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Polymer Nanofibers for Biomedical Engineering

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Abstract

Recent advancements in the electrospinning method enable the production of ultrafine solid and continuous fibers with diameters ranging from a few nanometers to a few hundred nanometers with controlled surface and morphological features. A wide range of biopolymers can be electrospun into mats with a specific fiber arrangement and structural integrity. These features of nanofiber mats are morphologically similar to the extracellular matrix of natural tissues, which are characterized by a wide pore diameter distribution, a high porosity, effective mechanical properties, and specific biochemical properties. This has resulted in various kinds of applications for polymer nanofibers in the field of biomedicine and biotechnology. The current emphasis of research is on exploiting these properties and focusing on determining the appropriate conditions for electrospinning various biopolymers for biomedical applications, including scaffolds used in tissue engineering, wound dressing, drug delivery, artificial organs, and vascular grafts, and for protective shields in specialty fabrics. This paper reviews the research on biomedical applications of electrospun nanofibers.

Key words : Polymer nanofibers, Electrospinning, Biomedical engineering

Ⅰ. INTRODUCTION

Nanofibers provide a connection between the nanoscale world and the macroscale world, as they have diameters in the nanometer range and they have a length of several meters. Polymer nanofibers are fibers with a diameter that is one or two orders of magnitude smaller than that of a conventional fiber[1]. These fibers have a very high surface area-to-mass ratio, in the range of 10 to 1000 m^2/g (when the diameter is around 500 nm)[2]. This makes them suitable for a broad range of applications. Scientists and engineers have produced polymer nanofibers for applications in the fields such as filtration, biomaterials, biomedical devices, chemical analysis, catalysis, aerospace, fiber reinforced composites, energy conversion, protective clothing, and agriculture. The creation of materials and devices on the nanometer scale offers unique benefits[3-8]:

(a) enhanced catalytic efficiency as a result of the high surface-to-volume ratios;
(b) increased material strength and hardness, because of fewer physical defects, a corollary effect of the ability to assemble nanoscale structures;
(c) multiple benefits related to the small physical dimensions;
(d) faster response and improved energy efficiency because of higher packing densities;
(e) possible miniaturization in devices, including biological structures, such as cells; and
(f) novel physical, electrical, chemical, optical, and magnetic properties that are ideal for specific applications.

Therefore, polymer nanofibers are regarded as a better candidate than bulk polymers for biomedical structural elements including: scaffolds used in tissue engineering, wound dressing, drug delivery, artificial organs, and vascular grafts. The major objectives of this article are: (a) to discuss briefly the mechanism and devices of electrospinning to fabricate nanofibers, and (b) to introduce applications of nanofibers in biomedical engineering.

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Ⅱ. ELECTROSPINNING

Among various processing techniques that can be used to manufacture nanoscale fibers, electrospinning is the only method capable of producing continuous polymer nanofibers [9]. Electrospinning technology is well suited to process natural biomaterials and synthetic biocompatible or bioabsorbable nanofibers for biomedical applications. This technique

may be considered as a variant of the electrostatic spraying (or electrospray) process[10]. Both these techniques involve the use of a high voltage to induce the formation of a liquid jet. In electrospraying, small droplets or particles are formed as a result of the varicose break up of an electrified jet that often forms from a solution with alow viscosity. In electrospinning, a solid fiber is generated as the electrified jet (composed of a highly viscous polymer solution) is continuously stretched because of the electrostatic repulsion between the surface charges and the evaporation of the solvent. Figures 1(a) and 1(b) show a schematic illustration of the basic setup for electrospinning and a typical morphology of randomly oriented electrospun nanofibers, respectively. The setup consists of three major components: a high voltage power supply, a spinneret (a metallic needle), and a collector (a grounded conductor).

The following parameters and processing variables influence the electrospinning process: (a) the system parameters, such as the solution properties (viscosity, conductivity, and surface tension), the molecular weight, the molecular weight distribution, and the architecture (e.g., branched or linear) of the polymer; and (b) the process parameters, such as the electric potential, distance between the spinneret needle tip and the collector, flow rate, the ambient parameters (temperature, humidity, and air velocity in the chamber), and finally, the motion of the collector[12,13]. For example, the polymer solution must have a concentration high enough to cause polymer entanglement, but not so high that the viscosity prevents polymer motion induced by the electric field. The solution must have a low enough surface tension, a high enough charge density, and a high enough viscosity to prevent the jet from collapsing into droplets before the solvent has evaporation. In particular, it is possible to control the shapes of nanofibers by changing the process parameters related to the electric field during electrospinning. Recently, Kim's group has developed the twisted nanofibers and aligned nanofibers using a modified electric field from an auxiliary electrode [14,15]. Figures 2(a) and 2(b) show a twisted nanofiber produced using an auxiliary electrode connected to a relay and aligned nanofibers fabricated using an assistant electrode that induces splitting electric fields, respectively.

Ⅲ. NANOFIBERS FOR TISSUE ENGINEERING

Electrospun nanofibrous structures meet the essential design criteria of an ideal tissue engineering scaffold on the basis of their ability to support and guide cell growth. Bowlin and his coworkers reported studies on the preparation of a scaffold by electrospinning biomaterials such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(ethylene-co-vinyl acetate) (PEVA), and type-I collagen[16]. Fang and his coworkers discussed electrospun poly(lactide-co-glycolide) (PLGA) nanofiber membranes for anti-adhesion applications[17]. Most publications have reported that electrospun nanofibrous structures are capable of supporting cell attachment and proliferation. An electrospun fibrous structure was developed for tissue engineering applications, composed of PLGA fibers ranging from 500 to 800 nm in diameter. The structural features were similar to the extracellular matrix of natural tissue, and were characterized in having a wide pore diameter distribution, a high porosity, and they have effective mechanical properties[18]. Matthews and his coworkers concluded that electrospinning can be adapted to produce tissue engineering scaffolds composed of collagen nanofibers (which had a

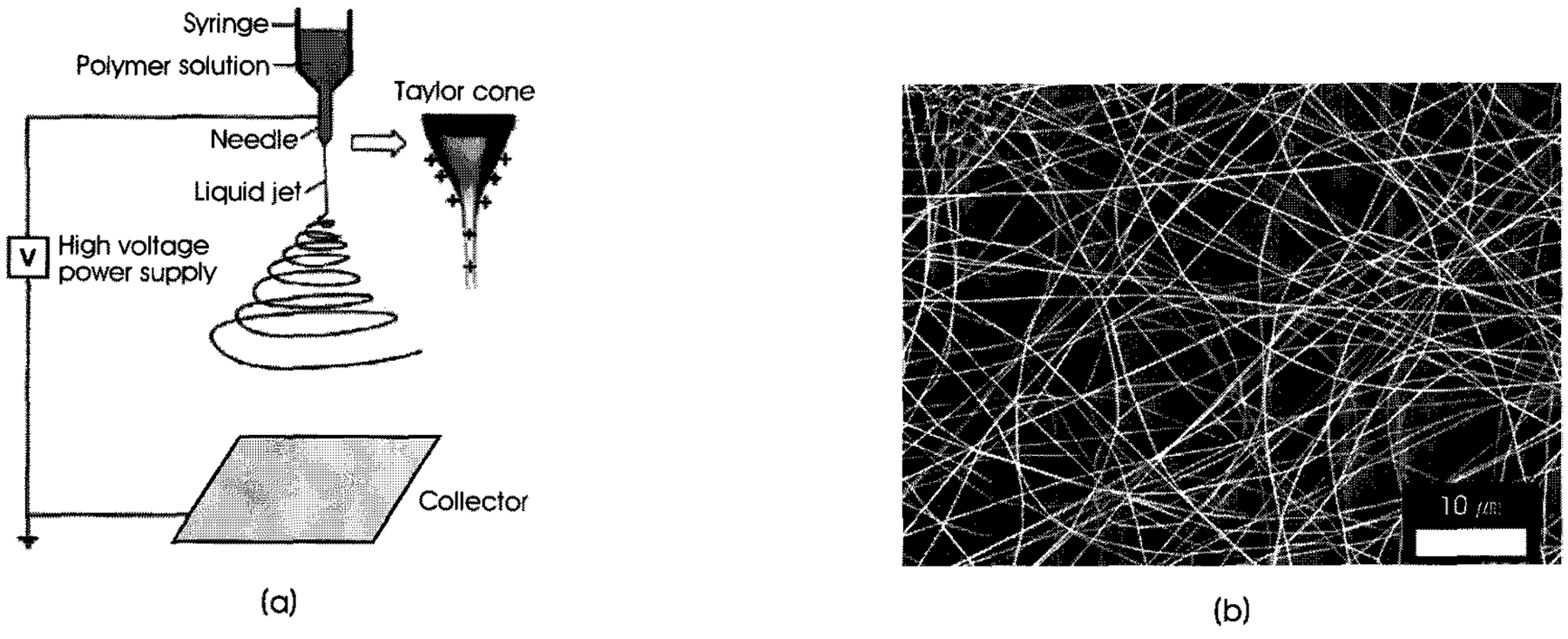


Fig. 1. (a) A schematic illustration of the basic set-up for electrospinning[11]. The insets show a drawing of an electrified Taylor cone. (b) Typical SEM image of the nonwoven mat of nanofibers deposited on the collector[5].

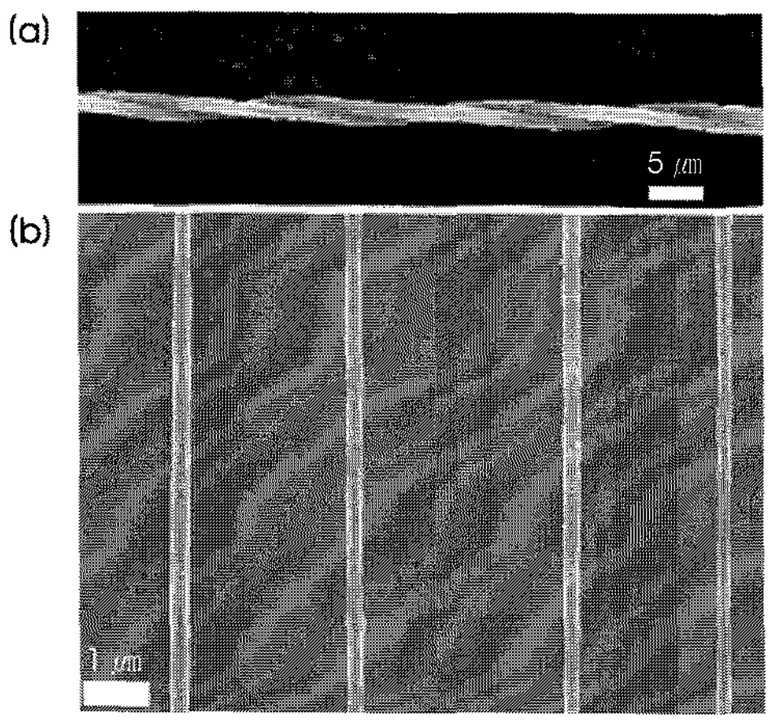


Fig. 2. SEM images showing (a) a twisted poly(ethylene oxide) (PEO) nanofiber obtained using an auxiliary electrode connected to a relay[14]and (b) four parallel poly(vinyl alcohol) (PVA) nanofibers aligned on the Si wafer using auxiliary parallel electrodes[15].

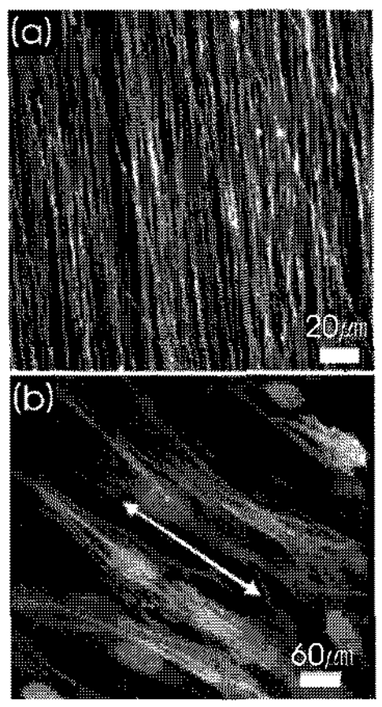


Fig. 3. (a) An aligned P(LLA-CL) nanofibrous scaffold (×20). (b) Smooth muscle cells on aligned nanofibers (laser scanning confocal microscope: a-actin protein, ×40)[22].

matrix composed of about 100 nm diameter fibers). They found that the structural properties of electrospun collagen varied with the tissue of origin, isotope, and the concentration of the collagen solution[19]. Huang and his coworkers provided a convenient, nontoxic, nondenaturing approach to the generation of collagen-containing nanofibers using components blended with type-I collagen and poly(ethylene oxide) (PEO) (with a diameter in the range of 100 to 150 nm)[20]. They suggested that the non-woven fibrous structure has potential applications in wound healing, tissue engineering, and as hemostatic agents[20]. The same group has also produced elastin mimetic fibers from peptide polymers to mimic the protein fibers found in arterial walls[21]. Cells seeded on these nanofibrous structures tend to maintain their phenotypic shape and guide growth according to the nanofiber orientation. Xu et al.[22] and Mo et al.[23] fabricated synthetic polymer scaffolds mimicking the native extracellular matrix by electrospinning poly(L-lactide-co-caprolactone) (P(LLA-CL)), and cultured the smooth muscle cells and endothelial cells showing the favorable behavior of the cells according to the alignment of P(LLA-CL) nanofibers forming scaffolds. Figures 3(a) and 3(b) show aligned (P(LLA-CL)) nanofibrous scaffolds and smooth muscle cells on the aligned nanofibers, respectively[22]. The aligned nanofibrous scaffolds shown in Figure 3(a) were fabricated employing the modified electrospinning setup[24,25].

Ⅳ. NANOFIBERS FOR REHABILITATION AND ARTIFICIAL MUSCLES

The aim of rehabilitation medicine is to regenerate or replace the soft and hard tissues, organs, muscles, and nerves responsible for human disabilities. Polymeric nanofibers are good candidates for human rehabilitation because of their unique structural and physical properties. Biocompatible and biodegradable nanofibers have been used for the replacement of structurally or physiologically deficient tissues and organs in humans. Polymers such as silicone rubber, nylons, polyesters, polyurethanes, and acrylics have been used in the field of rehabilitation in biomedical applications[26]. Some of the uses of biomaterials include dental implants, bone replacements and cements, heart valves, in cosmetic surgery, and in vascular grafts[27]. Dubrow et al. described various medical devices, such as catheters, vascular grafts, and implants (dental and orthopaedic), that utilizes nanofiber matrices to enhance surface area of the implants[28]. Furthermore the nanofibers can be attached to the body of the medical device by covalent linking, or grown directly on the surface[28]. Figure 4 illustrates a particular embodiment applied to an orthopedic implant. The addition of the nanosurface enhances the properties of the device used in ways, such as increased hydrophobicity, adhesion, and biointegration. Reneker and his coworkers produced a skin mask by directly electrospinning fibers onto the skin surface in order to protect or heal wounds[29]. Electrospinning can also be used to create biocompatible thin films with useful coating designs and surface structures that can be deposited on implantable devices to facilitate the integration of these devices in the body. Silk-like polymers with a fibronectin functionality (extracellular matrix proteins) have been electrospun to make biocompatible films used for prosthetic devices implanted in the central nervous system[30]. Ionic electrospun nanofibers that are sensitive to chemical or elec-

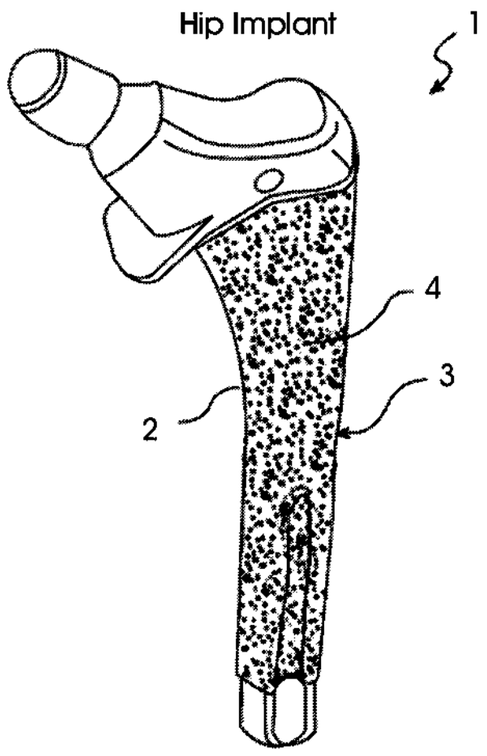
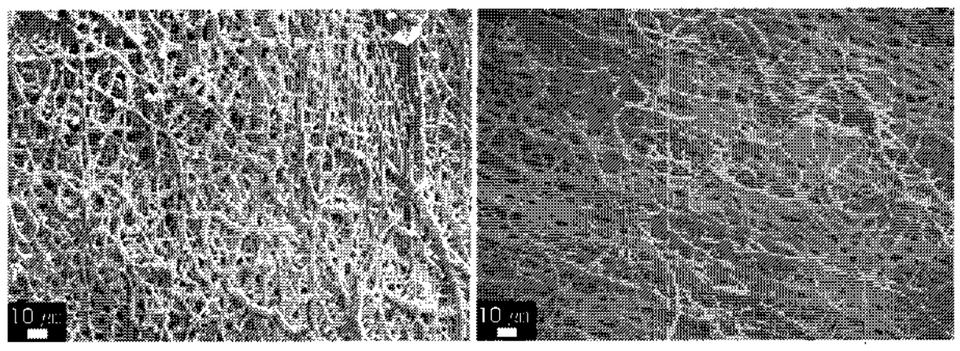


Fig. 4. A scheme illustrating thatan orthopedic implant (1) in the form of hip stem (3) comprises a substrate (2) and porous layer (4). Porous layer (4) can include beads, fibers, wire mesh and other known materials and shapes thereof used to form porous layer (4)[28].



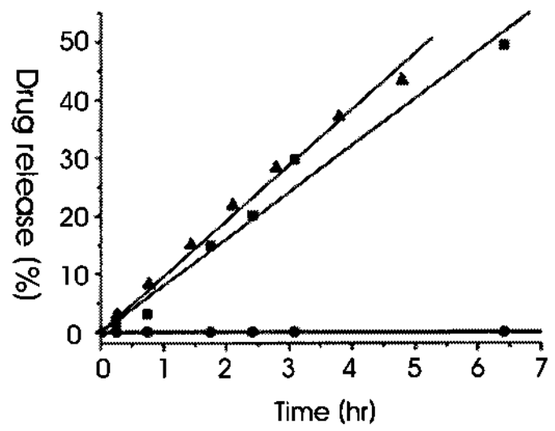


Fig. 5. SEM images of poly(ethylene-co-vinyl acetate) (PEVA) electrospun fibers (a) before drug release, and (b) after drug release[37]. (c) Release of rifampin from electrospun fibers vs. time. Circles = no proteinase K added with 15 wt.% rifampin; squares = concentration of proteinase K = 3 ㎍/ml with15 wt.% rifampin; and triangles = concentration of proteinase K = 3 ㎍/ml with 25 wt.% rifampin[36].

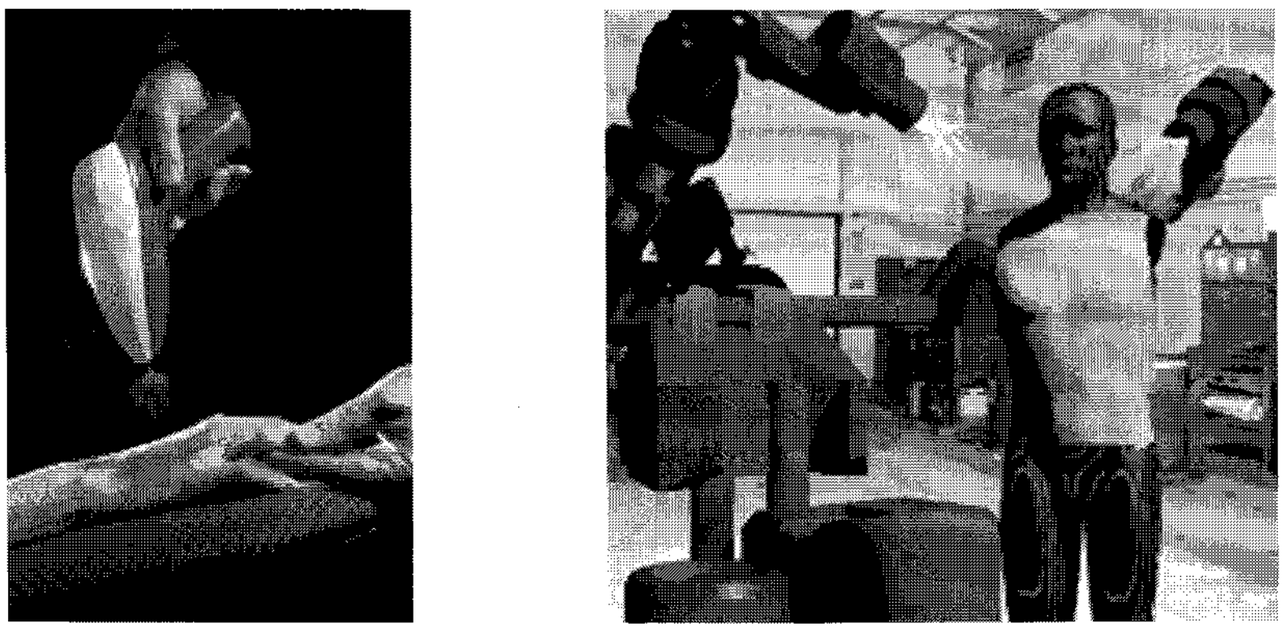
trical stimuli have been shown to have potential inartificial muscles, with a similar function to natural muscles. Samatam and his coworkers fabricated electrospun poly(acrylonitrile) (PAN) nanofibers that showed fast changes in the diameter of the fiber in acidic and basic solutions[31].

V. NANOFIBERS FOR BIOCAPSULES AND DRUG DELIVERY

It is desirable to encapsulate a drug, nano- or microparticles, and vesicles inside nanofibers because of their biocompatibiliy, release efficiency, and uniformity in a shape. Reneker's group presented studies on the encapsulation of particles into electrospun polymeric nanofibers[32]. This was achieved by adding insoluble particles to the polymer solution. They also incorporated biomaterials for wound healing or other substances that functionalized the fiber, such as soluble drugs and antibacterial agents. Electrospun polymeric fiber mats have been exploited in drug-delivery vehicles with promising results, because of their many advantages over conventional dosage forms, such as an improved therapeutic effect, a reduced toxicity, and more convenience[33]. The fiber mats have been made from PLA, PEVA, or a 50:50 blend of these two compounds. PLA has been widely used for drug delivery in biomedical applications because of its biodegradability, biocompatibility, good mechanical properties, and ability to be dissolved in common solvents for processing[34,35]. Figures 5(a) and 5(b) show typical morphologies of electrospun fibers before and after drug release, respectively. Electrospun fibers can overcome the low efficiency of drug delivery system and be tailored to stably release drugs at the initial stages. Electrospun fibers containing several percent of rifampin were prepared and the drug was capsulated inside the fibers[36]. Along with biodegradability, the fiber based system showed a constant drug release, and no sudden burst release was observed (Figure 5(c)). Therefore, such ultrafine fiber mats containing drugs would be also suitable for future clinical applications.

VI. NANOFIBERS FOR WOND DRESSING AND PROTECTIVE CLOTHING

Biomedical applications of electrospun nanofibers include the areas of treatment of wounds or burns of a human skin and protective clothing. Biodegradable fine fibers can be directly sprayed/spun onto the injured location of skin to form a fibrous dressing, which can let wounds heal by encouraging the normal skin growth and eliminate the formation of scar tissue which would occur in a traditional treatment[38]. Figures 6(a) and 6(b) show the photograph of wound dressing



(a) (b)

Fig. 6. (a) Nanofibers for wound dressing[41]. (b) A scheme illustration showing how garments can be made by spraying fibers[42].

using electrospun nanofibers and the scheme of garments made by spraying fibers, respectively. Of particular interest is the application of electrospun membranes composed of elastomeric fibers in the development of several protective clothing applications. Much work has carried out with the aim of developing garments that reduce the risks of chemical exposure for soldiers[39]. The idea is to interlace several types of polymers and fibers to make protective ultra thin layers that can enhance environmental resistance. At the Eighth International Conference on Textile Coating and Laminating the US Army presented its method to achieve these goals using electrospinning for protective garments[40]. They produced membranes for laminated fabrics, as well as fibrous coating structures.

Ⅶ. CONCLUSIONS

Various kinds of biopolymers such as natural, synthetic, and their blends have been electrospun to form nanoscale fibers or mats. These types of fibers provide excellent physical and chemical properties because of their unique nanostructures. Such nanofibers are used in biomedical applications, including scaffolds for the cell culture, wound dressings, artificial organs and muscles, drug delivery systems, and vascular grafts. Bio-applications based on nanofibers are very broad and interdisciplinary areas of research and are the subject of worldwide development activity. These areas have been growing rapidly over the past few years since the realization that creating new structures and devices from nanoscale, continuous fibers enables us to access new and improved properties and functionalities. In the future, the importance of biomedical engineering research using nanofibers will lie in its ability to improve health care and rehabilitate patients with physical impairments.

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REFERENCES

[1] Y. Dzenis, "Spinning continuous fibers for nanotechnology," *Science*, vol. 304, pp. 1917-1919, 2004.

[2] J. Venugopal, Y. Z. Zhang, and S. Ramakrishna, "Electrospun nanofibers: biomedical applications," *Proc. IMechE Part N: J. Nanoengineering and Nanosystems*, vol. 218, pp. 35-45, 2005.

[3] D. Li, Y. Wang, and Y. Xia, "Electrospinning of polymeric and ceramic nanofibers as uniaxially aligned arrays," *Nano Lett.*, vol. 3, pp. 1167-1171, 2003.

[4] A. Arinstein, M. Burman, O. Gendelman, and E. Zussman, "Effect of supramolecular structure on polymer nanofibre elasticity," *Nature Nanotechnology*, vol. 2, pp. 59-62, 2007.

[5] M. K. Shin, S. I. Kim, S. J. Kim, S.-K. Kim, H. Lee, and G. M. Spinks, "Size-dependent elastic modulus of single electroactive polymer nanofibers," *Appl. Phys. Lett.*, vol. 88, pp. 231929 (3pp.), 2006.

[6] R. Samatham, I.-S. Park, K. J. Kim, J.-D. Nam, N. Whisman, and J. Adams, "Electrospun nanoscale polyacrylonitrile artificial muscle," *Smart Mater. Struct.*, vol. 15, pp. N152-N156, 2006.

[7] J. Zeng, A. Aigner, F. Czubayko, T. Kissel, J. H. Wendorff, and A. Greiner, "Poly(vinyl alcohol) nanofibers by electrospinning as a protein delivery system and the retardation of enzyme release by additional polymer coatings," *Biomacromolecules*, vol. 6, pp. 1484-1488, 2005.

[8] E. P. S. Tan, S. Y. Ng, and C. T. Lim, "Tensile testing of a single ultrafine polymeric fiber," *Biomaterials*, vol. 26, pp. 1453-1456, 2005.

[9] D. H. Reneker and I. Chun, "Nanometre diameter fibres of polymer, produced by electrospinning," *Nanotechnology*, vol. 7, pp. 216-223, 1996.

[10] J. M. Deitzel, J. Kleinmeyer, D. Harris, and N. C. Beck Tan, "The effect of processing variables on the morphology of electrospun nanofibers and textiles," *Polymer*, vol. 42, pp. 261-272, 2001.
[11] D. Li and Y. Xia, "Electrospinning of Nanofibers: Reinventing the Wheel?," *Adv. Mater.*, vol. 16 , pp. 1151-1170, 2004.
[12] D. H. Reneker, A. L. Yarin, H. Fong, and S. Koombhongse, "Bending instability of electrically charged liquid jets of polymer solutions in electrospinning," *J. Appl. Phys.*, vol. 87, pp. 4531-4547, 2000.
[13] A. Vaseashta, "Controlled formation of multiple Taylor cones in electrospinning process," *Appl. Phys. Lett.*, vol. 90, pp. 093115 (3pp.), 2007.
[14] B. K. Gu, M. K. Shin, K. W. Sohn, S. I. Kim, S. J. Kim, S.-K. Kim, H. Lee, and J. S. Park, "Direct fabrication of twisted nanofibers by electrospinning," *Appl. Phys. Lett.*, vol. 90, pp. 263902 (3 pp.), 2007.
[15] M. K. Shin, S. I. Kim, and S. J. Kim, "Alignment of polymeric nanofibers using a filtering effect," *J. Nanosci. Nanotechnol.*, In press, 2008.
[16] G. L. Bowlin, J. A. Matthews, D. G. Simpson, E. R. Kenawy, and G. E. Wnek, "Electrospinning biomaterials," *J. Text. Apparel Technol. Mgmt.*, vol. 1. Special issue: The Fiber Society Spring 2001 Conference, Raleigh, North Carolina, USA.
[17] D. Fang, X. Xong, W. Chen, S. Cruz, B. Hsiao, and B. Chu, "Nanostructured electrospun poly-D,L-lactideco-glycolide membranes for anti-adhesion applications," *J. Text. Apparel Technol. Mgmt.*, vol. 1. Special issue: The Fiber Society Spring 2001 Conference, Raleigh, North Carolina, USA.
[18] W. J. Li, C. T. Laurencin, E. J. Caterson, R. S. Tuan, and F. K. Ko, "Electrospun nanofibrous structure: a novel scaffold for tissue engineering," *J. Biomed. Mater. Res.*, vol. 60, pp. 613-621, 2002.
[19] J. A. Matthews, G. E. Wnek, D. G. Simpson, and G. L. Bowlin, "Electrospinning of collagen nanofibers," *Biomacromolecules*, vol. 3, pp. 232-238, 2002.
[20] L. Huang, K. Nagapundi, and E. L. Chaikof, "Engineered collagen PEO nanofibers and fabrics. J. Biomater," *Sci. Polym. Ed.*, vol. 12, pp. 979-993, 2001.
[21] L. Huang, R. A. MacMillian, R. P. Apkarian, B. Pourdeyhimi, V. P. Conticello, and E. L. Chaikof, "Generation of synthetic elastin mimetic small diameter fibers and fiber networks," *Macromolecules*, vol. 33, pp. 2899-2997, 2000.
[22] C. Y. Xu, R. Inai, M. Kotaki, and S. Ramakrishna, "Aligned biodegradable nanofibrous structure: a potential scaffold for blood vessel engineering," *Biomaterials*, vol. 25, pp. 877-886, 2004.
[23] X. M. Mo, C. Y. Xu, M. Kotaki, and S. Ramakrishna, "Electrospun P(LLA-CL) nanofiber: a biomimitic extracellular matrix for smooth muscle cell and endothelial cell proliferation," *Biomaterials*, vol. 25, pp. 1883-1890, 2004.
[24] D. Li, Y. Wang, and Y. Xia, "Electrospinning of Polymeric and Ceramic Nanofibers as Uniaxially Aligned Arrays," *Nano Lett.*, vol. 3, pp. 1167-1171, 2003.
[25] M. K. Shin, S. I. Kim, and S. J. Kim, "Controlled assembly of polymer nanofibers: From helical springs to fully extended," *Appl. Phys. Lett.*, vol. 88, pp. 223109 (3pp.), 2006.
[26] M. J. Miller, and G. R. D. Evans, "Tissue engineering and plastic surgery," In Frontiers in Tissue Engineering (Eds C. W. Patrick, A. G. Mikos, and L. V. McIntire), pp. 213-232 (Pergamon, New York, USA), 1998.
[27] B. D. Ratner, "New ideas in biomaterials science a path to engineered biomaterials," *J. Biomed. Mater. Res.*, vol. 27, pp. 837-850, 1993.
[28] R. S. Dubrow, L. A. Bock, R. H. Daniels, V. D. Hardev, C. Niu, V. Sahi, US Patent No. 2006204738, 2006.
[29] D. J. Smith, D. H. Reneker, A. T. McManus, H. L. Schreuder-Gibson, C. Mello, and M. S. Sennett, "Electrospun fibers and an apparatus therefore," US Patent No. 6753454, 2004.
[30] C. J. Buchko, L. C. Chen, Y. Shen, and D. C. Martin, "Processing and microstructural characterization of porous biocompatible protein thin films," *Polymer.*, vol. 40, pp. 7397-7407, 1999.
[31] R. Samatham, I.-S. Park, K. J. Kim, J.-D. Nam, N. Whisman, and J. Adams, "Electrospun nanoscale polyacrylonitrile artificial muscle," *Smart Mater. Struct.*, vol. 15, N152-N156, 2006.
[32] W. Kataphinan, S. Dabney, D. Smith, and D. H. Reneker, "Fabrication of electrospun and encapsulation into polymer nanofibers," J. Text. Apparel Technol. Mgmt., vol. 1. Special issue: *The Fiber Society Spring 2001 Conference*, Raleigh, North Carolina, USA.
[33] E.-R. Kenawy, G. L. Bowlin, and K. Mansfield, "Release of tetracycline hydrochloride from electrospun poly(ethylene-co -vinylacetate), poly(lactic acid) and a Blend," *J. Controlled Release*, vol. 81, pp. 57-64, 2002.
[34] K. Kim, M. Yu, X. Zong, J. Chiu, D. Fang, B. S. Hsiao, B. Chu, and M. Hadjiargyrou, "Control of degradation rate and hydrophilicity in electrospun non-woven poly(D,L-lactide) nanofiber scaffolds for biomedical applications," *Biomaterials*, vol. 24, pp. 4977-4985, 2003.
[35] T. Nakamura, S. Hitomi, S. Watanabe, Y. Shimizu, K. Jamshidi, S. H. Hyon, and Y. Ikada, "Bioabsorption of polylactides with different molecular properties," *J. Biomed. Mater. Res.*, vol. 23, pp. 1115-1130, 1989.
[36] J. Zeng, X. Xu, X. Chen, Q. Liang, X. Bian, L.Yang, and X. Jing, "Biodegradable electrospun fibers for drug delivery," *J. Controlled Release*, vol. 92, pp. 227 -231, 2003.
[37] E.-R. Kenawy, G. L. Bowlin, K. Mansfield, J. Layman, D. G. Simpson, E. H. Sanders, and G. E. Wnek, "Release of tetracycline hydrochloride from electrospun poly(ethylene-co-vinylacetate), poly(lactic acid), and a blend," *J. Controlled Release*, vol. 81, pp. 57-64, 2002.
[38] H. J. Jin, S. Fridrikh, G. C. Rutledge, and D. Kaplan, "Electrospinning bombyx mori silk with poly(ethylene oxide)," *Abstracts of Papers American Chemical Society*, vol. 224, pp. 408, 2002.
[39] S. E. Ross, "Electrospinning: the quest for nanofibers," *Int. Fibre J.*, vol. 16, pp. 50-53, 2001.
[40] H. Schreuder-Gibson, International Conference on textile coating and laminating: preparing for the future a new millennium, 8th, Frankfurt, Germany, 1998, Paper No 17/ 11-Paper No 17/24.
[41] www.electrosols.com
[42] D. Adam, "A fine set of threads," *Nature*, vol. 411, pp. 236, 2001.