (PBAd) polymer blends to evaluate their potential as sustainable pharmaceutical patches for transdermal delivery of anti-rheumatoid agents. Compared with PLA fibers, PLA/PBAd blends showed significantly longer release profile due to the slower diffusion of the drug from the polymer matrix. In another study, Zhu et al. [117] employed blending eletrospinning rotating-collection method to develop a biodegradable paclitaxel/PCL microfibrous membrane-covered stent for the treatment of benign esophageal strictures. Paclitaxel was released from the stent mainly via diffusion and showed stable release profile for up to 32 days at a pH 4.0. Furthermore, significant inhibition of proliferation of smooth muscle cells was observed *in vitro*. An *in vivo* esophageal stricture model showed that the drug-loaded stent resulted in decreased tissue inflammation and collagen fiber production and easy removal of the stent from the esophagus, with no detrimental effects on the normal esophageal tissues. Thus, this novel stent is considered as potential clinical esophageal stricture therapy to effectively attenuate stent-induced inflammation and scar formation.

In short, Electrospun polymeric micro/nanofibrous scaffolds play a critical role in drug delivery due to the large specific surface area and ECM-like physical structure which promote cell adhesion, migration, proliferation, and differentiation . Due to their widespread popularity as drug delivery vehicles, electrospun fibers are increasingly applied in both tissue regeneration and therapeutic delivery.

5. Conclusion and prospective

Electrospun polymeric micro/nanofibrous scaffolds have gained significant popularity for use in long-term drug release due to several advantages including an inherently high surface area-to-volume ratio, tunable fiber diameter, high porosity, and ECM-like structure. In addition to these factors, their cost-effective production renders these scaffolds highly applicable to a multitude of disease states. A rich variety of materials, including natural, synthetic, and their composite polymers have been successfully electrospun into micro/nanofibers with different properties to deliver an array of hydrophilic and hydrophobic drugs as well as biomacromolecules like GFs and genes. Different loading techniques such as surface modification, blending, coaxial and emulsion electrospinning, and encapsulation of drug-loaded NPs into micro/nanofibers have been shown to greatly influence the drug release profiles, rendering such systems very controllable and attenuating common issues such as an

initial burst release of drugs. Thus far, these electrospun scaffolds have proven to be a promising long-term drug delivery platform for the support of bone, skin and nerve regeneration as well as for cancer and adhesion treatment. Despite significant progress in the field of electrospun scaffolds, four important issues remain to be solved for clinical translatability: (1) polymers require further optimization for better controllable degradation rates, (2) new electrospinning strategies will have to be developed to improve loading and extend release periods of hydrophilic drugs, (3) core-shell structured scaffolds need to be further evaluated in the context of multi-drug delivery and preservation of bioactivities of unstable drugs, and (4) scaffolds require further investigation in *in vivo* and then clinical settings to confirm their applicability. In conclusion, disease treatment and tissue regeneration are complex processes, which in most cases require the accurate orchestration of various drugs and GFs at various concentrations for different periods of time. By selecting the appropriate polymer type and designing effective drug loading strategies and release routes, so-called “smart” devices may be developed for successful clinical applications.

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Figures

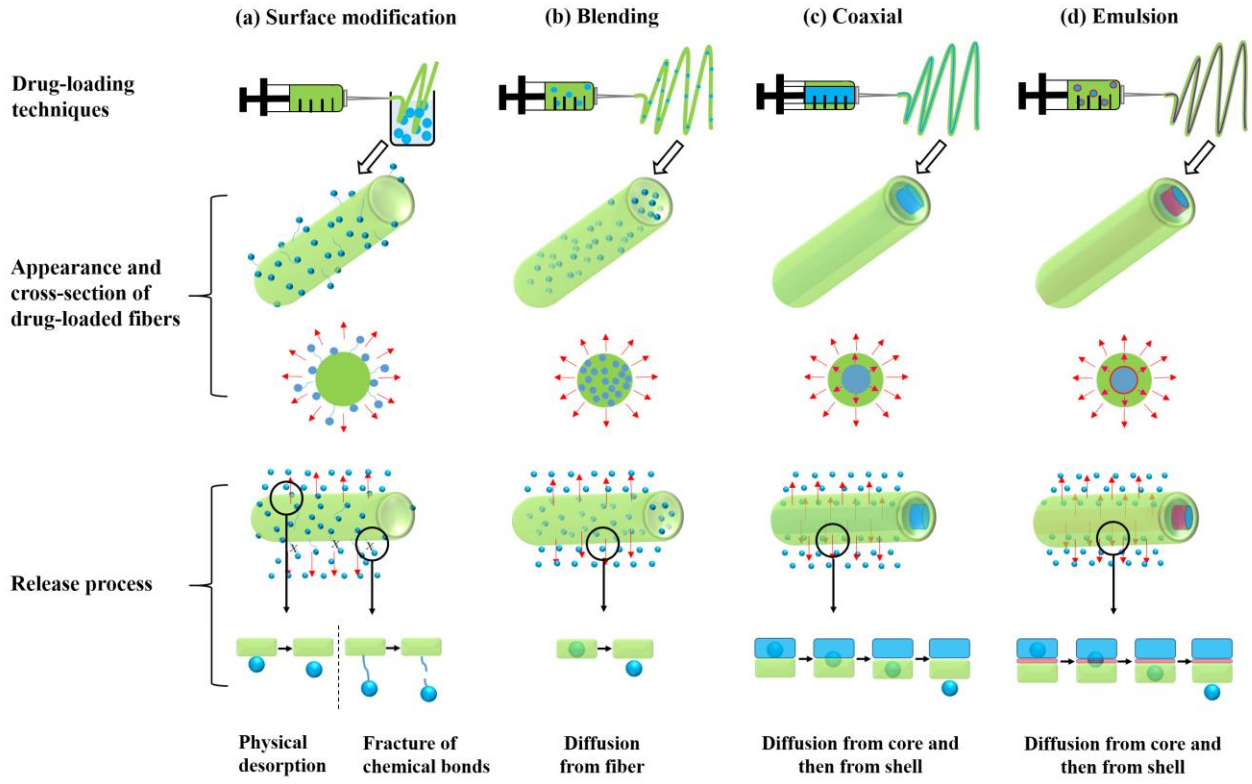

FIGURE 1

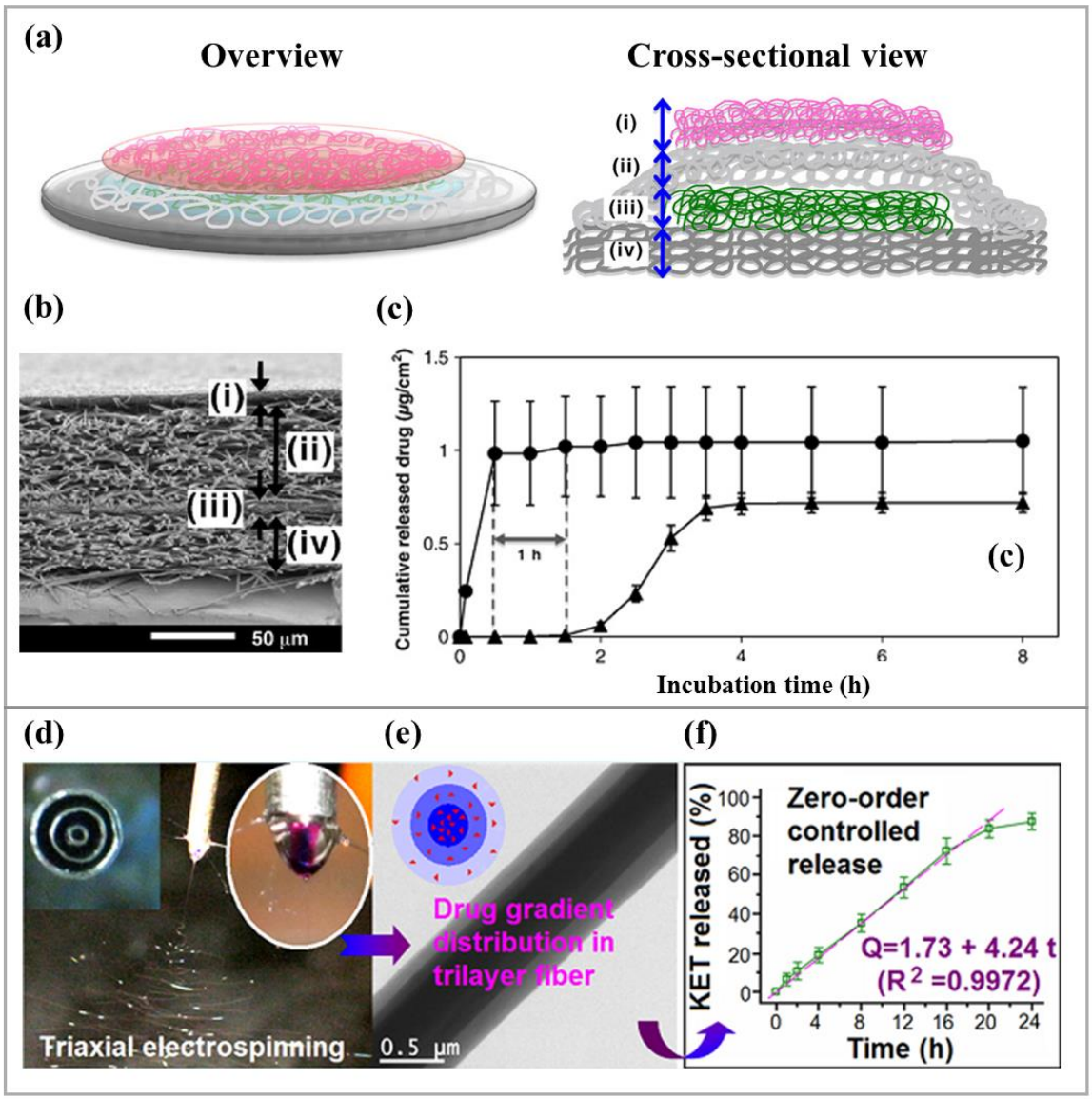
(a)
Overview
Cross-sectional view
(i)
(ii)
(iii)
(iv)
(b)
(c)
50 μm
Cumulative released drug (μg/cm²)
1 h
Incubation time (h)
(d)
(e)
(f)
Triaxial electrospinning
0.5 μm
Drug gradient distribution in trilayer fiber
KET released (%)
Zero-order controlled release
Q=1.73 + 4.24 t
(R² =0.9972)
Time (h)

FIGURE 2

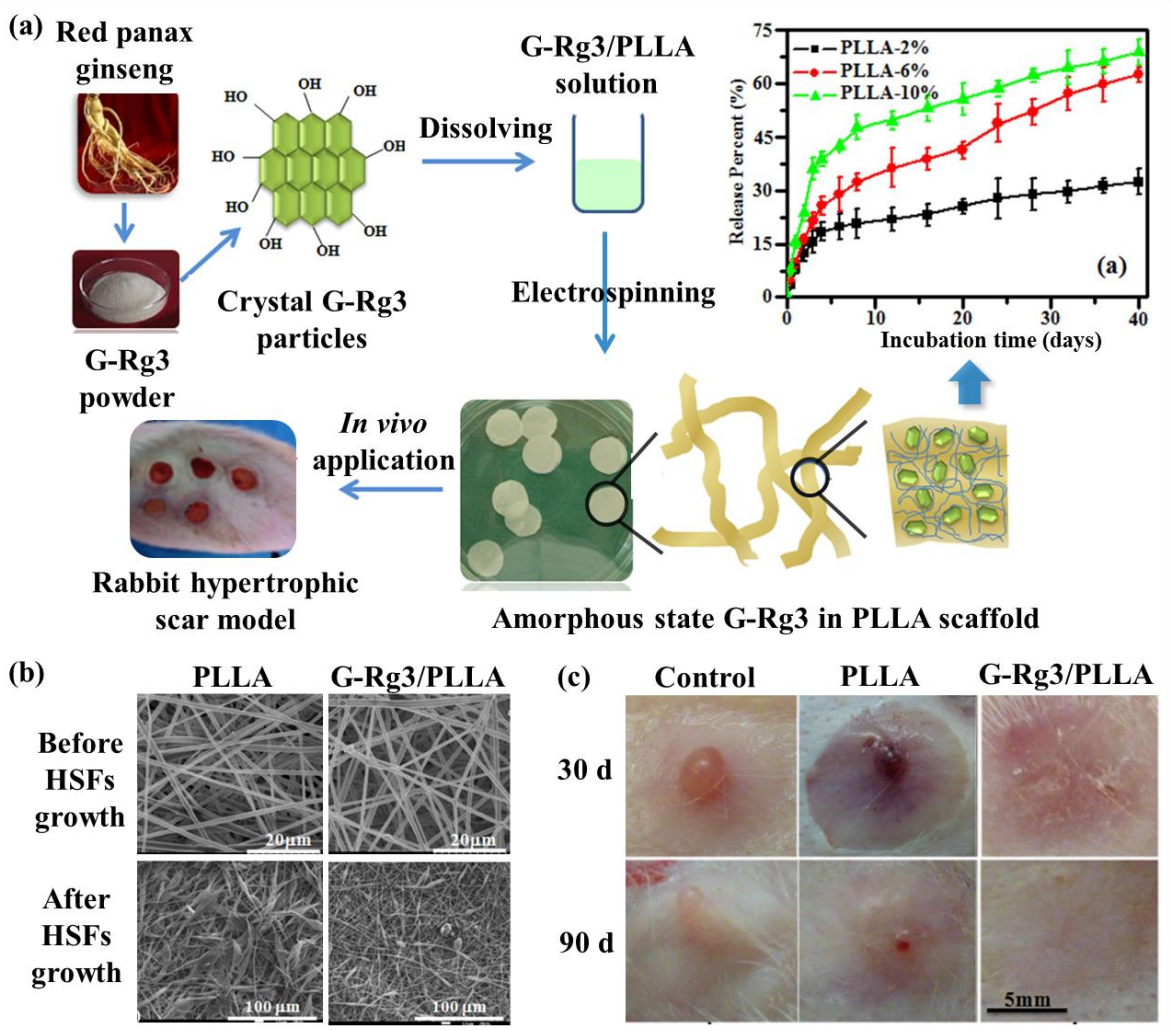
(a)
Red panax ginseng
G-Rg3 powder
Crystal G-Rg3 particles
Dissolving
G-Rg3/PLLA solution
Electrospinning
PLLA-2%
PLLA-6%
PLLA-10%
Release Percent (%)
Incubation time (days)
(a)
In vivo application
Rabbit hypertrophic scar model
Amorphous state G-Rg3 in PLLA scaffold
(b)
PLLA
G-Rg3/PLLA
Before HSFs growth
After HSFs growth
20μm
100 μm
(c)
Control
PLLA
G-Rg3/PLLA
30 d
90 d
5mm

FIGURE 3

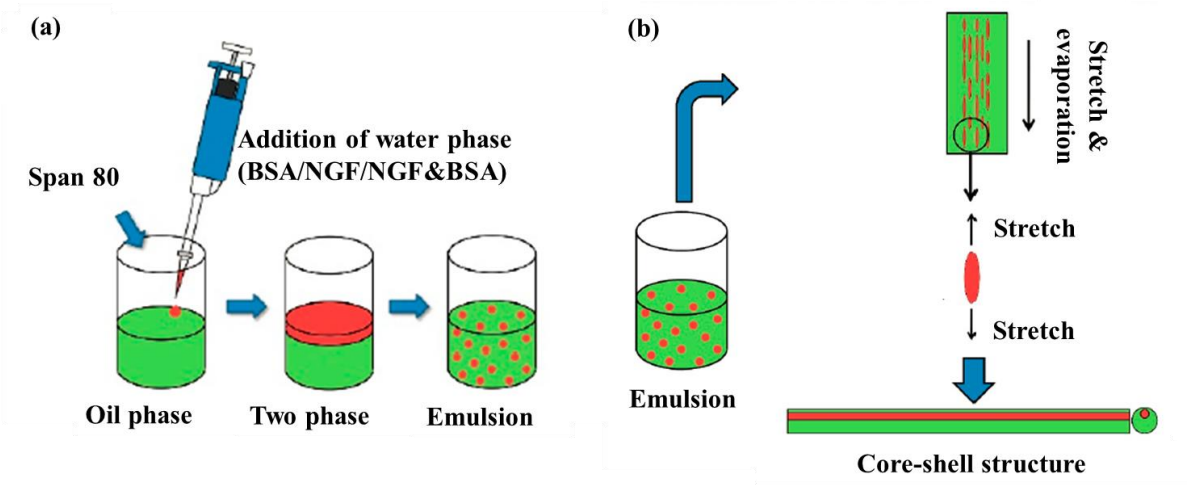
(a)
Span 80
Addition of water phase
(BSA/NGF/NGF&BSA)
Oil phase
Two phase
Emulsion
(b)
Emulsion
Stretch &
evaporation
Stretch
Stretch
Core-shell structure

FIGURE 4

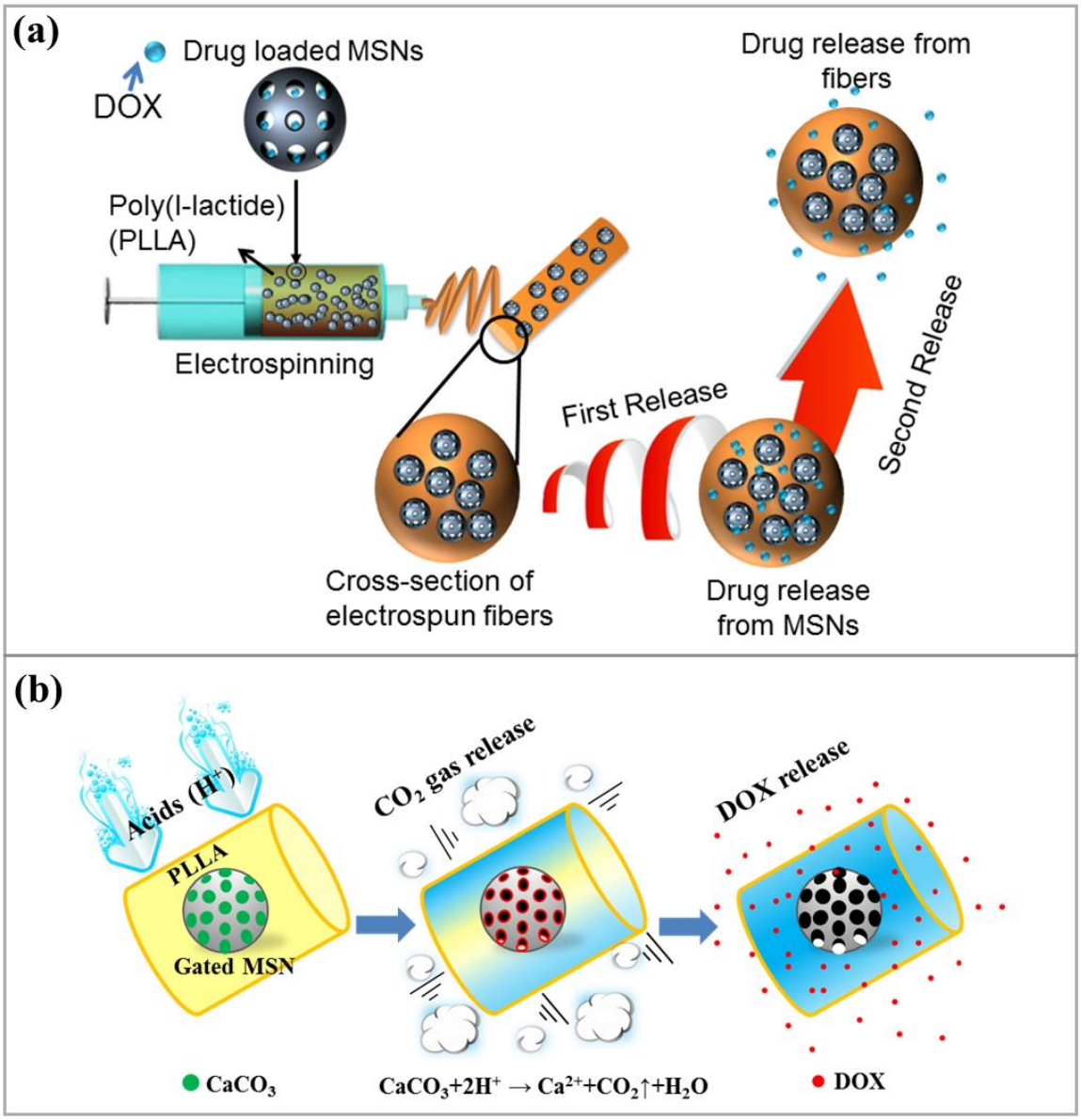
(a)
Drug loaded MSNs
DOX
Poly(l-lactide)
(PLLA)
Electrospinning
Drug release from
fibers
First Release
Second Release
Cross-section of
electrospun fibers
Drug release
from MSNs
(b)
Acids (H+)
PLLA
Gated MSN
CO2 gas release
DOX release
CaCO3
CaCO3+2H+ → Ca2++CO2↑+H2O
DOX

FIGURE 5

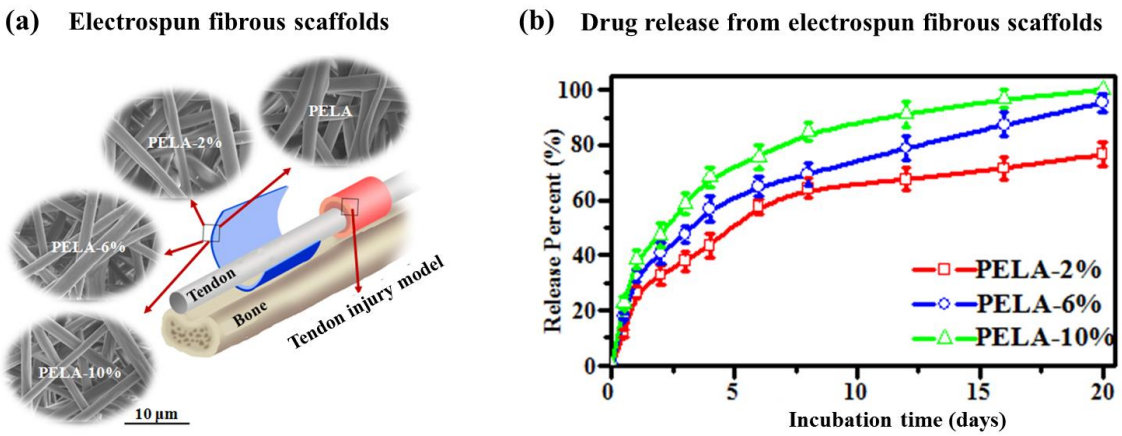
(a) Electrospun fibrous scaffolds
PELA
PELA-2%
PELA-6%
PELA-10%
Tendon
Bone
Tendon injury model
10 μm
(b) Drug release from electrospun fibrous scaffolds
Release Percent (%)
Incubation time (days)
PELA-2%
PELA-6%
PELA-10%
0
20
40
60
80
100
0
5
10
15
20

FIGURE 6

Figure Captions

FIGURE 1. Drug loading and release from polymeric micro/nanofibers fabricated by (a) surface modification, (b) blending, (c) coaxial and (d) emulsion electrospinning. The green color stands for polymer, blue for drugs and maroon for surfactant. The red arrows represent the direction of the drug release.

FIGURE 2. Multilayered drug-loading techniques. (a) Graphical demonstration of overview and cross-sectional view of tetra-layered nanofiber meshes. (b) Scanning electron microscopy (SEM) images of cross-sections of tetra-layered nanofiber meshes. Layers are (i) chromazurol B (ChroB) mesh, (ii) barrier mesh, (iii) 5,10,15,20 - tetraphenyl - 21H, 23H - porphinetetrasulfonic acid disulfuric acid (TPPS) mesh, and (iv) basement mesh. (c) Release profile of drug-loaded meshes of the tetra-layered nanofiber meshes. Closed circles and triangles represent release profiles of TPPS and ChroB, respectively. (d) Digital photographs showing the triaxial electrospinning process. The upper left and right insets show the structure of spinneret and a typical compound Taylor cone, respectively. (e) TEM image of a trilayer nanofiber. The upper-left insets show drug gradient distribution in trilayer fiber. (f) *In vitro* dissolution test results for the trilayer nanofibers. Images (a-c) were taken from [67] with permission whereas images (d-f) were taken from [68] with permission.

FIGURE 3. G-Rg3 coated electrospun PLLA fibrous scaffolds for inhibition of hypertrophic scar formation. (a) Schematics showing fabrication and application of G-Rg3 coated electrospun PLLA fibrous scaffolds for inhibition of hypertrophic scar formation. The inset shows *in vitro* cumulative percentage release of G-Rg3 (2%, 6% and 10%) from electrospun fibers after immersion in PBS. (b) SEM images showing the adhesion of human hypertrophic scar fibroblasts (HSFs) on the naked PLLA and G-Rg3 coated PLLA scaffolds. (c) Therapeutic efficacy of G-Rg3 coated electrospun PLLA fibrous scaffolds for inhibition of hypertrophic scar formation using a rabbit ear model. Images were modified from [90] with permission.

FIGURE 4. Schematic illustration of emulsion electrospinning of NGF loaded electrospun PCL fibrous scaffolds. (a) The process of emulsion preparation. (b) The formation of core-shell fibers using emulsion electrospinning. Red color represents water phase containing

water soluble drugs and green color indicates PCL phase. Images were modified from [102] with permission.

FIGURE 5. Electrospun polymeric fibers containing MSNs for extended drug delivery. (a) Schematic illustration of a composite drug release system for extended drug release. The chemotherapeutic agent DOX was loaded onto MSNs, which were dispersed within PLLA solution and then electrospun to obtain PLLA fibers. DOX was released first from MSN core to the PLLA shell and from the PLLA shell into the surrounding medium. By extending the drug diffusion route, the drug release was prolonged. (b) Schematic illustration of a tumor-triggered controlled drug release system. Infiltration of protons (H^+) into the electrospun PLLA fibers results in the unplugging of the $CaCO_3$ cap to unveil the DOX molecules trapped inside the MSN pores. Water penetration into the PLLA fibers facilitates the DOX release. Image was taken from [11] with permission.

FIGURE 6. Electrospun PELA nanofibers for prevention of tendon adhesion. (a) Schematic illustration of celecoxib-loaded PELA fibrous membrane and SEM images showing the morphology of drug-loaded PELA fibers. (b) Cumulative celecoxib release from electrospun PELA fibers after incubation in PBS at 37 °C. Image was taken from [114] with permission.

Table

TABLE 1

Polymer[a]	Integrin binding sites	Physicochemical properties		Mechanical properties		Biodegradation	
		Hydrophilic	Hydrophobic	Strong	Weak	Hydrolytic	Enzymatic
NATURAL							
Collagen	√	√			√		√
Gelatin	√	√			√		√
Silk fibroin	×	√		√			√
Chitosan	×	√			√		√
HA	×	√			√		√
SYNTHETIC							
PVA	×	√		√			√
PLA	×		√	√		√	
PGA	×		√	√		√	
PLGA	×		√	√		√	
PCL	×		√	√		√	

[a]: all listed polymers possess favorable biocompatibility.

HA = hyaluronic acid; PVA = polyvinyl alcohol; PLA = polylactic acid; PGA = polyglycolic acid; PLGA = polylactic-co-glycolic acid; PCL = poly-ε-caprolactone.

Table Captions

TABLE 1. Most commonly used natural and synthetic polymers for the development of electrospun polymeric micro/nanofibers for drug delivery.