

RESEARCH ARTICLE

Evaluation of the Effective Electrospinning Parameters Controlling Kefiran Nanofibers Diameter Using Modelling Artificial Neural Networks

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ABSTRACT

Objective(s): This paper investigates the validity of Artificial Neural Networks (ANN) model in the prediction of electrospun kefiran nanofibers diameter using 4 effective parameters involved in electrospinning process. Polymer concentration, applied voltage, flow rate and nozzle to collector distance were used as variable parameters to design various sets of electrospinning experiments for production of electrospun kefiran nanofibers.

Methods: The Scanning Electron Microscopy (SEM) was used to investigate the morphology and evaluate the size of the nanofiber. Data set was drawn using k fold cross-validation method, which was the most suitable scheme for the volume of the data in this work. Data were partitioned into the five series and trained and tested via ANN method.

Results: The Scanning Electron Microscopy (SEM) images of the generated nanofiber samples were confirmed that all of the samples were fine and defect-free. Our results indicated that the network including four input variables, three hidden layers with 10, 18 and 9 nodes in each layer, respectively, and one output layer obtained the highest efficiency in the testing set. The mean squared error (MSE) and linear regression (R) between observed and predicted nanofibers diameter were 0.0452 and 0.950, respectively.

Conclusions: The results demonstrated that the proposed neural network was appropriately performed in assessing the input parameters and prediction of nanofibers diameter.

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INTRODUCTION

Nanofibers, as one of the one-dimensional nanostructures, have attracted much attention due to their unique characteristics and fascinating potential applications in many fields [1]. Several methods exist for fabrication of nanofibers including drawing [2], template synthesis [3], phase separation [4], self-assembly [5] and electrospinning [6]. Among these methods, electrospinning seems to be the most common method due to its simplicity,

cost-effectiveness and controllability over nanofibers size and morphology [7, 8]. Moreover, electrospun nanofibers have several properties like a high surface to volume ratio, tunable porosity and ease of functionalization which give them a wide range of applications [9-11] including: 1) healthcare applications, such as scaffold in tissue engineering [12], wound healing bandages [13] and drug carrier [14, 15] with controlled release, 2) in biotechnology and environmental engineering

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as separation membrane [16] 3) in defense and security applications as protective garment [9] and 4) in energy generation used in polymeric batteries [17].

For improving the efficacy of electrospun nanofibers, their properties should be adjusted in the required ranges. Among these, nanofibers diameter plays a determinative role in nanofibers application. For example, the porosity and pore size of nanofibers can be modified by changing fibers diameter, while enhancing the overall porosity and pore size of nanofibers scaffolds can improve cell spreading, proliferation and infiltration [18]. Besides, human embryonic stem cells process is affected due to alteration in nanofibers diameter [19] and the pattern of differentiation and infiltration of osteoblastic cells are different in various fibers diameter [20]. Hence, it is important to control the electrospun nanofibers diameter as scaffolds, to manage its interactions with cells.

Several parameters influence nanofibers diameter and morphology which can be categorized into two main groups: external and internal factors. The type of the applied polymer and solvent, polymer solution feeding rate, applied voltage, and the distance between the nozzle and the collector plate are the external factors whereas the nature of solvents, and surface tension, viscosity, conductivity and concentration of the solution are considered as the internal factors [36]. Each group of parameters includes many variables and the simultaneous evaluation of factors affecting nanofibers diameter becomes very complex in experimental works, whereas suitable theoretical methods can be used for simultaneous evaluation of the effective parameters on electrospinning.

One of the effective methods successfully used for modeling electrospinning process is artificial neural networks (ANNs) [21]. ANN is inspired by human brain, in which 3-4 billions of nerve cells, called neurons, are interconnected to form the biological neural network. The neuron constructed in a mathematical model by ANNs is called node or an artificial neuron. These artificial neurons contain a network with several layers [22]. As a computational method, the well- designed ANNs are trained by a series of input data that on the basis of the previous experience are able to produce an acceptable output for new inputs [23].

Artificial neural networks (ANNs) have been

recently used to evaluate the interactions of applied electrospinning parameters with electrospun nanofibers diameter [24, 25]. Mirzaei et al. used ANNs and the correlation coefficient, R-squared (R²), between the predicted values of the nanofibers mean diameter and experimental amount for investigating the relationships between the electrospinning parameters with the diameter of polyethylene oxide (PEO) nanofibers. The influence of four parameters, including: PEO and acetic acid concentration, applied voltage, and temperature of the electrospinning media on the nanofibers mean diameter were evaluated. The results indicated the reliability of ANN model in identifying the relation between fibers diameter and aforementioned parameters [21]. The effect of concentration, conductivity, flow rate, and electric field strength on the electrospun polyethylene oxide (PEO) nanofibers diameter was also modeled by ANNs and k-fold cross-validation method by Sarkar et al [26]. The outcome of this study showed the viability of the neural network in fibers diameter prediction. Besides, Samadian et al. [27] applied ANN to optimize conductivity of carbon nanofibers (CNFs). In their study, simulated body fluid (SBF) concentration, immersion time and nanofibers diameter were exploited as input variables. They found out that diminishing CNFs' diameter, SBF concentration and immersion time could enhance conductivity in mineralized CNFs. The results of these studies demonstrated that the ANN models could be used to investigate the interactions and influences of different parameters on the nanofibers diameter.

Kefiran is a microbial polysaccharide and a water-soluble glucogalactan extracted from the flora of kefir grains and is widely used in food industry as texturing and gelling agent [28]. Several important advantages such as antibacterial, antifungal and antitumoural activities are suggested for it [29, 30]. Furthermore, kefiran can be easily isolated from the kefir grains in deproteinized whey powder with high yields [31] and could be a good candidate as a base material for food packaging [32-34].

There are few works to predict different polymer nanofibers diameter via neural networks. In our previous work, kefiran electrospun nanofibers were successfully fabricated and characterized [35]. In this paper, the prediction of kefiran nanofibers diameter using modeling ANN have been studied,

Table 1. list of input variable for electrospinning

Independent input variable	Description
X ₁	Polymer Concentration(w/v)
X ₂	Applied voltage(kV)
X ₃	Rate Flow (ml/h)
X ₄	Distance (cm)

and various sets of electrospinning were used to prepare kefir nanofibers. Moreover, the validity of ANN models in prediction of kefir nanofibers diameter is evaluated.

MATERIALS AND METHODS

In this study, the following materials were used: Kefir grains, as the starter culture, were purchased from a household in Tehran and the electrospinning process performed using Electroris (FNM Ltd., Iran, www.fnm.ir).

Starter culture

Kefir grains, as the starter culture, were cultured in milk and maintained in a closed plastic container for 24 hours at room temperature. The medium (milk) was replaced each day with fresh milk. This process was repeated for seven subsequent days to activate the grains.

Isolation and purification of kefiran

Kefiran in kefir grains was extracted through the defined method [31]. Briefly, a certain amount of kefir grains were poured in boiling distilled water (1/10 W/V) and stirred vigorously for 30 minutes. The mixture was centrifuged at 10,000 g for 20 min at 20 °C. The obtained supernatant was added to two volumes of cold ethanol (96% mark alcohol) to precipitate soluble kefiran and left at -20 °C overnight. The mixture was centrifuged at 10,000 g for 20 min at 4 °C. The pellets were collected and dissolved in hot water. The precipitation procedure was repeated two more times. The final precipitate was dissolved in hot distilled water and dehydrated at room temperature to form pure kefiran.

Preparation of the solution

Kefiran solutions were prepared by dissolving different amounts of purified kefiran in distilled water at 100 °C temperature until the polymer is completely

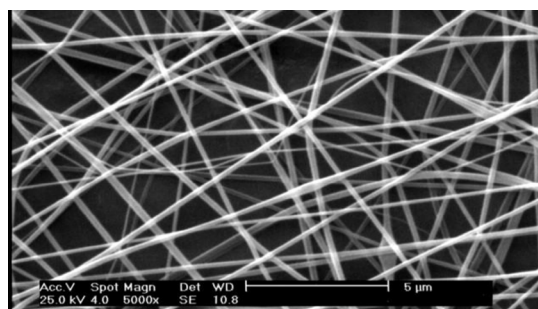


Fig. 1. A) SEM image of electrospun kefiran nanofibers of sample NO. 4 with an average diameter of 213nm.

dissolved to obtain homogenous solution.

Fabrication of electrospun nanofibers

The electrospinning process was conducted by Electroris (FNM, Tehran, Iran). A commercial plastic syringe, fitted with an 18-gauge (1.41 mm inner diameter), was used as polymer solution reservoir and equipped with a stainless steel blunted needle as a nozzle. The polymer solution was fed to the tip of the nozzle by the use of a syringe pump. A high voltage power, connected to the nozzle, electrified the polymer and a charged jet was ejected from the tip. Toward the collector, the solvent was evaporated, and kefiran nanofiber was deposited on the collector (rotating cylinder wrapped with foil). Electrospinning process was conducted based on the changing four independent variables including kefiran solution concentration, applied voltage, tip to collector distance and feeding rate, listed in Table 1.

The conductive collector (drum) was fixed at 200 rpm for all samples.

Nanofiber characterization

A piece of every electrospun nanofiber sample was coated with gold by sputtering (Bal-Tec, SCD 005, USA) and scanning electron microscope (SEM) (XL 30, Philips, USA) images were taken at an accelerating voltage of 25 kV. For each sample, the average fiber diameter was estimated from 50 nanofiber diameters, selected randomly via image analysis (Fig. 1).

Network models designing

The ANNs were designed to predict nanofibers diameter, and the accuracy of the predictions was investigated by MATLAB software. Regarding to

the previous studies, k fold cross-validation method was applied to obtain better results.

Several various experiments were designed based on different amount of four effective variables including kefir concentration (X1) (w/v), the applied voltage (X2) (kV), rate flow (X3) (ml/h), and distance (X4) (Table 1).

The empirical data are divided into the two groups, namely training and testing categories. Training data adjusts the network weights and the efficiency of the trained network is assessed by testing data.

According to the literature, using simple dataset for prediction by ANN is not proper when the database volume is small [26]. Besides, a large amount of database may also decrease the reliability of the ANN models to estimate subsequent samples if a simple training-test dataset dividing procedure is used. In order to solve these problems, k-fold cross-validation could be used instead of the simple training-test dataset dividing process to reduce the bias [37].

In this method, database randomly partitioned into the k equal subsets (Table 2) including testing and training sets, and function of approximation repeated k times to fit a function using training dataset. At every step, k-1 subsets are collected as the training set and one remaining of the k subsets is considered as the test set. Finally, the mean squared error (MSE) across all k trials is estimated and referred to as a criterion for the network validity.

Network training using k fold cross-validation procedure

25 samples of nanofibers fabricated by electrospinning were applied as ANN models training-testing dataset. SEM images of the samples showed that all the generated nanofibers were smooth and without any defect (Table 3). Before using ANN networks, data normalization was performed, so that all data has a mean of zero and variance of one.

The data normalization is assumed by:

Table 2. Training-testing partition pairs using five folds cross-validation method

Partition pairs	Training set	Testing set
1	Partition {1,2,3,4}	Partition {5}
2	Partition {1,2,3,5}	Partition {4}
3	Partition {1,2,4,5}	Partition {3}
4	Partition {1,3,4,5}	Partition {2}
5	Partition {2,3,4,5}	Partition {1}

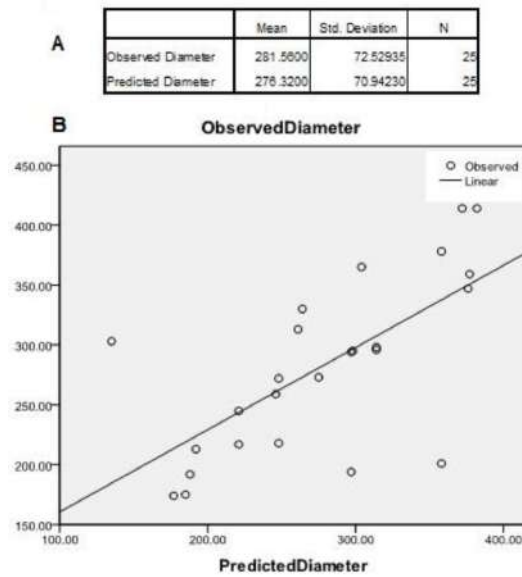


Fig. 2. A) Descriptive statistics of observed and predicted mean diameter B) Regression plot between observed diameters and predicted diameters.

$$y_{norm} = (y_{max} - y_{min})(x - x_{min}) / (x_{max} - x_{min}) + y_{min} \quad (1)$$

where, y_{min} and y_{max} are equal to -1 and 1 respectively. The parameter of x is the data that should be normalized. x_{max} and x_{min} are the maximum and minimum values of x, respectively.

ANN network Training

In this work, five neural networks with various structures including four input units, one output unit and various hidden layers with different nodes were designed. Training dataset was used to train the network and the testing data was applied to test the network.

RESULTS AND DISCUSSION

The mean square error and correlation coefficient (R) of the test dataset obtained from ANN models is seen in Table 4s. (Hidden layers = 4) (Number of a nodes in hidden layers = 10, 15, 10, 5, respectively). Mean square prediction error (MSPE) is given by equation (2):

$$MSPE_n = \frac{100}{Nte\sigma_{dn}^2} \sum_{i=1}^{Nte} (d_n(i) - d_{pn}(i))^2, n = 1, \dots, 5 \quad (2)$$

Where d_n and d_{pn} are observed and predicted size of nanofibers in n network respectively. Variables of Nte are the numbers of samples used for network

Table 3. Training Data Set for ANNs Modeling

Sample NO	concentration (wt%)	Rate flow (ml/h)	Applied voltage (Kv)	Distance (cm)	Observed Diameter (nm)	Predicted Diameter (nm)
1	6	1.7	10	14	175	185
2	6	1.7	10	20	192	188
3	6	2.3	10	14	217	221
4	6	2.3	10	20	213	192
5	6	2	15	17	194	297
6	6	1.7	20	14	174	177
7	6	1.7	20	20	201	358
8	6	2.3	20	14	218	248
9	6	2.3	20	20	245	221
10	8	2	10	17	259	246
11	8	1.7	15	17	313	261
12	8	2	15	14	296	314
13	8	2	15	17	295	298
14	8	2	15	17	273	275
15	8	2	15	20	294	297
16	8	2.3	15	17	303	135
17	8	2	20	17	272	248
18	10	1.7	10	14	330	264
19	10	1.7	10	20	365	304
20	10	2.3	10	14	378	358
21	10	2.3	10	20	414	372
22	10	2	15	17	414	382
23	10	1.7	20	14	298	314
24	10	1.7	20	20	359	377
25	10	2.3	20	14	347	376

testing and σ_{dn}^2 is the variance of d_n . Spss 17 software was used to analysis the observed and predicted average fibers diameter and calculated the standard deviation (Fig 2A). A linear regression correlation between the observed and predicted diameter of the fibers was obtained and plotted in Fig 2B.

The Pearson correlation coefficient between the observed and predicted fibers diameter was achieved equal to 0.671 that is significant at the 0.01% level. Considering the very high degrees of complexity in relations between the processing conditions and the diameter of the electrospun nanofibers, these values indicate a satisfactory trained model [38]. Similarly, the R-squared of 0.950 for test validation obtained in ANN model

designed for predicting PEO nanofibers diameter [21].

The Pearson correlation coefficients (r) between the observed (d_n) and predicted (d_{pn}) nanofibers diameter is given by equation (3):

$$r = \frac{n(\sum d_n d_{pn}) - (\sum d_n)(\sum d_{pn})}{\sqrt{[n(\sum d_n^2) - (\sum d_n)^2][n(\sum d_{pn}^2) - (\sum d_{pn})^2]}} \quad (3)$$

In this equation, n is the number of data.

3D Plots of Kefiran nanofibers diameters predicted patterns

In order to understand the effects of various selected parameters (kefir concentration, applied voltage, distance between nozzle and collector and flow rate) on kefir nanofibers diameter (Figures 3 to

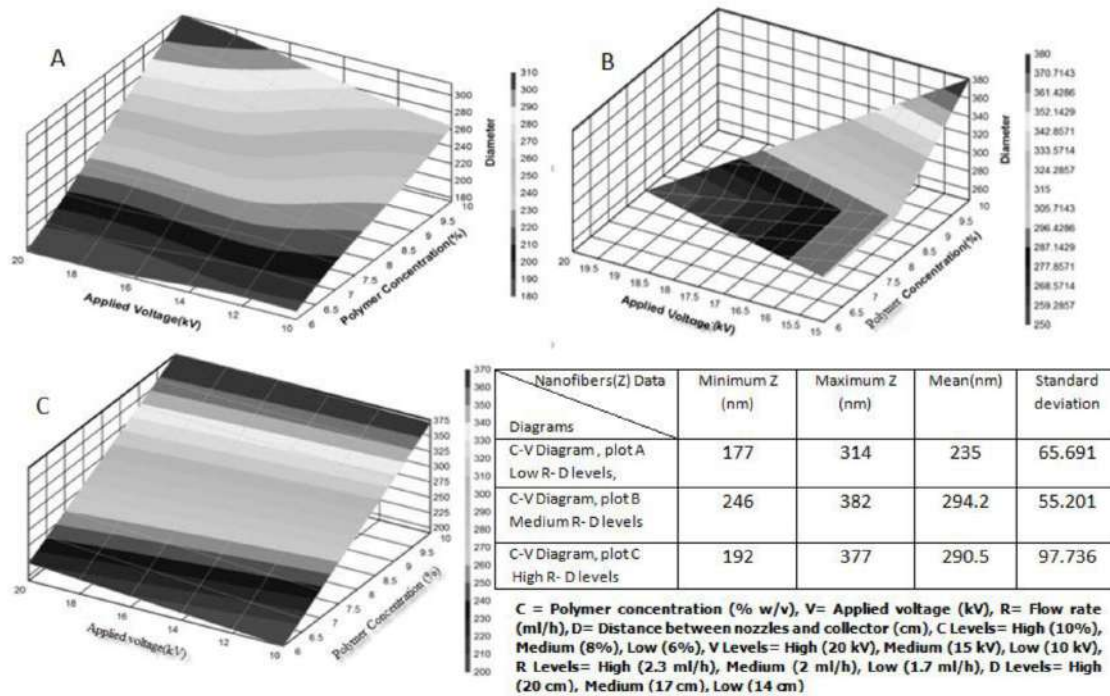


Fig. 3. The data and 3 D plots of nanofibers diameter predicted by ANN fixed in mentioned levels (C-V diagrams)

8), 3D Plots are indicated at defined levels. The results show that the minimum size of the fibers is about 235 nm in the level of low flow rate - low distance between the nozzles and collector (Low R- Low D level) (Figure 3). On the other hand, the maximum size of the fibers is approximately 294 nm within the medium flow rate – medium distance between nozzles and collector level (Medium R- D levels). The results show that at the Low R- Low D range, the nanofibers diameter increased as the polymer concentration enhanced and the largest nanofiber diameter is obtained at the highest applied voltage and polymer concentration. These results indicated

a direct relationship between these parameters and nanofibers size in this level. However, the maximum size of the nanofibers was reported at the lowest applied voltage and the highest polymer concentration, within Med R-Med D level. These results indicate the interaction between the flow rate, distance between the nozzle, and collector, and applied voltage with the fibers size.

The results show that in the Low V-Low D level, the minimum mean diameter of the nanofibers was about 257nm. In contrast, the size of the nanofibers enhanced via increasing the voltage and distance between the nozzle and collector. In this situation, the average size of the nanofibers was about 301 nm (Figure 4).

Also, 3D graphs show that in Low V-Low D level, the fibers diameter is increased by enhancing polymer concentration, whereas at the lower polymer concentration, increasing flow rate do not have considerable effect on the nanofibers diameter. The influence of the flow rate on the fibers size increased at higher concentration of the polymer. For instance, by enhancing the flow rate from 1.7ml/h to 2.3ml/h in 10% (w/w) polymer solution, fiber diameter increased from 260nm to 350nm. 3D plots results within the range of High

Table 4. Results of MSE and linear regression in tests data

DATA Set	TEST MSE	TEST R
1	0.0110	0.936
2	0.0519	0.963
3	0.0554	0.955
4	0.0851	0.930
5	0.0443	0.968
Mean	0.0452	0.950

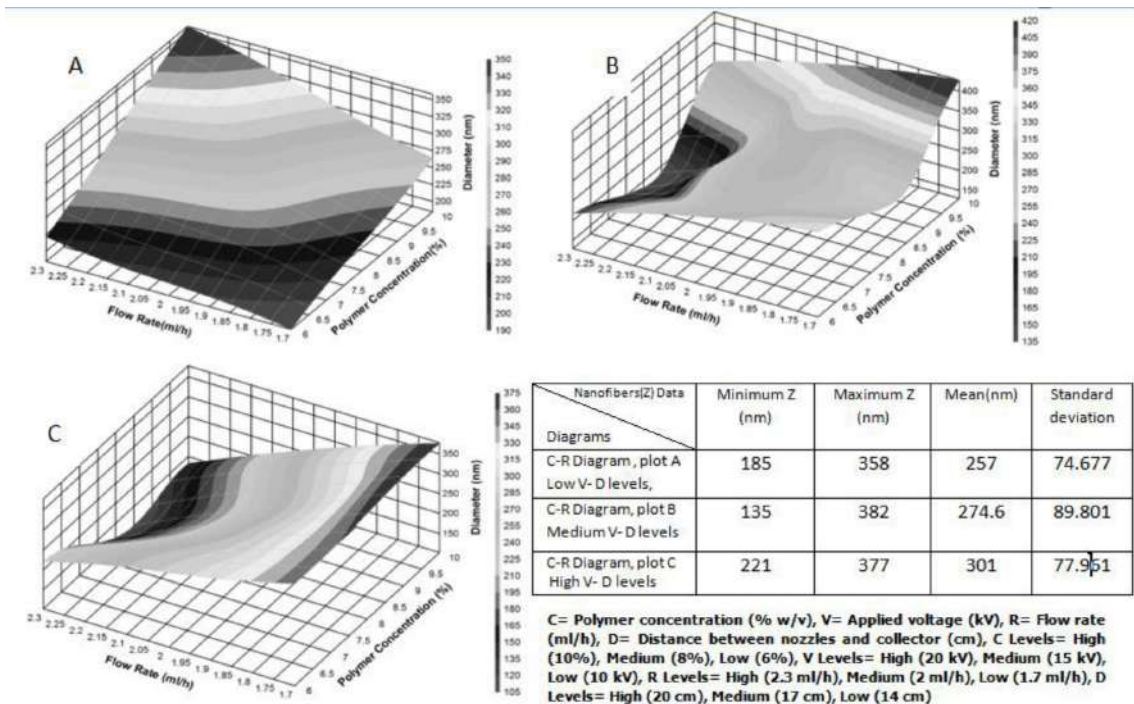


Fig. 4. The data and 3 D plots of nanofibers diameter predicted by ANN fixed in mentioned levels (C-R diagrams)

V-High D and Medium V- Medium D showed that the flow rate is inversely related to the fibers size while it has a direct relationship with the fibers diameter in the Low V-Low D area. Therefore, to produce nanofibers with determined

Based on the results of the graph, minimum fibers mean diameter in the range of the low voltage and flow rate was about 235nm (Figure 5). The maximum size of the fibers is seen in the Med V and Med R area (about 317nm).

The plot shows that distance between the collector and nozzle has insignificant effects on the fibers diameter, solely. The direct relation between polymer concentration and the fibers diameter is demonstrated like in the other plots. Base on the plots data, in the High V-High R region, increasing the distance results in smaller fibers at a constant concentration which was not seen in other plots. This result can be due to the internal interaction between parameters which needs further more precise investigation.

The minimum mean diameter of Kefiran fibers (about 207 nm) was seen in the Low C-Low D area (Figure 6). In contrast, the maximum mean size of the nanofibers (about 358 nm) was reported in the

High C-High D area. Ascending peak of the fibers diameter can be obtained with increasing flow rate in the Low C-Low D and High C-High D levels, unlike the Med C –Med D level that the descending peak was observed with increasing the flow rate of polymer solution.

The obtained results show that increase and decrease in applied voltage do not have considerable effects on the fibers size. Although, there is an exception in the High C-High D area, in which increasing applied voltage produced thicker nanofibers.

The results show that the minimum mean size of the fibers (about 227 nm) is obtained in the Low C-Low R area (Figure 7). The maximum mean diameter of the fibers was about 370 nm which is related to the High C-High R area. In the Low C-Low R area, the fibers diameter show non-significant alteration by changing the distance between 14 to 16 cm and the applied voltage from 10 to 14 kV. However, simultaneously increasing in the applied voltage and distance from 14 to 20 kV and 16 to 20 cm, respectively, result in proportional augmentation in the fibers sizes. Furthermore, in the High C-High R graphs, distance and applied voltage also show a direct relationship with fibers diameter, whereas

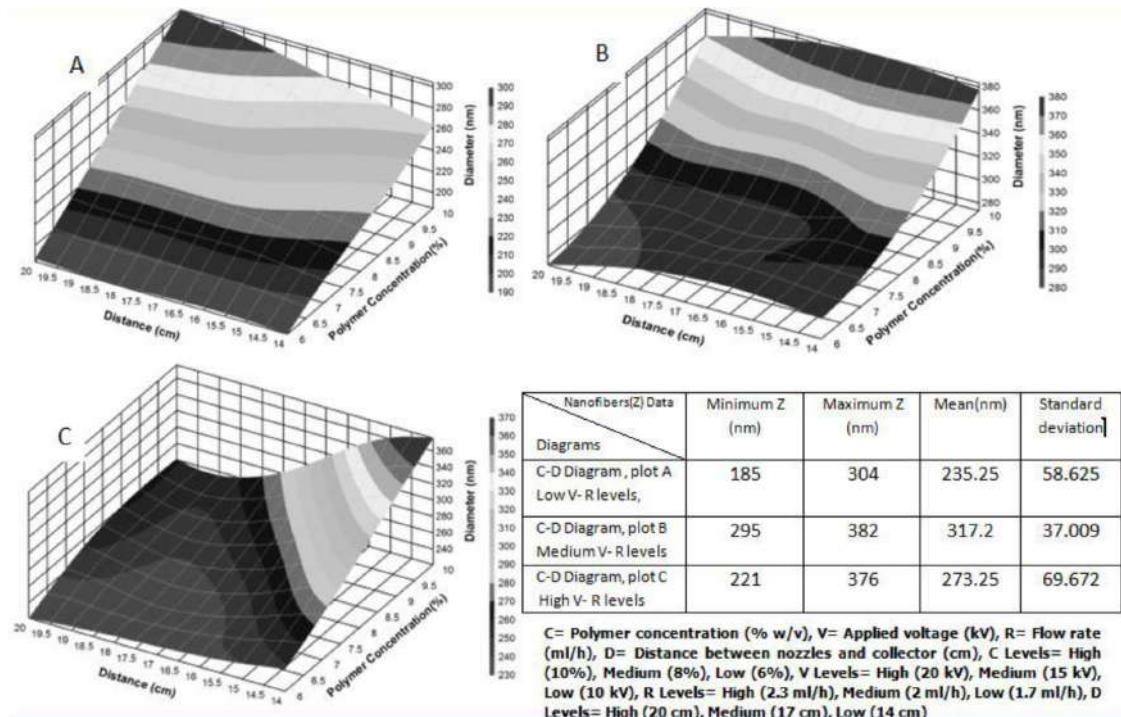


Fig. 5. The data and 3 D plots of nanofibers diameter predicted by ANN fixed in mentioned levels (C-D diagrams)

in the Medium C- Medium R area, results are different. In this area, the largest size of the fibers is observed at the medium voltage (16-18kV) and low distance (14-15 cm) level. Plots demonstrate the reciprocal effects of the polymer concentration and flow rate on the fibers diameter in the medium area. These interactions can be assessed in further complementary studies.

The results of the table showed that the minimum mean size of the fibers (196.5 nm) is related to the Low C-Low V area (Figure 8s). The maximum mean size of the fibers (about 328 nm) obtained in the High C-High V stage. The results of the Low C-Low V and Medium C-Medium V plots almost followed the same trend, and the largest fibers are obtained at the lowest distance (14-15cm) and the highest flow rate (2ml/h) in these areas. The results of the plots also show that in these areas, the fiber diameter decreased as the distance increased. Based on these results, the amount of the flow rate has a direct relation to the fibers size. Besides, changing the distance at a constant flow rate does not have considerable effects on the fibers diameter.

In the High C-High V area, the maximum size of the fibers is seen at the high range of flow rate (2.3 ml/h) and distance (17-18cm) that can be due to the

interaction between the high concentration of the polymer, the applied voltage, the flow rate and the distance. These complex communications between the applied parameter and the nanofibers diameter could be evaluated in further studies. The results of the plots revealed that the nanofibers diameter has an indirect relationship with the distance between nozzle and collector.

CONCLUSIONS

In this paper, the validity of the artificial neural network (ANN) models was evaluated for prediction of electrospun kefiran nanofibers diameter. In this research, various experiments were designed via changing four main involved parameters in electrospinning process including: polymer concentration, applied voltage, flow rate and nozzle to collector distance. SEM images of all experiments showed that all of the produced nanofibers were fine and defect-free. The nanofibers diameter was predicted through the designed ANN models, and the best ANN with acceptable MSE and regression coefficient was selected. In the selected ANN, the correlation between observed and predicted fibers diameter was significant and confirmed that the ANN model was fitted with

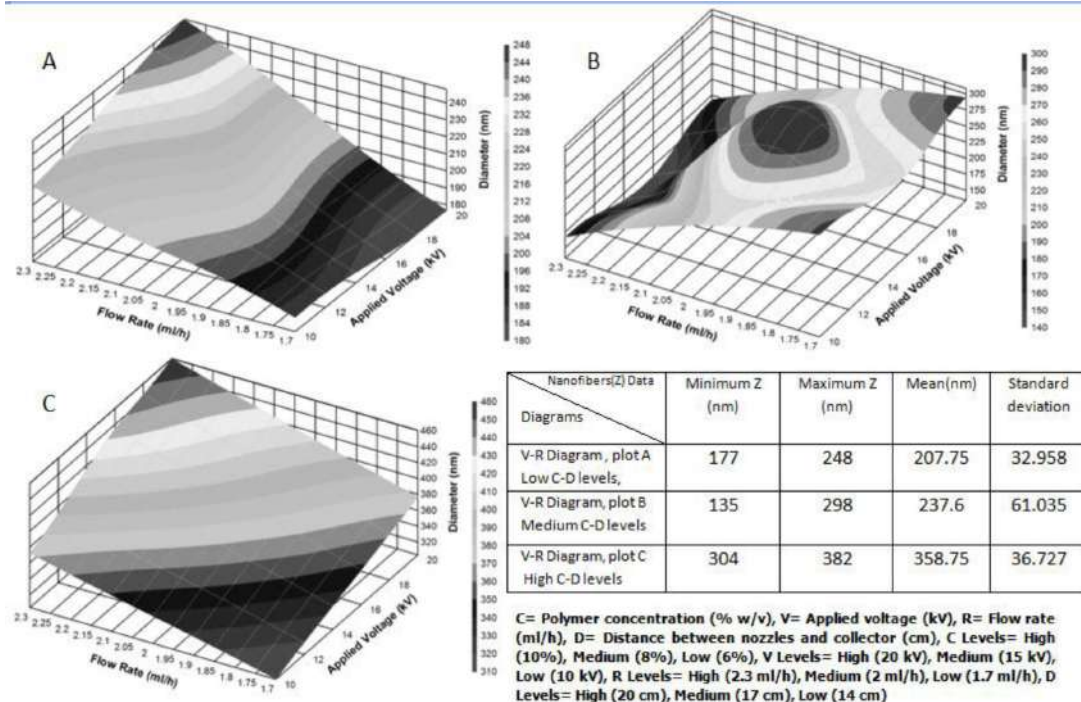


Fig. 6. The data and 3 D plots of nanofibers diameter predicted by ANN fixed in mentioned levels (V-R Diagrams)

experimental data. Also, our results indicated that the ANN is an appropriate method for prediction of kefiran electrospun nanofiber based on the four input variables. Besides, other sets of variables and polymers could be placed in ANN models to develop the insight into the nanofibers diameter prediction.

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

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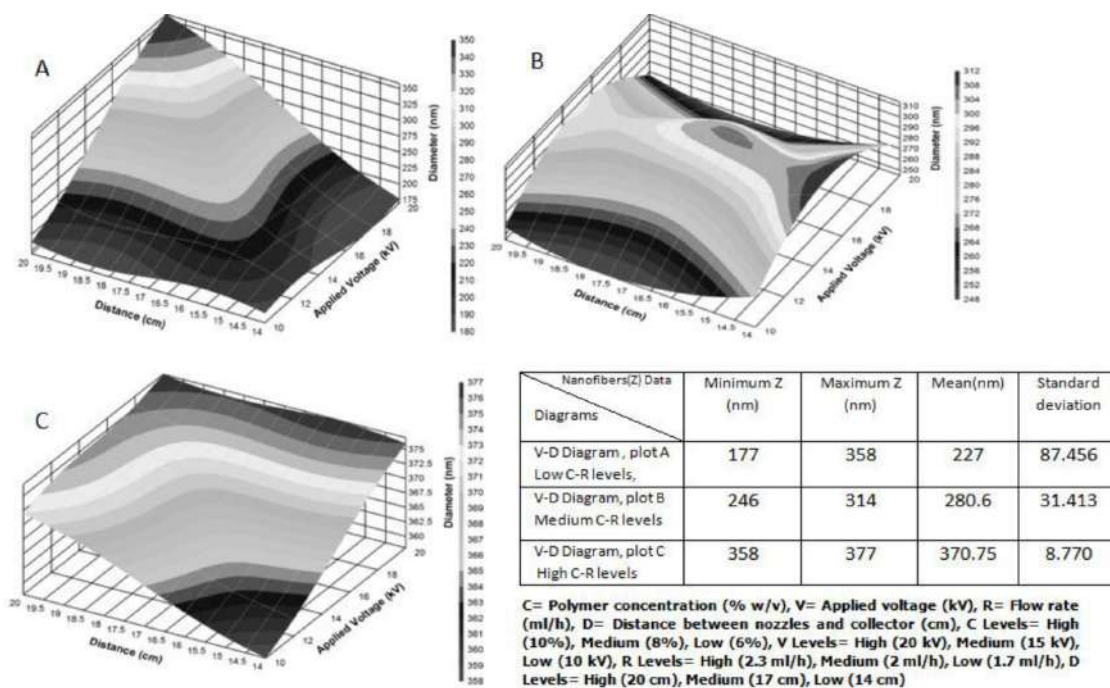


Fig. 7. The data and 3 D plots of nanofibers diameter predicted by ANN fixed in mentioned levels (V-D Diagrams)

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