

ELECTROSPUN BIOMATERIAL FOR BIOMEDICAL APPLICATION

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SUMMARY

Nanostructured fibrous materials have been made more readily available in large part owing to recent advances in electrospinning and related technologies. Development of nanofibers by using the technique of electrospinning is having a new momentum. The nonwoven structure has unique features, including interconnected pores and a very large surface-to-volume ratio, which enable such nanofibrous scaffolds to have many biomedical and industrial applications, such as tissue engineering, wound dressing, enzyme immobilization and drug delivery. The chemical composition of electrospun membranes can be adjusted through the use of different polymers, In this paper, nanoscaffolds developed by using electrospinning and its applications in tissue engineering, drug delivery and wound healing are reviewed.

KEY WORDS: Electrospinning; Nanofibers; Scaffolds

1.INTRODUCTION

During the past two decades significant advances have been made in the development of biodegradable polymeric biomaterials for biomedical applications¹⁻³. There are several reasons for the favorable consideration of biodegradable over biostable materials for biomedical applications. A biomaterial can be defined as a material intended to interface with biological systems to evaluate, treat, augment or replace any tissue, organ or function of the body⁴. Both synthetic polymers and biologically derived (or natural) polymers have been extensively investigated as biodegradable polymeric biomaterials. Biodegradation of polymeric biomaterials involves cleavage of hydrolytically or enzymatically sensitive bonds in the polymer leading to polymer

erosion⁵. The essential prerequisite to qualify a material as a biomaterial is biocompatibility, which is the ability of a material to perform with an appropriate host response in a specific application.

The usage of electrospun nanofibrous scaffolds for biomedical applications has attracted a great deal of attention in the past several years. For examples, nanofibrous scaffolds have been demonstrated as suitable substrates for tissue engineering⁶⁻⁹, immobilized enzymes and catalyst¹⁰⁻¹³, wound dressing¹⁴⁻¹⁵ and artificial blood vessels¹⁶⁻¹⁷. They have also been used as barriers for the prevention of post-operative induced adhesion¹⁸⁻¹⁹ and vehicles for controlled drug (gene) delivery²⁰⁻²⁴. The current paper reports on biodegradable nanomats produced by e-spinning, for

potential application in biomedical applications are reviewed.

Among various processing techniques, electrospinning is the only method capable of producing continuous polymer nanofibres²⁰. Electrospinning is a unique technology that can produce non-woven fibrous articles with fiber diameters ranging from tens of nanometers to microns, a size range that is otherwise difficult to access by conventional non-woven fiber fabrication techniques^{25,26}. The electrospinning technology is well suited to process natural biomaterials and synthetic biocompatible or bioabsorbable nanofibers for biomedical applications. The major driving force being the long-term biocompatibility issues with many of the existing permanent implants and many levels of ethical and technical issues associated with revision surgeries. Linear aliphatic polyesters such as polyglycolide, polylactide, and their random copolymer poly(glycolide- co-lactide) are often used as the base materials for implant devices, such as suture fibers and scaffolds^{27,28}. These materials meet several controlled-release criteria, i.e. they are biocompatible and biodegradable and they can provide a high efficiency of drug loading. For a successful application to a specific target, the nanofibrous scaffold must exhibit suitable physical and biological properties closely matching the desired requirements. The use of nanofibers in tissue restoration is expected to result in an efficient, compact organ and a rapid recovery process due to the large surface area offered by nanofibers Scaffold materials produced from nanofibers offer a large surface area that can support cell growth. For example, in tissue engineering, the electrospun scaffold should physically resemble the nanofibrous features of extracellular

matrix (ECM) with suitable mechanical properties. It should also be able to promote cell adhesion, spreading and proliferation. For wound dressing, the nanofibrous scaffold should not only serve as a substrate for tissue regeneration, but also may deliver suitable bioactive agents, including drugs (e.g. antibiotic agent), within a controlled manner during healing. For electrospun nanofibrous scaffolds in biomedical applications, its physical and biological properties, such as hydrophilicity, mechanical modulus and strength, biodegradability, biocompatibility, and specific cell interactions, are largely determined by the materials' chemical compositions²⁹. Based on polymer physics, copolymerization and polymer blending are two effective means to combine different polymers to yield new materials properties. Thus, by selecting a combination of proper components and by adjusting the component ratio, properties of electrospun scaffolds can be tailored with desired new functions. For example, many kinds of copolymers and polymer mixtures, such as poly(lactide-co glycolide)¹⁸, poly(ethylene- co-vinyl alcohol)³⁰, mixtures of collagen with elastin³¹, and mixtures of chitosan with poly(ethylene oxide) (PEO or PEG when the molecular weight is small, say less than 5000 Da)³², have been electrospun to fabricate nanofibrous scaffolds for biomedical applications, but with varying degrees of success.

2. Electrospinning

Electrospinning, a spinning technique, is a unique approach using electrostatic forces to produce fine fibers of thinner diameter (from nanometer to micrometer). Electrospun fibers have small pore size and high surface area than those obtained

from conventional spinning processes. Interest in the electrospinning process has increased in recent years^{26, 33}, and this technology has been exploited for a wide range of applications. Various techniques such as electrostatic precipitators and pesticide sprayers work similarly to the electrospinning process and this process, mainly based on the principle that strong mutual electrical repulsive forces overcome weaker forces of surface tension in the charged polymer liquid³⁴. The emphasis of current research is focus on determining appropriate conditions for electrospinning various polymers and biopolymers for eventual applications. Soluble drugs or bacterial agents can be added and electrospun into non-woven mats³⁵. There is also evidence of sizable static charges in electrospun fibers that could be effectively handled to produce three dimensional structures. Processing parameters of nanofibers have been considered to applied voltage, the solution flow rate, polymer concentration, molecular weight, and distance between the syringe needle tip to ground collection plate³⁶. Solution viscosity has been found to influence fibre diameter, initiating droplet shape, and the jet trajectory. Increasing solution viscosity has been associated with the production of larger diameter fibres³⁷. Most of the literature on electrospinning has explored the types of polymer solvent systems from which fibers can be produced.

2.1 Electrospinning Set-up

The advantages of the electrospinning process are its technical simplicity and its easy adaptability. The apparatus used for electrospinning is simple in construction. Basically an electrospinning system consists of three major components which are (i) a high voltage power supply with

positive or negative polarity, (ii) a syringe pump with capillaries or tubes to carry the solution from the syringe or pipette to the spinnerets, and (iii) a grounded collecting plate (usually a metal screen, plate, or rotating mandrel). The collector can be made of any shape according to the requirements, like a flat plate, rotating drum, etc. Currently, there are two standard electrospinning setups, vertical and horizontal. With the expansion of this technology, several research groups have developed more sophisticated systems that can fabricate more complex nanofibrous structures in a more controlled and efficient manner³⁸⁻⁴¹. A schematic of the electrospinning process is shown in Figure 1.

2.2 Process of Electrospinning

The solution or the melt that has to be spun is forced through a syringe pump. At the end of the capillary, the polymer solution held by its surface tension which is subjected to an electric field and an electric charge is induced on the liquid surface due to this electric field. The pendant hemispherical polymer drop takes a cone like projection in the presence of an electric field at the end. When the applied potential reaches a critical value, the repulsive electrical forces overcome the surface tension forces. Eventually, a charged jet of the solution is ejected from the tip of the Taylor cone and an unstable and a rapid whipping of the jet occurs in the space between the capillary tip and collector which leads to evaporation of the solvent, leaving a polymer behind⁴²⁻⁴⁴. For instance, the polymer solution must have a concentration high enough to cause polymer entanglements yet not so high that the viscosity prevents polymer motion induced by the electric field. The solution must also have a surface tension

low enough, a charge density high enough, and a viscosity high enough to prevent the jet from collapsing into droplets before the solvent has evaporated. Morphological changes can occur upon decreasing the distance between the syringe needle and the substrate. Increasing the distance or decreasing the electrical field decreases the bead density, regardless of the concentration of the polymer in the solution³⁷⁻⁴⁵.

3. Application

3.1 Scaffolds for Tissue Engineering

The biomedical role of nanofibers of biomaterials both natural and synthetic has extended into various specific applications with tissue engineering being the most widely studied. Nanofibers with high surface area and porosity have enormous scope for applications in engineering mechanically stable and biologically functional tissue scaffolds. The utilization of electrospun scaffolds as cell delivery vehicles has been substantially increased in recent years owing, in part, to the physical similarities between the nanofibrous scaffolds and the extracellular matrix (ECM) found in native tissues⁴⁶. Scaffolds and synthetic matrices mimic the structure and biological functions of the natural extracellular matrix (ECM). The tissue scaffolding material must be selected carefully to ensure its biocompatibility with the body cells. The biocompatibility depends on the surface chemistry of the scaffolds, which is influenced by the material properties. Nanoscale fibrous scaffolds provide an optimal template for cells to seed, migrate and grow⁴⁷. The inherent architecture of electrospun scaffolds provides a favorable substrate to more accurately assess cellular behavior

in vitro. Electrospun biocompatible polymer nanofibers can also be deposited as thin porous mats onto a hard tissue prosthetic device designed to be implanted into the human body. Scaffold structure and morphology can also be altered postproduction to closely match those of native tissues, mimicking the native physiological environment, for example an injury site. Thus, the scaffold would be constructed with the predominant protein(s) that are present in the ECM. For example, poly(amino acid)s [e.g., poly(aspartic acid)] have been investigated as to serving as a bioactive moiety in polymeric scaffolds⁴⁸. For these scaffolds, the presence of poly(aspartic acid) was beneficial for osteoblast adhesion, proliferation, and differentiation after seven days. New type of guided bone regeneration membranes were synthesized by electrospinning polycaprolactone (PCL) and PCL/CaCO₃ composite nanofibers⁴⁹. The authors concluded that membranes rich in PCL had better cell attachment and proliferation than those of CaCO₃ rich membranes. Tissue engineering was advanced when synthetic polymer/DNA composite scaffolds for therapeutic application in gene delivery were electrospun composed of poly(lactide-co-glycolide) (PLGA) PEG²⁴. Variations in the PLGA to PLA-PEG ratio were observed to vastly affect the overall structural morphology, rate and efficiency of DNA release from 68 to 80% of the initially load. The synthetic tensile moduli and strain resemble those of skin and cartilage. Another example is collagen nanofibers; type I and type III collagen are the predominant structural elements of the ECM in many tissues. The electrospun fibers closely resemble the natural dimensions and architecture of collagen fibrils making up the ECM and support cell growth and penetration within the scaffold⁵⁰. Indeed, researchers

investigating scaffolds that incorporate both synthetic and natural polymers have reported a combinatory effect of enhancing cell adhesion by modifying poly(lactic acid) (PLA) or poly(glycolic acid) (PGA) derivatives with collagen^{51,52}. Another group has electrospun a mixture of aqueous regenerated silkworm solution with polyethylene oxide (PEO)⁵³. The silk fibroin-based fibers with an average diameter of 700 nm were tested for supported human bone marrow stromal cell attachment and proliferation over 14 days. Further studies examining the precise polymeric interactions within electrospun nanofibers and their subsequent effects on cellular behavior are warranted. Poly (D, L-lactide-*co*-glycolide) (PLGA), the commonly used biodegradable polymer in tissue engineering while electrospinning, produced highly suitable tissue scaffolds that have high porosity, pore diameter, and pore volume⁵⁴.

3.2 Drug Delivery

Drug delivery and pharmaceutical composition Delivery of drug/ pharmaceuticals to patients in the most physiologically acceptable manner has always been an important concern in medicine. In general, the smaller the dimensions of the drug and the coating material required to encapsulate the drug, the better the drug to be absorbed by human being. Drug delivery with polymer nanofibers is based on the principle that dissolution rate of a particulate drug increases with increasing surface area of both the drug and the corresponding carrier if needed. With the massive proliferation in the primary literature on electrospinning, a relatively small amount of these reported data deals specifically with the use of the technology in the

delivery of drugs. Nanofiber mats due to their high functional characteristics find application as drug carriers for the drug delivery system. Researchers in this nascent field have started to demonstrate rapid progress and understanding of the factors involved in the formulation, incorporation, and controlled, sustained release of a repertoire of molecules with vastly different characteristics. Controlled delivery of drugs at a defined rate over a definite period of treatment is possible with biocompatible delivery matrices of either biodegradable or non biodegradable polymers. Undoubtedly, more data and reports further demonstrating the efficacy of using electrospinning in the generation and production of biodegradable scaffolds capable of delivering bioactive molecules. Kenawy *et al.* investigated the drug delivery potential of electrospun polymers by spinning poly (ethylene-*co*-vinyl acetate) (PEVA) and poly lactic acid with ethanol and tetracycline hydrochloride as the model drug⁵⁵. The release of tetracycline from the electrospun mats was found much greater than from the cast films. They observed that the electrospun PEVA and 50/50 PLA/PEVA mats gave very smooth release of tetracycline over a period of five days. In another work by⁵⁶, bioabsorbable nanofiber membranes of poly(lactic acid) targeted for the prevention of surgery induced adhesions, were also used for loading an antibiotic drug Mefoxin. Preliminary efficiency of this nanofiber membrane compared with bulk film was demonstrated. Ignatius & Baldoni⁵⁷ described electrospun polymer nanofibers for pharmaceutical compositions, which can be designed to provide rapid, immediate, delayed, or modified dissolution, such as sustained and/or pulsatile release characteristics. Owing to the solvent requirements in the electrospinning process, whereby the

majority of polymers utilized require dissolution in organic solutions, e.g., N,N-dimethylformamide (DMF), tetrahydrofuran (THF), and hexafluoroisopropanol (HFTP), with low aqueous content, the challenges faced in the formulation and incorporation of bioactive molecules need to be addressed separately for hydrophobic, hydrophilic, and charged molecules.

3.3 Wound Dressing

Dressings for human wounds have been aimed at protection, removal of exudates, inhibition of exogenous microorganism invasion, and improved appearance. Wound areas that are kept just damp may heal faster, but accumulation of exudates under the dressing can cause infection. For wound healing, an ideal dressing should have certain characteristics such as haemostatic ability, efficiency as bacterial barrier, absorption ability of excess exudates (wound fluid/pus), appropriate water vapor transmission rate, adequate gaseous exchange ability, ability to conform to the contour of the wound area, functional adhesion, i.e., adherent to healthy tissue but non-adherent to wound tissue, painless to patient and ease of removal, and low cost⁵⁸. A wound dressing with electrospun polymeric nanofibrous membrane can meet most of the requirements outlined. With the aid of electric field, fine fibers of biodegradable polymers can be directly sprayed/spun onto the injured location of skin to form a fibrous mat dressing, which can let wounds heal by encouraging the formation of normal skin growth and eliminate the formation of scar tissue which would occur in a traditional treatment⁵⁹⁻⁶¹. Non-woven nanofibrous membrane mats for wound dressing usually have pore sizes ranging from 500 nm to 1 mm, small enough to protect the

wound from bacterial penetration via aerosol particle capturing mechanisms. High surface area of 5–100 m²/g is extremely efficient for fluid absorption and dermal delivery. Nanofibrous structures provide the nonwoven textile with desirable properties and there are also reports of cytocompatibility and cell behavior of normal human keratinocytes and fibroblasts onto electrospun silk fibroin nanofibrous membranes. Researchers have investigated the wound-healing properties of mats of electrospun type I collagen fibers on wounds in mice and they found that healing of the wounds was better with the nanofiber mats than with conventional wound care, especially in the early stages of the healing process^{21, 45, 59, 62-64}. Apart from electrospun collagen, silk, polyurethane, polycaprolactone fiber are also frequently used in wound dressing^{14, 60}. Jia et al. have prepared non-woven antibacterial poly(vinyl alcohol) (PVA) membrane by electrospinning of PVA aqueous solution with addition of Ag⁺-loaded Zirconium phosphate nanoparticles for potential use in wound healing materials and antimicrobial tests proved the efficacy of nanoparticles containing nanofibers against tested strains⁶⁵.

4. Conclusion

In nanoscience and nanotechnology, the electrospinning technique provides an inexpensive and easy way to produce nanofibers from many types of polymers. The specific advantages of electrospun scaffolds (high surface-to-volume ratio, controlled porosity, and flexibility to conform to a wide variety of sizes and shapes) make them superior to scaffolds generated by most other techniques for a wide variety of applications. In addition, electrospun scaffold composition and fabrication can be used to provide

functionality. Collectively, these advantages are reflected in the wide diversity of scaffolds generated with the intended purposes from biomedical applications. Nanofibers are used in biomedical applications including drug-delivery and wound dressing systems, and structural elements in tissue engineering. It can be clearly seen that polymeric nanofiber-based scaffolds have a potential for a wide range of applications in tissue repair and regeneration. Their place in tissue engineering is expanding rapidly and the potential of a variety of polymers as scaffold candidates in mimicking the ECM has been already demonstrated. However, employing drug and morphogen release properties will confer extra properties on multifunctional scaffolds and mimic further native ECM. Thus, the convergence of tissue engineering, nanotechnology, drug release and wound dressing technologies is expected to address more of the current challenges which relate to the success and functionality of engineered grafts for regenerative medicine. There is room for much improvement in processing technologies, regarding the formation of three-dimensional constructs and incorporation of molecules/particles for subsequent controlled release.

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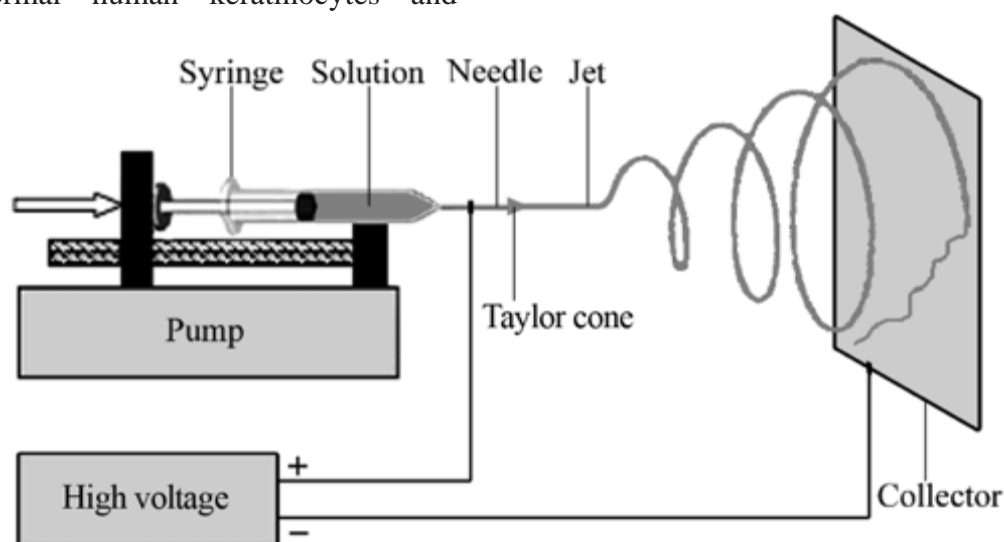


Fig. 1 Systematic set-up of electrospinning