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ORIGINAL ARTICLE / ÖZGÜN MAKALE

FABRICATION AND CONTROLLING MORPHOLOGY OF POLYETHYLENE OXIDE/SODIUM ALGINATE BEADS AND/OR FIBERS: EFFECT OF VISCOSITY AND CONDUCTIVITY IN ELECTROSPINNING

POLİETİLEN OKSİT/SODYUM ALJİNAT BONCUKLARININ VE/VEYA LİFLERİNİN ÜRETİMİ VE MORFOLOJİK KONTROLÜ: ELEKTROEĞİRMEDE VİSKOZİTE VE İLETKENLİĞİN ETKİSİ

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ABSTRACT

Objective: *The aim of the study is to determine the viscosity and conductivity of PEO/NaAlg polymer solutions, to formulate PEO/NaAlg beads, bead-on-string fibers and fibers via electrospinning, and to perform advanced morphological characterization studies on them.*
Material and Method: *Effect of PEO and NaAlg concentration and ratio of them on spinnability, viscosity and conductivity of solutions, and also on the morphological properties of PEO/NaAlg electrospun fibers, and beads (length, width and aspect ratio of beads, number of beads and bead area) were investigated.*
Result and Discussion: *As a result, electrospun materials were produced using PEO/NaAlg beads and/or fibers, which are valuable for medical and biological applications such as tissue engineering, wound dressing, drug delivery system. Viscosity and conductivity of solutions, and morphological properties of the obtained materials were found to be affected by PEO and NaAlg concentration and the ratio of them. Spinnability was improved thanks to the increase in conductivity in the presence of PEO. The lower viscosity and conductivity resulted in the production of beads that were generally smaller and greater in number in the material and having higher area. The morphological properties of PEO/NaAlg electrospun materials can be modified by controlling the parameters examined in the study.*

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ÖZ

Amaç: *Çalışmanın amacı, PEO/NaAlg polimer çözeltilerinin viskozite ve iletkenliklerini belirlemek, PEO/NaAlg boncukları, boncuk-iplik lifleri ve lifleri elektroeğirme yöntemiyle formüle etmek ve bunlar üzerinde ileri morfolojik karakterizasyon çalışmaları yapmaktır.*
Gereç ve Yöntem: *PEO ve NaAlg derişiminin ve oranlarının çözeltilerin eğrilebilirliği, viskozitesi ve iletkenliği ve ayrıca PEO/NaAlg elektroeğrilmiş liflerin ve boncukların morfolojik özellikleri (boncukların uzunluğu, genişliği ve en boy oranı, boncuk sayısı) üzerindeki etkisi incelenmiştir.*
Sonuç ve Tartışma: *Sonuç olarak, doku mühendisliği, yara örtüsü, ilaç taşıyıcı sistem gibi tıbbi ve biyolojik uygulamalar için değerli olan PEO/NaAlg boncuklar ve/veya lifler elektroeğirme yöntemiyle üretilmiştir. Çözeltilerin viskozite ve iletkenliği ile üretilen materyalin morfolojik özelliklerinin PEO ve NaAlg derişiminden ve oranlarından etkilendiği bulunmuştur. PEO varlığında iletkenlikteki artış sayesinde eğrilebilirlik iyileştirilmiştir. Daha düşük viskozite ve iletkenlik, genellikle daha küçük, daha fazla sayıda ve daha büyük alana sahip boncukların üretilmesine neden olmuştur. PEO/NaAlg elektroeğrilmiş materyallerin morfolojik özellikleri, çalışmada incelenen parametreler kontrol edilerek değiştirilebilir.*
Anahtar Kelimeler: *Elektrik iletkenliği, elektroeğirme, elektroeğrilmiş boncuklar, polietilen oksit(PEO)/sodyum aljinat (NaAlj), viskozite*

INTRODUCTION

Electrospinning is a reproducible, one-step, inexpensive method that allows the production of beads and/or fibers with many polymers and solvents. In electrospinning, a jet is created by applying a high voltage over a polymer solution/emulsion to create an intense electric field on a droplet at the tip of a needle. The jets are then collected on a metal collector and the dried electrospun materials can be used for many purposes such as wound healing, drug delivery system and tissue engineering applications [1,2].

Sodium alginate (NaAlg) is a natural linear polysaccharide polymer of mannuronic acid and β-D-α-L-guluronic acid. It is extracted from brown seaweed or produced from the bacteria (Pseudomonas and Azotobacter). It is a hyrophilic polymer widely used in the pharmaceutical industy due to being nontoxic, biocompatible, biodegredable and has unique gel ability, swelling, film-forming and mucoahesive properties. It is also known to be antibacterial, antiinflammatory and antioxidant. In addition, NaAlg-based drug delivery systems draw attention with their advantages such as controlled release, better efficacy at lower doses and frequency of administration, and therefore reducing toxicity. Thus, NaAlg has a wide range of uses in the pharmaceutical industry such as wound dressing, tissue scaffolding, skin healing and drug delivery system [3-7]. Despite all these advantages, spinnability of pure alginate is a great challenge due to its polyelectrolyte structure, high viscosity and limited solubility. In the study, polyethylene oxide (PEO), flexible and uncharged polymer, was preferred because of its ability to improve the spinnability of NaAlg, by reducing the repulsive force between polyanionic molecules when added to NaAlg [7].

PEO is another preferred hydrophilic polymer in the pharmaceutical industry. It has a repeating structural unit of CH_2CH_2O and has a wide range of different molecular weights (100 000 to 8 000 000). It is also known as poly(ethylene glycol). PEO is preferred as a drug delivery system and biomaterial thanks to its advantages such as high biocompatibility, nontoxicity, ease of production, and insensitivity to the pH of physiological fluids [8]. Unlike NaAlg, PEO is a linear polymer and can easily spinnable.

Viscosity and conductivity of solutions are crucial parameters in the electrospinning. The viscosity plays critical role in the formation of stable taylor cone on the droplet, so it is one of the most effective parameters on the production of beads or fibers and their morphological characterization [1,9-11]. Since the polymer solution must be stretched by the charges collected on the drop at the needle tip, the solution must have sufficient electrical conductivity for electrospinning. The spinnability of solutions, the production of beads or fibers and their morphology are directly affected by the electrical conductivity of the solutions [9,12,13]. Therefore, viscosity and conductivity of the polymer solutions were determined in this study.

Although at first bead-on-string fibers were considered to be useless in electrospinning, nowadays it is thought that beads can be used, especially for high drug loading [14]. In the future, electrospinning may be a preferred method for the production of beads, especially to be used for purposes such as scaffold or wound dressing, as it enables the production of beads in the form of scaffolds. At the same time, in order to obtain beadless fiber, the factors affecting bead formation should be clarified. The main objective of this study is to determine the viscosity and conductivity of PEO/NaAlg polymer solutions, to formulate PEO/NaAlg beads, bead-on-string fibers and fibers via electrospinning, and to perform advanced morphological characterization studies on them. Although there are many studies in the literature examining the production and morphology of the fibers in materials produced by electrospinning, there are not enough studies on the production of beads by electrospinning and the detailed characterization of the produced beads. The study is the first to investigate the effects of the use of mixtures of different polymers at different concentrations and in different ratios on the effects of viscosity and conductivity of the polymer solutions and on the advanced morphological properties of beads (average length and width of beads, aspect ratio of beads, number of beads and bead area), and as well as fibers in electrospun materials. The current study provides fabrication and morphological characterization of PEO/NaAlg beads and/or fibers which are valuable for producing electrospun materials for medical and biological applications such as tissue engineering, wound dressing, drug delivery system.

MATERIAL AND METHOD

Materials

PEO (MW 400.000) and NaAlg were obtained from Sigma-Aldrich. All chemicals used were of analytical grade.

Preparation of PEO/NaAlg Electrospun Materials via Electrospinning

3-5% w/v PEO and 1-2% w/v NaAlg were dissolved in distilled water. They were mixed in different proportions for different formulations and poured in a syringe. Then, the syringe was fixed in a syringe pump. Flow rate (1 ml/h), voltage (16 kV) and needle tip-collector distance (14 cm) were set from the electrospinning device (Ne-200, Inovenso, Turkey). The collector of the device was covered by aluminum foil and they were dried at room temperature for 48 h. PEO/NaAlg electrospun materials produced in the study were given in Table 1.

Table 1. PEO/NaAlg electrospun materials prepared in the study

	PEO (w/v%)	**NaAlg (w/v%)**	**Ratio of PEO:NaAlg (w/w)**
F1	3	1	1:1
F2	3	1	2:1
F3	3	2	1:1
F4	3	2	2:1
F5	4	1	2:1
F6	5	1	2:1
F7	4	2	1:1

Viscosity of Polymer Solutions

The viscosity of the polymer solutions were determined by Brookfield Viscometer (LVDV-I Prime, U.S.A.) at 100 rpm (spindle no: 14). All the tests were done in triplicate at room temperature. Values were expressed as mean viscosity [millipascal-second (mPa·s)] ± standard deviation.

Electrical Conductivity of Polymer Solutions

Electrical conductivity was measured by an electric conductivity meter (SevenEasy Conductivity, Mettler-Toledo, Switzerland) at room temperature (n=3). Values were expressed as mean conductivity [milisiemens (mS)] ± standard deviation.

Morphologies of Electrospun Fibers and/or Beads

Morphologies of the beads and/or fibers were examined by scanning electron microscope (SEM) (QUANTA 400 F Field Emission SEM, Holland). Electrospun mats were coated with gold before SEM analysis. The length and width of beads and mean diameters of fibers were determined by the measurement of 100 beads/fibers using SEM images via Image J. Aspect ratio of beads divided by lengths and widths for each beads was calculated (n=100). Number of beads and bead area % were also determined using SEM images via Image J.

Statistical Analysis

Statistical analysis was done using SPSS 18.0 (SPSS, Chicago, IL). The significance was determined with one-way ANOVA result with Tukey's post hoc test. The data of $p<0.05$ was considered significant. Values were expressed as mean ± SD.

RESULT AND DISCUSSION

Viscosity and Conductivity of Solutions

The viscosity and conductivity of the aqueous solutions of PEO and NaAlg at the concentrations used in the study were given in Table 2.

Table 2. Viscosity and conductivity of the aqueous solutions of PEO and NaAlg[a]

	Viscosity (mPa·s)	Conductivity (mS)
3% PEO	84.4±0	123.2±0.4
4% PEO	237.2±1.3	116.3±0.6
5% PEO	724.1±2.4	115.1±0.2
1% NaAlg	27.3±0.4	32.2±1.1
2% NaAlg	294.5±2.1	44.1±0.8

[a]Values are expressed as mean± standard deviation (n=3)

It is known that the viscosity of the polymer solution plays an important role in the electrospinning process. An ideal (neither low nor high) viscosity is desirable for the spinnability and especially fiber formation rather than beads. The viscosity of the polymer solution should be low enough not to prevent jet formation by the electric field, and high enough to allow the polymer solution to form a taylor cone without flowing at the needle tip [1,9-11]. While the viscosity of PEO solutions was 84-724 mPa·s, it varied between 27-295 mPa·s in NaAlg solutions. There was a significant difference between the viscosities of all the polymer solutions ($p<0.05$). As expected, the increase in both PEO and NaAlg concentrations resulted in an increase in viscosity ($p<0.05$) (Table 2).

Conductivity of PEO solutions ranged from 115 to 123 mS, while the conductivity of NaAlg solutions ranged from 32 to 44 mS. It was remarkable that the conductivity of NaAlg solutions was very low (approximately 3-4 times) compared to PEO solutions ($p<0.05$) (Table 2).

The viscosity and conductivity of the polymer solutions, in which the electrospun materials were produced, were given in Table 3.

The viscosity of polymer solutions producing electrospun materials ranged from 47 to 248 mPa·s and was related to the amount of PEO and NaAlg they contained. Except for F6 and F7 ($p>0.05$), there was a significant difference between the viscosities of the formulations ($p<0.05$). The viscosity increased with the increasing PEO and NaAlg concentration and the ratio of PEO to NaAlg ($p<0.05$) (Table 3).

Table 3. Viscosity and conductivity of polymer solutions which produced electrospun materials[a]

	Viscosity (mPa·s)	Conductivity (mS)
F1	46.9±0	144.3±0.4
F2	64.8±0.4	141.9±0.5
F3	120.5±1.6	134.8±0.3
F4	151.2±1.4	139.5±0.8
F5	133.2±1.4	142.1±0.3
F6	245.6±1.0	144.4±0.4
F7	247.9±0.6	137.5±0.6

[a]Values are expressed as mean± standard deviation (n=3)

The conductivity of the solutions is another parameter in the electrospinning process. It affects the spinnability of solutions, the production of beads or fibers and their morphology. Low electrical conductivity of the polymer solution leads to bead formation. It is also known that the increase in the electrical conductivity causes an increase in the stretching forces on the jet, leading to the formation of finer jets and finer fibers. As a result, high electrical conductivity leads to finer fiber production with fewer beads [9,12]. It explained the smooth fiber production with very few beads in the F6 which had the highest electrical conductivity (144 mS). While the conductivity in F1 (144.3 mS) was similar to that of F6 (144.4 mS) ($p>0.05$), the formation of beads instead of fibers in F1 was due to the insufficient viscosity of F1 compared to F6 ($p<0.05$). In addition, although the viscosity of F7 (248 mPa·s) was similar to that of F6 (246 mPa·s) ($p>0.05$), the beaded fibers were formen in F7, unlike F6, which formed smooth fibers. This was due to F7 not having high enough conductivity. In conclusion, the current study has proven that both viscosity and electrical conductivity are highly effective in producing fibers or beads, and it is not sufficient for fiber production to be ideal of only one of them.

Preparation and Morphology of PEO/ NaAlg Electrospun Materials

PEO/NaAlg beads and fibers were produced successfully by altering the formulation parameters, viscosity and conductivity. The concentration of PEO (3-5%) and NaAlg (1-2%) and the polymer ratio (1:1 and 2:1) affected the viscosity and conductivity of the polymer solutions and the advanced morphological properties of fibers (diameter and distribution) and beads (mean length and width of beads, aspect ratio of beads, number of beads, and bead area) in electrospun materials. For this purpose, various formulations given in Table 1 were prepared.

The spinnability of pure PEO and NaAlg was also determined. While pure PEO was spinnable, pure NaAlg was not suitable for electrospinning. Because the electrical conductivity of NaAlg aqueous solutions was not sufficient to stretch the charges collected on the drop at the needle tip [9,12]. As seen in Table 2, the conductivity of the NaAlg solutions was 32 and 44 mS, which was quite low compared to PEO solutions ($p<0.05$). In fact, one of the main goals of using PEO was to improve the spinnabililty of NaAlg. Hu et al. claimed that reducing the repulsive force between the polyanionic molecules of NaAlg via hydrogen bonding in the presence of PEO allows fiber production [7]. In addition, the current study also proved that NaAlg could not spin due to its very low conductivity and the increase in conductivity in the presence of PEO improved the spinnability.

The effect of NaAlg concentration and PEO/NaAlg ratio on the morphological properties of beads and fibers of PEO/NaAlg electrospun materials were given in Figure 1 and Table 4.

It was observed from the SEM images that the F1-F4 formulations had a high bead ratio (53-85%) and consisted of many beads with few fibers (Figure 1, Table 4). Increasing the PEO/ NaAlg ratio from 1:1 (F1 and F3) to 2:1 (F2 and F4) increased the viscosity, resulting in an increase in the average width and aspect ratio of the beads, while decreasing the bead area in percent ($p<0.05$). As a result, increasing PEO content and decreasing NaAlg content resulted in the formation of more elliptical beads rather than spherical beads with smaller area in the electrospun material. The main reason was that increasing viscosity reduces bead formation and increases fiber formation ($p<0.05$) (Table 3) [15]. In fact, the decrease in viscosity increased the aspect ratio of the beads ($p<0.05$), indicating a transition from beads to fiber. It is known that increasing the viscosity of the solution causes the formation of thicker fibers by electrospinning [16,17]. On the contrary, in our study, although the viscosity always increased with the increase in PEO/NaAlg concentration, there was not always an increase in fiber diameter. There was even a reduction in fiber diameters in the F1-F2 formulations (Figure 1, Table 4).

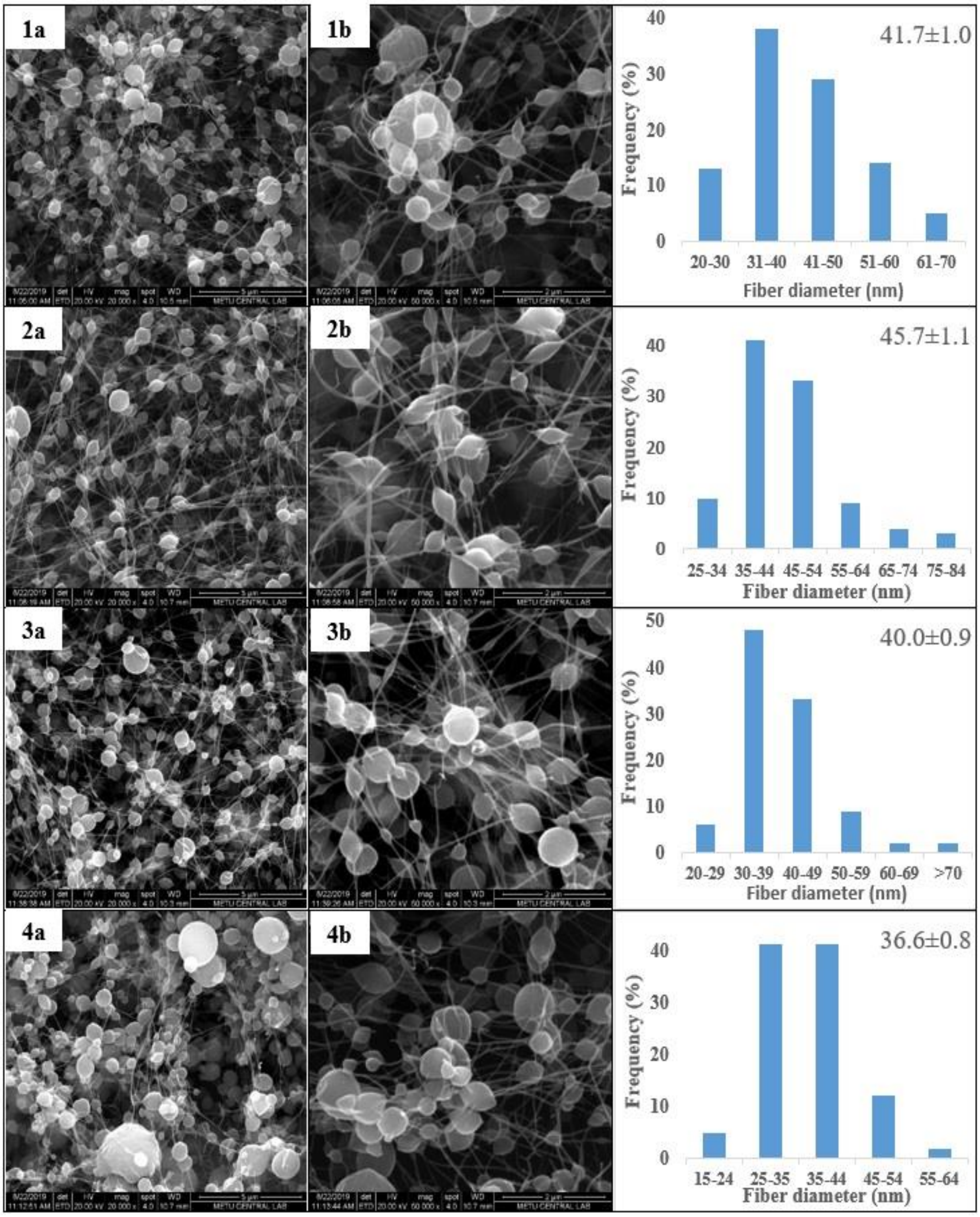

Figure 1. Effect of NaAlg concentration and the ratio of PEO/NaAlg on the morphology and fiber diameter distribution of the electrospun materials[a]

[a]Containing 3%PEO and 1%NaAlg in the ratio of PEO/NaAlg of [F1: (1-1), and F2: (2-1)] and 2%SA in the ratio of [F3: (1-1), and F4: (2-1)] (magnification = a: 20.000×, b: 50.000×)

Table 4. Effect of NaAlg concentration and the ratio of PEO/NaAlg on the morphological properties of beads of PEO/NaAlg electrospun materials[ab]

	F1	F2	F3	F4
The structure	Many beads+fibers	Beads+fibers	Many beads+fibers	Beads+fibers
Bead area %	85.4	53.1	67.1	52.77
Number (beads/µm^2)	3.11±0.03	1.98±0.02	2.63±0.03	3.35±0.32
Aspect ratio of beads	1.20±0.04	1.76±0.53	1.39±0.03	1.48±0.04
Average length of beads (nm)	632.7±32.7	756.5±22.8	660.9±21.5	562.0±35.6
Average width of beads (nm)	552.8±28.4	451.6±21.2	491.6±21.8	388.4±27.1

[a]Values are expressed as mean± standard deviation (n=3)
[b]Containing 3%PEO and 1%NaAlg in the ratio of PEO/NaAlg of [F1: (1-1), and F2: (2-1)] and 2%SA in the ratio of [F3: (1-1), and F4: (2-1)]

In the current study, increasing the PEO:NaAlg ratio from 1:1 to 2:1 resulted in both a decrease (F1 to F2) and an increase (F3 to F4) in conductivity, while increasing the viscosity ($p<0.05$). The increase in conductivity led to the formation of more beads (increase in numbers of beads/µm^2) which had greater length, and thinner fibers in both groups independent of the increase in viscosity ($p<0.05$). It clearly proved the effect of the increase in conductivity on the number of beads, length of beads and diameter of fibers ($p<0.05$). As the electric charge density in the ejected jets increases with the increase in electrical conductivity, it causes stronger elongation forces. Since the excess charges will create a self-repunsion force, it leads to the formation of finer jets and thus finer fibers [18-20]. In previous studies, it was also stated that the low electrical conductivity of the polymer solution used resulted in thinner fibers and more beads [12,21]. In conclusion, the present study proved that the conductivity of polymer solutions is more effective than the viscosity on the properties of electrospun materials.

Increasing the NaAlg concentration from 1% to 2% also led to a reduction in bead area due to reduced conductivity (Table 3). While the decrease was statistically significant for F1-F3 ($p<0.05$), it was not statistically significant for F2-F4 ($p>0.05$). This can be explained by the fact that the decrease in conductivity between F1-F3 is greater than the decrease between F2-F4 (Table 3). NaAlg concentration and PEO:NaAlg ratio had no significant effect on fiber diameter ($p>0.05$). This proved that the increase in viscosity and decrease in conductivity were more effective on bead formation and morphology rather than the fiber diameters.

Effect of PEO concentration on the morphological properties of fibers and beads of PEO/NaAlg electrospun materials were given in Figure 2 and Table 5.

While the bead area was 53.1% for 3% PEO (F2), it decreased to 13.7% when the PEO concentration was increased to 4% (F5) and to 10.7% when increased to 5% (F6) ($p<0.05$). Similarly, the number of beads also decreased (Figure 2 and Table 5) ($p<0.05$). As a result, the bead area and number of beads were directly related to the PEO concentration. The fiber diameter was also affected by the PEO concentration, and the increase in concentration resulted in thicker fiber production. These might be brought on by the increasing both viscosity and conductivity of solutions with increasing PEO concentration (Table 3) ($p<0.05$). It is known that high electrical conductivity leads to finer fiber production with fewer beads [9,12], while high viscosity leads to thicker fiber production with fewer beads [1,13]. In F6, many fibers with few bead-on-string fibers were produced due to the highest viscosity, whereas beads were dominant at lower viscosities. Therefore, fewer beads were formed with the increase in both viscosity and conductivity ($p<0.05$), the increase in viscosity was more effective on the the fiber diameter than the increase in conductivity, and an increase in fiber diameters was observed. Moreover, the increase in PEO concentration also caused an increase in length and width of beads

($p<0.05$). As a result, it was shown that the increase in concentration and viscosity resulted in the production of fewer but larger beads.

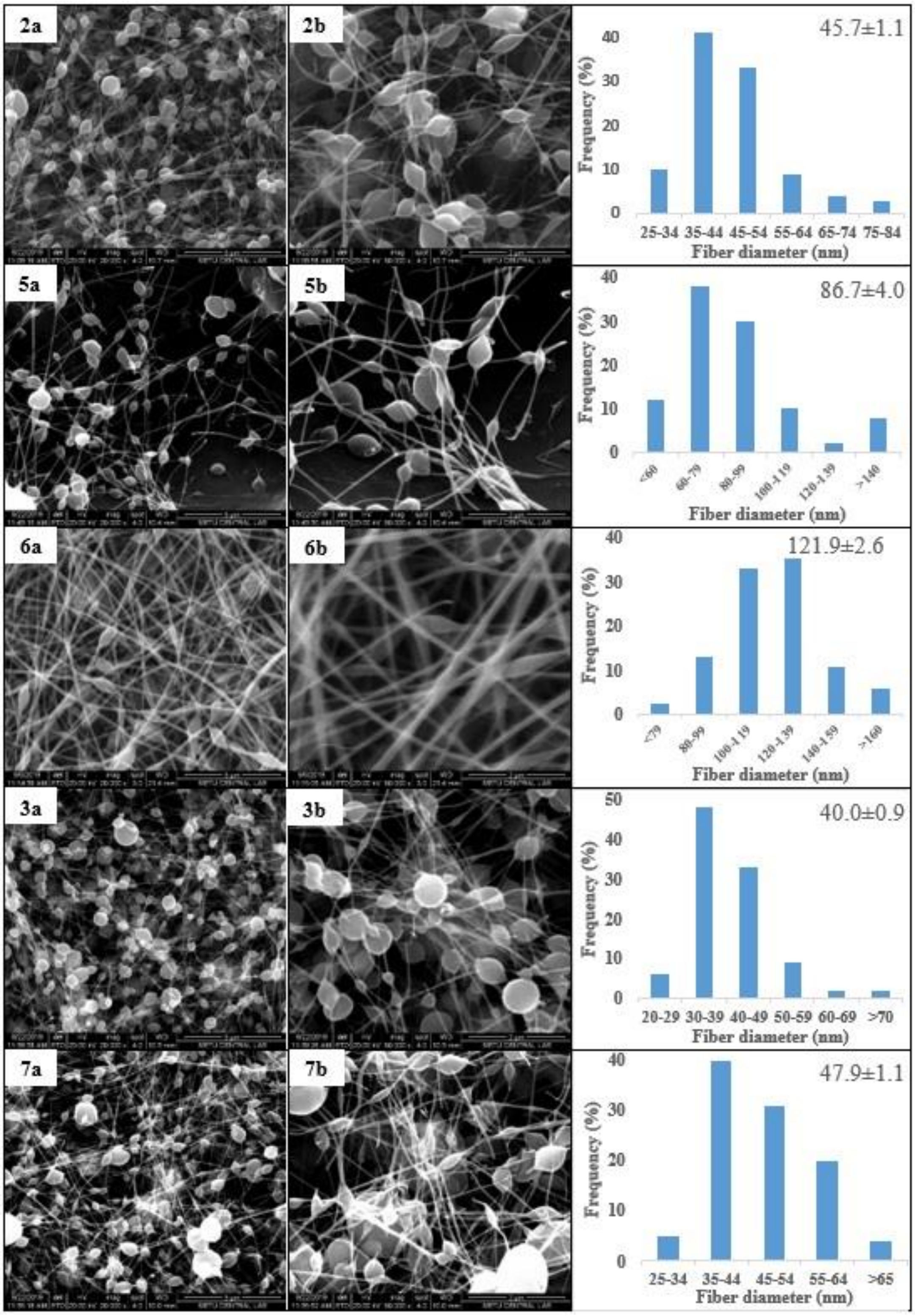

Figure 2. Effect of PEO concentration on the morphology and fiber diameter distribution of the electrospun materials (magnification = a: 20.000×, b: 50.000×)[a]

[a]F2, F5 and F6 containing 1% NaAlg in the ratio of PEO/NaAlg of 2:1 [F2: 3% PEO, F5: 4% PEO, F6: 5% PEO], F3 and F7 containing 2% NaAlg in the ratio of PEO/NaAlg of 1:1 [F3: 3% PEO, F7: 4% PEO].

Table 5. Effect of PEO concentration on the morphological properties of beads of PEO/NaAlg electrospun materials[ab]

	F2	F5	F6	F3	F7
The structure	Beads+fibers	Few beads +few fibers	Many fibers +few bead-on-string fibers	Many beads+fibers	Beads+fibers
Bead area %	53.1	13.7	10.7	67.1	45.8
Number (beads/µm^2)	1.98±0.02	0.46±0.01	0.13±0.01	2.63±0.03	1.69±0.07
Aspect ratio of beads	1.76±0.53	1.55±0.04	2.56±0.08	1.39±0.03	1.62±0.05
Average length of beads (nm)	756.5±22.8	757.3±23.7	1623.0±36.5	660.9±21.5	731.7±36.9
Average width of beads (nm)	451.6±21.2	500.9±18.2	645.0±18.3	491.6±21.8	471.4±31.4

[a]Values are expressed as mean± standard deviation (n=3)
[b]F2, F5 and F6 containing 1% NaAlg in the ratio of PEO/NaAlg of 2:1 [F2: 3% PEO, F5: 4% PEO, F6: 5% PEO], F3 and F7 containing 2% NaAlg in the ratio of PEO/NaAlg of 1:1 [F3: 3% PEO, F7: 4% PEO]

As a conclude, the study is the first to describe in detail the effects of the use of PEO and NaAlg at different concentrations and ratios on the viscosity and conductivity of the polymer solutions and hence on the advanced morphological properties of beads and fibers in electrospun materials. Viscosity and conductivity of solutions, and morphological properties of the obtained materials were found to be affected by PEO and NaAlg concentration and the ratio of them. Spinnability was improved thanks to the increase in conductivity in the presence of PEO. Morphological properties of PEO/NaAlg electrospun materials can be modified by controlling the parameters examined in the study. The lower viscosity and conductivity resulted in the production of generally smaller beads, having greater in number and in area in the electrospun material. Consequently, lower viscosity and conductivity may be preferred for bead production, while higher viscosity and conductivity are required for fiber production. However, it should be noted that sufficiently high viscosity and conductivity are required for the electrospinning process. The current study also points to the production and morphological characterization of PEO/NaAlg electrospun material, which is valuable for medical and biological applications such as tissue engineering, wound dressing, drug delivery system.

AUTHOR CONTRIBUTIONS

Concept: T.E.B.; Design: T.E.B.; Control: T.E.B.; Sources: T.E.B.; Materials: T.E.B.; Data Collection and/or Processing: T.E.B.; Analysis and/or Interpretation: T.E.B.; Literature Review: T.E.B.; Manuscript Writing: T.E.B.; Critical Review: T.E.B.; Other: -

CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

ETHICS COMMITTEE APPROVAL

The authors declare that the ethics committee approval is not required for this study.

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