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Research Article

Determination of Electrospinning Parameters' Strength in Poly(D,L)-lactide-co-glycolide Micro/Nanofiber Diameter Tailoring

Yi-Pin Chen,[1,2] Hsin-Yi Liu,[3] Yen-Wei Liu,[3] Tzung-Yan Lee,[4,5] and Shih-Jung Liu[3,6]

[1]*Graduate Institute of Clinical Medical Sciences, College of Medicine, Chang Gung University, Tao-Yuan, Taiwan*
[2]*Department of Obstetrics and Gynecology, Keelung Chang Gung Memorial Hospital, Keelung, Taiwan*
[3]*Department of Mechanical Engineering, Chang Gung University, Tao-Yuan, Taiwan*
[4]*Graduate Institute of Traditional Chinese Medicine, School of Chinese Medicine, College of Medicine, Chang Gung University, Tao-Yuan, Taiwan*
[5]*Department of Traditional Chinese Medicine, Keelung Chang Gung Memorial Hospital, Keelung, Taiwan*
[6]*Department of Orthopedic Surgery, Chang Gung Memorial Hospital-Linkou, Tao-Yuan, Taiwan*

Correspondence should be addressed to Shih-Jung Liu; shihjung@mail.cgu.edu.tw

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Electrospinning has received increasing interest and attention in recent years for fabricating micro/nanofibers of various materials; this is due to its versatility and capability of multiple field applications, including filtration, biosensors, tissue engineering, wound dressings, drug delivery, and composites. Nonetheless, the optimization of the electrospinning process is based on a time-consuming trial-and-error procedure. An empirical study, in conformity with the Taguchi orthogonal matrix design, was carried out to investigate the influence of various processing variables on the electrospinning of resorbable poly(D,L)-lactide-co-glycolide (PLGA). Three different solvents, hexafluoro-2-propanol (HFIP), dichloromethane (DCM), and trichloromethane (TCM), were employed. Five variables were selected for evaluation, including PLGA concentration, the solution's flow rate from the nozzle, the distance between the nozzle and ground collection, the voltage, and the type of solvents. After electrospinning, we performed a morphological analysis of nanofibers by scanning electron microscopy (SEM) and measured the fiber size by the evaluation of SEM images. Among the variables selected, the type of solvent and the applied voltage were found to be the principal variables influencing the diameter distribution of electrospun PLGA fibers. Nanofibers with the smallest fiber size (466.25 ± 158.38 nm) could be obtained with HFIP solvent and an applied voltage of 15 kV.

1. Introduction

In recent years, there has been an increasing interest in exploiting the electrospinning technology to produce nanoscale fibers of various materials, including natural and synthetic polymers, metals, ceramics, and composites [1]. Electrospinning, a broadly used technology for electrostatic fiber formation, which utilizes electrical forces to produce polymeric fibers of both natural and synthetic polymers, has received tremendous attention over the past decade [2]. The process utilizes electrostatic forces to prepare fiber mats from polymer melts or solutions. Manufactured fibers possess a finer diameter (ranging from few nanometers to several micrometers) and a greater surface area than fibers produced by the conventional spinning process.

Electrospinning is a relatively energetic yet easy technique in producing micro/nanofibers from a wide variety of polymers. Electrospun micro/nanofibers also provide various advantages, including a high surface area and porosity, tunable micro/nanofiber composition, and the capacity to conform to a wide variety of sizes and shapes. Given the strength of these advantages, electrospun micro/nanofibers have been extensively researched during the past decade for various applications, such as filtration [3], biosensors [4],

tissue engineering [5], wound dressings [6, 7], drug delivery [8], and composites [9]. Despite the several advantages offered by electrospinning, there are still challenges that demand proper consideration. One central challenge pertains to the optimization of this spinning process. To date, various work has been completed to investigate the influence of processing parameters on the electrospinning of different materials, including collagen [10, 11], wheat gluten [11], polystyrene [12], polycaprolactone [13], poly(L-lactide--co-epsilon-caprolactone) [14], chitosan-gelatin blend [15], poly(vinyl alcohol) [16], polylactide [16], polydimethlsiloxane [17], polyamide [18, 19], silica [20], silk fibroin [21], peptide-based supramolecular polymers [22], and halloysite nanotubes/polyvinylpyrrolidone composite [23]. However, research on the electrospinning of poly(D,L)-lactide-co-glycolide (PLGA) has been few. Meng et al. [24] explored the electrospinning of PLGA/gelatin randomly oriented and aligned nanofibers as potential scaffold in tissue engineering. Liu et al. [25] investigated the influence of solvent type and solvent composition on the physical properties of electrospun nanofibers. Brown et al. [26] examined how nanofibrous PLGA electrospun scaffolds modified with type I collagen influence hepatocyte function and support viability in vitro.

PLGA is one of the extensively coveted resorbable polymers, mainly due to its availability in different molecular weights, compositions, and degradation rates for medical devices and drug deliveries [27, 28]. The transformation of PLGA into textile structures such as micro/nanofibers, using the electrospinning technique, is complicated and depends on different variables during the process [3]. Optimization of the electrospinning process of PLGA micro/nanofibers is therefore highly desirable.

Thus far, various efforts have been completed to investigate the influence of processing parameters on the diameter distribution of nanofibers [29–33]. However, these studies employed a factorial design approach to judge whether there is a link between variables, while reducing the possibility of experimental error and confounding variables. The main disadvantage of the approach lies in the difficulty of experimenting with more than two factors, or many levels simultaneously, which jeopardizes a great amount of work. Furthermore, the approach could not identify the relative importance of each variable in influencing the final micro/-nanofiber diameters.

In this study, we aimed to assess the electrospinning parameters' strength in fiber diameter, tailored to heighten the electrospinning process of PLGA materials, which have a LA : GA ratio of 50 : 50 and are thus selected for this work. Experiments were carried out on an electrospinning setup, consisting of a syringe and nozzle, a ground electrode, a collection sheet, and a high-voltage supply. Several properties can be affected by processing variables during electrospinning, including spinnability, fiber diameter and uniformity, and mechanical properties. Among these, the decrease in fiber size improves the overall separation efficiency of nanofibers in the water filtration process [34]. Additionally, the nanoscale diameter of the fibers resembles certain supramolecular features of the extracellular matrix, which is favorable for cell attachment and proliferation [14]. For simplicity, the fiber diameter was selected as the target for process optimization.

An empirical study was conducted, in line with the Taguchi orthogonal array design [35], to investigate the effect of different processing variables, including polymer concentration, flow rate of solution from the nozzle, distance between the nozzle and the collecting plate, voltage, and type of solvents, on the diameter distribution of electrospun micro/nanofibers. This enables the researcher to statistically acquire the same information as a full-factorial experimental design, but with a lower number of experiments for electrospinning process optimization. The properties acquired from every experiment were analyzed statistically. In line with Taguchi, a signal-to-noise (S/N) ratio is the statistical quantity denoting the strength of a response signal, divided by the strength of the disparity in the signal from the noise. Signal factors are the ones that designate the desired value of the outcomes' response. Noise factors are those that may not be easily managed, as they give rise to the response to depart from the desired target by the signal, resulting in "quality loss." The S/N ratio originates from loss function (a quadratic function proposed by Taguchi [36] to depict deviation of the quality of interest from its target value), which postulates different forms that rely on optimization objectives: maximization of the S/N ratio results in the minimization of any property responsive to noise. To optimize the fiber diameter, the formulation of the smallest product characteristic in the Taguchi analysis was adapted for analysis: this is the optimum factor level with the greatest S/N ratio in order to minimize sensitivity over a wide range of noises.

2. Materials and Methods

2.1. Polymeric Materials and Experimental Setup. The polymeric material used in this study was commercially available as poly(D,L)-lactide-co-glycolide (PLGA) (Resomer RG 503, Boehringer, Ingelheim, Germany) and has a LA : GA ratio of 50 : 50 and a molecular weight of 33,000 Da. Hexafluoro-2-propanol (HFIP), dichloromethane (DCM), and trichloromethane (TCM) were acquired from Sigma-Aldrich (Saint Louis, MO, U.S.A.).

Micro/nanofibers were prepared with lab-made electrospinning equipment, which included a nozzle and a 26 G (0.4 mm) needle, an aluminum plate, and a high-voltage power supply (Figure 1). The high-voltage power supply was linked to the needle. For electrospinning of PLGA micro/nanofibers, a predetermined weight/volume ratio of PLGA/solvent was first mixed for 24 h under magnetic stirring. The solutions were transported by a syringe pump with a predetermined volumetric flow rate for spinning.

Five processing variables were chosen as factors for assessment, including PLGA concentration in the solution, volumetric flow rate of the PLGA solution, distance between the needle and ground collection, positive voltage applied to polymer solutions, and the type of solvent used. The concentrations of PLGA in different solutions were 25, 28, and 30%. The flow rates of the solutions were 0.6, 0.9, and 1.2 mL/h. The nozzle-collector distances were set at 8, 12, and 15 cm.

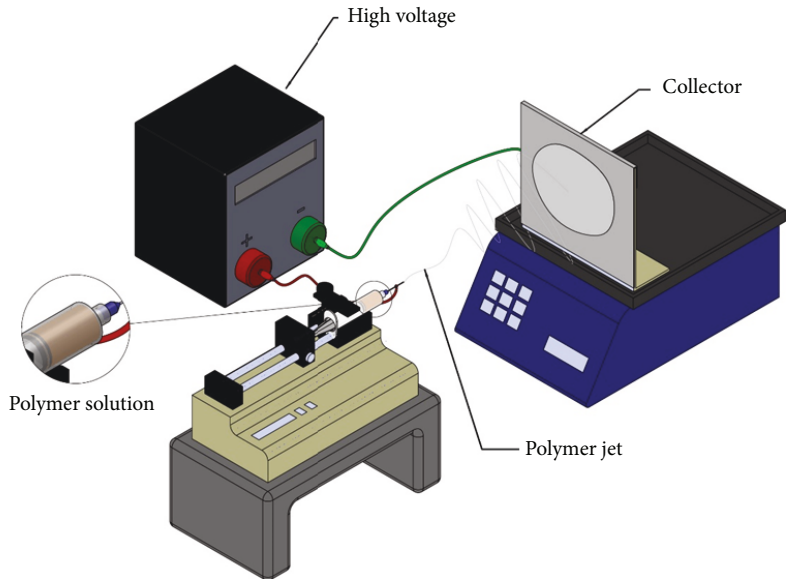

Figure 1: The electrospinning setup employed in this study.

The voltages were maintained at 15, 18, and 20 kV. Three types of solvents were employed: HFIP, DCM, and TCM, as listed in Table 1.

2.2. Experimental Variables and Design. In order to determine the influence of these five variables, each variable with three levels, it would require a great number of test trials (3^5 runs). A Taguchi-based robust design [35] was used to decrease experimental runs. The experimental procedure was composed of 18 tests, designed on the basis of the L18 array (Table 2). Three samples were assessed for each experimental run. The electrospinning of fibers with nanoscale size was the object of this study; thus, optimized processing variables were acquired by incorporating all factor levels with the smallest fiber diameter distribution.

2.3. Fiber Characterization. The morphological structure of spun micro/nanofibers was inspected under a JSM-7500F field emission scanning electron microscope (JEOL, Tokyo, Japan), after the fibers were coated with gold. The average diameter and diameter distribution were acquired by evaluating 50 randomly selected fibers from the SEM images for each test sample ($n = 3$) using a commercial ImageJ image software (National Institutes of Health, Bethesda, MD, USA).

The porosity of electrospun micro/nanofibers was computed with the below expression:

$$\text{Porosity}\,(\%) = \left\{1 - \frac{\rho_{\text{membrane}}}{\rho_{\text{polymer}}}\right\}, \tag{1}$$

where ρ_{membrane} and ρ_{polymer} denote densities of micro/nanofibers and pure PLGA, respectively.

3. Results and Discussions

In this study, experiments were successfully completed on the electrospinning setup. Figure 2 shows the SEM images and the fiber diameter distribution of electrospun fibers from the 18 processing conditions, while Table 2 lists the calculated average fiber diameters and their standard deviations (SDs). The Taguchi analysis can be divided into (1) calculation of S/N ratios, (2) estimation of mean, and (3) verification experiments. The diameters of each experimental trial are evaluated statistically.

3.1. Process Optimization in Line with the Experimental Design

3.1.1. Calculation of S/N Ratios. The ratio of signal-to-noise (S/N) is the value showing the strength of a response signal in respect to the strength of the signal variation as a function of its noise. It is an ideal metric for deciding the best values/levels for the control factors [36].

$$\frac{S}{N} = -10\log_{10}\left[\left(\frac{1}{n}\right)\sum_{i=1}^{n}\left(\bar{y}^2 + {S_n}^2\right)\right], \tag{2}$$

where $\bar{y}$ and S_n are the average value and deviation of the calculated fiber diameter, respectively, with n representing the number of specimens for each test run. Factor levels with the greatest S/N ratios minimize noise sensitivity and thereby create optimum conditions.

The change of fiber diameter due to various processing variables and noise was evaluated statistically. The S/N ratios for the fiber diameters were computed for the main experiments, and the results are listed in Table 2 as well as displayed in Figure 3. In conformity with these figures, the optimum factor levels for achieving the minimum diameter distribution for electrospun fibers were estimated to be

Table 1: Factors and factor levels selected for the analysis.

Factors	A Type of solvent	B PLGA concentration (%)	C Flow rate (mL/min)	D Voltage (kV)	E Nozzle-collector distance (cm)
Level 1	HFIP	25	0.6	15	8
Level 2	DCM	28	0.9	18	12
Level 3	TEM	30	1.2	20	15

HFIP: hexafluoro-2-propanol; DCM: dichloromethane; TCM: trichloromethane.

Table 2: L'18 (3^5) orthogonal array utilized in the experiments.

Exp	A	B	C	D	E	$\bar{y}$ (nm)	S_n (nm)	S/N (dB)
1	1	1	1	1	1	1129.8	648.4	-62.2
2	2	2	2	2	2	3689.5	2424.6	-72.8
3	3	3	3	3	3	4774.0	2292.8	-74.4
4	1	1	2	2	3	1414.6	949.6	-64.6
5	2	2	3	3	1	2165.0	637.0	-67.0
6	3	3	1	1	2	1746.0	1079.4	-66.2
7	1	2	1	3	2	24594.4	5061.7	-87.9
8	2	3	2	1	3	3437.5	2135.5	-72.1
9	3	1	3	2	1	2298.1	780.9	-67.7
10	1	3	3	2	2	4121.6	2462.6	-73.6
11	2	1	1	3	3	2091.6	1535.7	-68.2
12	3	2	2	1	1	980.8	492.1	-60.8
13	1	3	3	1	3	1861.6	2437.1	-69.7
14	2	1	1	2	1	1869.3	592.5	-65.8
15	3	2	2	3	2	4207.6	4966.0	-76.2
16	1	2	2	3	1	1189.8	638.6	-62.6
17	2	3	3	1	2	1753.8	848.8	-65.7
18	3	1	1	2	3	1938.2	768.2	-66.3

A1/B3/C1/D1/E2. These optimal factor levels denote the use of HFIP as the solvent, a PLGA concentration of 30%, a flow rate of 0.6 mL/h, a voltage of 15 kV, and a nozzle-collector distance of 8 cm.

3.1.2. Estimation of the Mean. The optimized levels of variables were not contained in the 18 tests in Table 2, so an alternative path was taken to estimate the response of the fiber diameter to optimum levels. We assumed that there was not any interplay among the chosen variables, and the estimated S/N ratio for the optimum levels, $\eta_{\mathrm{A1B3C1D1E2}}$, is:

$$\eta_{A1B3C1D1E2} = \eta_{\mathrm{m}} + (\eta_{A1} - \eta_{\mathrm{m}}) + (\eta_{B3} - \eta_{\mathrm{m}}) + (\eta_{C1} - \eta_{\mathrm{m}}) + (\eta_{D1} - \eta_{\mathrm{m}}) + (\eta_{E2} - \eta_{\mathrm{m}}) = \eta_{A1} + \eta_{B3} + \eta_{C1} + \eta_{D1} + \eta_{E2} - 4\eta_{\mathrm{m}}, \quad (3)$$

where η_{m} denotes the mean S/N ratio for the 18 experimental runs in Table 2, and η_{FN} denotes the S/N ratio for variable F and level N. Accordingly, the estimated S/N ratio of the fiber diameter for optimum variable levels, A1/B3/C1/D1/E2, was -58.30 dB. The estimated value was undoubtedly greater than that realized in Table 2.

3.1.3. Verification Experiment. A verification experimental run was completed on the basis of the optimum variable levels of A1/B3/C1/D1/E2. Figure 4 displays the SEM image of the electrospun fibers. The average fiber diameter was 466.25 ± 158.38 nm. The diameter was reduced with regard to the diameters achieved in Table 2. In addition, the calculated S/N ratio (for the fiber diameter of 466.25 ± 158.38 n m based on Equation 2) was -53.84 dB, which was obviously greater than the estimated value of -58.30 dB. This demonstrates that the diameter of electrospun fibers was satisfactorily decreased using optimized factor levels.

3.2. Significance of Processing Variables. The S/N ratio is an important measure of robustness to identify control factors that reduce variability in a product or process by minimizing the influence of uncontrollable (noise) factors [35]. The significance of each processing variable on product quality can be determined by the variation of S/N. In line with Figure 3, the significance of each variable on the diameter of electrospun PLGA micro/nanofibers was, from high to low, solvent type (ΔS/N = 9.4 dB), voltage (ΔS/N = 6.6 dB), solution flow rate (ΔS/N = 1.7 dB), polymer concentration (ΔS/N = 1.5 dB), and nozzle-collector distance (ΔS/N = 0.2 dB). For variables in this analysis, the type of solvent and the applied voltage were discovered to be the most salient factors in terms of influencing the diameter distribution of electrospun PLGA micro/nanofibers.

3.3. Effects of Electrospinning Parameters. In conformity with Figure 3, electrospun micro/nanofibers of the smallest fiber diameters (466.25 ± 158.38 nm) can be acquired by adopting the HFIP as the solvent. In addition, HFIP was generally found to electrospin the micro/nanofibers with a narrower fiber diameter distribution (e.g., tests 1, 4, 7, 13, and 16 in Figure 2), when compared to DCM and TCM. HFIP is a colorless, volatile liquid characterized by a strong, pungent odor. It is a fluorinated alcohol frequently used as solvent for polymer systems. When compared to DCM or TCM, HFIP shows strong hydrogen bonding properties for better dissolving a number of molecules with oxygen atoms, double bonds, or amine groups. It is easier for the HFIP-dissolved PLGA solution to be stretched by external electrical forces. Spun fibers thus showed the smallest diameter distribution [14].

The experimental results suggested that micro/nanofibers with the smallest diameter (466.25 ± 158.38 nm) can be obtained by applying the lowest electrical voltage (15 kV). During the electrospinning process, the polymeric solution ejected from the nozzle was stretched by external forces from electrical fields. If the applied voltage is too high (above

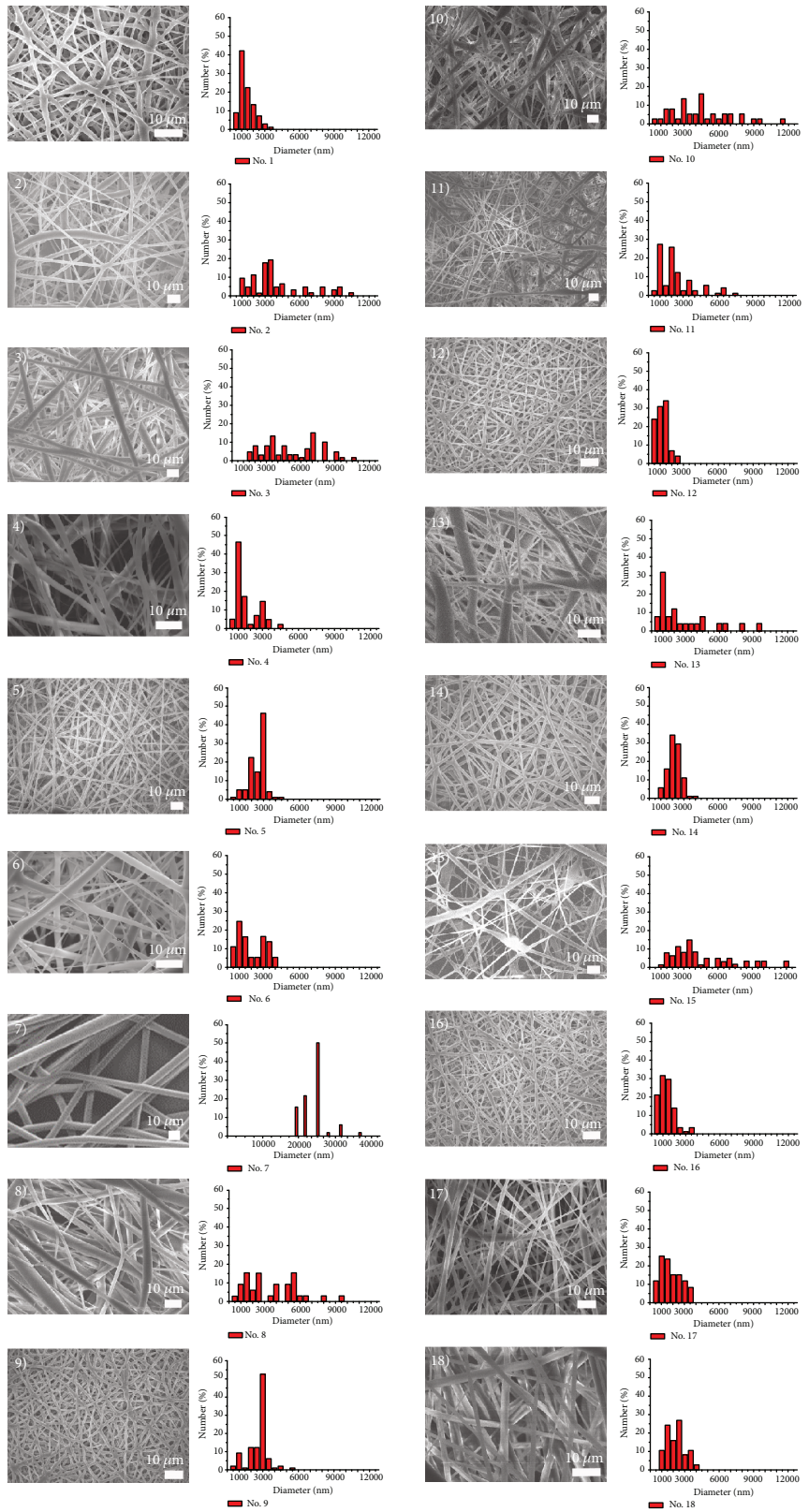

Figure 2: SEM images and fiber diameter distribution of electrospun micro/nanofibers for the 18 test trials in the main experiment.

15 kV), the solution might be overstretched and then become unstable, breaking into tiny particles rather than forming fibers [20].

The experimental outcomes indicate that fibers electrospun with a flow rate of 0.9 mL/min resulted in fibers of smaller diameter distribution. A lower flow rate of solution

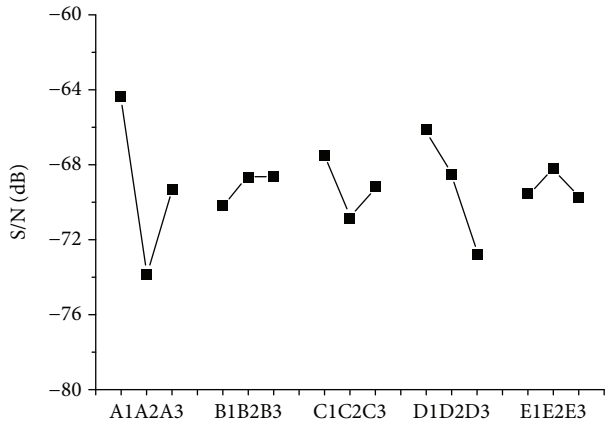

Figure 3: Alteration of the S/N ratio with various factor levels.

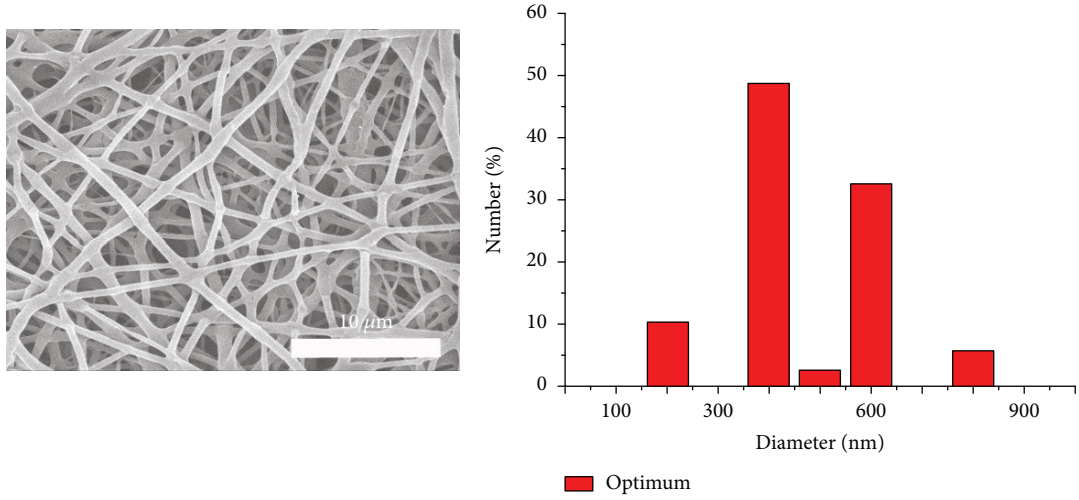

Figure 4: SEM image and fiber diameter distribution of electrospun micro/nanofibers using the optimum processing condition (the use of HFIP as the solvent, a PLGA concentration of 30%, a flow rate of 0.6 mL/h, a voltage of 15 kV, and a nozzle-collector distance of 8 cm).

generally leads to less resistance of the external stretching forces by the electrical field, with the solution becoming more extended. Electrospun fibers exhibited a smaller diameter distribution. However, if the flow rate is too low (0.6 mL/min), the solution might be overstretched and break into tiny particles. On the other hand, the empirical data suggest that the 30% PLGA concentration should be utilized to obtain micro/nanofibers with the smallest fiber diameters (466.25 ± 158.38 nm). This might be due to the fact that a high enough polymeric concentration in the solution will trigger considerable chain entanglements in the polymeric materials. The solution thus possesses enough strength to be stretched by the external electrical force. Electrospun micro/nanofibers thus showed a more uniform and smaller fiber diameter distribution.

A nozzle-collector distance of 12 cm was found to electrospin the PLGA with a smaller fiber diameter. Within a too short nozzle-collector distance (8 cm), the PLGA solution may not be sufficiently stretched after it is ejected from the nozzle. If the nozzle-collector distance is too large (15 cm), the solution may, however, break into tiny particles rather than form into fibers.

The correlation between fiber diameter and porosity for the 18 experimental runs in this study was also examined. The results in Figure 5 suggest that the porosity generally increased with fiber diameter (from 0.67 to 0.78). This might be due to the fact that it is more difficult for micro/nanofibers of greater diameters to accumulate compactly on the collector during the electrospinning process: spun porosities increased accordingly.

This study has successfully employed the Taguchi experimental design to minimize fiber diameters of electrospun PLGA micro/nanofibers. Despite that the fiber diameter was only selected as the target of optimization, the same scheme can be applied to maximize the electrospun qualities of other natural or synthetic materials. Furthermore, if a specific fiber diameter or other property is needed, one can use the relevant Taguchi formulation [36] to acquire micro/nanofibers of the desired property. This highlights

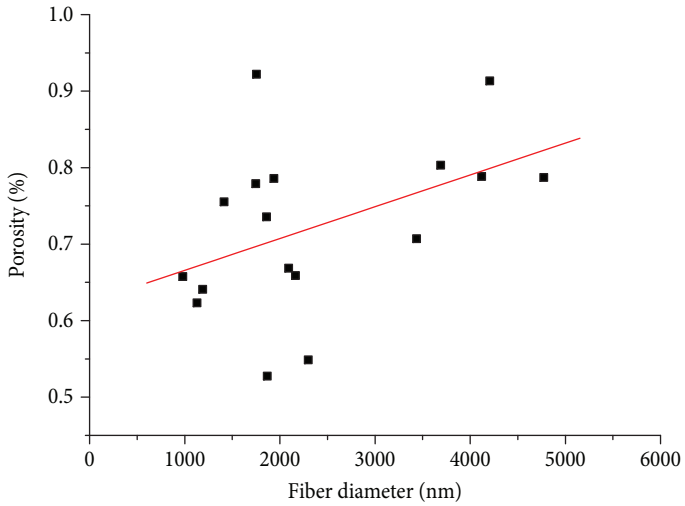

Figure 5: Correlation between micro/nanofiber diameter and fiber porosity (the line is the linear curve fitting).

the feasibility of the experimental design in manufacturing fibrous membranes for a number of applications.

4. Conclusions

The experimental results indicate that the type of solvent and the applied voltage are key factors in affecting the fiber diameter distribution of electrospun micro/nanofibers. HFIP electrospun PLGA micro/nanofibers with the smallest diameter distribution (466.25 ± 158.38 nm) mainly result from its strong hydrogen bonding properties for PLGA dissolution. When the applied voltage was too high (higher than 15 kV), the PLGA solution was overstretched and the solution breaks into tiny particles rather than forming into fibers. In addition, the porosity of electrospun PLGA mats increases with fiber diameter (from 0.67 to 0.78), owing to the fact that it is more difficult for micro/nanofibers with large diameters to accumulate compactly on the collector during the electrospinning process.

In this study, the key processing parameters that influence the distribution of PLGA micro/nanofibers have been identified by employing the Taguchi technique. This provides significant advantages in terms of effectively tailoring the electrospun fiber diameters and morphology.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Authors' Contributions

The following are the authors' contributions in this study: conceptualization: Y.-P.C. and S.-J.L.; funding acquisition S.-J.L.; investigation: H.-Y.L. and Y.-W.L.; writing: Y.-P.C. and S.-J.L.; writing -review and editing: T.-Y.L.; and supervision: S.-J.L.

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