Effect of Solution Properties on Nanofibrous Structure of Electrospun Poly(lactic-*co*-glycolic acid)

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ABSTRACT: Electrospinning of poly(lactic-*co*-glycolic acid) (PLGA) in chloroform or 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) was investigated, focusing on its solution parameters, to develop nonwoven biodegradable nanofibrous structures for tissue engineering. PLGA nanofibers were obtained by electrospinning of 15 wt % PLGA solution and the resulting average fiber diameters were varied with the range of 270–760 nm, depending on solution property. When small amounts of benzyl triethylammonium chloride (BTEAC) was added to the PLGA/chloroform solution, the average diameter was decreased from 760 to 450 nm and the fibers were densely amounted in a straight shape. In addition, the average fiber diameter (270 nm) of nanofibers electrospun from polar HFIP solvent was much smaller than that (760 nm) of nanofibers electrospun from nonpolar chloroform solvent. Therefore, it could be concluded that conductivity or dielectric constant of the PLGA solution was a major parameter affecting the morphology and diameter of the electrospun PLGA fibers. © 2005 Wiley Periodicals, Inc. J Appl Polym Sci 99: 1214–1221, 2006

Key words: electrospinning; nanofiber; additive; solution properties; polyesters

INTRODUCTION

Ultrafine polymer fibers exhibiting high surface area to volume and length to diameter ratios can be prepared *via* electrospinning. These characteristics are essential for various advanced applications such as separation membranes, wound dressing materials, artificial blood vessels, sensors, composite reinforcement, etc.[1–4] In electrospinning, polymer solution is placed in a container having a millimeter size capillary. When a strong electrostatic force is applied to the capillary, the polymer solution is ejected from the capillary and deposited as a nonwoven fibrous structure on a template serving as the ground for the electric charges. The morphology of ultrafine fibers produced by electrospinning strongly depends on the solution properties such as polymer concentration, nature of solvent (volatility and polarity), as well as processing parameters.

Recently, many researchers are trying to employ the electrospinning technique to prepare microporous biodegradable or biocompatible scaffolds.[5–9] Li et al.[5] prepared poly(D,L-lactide-*co*-glycolide) ultrafine fibers via electrospinning, showing a morphological similarity to the extracellular matrix (ECM) of natural tissue in the diameter range from 500 to 800 nm. Yoshimoto et al.[6] reported that electrospun nonwoven poly(ε-caprolactone) could be a useful scaffold for bone tissue engineering. Luu et al.[8] fabricated synthetic polymer (PLGA and PLA-PEO copolymer)/DNA composite scaffolds for therapeutic application in gene delivery for tissue engineering. Matthews et al.[9] studied how electrospinning can be adapted to produce tissue-engineering scaffolds composed of collagen nanofibers (a matrix composed of 100 nm fiber). They found that the structural properties of electrospun collagen varied with the tissue of origin, the isotope, and the concentration of the collagen solution.

Among the biodegradable polymers, poly(L-lactic acid) (PLA), poly(glycolic acid) (PGA), and their copolymers have been extending their applications to surgical sutures, implant materials, drug carriers, and scaffolds for tissue engineering, because they have a diverse biodegradability, good mechanical property, and biocompatibility, and because they have received FDA approval for medical devices. In this study, nonwoven nanofibrous structures of poly(lactic-*co*-glycolic acid) (PLGA) were produced via electrospinning to develop biodegradable scaffolds. To obtain nanofibrous structure having various average diameters and porosities, electrospinning of PLGA was also carried out with quaternary ammonium salt (BTEAC), which was soluble in the electrospinning solvent of PLGA

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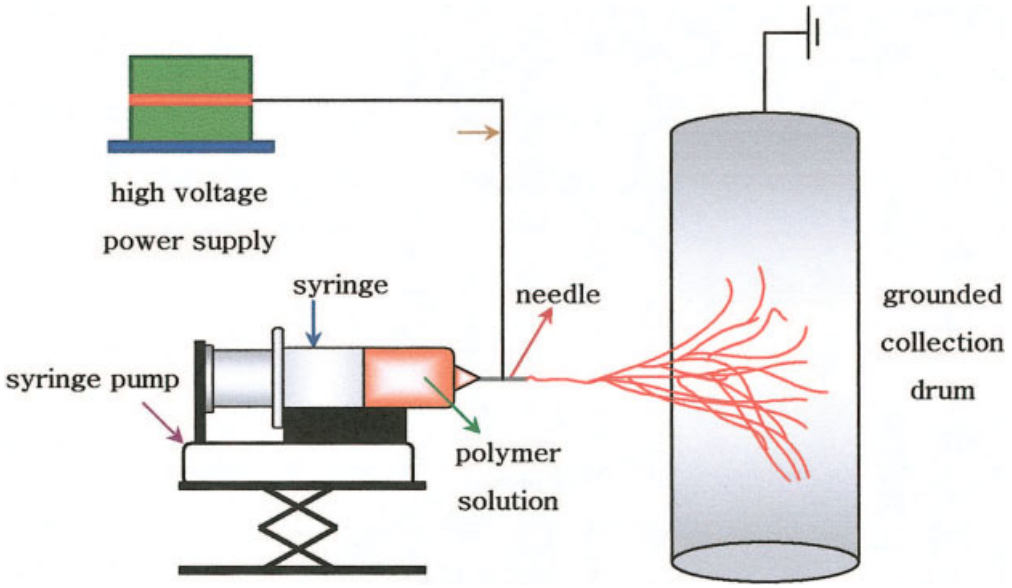


Figure 1 Schematic diagram of electrospinning apparatus.[Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

and easily removable from the resulting ultrafine fibers. The changes in the fiber diameter and morphology by adding salt or changing solvent were investigated in terms of solution viscosity, surface tension, dielectric constant, and conductivity.

EXPERIMENTAL

Materials

PLGA (50/50) copolymers (MW = 25,000) was kindly supplied by Purac Co. Chloroform, 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), and benzyl triethylammonium chloride (BTEAC) were purchased from Aldrich Co. and used as received.

Electrospinning

A schematic diagram of the electrospinning apparatus for producing ultrafine PLGA fibers is shown in Figure 1. The electrospinning setup utilized in this study consisted of a syringe and needle (ID = 0.84 mm), a ground electrode (d = 21.5 cm, stainless steel sheet on

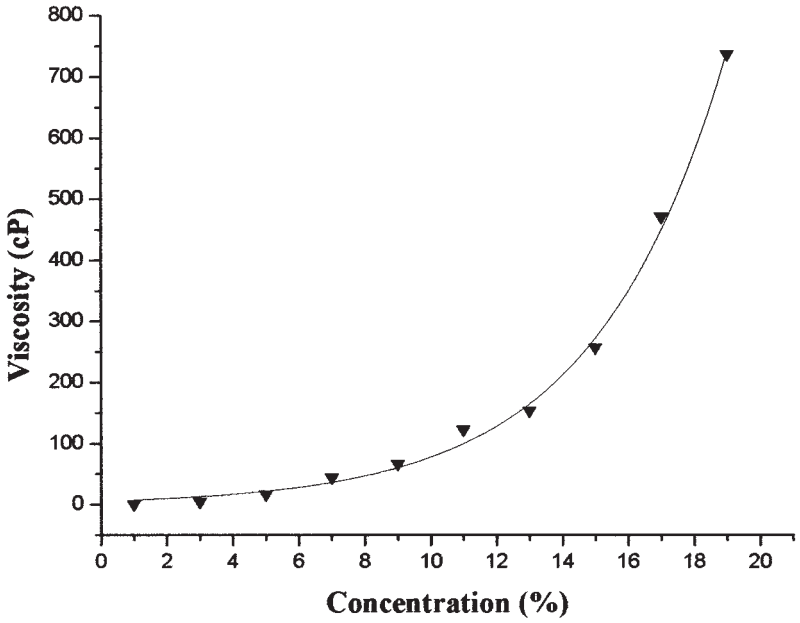


Figure 2 Relationship between concentration and viscosity of the PLGA solution in chloroform.

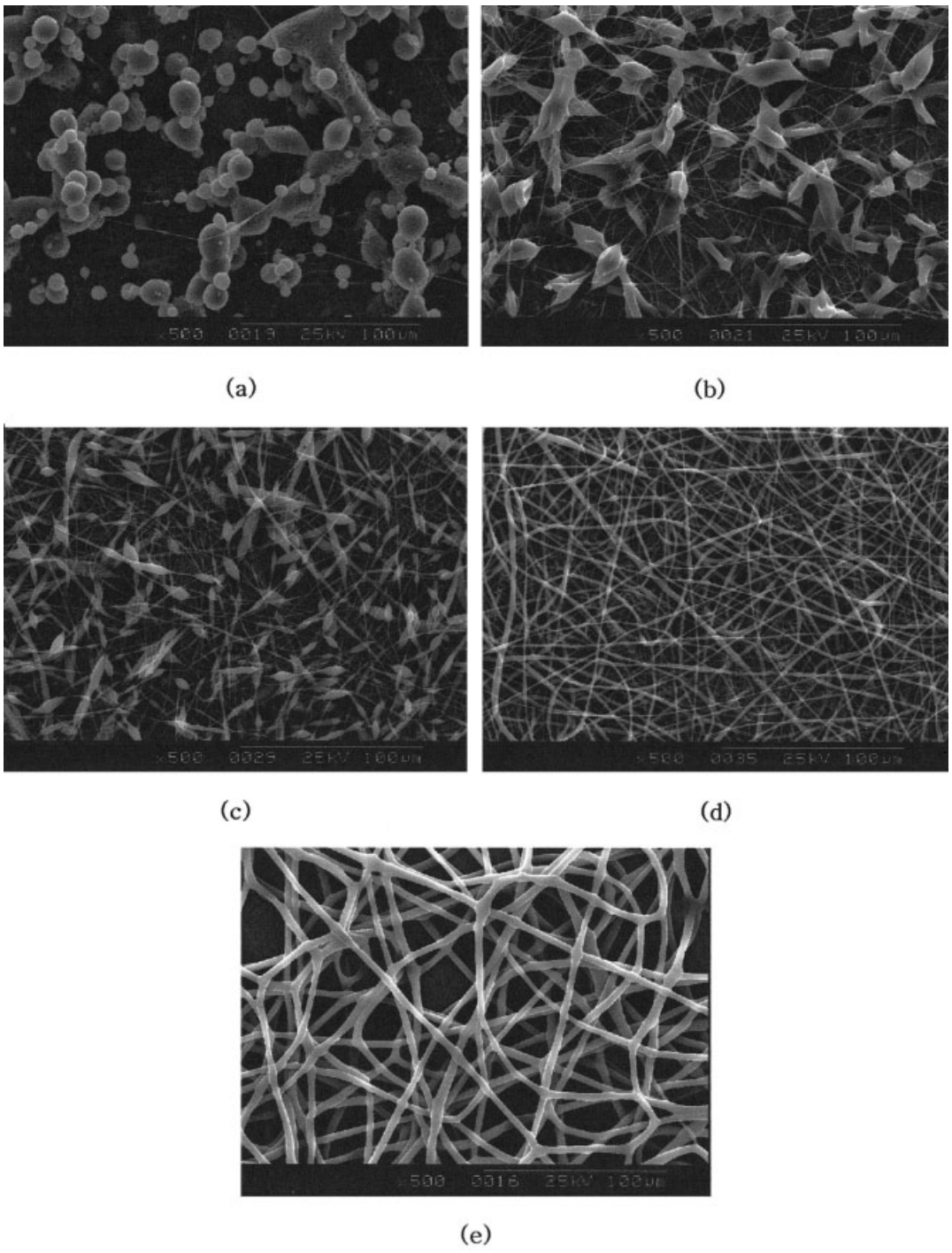


Figure 3 SEM micrographs of electrospun PLGA fibers at different concentrations in chloroform: (a) 9%, (b) 11%, (c) 13%, (d) 15%, and (e) 17%.

a drum whose rotation speed can be varied), and a high voltage supply (Chungpa EMT, CPS-40K03). The needle was connected to the high voltage supply, which can generate positive DC voltages up to 40 kV. For the electrospinning of PLGA fibers, PLGA was first dissolved in chloroform or HFIP and delivered by a syringe pump (KD Scientific, Model 100) with the mass flow rate of 4 mL/h. The distance between the needle tip and the ground electrode was in a range of 5–10 cm and the positive voltage applied to polymer solutions were in the range of 15–20 kV. All experiments were carried out at room temperature.

Measurements

The viscosity of PLGA solution was determined by using a Brookfield digital viscometer (Model DV-E)

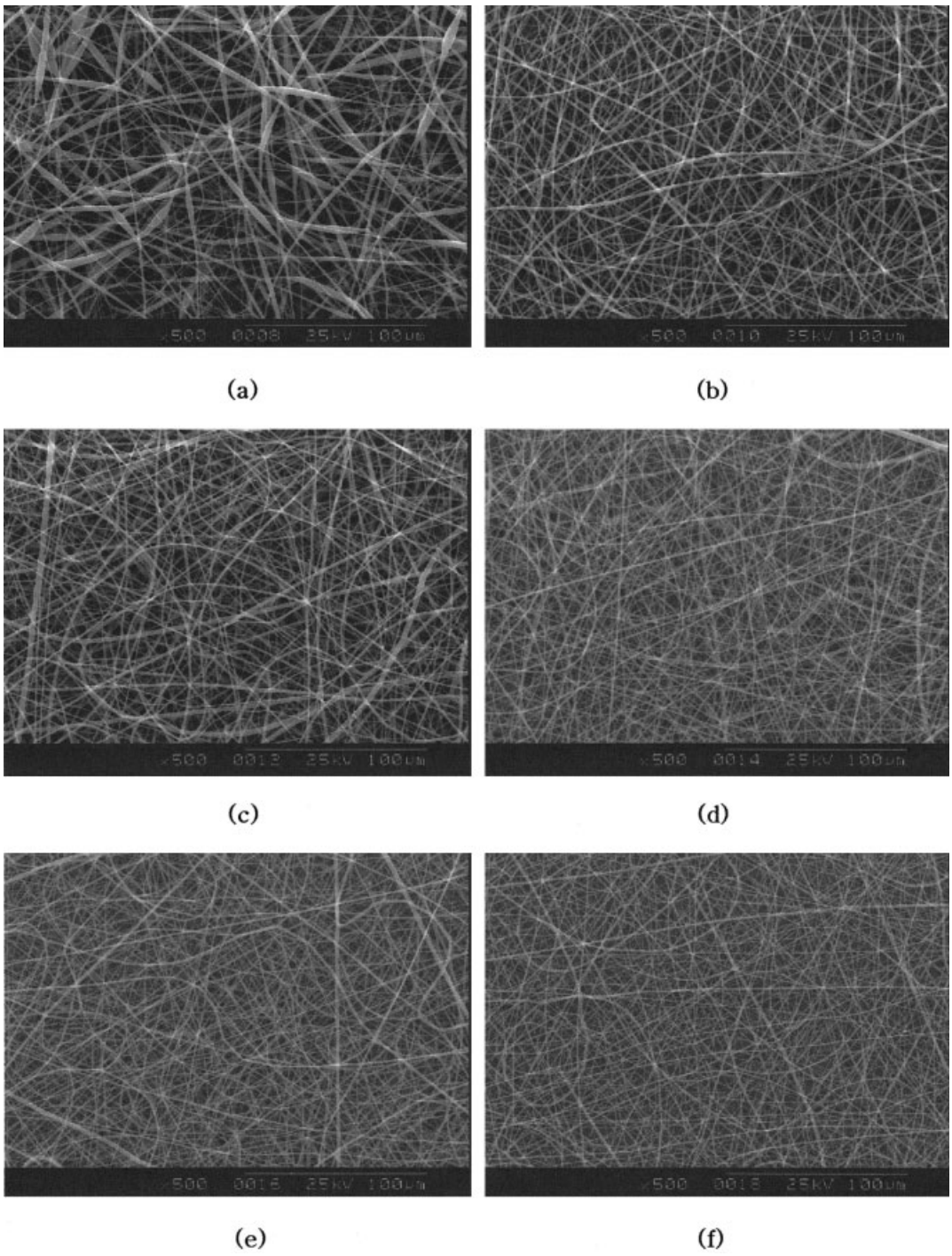


Figure 4 SEM micrographs of nanofibers electrospun from PLGA solution with different amounts of BTEAC: (a) 0.1 wt %, (b) 0.5 wt %, (c) 1.0 wt %, (d) 2.0 wt %, (e) 3.0 wt %, and (f) 4.0 wt %.

at 25°C. Surface tension and conductivity of polymer solution were determined by using a tensiometer (Kruss K8) and a conductivity meter (Jenway 4310), respectively. The morphology of electrospun PLGA fibers was observed on a scanning electron microscope (SEM) (Hidachi *S*-2350) after gold coating. The average diameter and diameter distribution were obtained by analyzing SEM images with a custom code image analysis program (Scope Eye II). Porosity and pore parameters in the interfiber region of PLGA nanofibers web were determined by mercury intrusion technique using an AutoPore III mercury porosimeter (Micromeritics Instrument Co.).

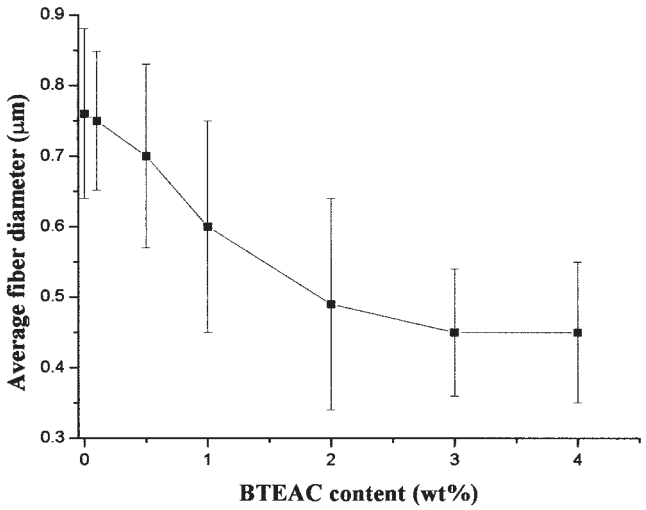


Figure 5 The average diameters of electrospun PLGA fibers with different amounts of BTEAC.

RESULTS AND DISCUSSION

Electrospinning of PLGA/chloroform

In electrospinning, viscosity of solution plays an important role in determining the range of concentrations from which continuous fibers can be obtained. At low viscosities, surface tension is the dominant factor and just bead or beaded-fiber form is formed. Above a critical concentration, continuous fibrous structure is obtained and its morphology is affected by the concentration of solution.[10,11] The formation of continuous fiber is attributed to the extensive chain entanglements in polymer solution. Figure 2 shows the change in solution viscosity with increasing the concentration of PLGA. The viscosity of PLGA increased rapidly at ~15% (w/v), indicating the extensive chain entanglement of PLGA occurred around this concentration. This stabilizes the liquid ejected and fibers form as the solvent evaporates. Figure 3 shows SEM micrographs of PLGA fibers electrospun from different concentrations. The distance between the needle tip and the ground electrode was 7 cm and a positive voltage was set at 17 kV. These conditions were determined by electrospinning of 15% of PLGA solution, which is considered to be high concentration for chain entanglement, and employed for all electrospinnings in this study. At concentrations below 9%, only large beads were generated [Figure 3(a)]. As the PLGA concentration increased, the beaded-fiber structure obtained at concentrations of 11–13% [Figure 3(b,c)] was changed to the continuous fibrous structure at concentration of 15% [Figure 3(d)]. The average fiber diameter of PLGA electrospun from a 15% PLGA solution was 760 nm, which is slightly larger to replace the natural ECM because it is composed of randomly oriented collagens in the diameter range of 50–500 nm.

Electrospinning of PLGA/chloroform with BTEAC salt

To obtain nanofibrous structures having a proper diameter, porosity, and mechanical properties, electrospinning of PLGA was carried out with BTEAC, which was chosen as salt because it is soluble in chloroform and easily removable from the resulting ultrafine fibers by a methanol treatment. The BTEAC can change

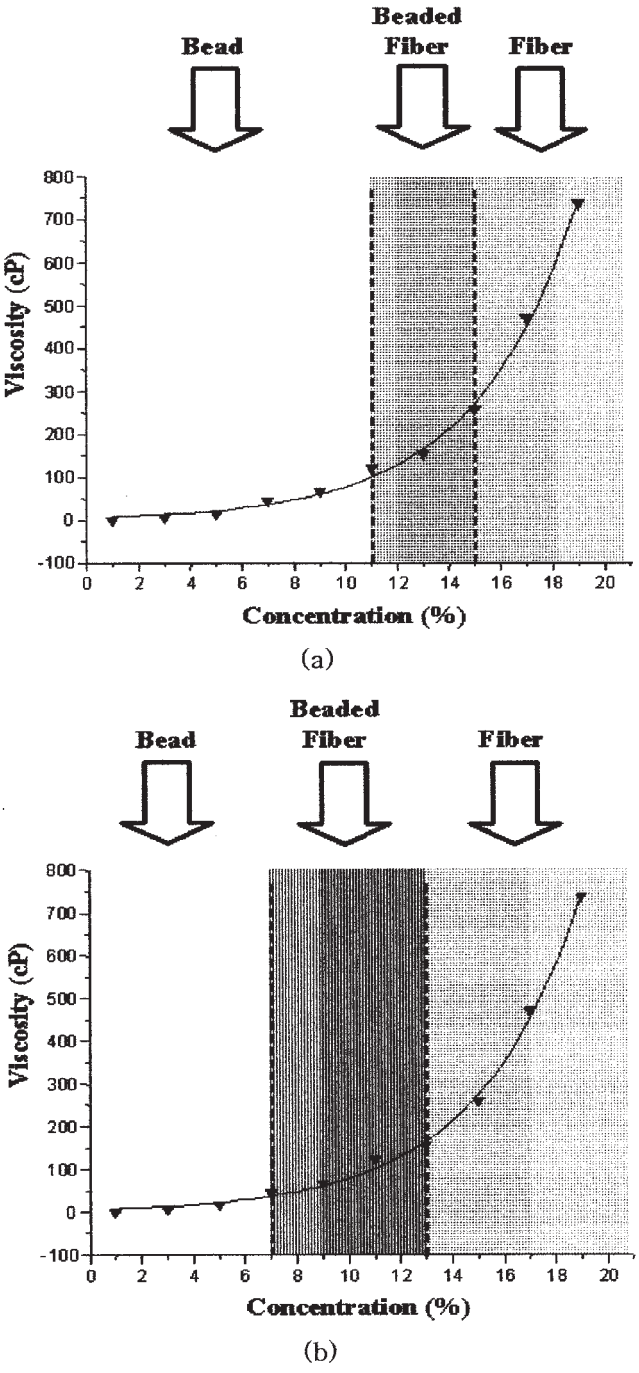


Figure 6 Shapes of the electrospun PLGA products *versus* concentrations of PLGA solution with or without 2 wt % BTEAC.

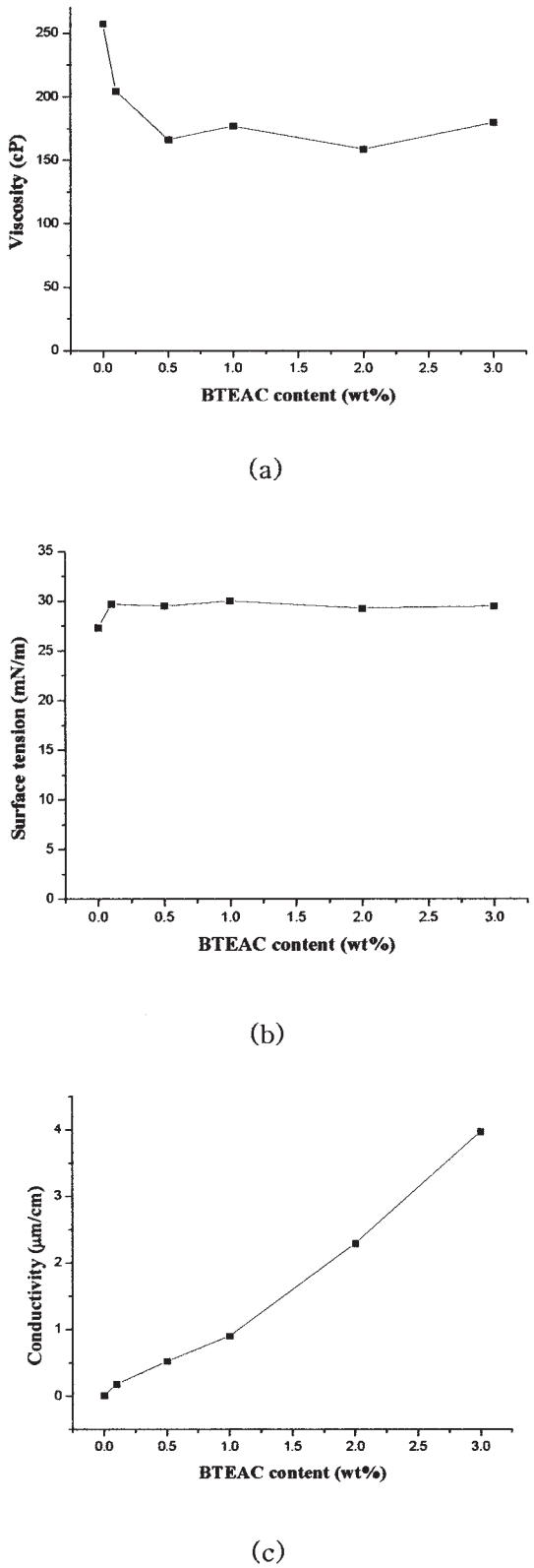


Figure 7 Changes in (a) viscosity, (b) surface tension, and (c) conductivity of the PLGA solution in chloroform, according to the content of BTEAC.

the solution properties of PLGA, such as surface tension and conductivity, and consequently it is expected that the diameter and morphology of electrospun PLGA fibers would be affected by its addition. It is known that the average diameter of electrospun ultrafine fibers decreased with the addition of salt and their morphologies were dependent on the type of salts.[12]

Figure 4 shows SEM micrographs of ultrafine PLGA fibers electrospun from a 15% PLGA solution with small amounts of BTEAC. The electrospun PLGA fibers were amounted in a straight shape, while those without BTEAC were in a bended shape. Figure 5 shows changes in the average fiber diameter of PLGA fibers electrospun with different amounts of BTEAC. The addition of small amounts of BTEAC to the PLGA solution caused a significant decrease in the average fiber diameters, and it was dependent on the amount of BTEAC added up to 3 wt % (based on PLGA weight in the solution). Figure 6 shows shapes of the electrospun PLGA products versus concentrations of PLGA solution with or without 2 wt % BTEAC. As shown in Figure 6, PLGA concentration ranges to form large beads, beaded-fibers, and continuous fibers, respectively, were shifted to lower concentrations when BTEAC of 2 wt %, based on PLGA weight in the solution, was added to PLGA solution. In addition, beaded-fibers were formed in broader range of PLGA concentration (from 11–15% to 7–13%). To explain these results, viscosity, surface tension, and conductivity of PLGA solutions with various amounts of BTEAC were measured (Fig. 7). The addition of BTEAC to PLGA solutions caused significant increase in conductivity of PLGA solutions with increasing amounts of BTEAC up to 3 wt %, whereas no significant change was observed in viscosity and surface tension of PLGA/chloroform solutions. Therefore, it was found that the conductivity of the PLGA solution was a major parameter affecting the morphology and diameter of the electrospun PLGA fibers.[13,14]

Figure 8 shows a photograph of nanofibers web electropun from PLGA solution, with or without 2 wt % BTEAC, for 10 min. With respect to jet formation, it was noticeable that the addition of BTEAC did not make the area of ejected jet broader during the electrospinning, but increases the density of ejected jet as shown in Figure 8. The addition of salt also increases the charge density in ejected jet, and thus, stronger elongation forces are imposed to the jet due to the self-repulsion of the excess charges under the electrical field, resulting in substantially straighter shape and smaller diameter of electrospun fibers. However, the effect of conductivity on the fiber diameter might be limited above a critical value because the average diameter of electrospun fibers did not further increase at above 3 wt % BTEAC. It is known that besides the density of charges carried by the jet, the size of the ions has an important impact on the resulting fiber diameter. Ions with smaller atomic radius have a higher charge density and thus a higher mobility under an external electric field.[12]

Figure 8 Photograph of PLGA fibers electrospun at a concentration of 15% for 10 min, with or without 2 wt % BTEAC.

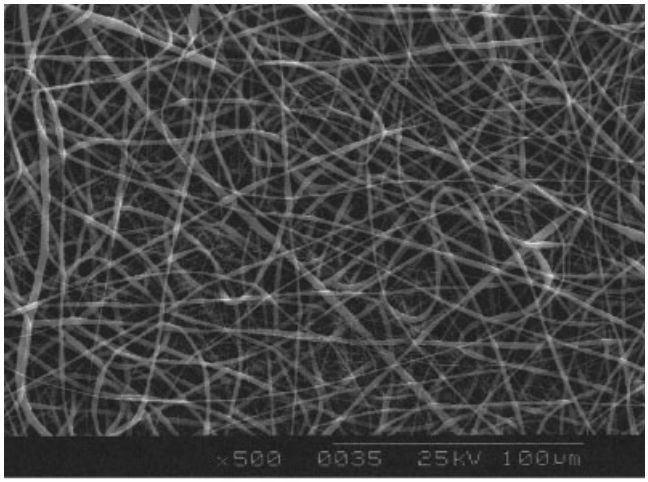
Pore parameters of nanofibers web electropun from PLGA solution with or without 2 wt % BTEAC were compared in Table I. Because of its smaller fiber diameter, the PLGA web electrospun with 2 wt % BTEAC had higher total pore area but lower porosity than the PLGA web without BTEAC.

Electrospinning of PLGA/HFIP

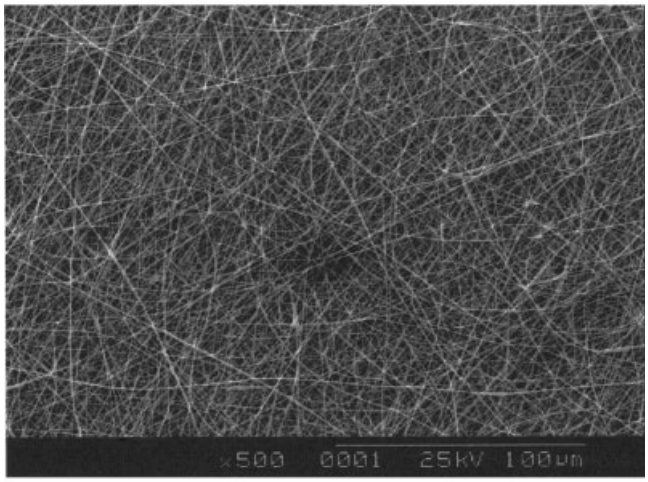
In the electrospinning process, the nature of solvent such as volatility and polarity (dielectric conatant) has a significant influence on the morphology and diameter of the electrospun fibers, similar to conductivity of solution. Bognitzki et al.[15] used highly volatile dichloromethane (boiling point, 40°C) as solvent and prepared PLGA fibers with a regular pore structure. In general, electrospinning of polymer in polar solvent produces the ultrathin fibers with a smaller average diameter, although the effect of polarity of solvent on the fiber diameter is not systematically studied yet. Figure 9 shows SEM micrographs of the ultrafine PLGA fibers electrospun from PLGA solution in chloroform (dielectric constant = 4.81 at 25°C) or HFIP (dielectric constant = 16.70 at 20°C). The average fiber diameter (270 nm) of nanofibers electrospun from polar HFIP solvent was much smaller than that (760 nm)

TABLE I
Pore Parameters of PLGA Nanofibers Web Electrospun with or without 2 wt% BTEAC

	15% PLGA	15% PLGA with 2 wt% BTEAC
Fiber diameter (nm)	760	490
Total pore area (m^2/g)	37.0	52.4
Porosity (%)	88.0	77.2



(a)



(b)

Figure 9 SEM micrographs of nanofibers electrospun from PLGA solution in chloroform (a) or HFIP (b).

of nanofibers electrospun from nonpolar chloroform solvent. Therefore, it could be concluded that the diameter of the electrospun PLGA nanofibers was strongly dependent on a dielectric constant of solvent.

CONCLUSIONS

PLGA nonwoven structures were obtained by electrospinning of PLGA/chloroform at concentration of 15% and the average fiber diameter was 760 nm. The addition of small amounts of BTEAC to the PLGA solution caused a significant decrease in the average fiber diameters to 450 nm and the fibers were amounted in a straight shape. With respect to jet formation, the addition of BTEAC to PLGA solution did not make the area of ejected jet broader, but increases the density of ejected jets during the electrospinning. Therefore, it was found that the conductivity of the PLGA solution was a major parameter affecting the morphology and diameter of the electrospun PLGA fibers, though the effect of conductivity on the fiber diameter was limited above a critical value. In addition, the diameter of the electrospun PLGA nanofibers was strongly dependent on a dielectric constant of solvent.

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