Chapter 5

ELECTROSPUN NANOFIBERS FROM BIOPOLYMERS AND THEIR BIOMEDICAL APPLICATIONS

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5.1 Introduction

Over the past decade electrospinning has been rediscovered as a process to generate ultrafine fibers, and a massive amount of research on the process and/or the product fibers has been published [1, 2, 3]. Electrospinning was originally pioneered by Formhals who filed for a patent on this process in 1934 [4]. Recent interest has been spurred by the fact that electrospun fibers have a high surface area-to-volume ratio. With such small diameter electrospun fibers enter the realm of nanomaterials. The medical relevance of nanomaterials has recently been reviewed [5]. Electrospun fibers are more exciting than most other nanofibers because their composition is highly diverse. Until recently, nanofibers have consisted largely of carbon nanotubes and other inorganic fibers. However, electrospun fibers can be fabricated of almost limitless materials from synthetic to natural polymers. Thus, the surface chemistry can be tailored to meet a large number of applications. The focus for electrospun products has so far included nonwovens for filtration [6], membranes for aerosol purification [7], thin coatings for defense and protection [8], and structures incorporated in composites [2]. Biomedical applications include more efficient wound healing and drug delivery devices, biocompatible scaffolding for tissue regeneration, bioerodable implant structures, and others [9, 10]. The purpose of this chapter is to briefly review some of the natural and synthetic biopolymers that can be electrospun into micro- and nanofibers and to show their value for future medical applications. Due to the enormous amount of research published

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in recent years only a brief review will be presented here, with the scope of this article being to introduce the reader to this rapidly emerging field.

5.2 Principle of electrospinning

Conventional fiber formation techniques are not capable of producing fibers smaller in diameter than 2 μm. For example, a commercial polyester fiber typically has a diameter of approximately 10 μm. For most technical and textile applications larger fiber diameters in the range of 10–500 μm are sufficient and appropriate for their intended usage. However, in cases where interfacial characteristics and porosity are of decisive importance, electrospinning enables the production of fibers with diameters of less than 500 nm and thus with a high surface area-to-volume ratio. These fibers can easily be formed into nonwoven mats offering advantages over inorganic nanotubes and nanowires as well as other forms of nanostructured materials such as beads, films, or foams.

Electrospinning is similar to the electrospraying technique [6]. Basically any polymer that can be dissolved or melted at moderately high temperatures and without decomposition can be used for electrospinning. Fibers electrospun from solution are generally finer than fibers spun from melt due to the evaporation of the solvent in the former case.

The basic experimental set-up is presented in Figure 5.1. Electrospinning can be performed using either a horizontal or vertical geometry. For less viscous polymer spinning solutions the horizontal geometry is more advantageous. An

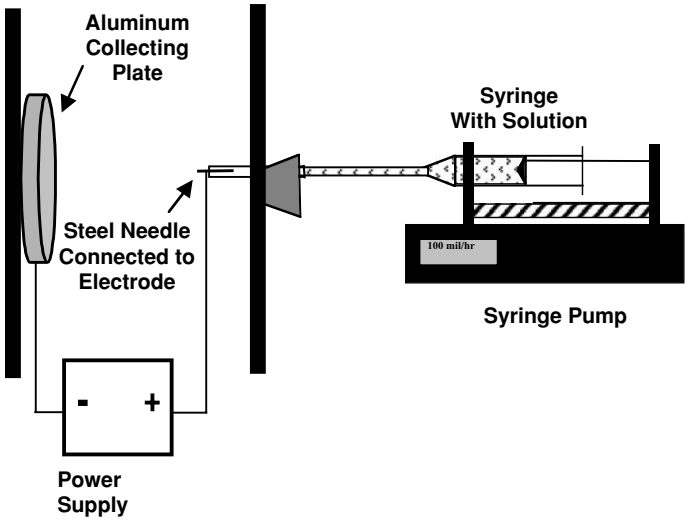


Figure 5.1. Schematic of the electrospinning apparatus

electric force, applied between the spinneret and a collector, draws the polymer jet toward the collection plate. The formation of nanoscale fibers is due to instabilities during spinning [6, 3], which cause the polymer jet to be elongated and possibly separated into smaller diameter fibers while whipping around or simply be stretched into finer fibers [3] before depositing on the target. Generally, the properties of the formed nanofiber web are determined by the polymer type and composition, the surface tension, viscosity, and conductivity of the spinning solution or melt, and the physical and geometrical parameters of the electrospinning, such as voltage and electrode distance. According to the model developed by the research group of Rutledge [11] the polymer jet reaches a terminal diameter which is determined by the characteristics of the polymer and its solvent, with the fluid's elastic properties being most vital for fiber formation.

The device used for electrospun biopolymers reported in this chapter involved a HV power supply from Gamma High Voltage Research with a range of 0–30 kV. A glass or plastic syringe with variable tip diameter was used as the spinneret. The product fibers were collected on different types of targets: scanning electron microscopic (SEM) stubs, rotating or stationary metal screens, knitted polyester tubing with a metal bar inside, paper, and glass, depending on the electrospun polymer. Details on polymer solution, specific solvent, voltage, electrode distance, etc. are given in ensuing sections.

5.3 Challenges of the process

Although conceptually a simple process, electrospinning has significant challenges. The major criticism of the electrospinning technique has been the comparatively slow, batch-wise production of the nanofibers. However, increasing commercialization of the process has led to technical advances; therefore the production rate should continually improve until an industrial scale process is more easily attained. For example, Donaldson Comp. [12] recently filed for a patent on electrospinning of nylon 6, 6,6, and 6,10 and blends for filter materials at a higher speed.

Electrospinning forms nanofibers as a product of instabilities of the polymer jet during spinning. This process causes the filament to stretch or possibly splice into even finer fibers. However, the whipping motion of the polymer jet randomizes the orientation of the nanofibers such that nonwoven mats are the simplest secondary structure to generate. Various different experimental designs have been constructed to improve the orientation and collection methods, as well as increase crystallinity and ultimately tensile strength by using a rotating drum [6, 1] or frame [2] as the collector. Charged rings have been proposed to help guide the jet stream. Electrospinning in a vacuum has also been explored [13].

Lee et al. [14] has identified numerous modifications regarding continuous as opposed to batch-wise fiber collection.

As a further challenge the web frequently contains fibers of varying diameters as well as individual fibers with varying thickness. In addition, small beads can form with the fibers. The formation of beads or fused crossover points is often due to delayed coagulation. This crisscross structure is undesired when fiber strand production is the goal of the electrospinning process. However, it can be useful as reinforcement of the nonwoven mat ensuring some stability to the fibrous web.

It is anticipated that electrospinning will continue to advance until the technical challenges will be overcome. In the meantime, it is likely that nanofibrous matted structures will be more fully explored.

5.4 Biopolymers for medical applications

For many biomedical applications, the slow production rate and web structure are not major disadvantages. This is especially true when the porosity and surface area properties are being exploited. Improvements in biomedical materials (implants, prosthetics, tissue replacement, and drug delivery devices) are continually in demand. Much of the current research is focused on natural materials for improved biocompatibility. Various physical and chemical properties define the potential biomedical use of a material. First, chemical reactions such as adsorption/recognition processes at the interface of the biomaterial influence biocompatibility. Also, physical properties, such as modulus of elasticity, need to match that of the neighboring tissue. Ideally, the device is truly integrated into the body's natural environment at a rate exactly equal to its being replaced by healthy tissue without causing an adverse reaction. In reality, distinction has to be made between those materials that are bioinert or cause no host response and no property changes over time, and those that biodegrade or bioresorb during which the implant decomposes in a natural, controlled manner with the degradation products being removed and replaced by the body in normal metabolic processes.

The physical compatibility of biomaterials includes variables such as structural integrity, strength, deformation resistance, fatigue properties, and modulus of elasticity. For prosthetic devices, carefully engineered metallic or ceramic biomaterials have adequate mechanical properties, wear, and corrosion resistance. However, metals and ceramics do not match both modulus and resiliency of living bone. Bone is continually undergoing fracture and repair processes whereas current synthetic materials do not have this property. Attempts to overcome this challenge have included making the surface or the entire material porous or biodegradable. Porous materials are used to encourage tissue growth into the prosthetic. Biodegradable materials are chosen so that the prosthetic

will gradually disappear and be replaced by living tissue. To date, neither approach has been highly successful.

Biopolymers are better suited for applications that require flexibility, elasticity, and shapeability. Examples for biopolymer stets include wound dressings, drug release devices, soft tissue replacements, cardiovascular grafts, and sutures. Research in biodegradable polymers has increased dramatically over the past decade and good reviews are available in the literature (see e.g., Refs. [15, 10]).

Materials with high surface area and extended pores have a built-in scaffold for cell adhesion and cell in-growth. Porous coatings and modifications that render the implant surface rough and irregular encourage cell adhesion and favorable interactions with biological tissue. Examples for surface modifications include plasma treatments and grafting of either charged molecules, hydrophobic side-chains, or peptides to enhance cell attachment [16]. Electrospinning offers a method to produce high surface-to-volume ratio materials with extended porous systems easily. Besides the scaffolding itself being made from electrospun fibers, an interphase in the form of electrospun coatings that could adhere to a prosthetic device could be made as a transition region to the host tissue [2]. In the following sections a few more specific examples of potential biomedical applications of the electrospinning technology will be introduced.

5.4.1 Collagen

Collagen is the most abundant protein in the body of invertebrates and forms the principal structural framework of connective tissue such as ligaments, skin, tendons, and other organs. It is composed of a triple helical arrangement of amino acids with glycine at about every third position and stabilized by hydrogen bonding [17, 16]. A total of 19 collagen types have been established which differ in the composition of their individual chains within the triple helix.

Electrospinning of collagen for scaffolding and tissue engineering has been intensively studied over the past few years. Collagen can be isolated from various sources, however reprocessing of the protein into structures mimicking natural arrangements and suitable for scaffolding has been a major challenge. The collagen source largely determines the properties of the reprocessed product fibers. Extensive work has been performed by Bowlin, Simpson, and coworkers [18] primarily on electrospinning of collagen type I from calf skin. Comparisons were drawn to electrospinning of collagen types I and III from human placenta. A patent covering the technology has been filed recently by Simpson et al. [19].

Figure 5.2 shows fibrous webs of acid-soluble collagen type III formed by electrospinning of a suspension of 0.04 g/mL collagen in 1,1,1,3,3,3

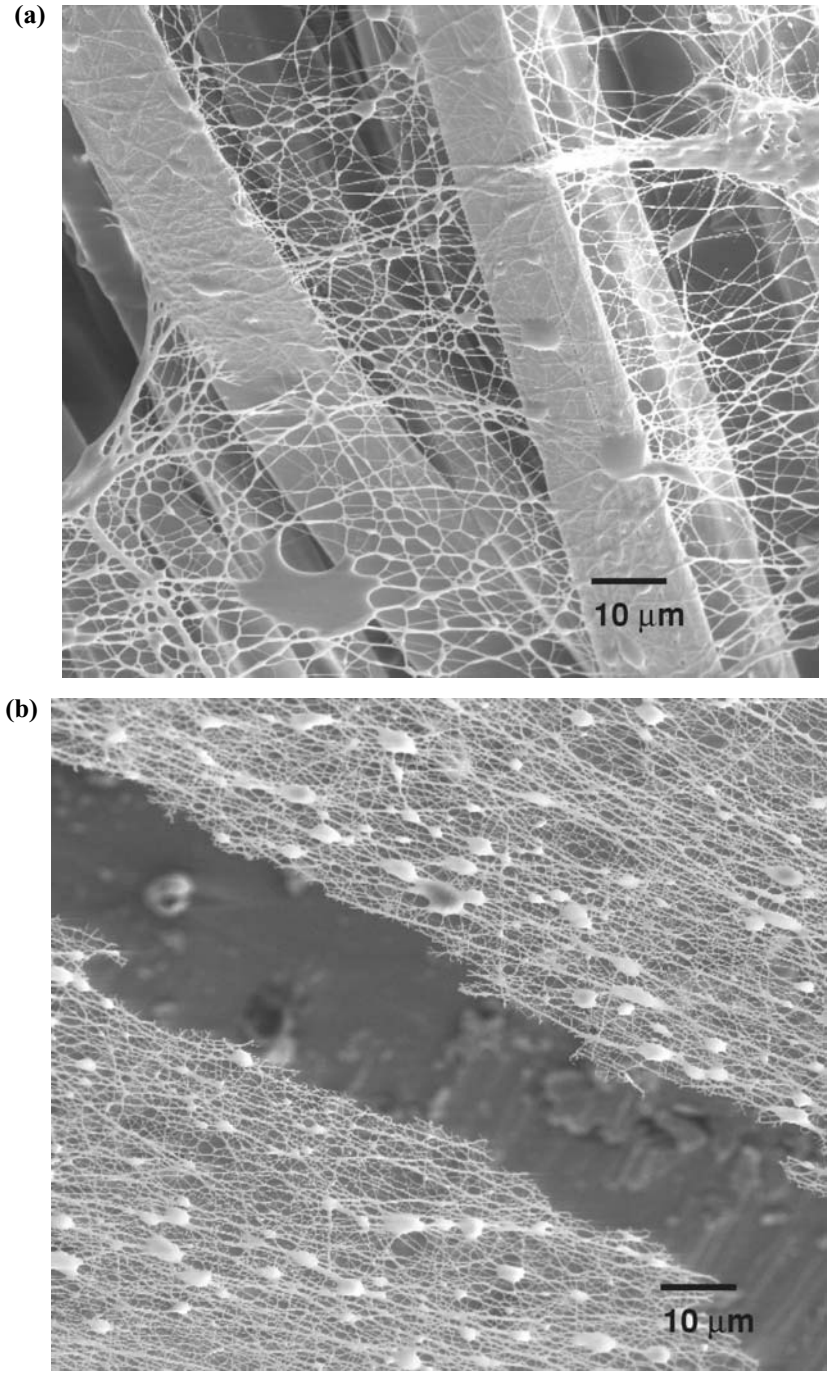
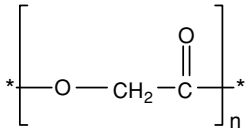


Figure 5.2. (a) Collagen spun on polyester scaffold (×500) and (b) a collagen web spun on a metal grid (×500)

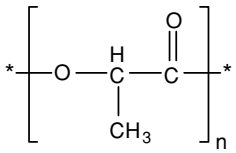
hexafluoro-2-propanol (HFP) [18] in our lab. The voltage was 25 kV and the distance between electrodes 25 cm. The collagen web was deposited on different carriers such as a knitted polyester tubing mounted on a metal or glass core [20]. Fused fibers and small droplets within the web might be able to provide some mechanical stability to the sample. Such structures are advantageous for tissue engineering but might also affect the elasticity of the nonwoven structure. Thus, we have attempted to control the coagulation behavior of the fibers and the formation of beads by adjusting the temperature in the electrospinning region during the process.

Multilayered structures of electrospun collagen type I from bovine skin, styrenated gelatin, and segmented polyurethane as well as mixed component systems electrospun from polyurethane and poly(ethylene oxide) by simultaneous electrospinning have been reported by Kidoaki et al. [21]. Morphology and tensile properties of each component were investigated and evaluated in regard to improved functionality of scaffolding materials. The function of polyurethane was to provide elastomeric characteristics, while the gelatin fibers were tested for drug releasing and collagen for cell adhesion capabilities.

5.4.2 Poly(lactic acid), poly(glycolic acid), and poly(lactide-*co*-glycolide)



Poly(glycolic acid)



Poly(lactic acid)

Biocompatible and biodegradable, poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and their copolymers are interesting materials for implants, sutures, and especially controlled drug release at high loading concentrations. The rate at which the drug is discharged into the biological system is determined by the degradation rate of the polymeric carrier. The degradation products, for instance lactic acid in the case of PLA decomposition, can easily be metabolized by the body.

Due to a fairly high melting temperature, PGA fiber formation has so far been limited to melt extrusion and drawing, producing fibers in the micrometer range. Boland et al. [22] could demonstrate that PGA can be electrospun from solution to produce nanofibers for tissue engineering.

Bognitzki et al. [23] used volatile solvents to create highly porous PLA fibers. While the fibers had a fairly large diameter in the micrometer range, regular pores developed of approximately 100 nm width and 250 nm length with

orientation along the fiber axis. The authors noticed a rapid phase separation due to the evaporation of the solvent, followed by rapid solidification. It is believed that these processes combined to produce the observed phenomenon of fibers with large pores.

Zong et al. [24] investigated the effect of ions (salts) on the morphology of electrospun amorphous poly(D,L-lactic acid) and semicrystalline poly(L-lactic acid) fibers. The salts served as mimics for ionic drugs (e.g., Mefoxin®, cefoxitin sodium) to be included at a later stage.

Copolymerized products of PLA and PGA are available at various ratios of lactide (LA) and glycolide (GA) and exhibit different levels of crystallinity and mechanical properties [15]. Commercially available copolymers from 90:10 GA:LA have been used as sutures (Vicryl®). Of course, these threads are not in the nanofiber range.

Depending on the composition of PLGA, micro- or nanofibers can be produced by electrospinning. Figure 5.3 shows a scanning electron micrograph of PLGA nanofibers electrospun from melt at 220 °C in our lab.

Electrospun PLGA fibers from melt were straight and fairly large in diameter with an overall average of more than 1.5 μm. The smallest fibers (diameter 1.28 μm (±0.4)) could be obtained at a voltage of 20 kV and an electrode distance of 12–15 cm. The advantage of melt-electrospinning in this case is the option to fairly easily co-extrude PLGA together with a second melt-spinnable polymer to form bicomponent fibers with diameters in the low micrometer range (the results of these experiments will be presented elsewhere).

Kim et al. [25] created scaffolding material from PLGA-poly(ethylene glycol) PEG-PLA diblock copolymer from *N*,*N*-dimethyl formamide solution and incorporated an antibiotic drug (cefoxitin sodium) which is intended to prevent infection after surgery. The drug has high water-solubility and low solubility in DMF. The release of the drug from the medicated electrospun web into water was monitored, and its effectiveness measured. Attempts were made to slow down the release of the antibiotic because it occurred at a rate that was higher than suitable for medical applications.

Kewany et al. [26] studied drug delivery from PLA, poly(ethylene-*co*-vinyl acetate) (PEVA), and a 1:1 blend of the two polymers electrospun from chloroform solution with tetracycline hydrochloride as the model drug. While PLA delivered the drug more or less instantaneously, the release from PEVA and from the blended nonwoven structures could more appropriately be extended over 5 days. This release rate was much closer to that desired for drug treatment.

A block copolymer of various concentrations of PGA and PEG containing additionally PLGA (75:35, LA:GA) was used as scaffolding material for release

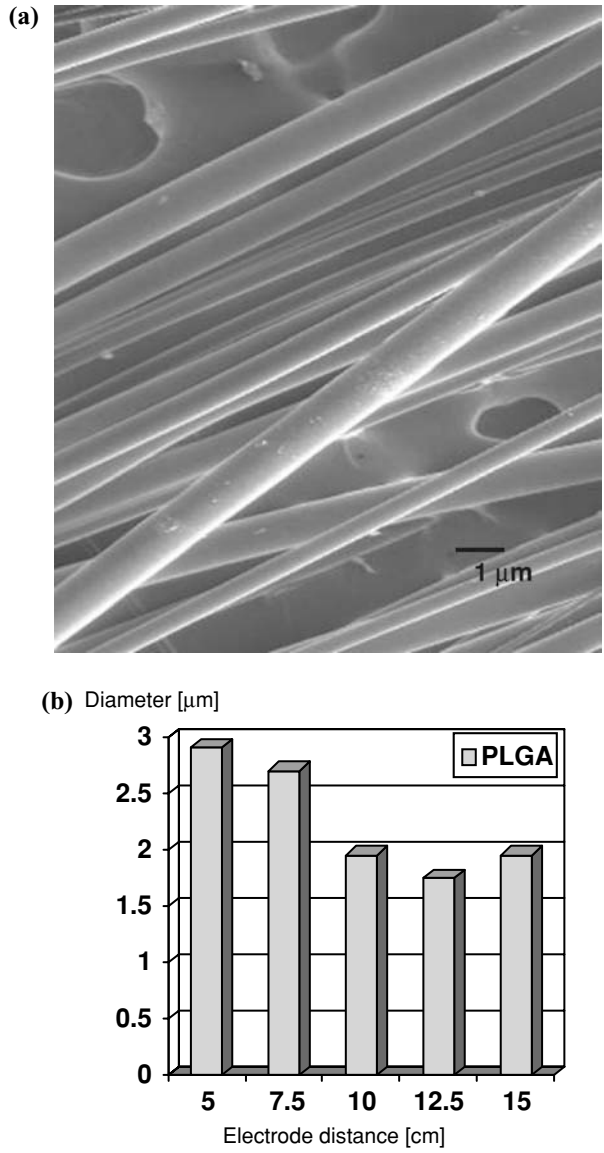
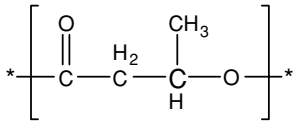


Figure 5.3. (a) Electrospun PLGA fibers from melt (15 kV, 7.5 cm electrode distance) and (b) relationship of electrode distance and diameter

of DNA [27]. The mechanical properties of the nonwoven product were tested as well as the structural integrity of the delivered plasmid DNA over 20 days. These results demonstrate that electrospun PLGA is promising as a preliminary candidate for DNA release for gene therapy.

5.4.3 Poly(3-hydroxybutyrate) and copolymers

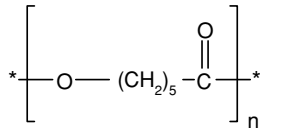


Poly(3-hydroxybutyrate)

Besides PLA, PGA and their copolymers bacterial polyesters poly(3-hydroxybutyrate) PHB and copolymers have been investigated for tissue and cartilage repair as it is compatible with various cell lines [28]. Due to the low mechanical strength of PHB, blends with other polymers have been explored.

PHB can be electrospun from 5% chloroform solution to fibers of less than 1 μm. Figure 5.4 shows fibers produced at a voltage of 10 kV and 7.5 cm electrode distance. The fibers had an average diameter of 860–720 nm (±100), depending on the specific experimental conditions, and a somewhat rough surface.

5.4.4 Poly(ε-caprolactone)



Poly(ε-caprolactone)

Poly(ε-caprolactone) (PCL) has been explored for biomedical applications as well as a potential polymer suitable for electrospinning due to its low melting point of 61 °C and its solubility in various solvents. Thus, PCL can be electrospun from solution as well as from melt. Like PLA, PCL biodegrades in a two-phase process but at a lower rate [29]. It has been recommended for use as a controlled drug delivery system.

Yoshimoto et al. [30] produced electrospun PCL fibers with an average diameter of 400 nm from a chloroform solution with the goal of creating scaffolds for bone tissue engineering. Depending on the spinning conditions the fibers were somewhat irregular in shape along the fiber axis. Their surfaces were also irregular, a characteristic which might aid cell attachment and migration within the scaffolding. Before these fibers were exposed to cell cultures, the PCL fibers were immersed in a collagen solution to encourage cell adhesion. Mineralization of the fibers was achieved within 2 weeks.

5.4.5 Nanoscale silk fibroin fibers

Electrospinning was used to produce silk fibroin fibers from *Bombyx mori* and *Samia cynthia ricini* by dissolving the fibroin in hexafluoroacetone (HFA)

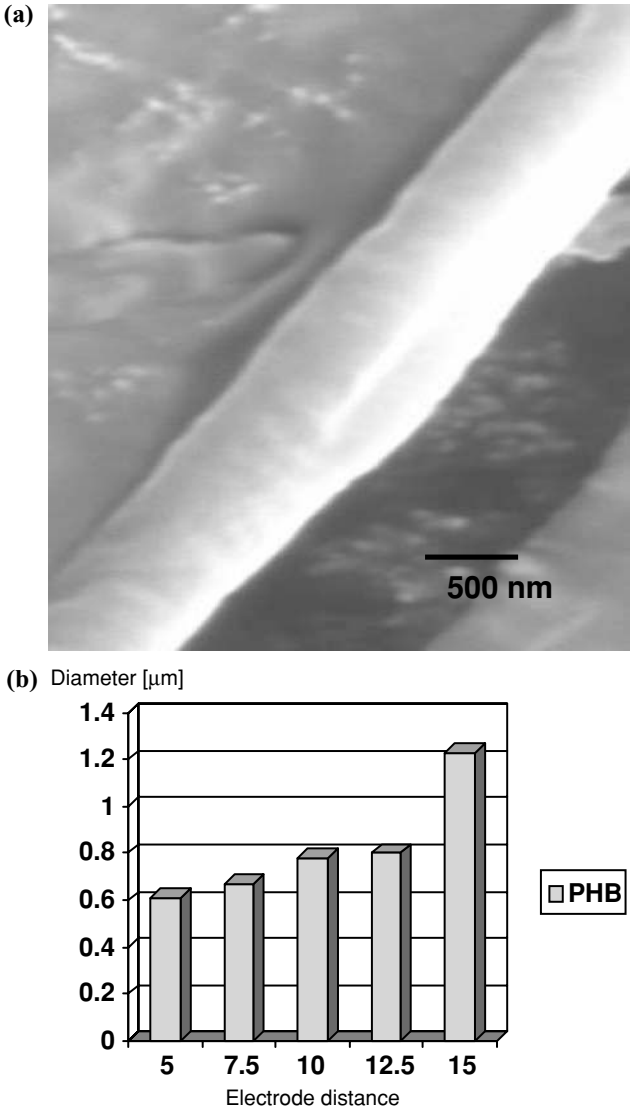


Figure 5.4. (a) PHB fibers electrospun from 5% chloroform solution and (b) the relationship of diameter and electrode distance

solution [31]. HFA was removed by exposing the electrospun fibers to methanol which served as a coagulant in the post-treatment process. Fiber diameters obtained ranged from 100 to 1000 nm. The research group also reported the production of fibers made from recombinant hybrid silk using a genetic engineering technique. Another possible option to produce nanofibers from silk fibroin by co-spinning with a polymer that electrospins easily was reported by Fridrikh [11].

5.4.6 Cellulose-based nanofibers

Cellulose-based materials are useful for wound dressings and, less importantly, for sutures and related applications. Natural cellulosic materials, such as cotton, decompose before they melt, and cannot be melt-spun. Efforts have been made to regenerate cellulose from solution so as to form nanofibers. Frey [32] successfully produced electrospun cellulose fibers from polar fluid/salt solutions. It is clear from this work that cellulose nanofibers could potentially be spun from inexpensive renewable resources or reclaimed cellulosic material.

Another experimental route to the production of nanofibers based on cellulose consists of derivatizing cellulose and subsequently removing the substituents at the cellulosic hydroxyl groups. For instance, cellulose acetate was electrospun from acetone, acetic acid, and dimethyl acetamide. These solvents and the resulting fibers were studied in connection with the type of collector used [33]. Depending on the composition of the solvent and the concentration of cellulose acetate, fibrous products or beads were obtained. Deacetylation with alcoholic sodium hydroxide solution was performed to various degrees of acetylation from 0.15 to 2.33 without major changes in surface characteristics.

Ding et al. [34] produced blended nanofibrous mats of cellulose acetate and poly(vinyl alcohol) PVA, extruded from separate syringes. Higher mechanical strength was achieved as the content of PVA was increased.

5.5 Conclusions

With the help of the electrostatic spinning technology, biopolymers can be formed into nanofibrous structures which have great potential for medical applications. Due to their small size, the electrospun fibers provide a large surface-to-volume ratio and could be used for drug delivery, scaffolds for tissue engineering, or provide support for bone repair. Due to the relative ease of the electrospinning technique a large number of different polymeric materials including natural fibers have already been explored or will be in the near future. Carefully tailored surface chemistries of these micro- and nanofibers will continue to expand their applications in the medical field.

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