

# EFFECT OF DIFFERENT PARAMETERS ON THE FABRICATION OF SUSTAINED RELEASE CELLULOSE ACETATE AND ETHYL CELLULOSE POLYMER BLENDS

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In this paper, the effects of solvent system, applied voltage and ratio of polymers on the morphological appearance and diameters of nanofibers electrospun from cellulose acetate (CA) and ethyl cellulose (EC) polymer blends have been investigated. Single solvent systems, *i.e.* acetone, N,N-dimethyl acetamide (N,N-DMAc), N,N-dimethyl formamide (N,N-DMF) and acetic acid, and mixed solvent systems, *i.e.* acetone+N,N-DMAc, acetone+N,N-DMF, acetone+N,N-DMAc+ethanol, were investigated. Electrospinning of polymer blends in acetone produced short and beaded nanofibers, while in N,N-DMAc, N,N-DMF and acetic acid, round, hollow and diffused microcapsules were produced, respectively. The effect of voltage on fiber morphology and diameter for solvent mixtures of acetone+N,N-DMAc and acetone+N,N-DMF was also investigated. Moreover, the effect of polymer ratio on fiber morphology and diameter for the solvent mixture of acetone+N,N-DMAc+ethanol was studied. Bead-free nanofibers were observed as the concentration of CA increased and EC decreased in the polymer blend solution. After immersion in distilled water for 24 h, the electrospun CA+EC nanofibers swelled appreciably (*i.e.* from 702 to 1250%) with minor weight loss (1.6-1.2%). It was also found that the viscosities of the blend solutions decreased with an increase in the conductivity and voltage applied.

**Keywords:** electrospinning, polymer blends, cellulose acetate, ethyl cellulose

## INTRODUCTION

In recent years, electrospinning has been considered as the most efficient method for the fabrication of both single polymers and polymer blends. With the advancement in nanotechnology, researchers have become interested in studying the unique properties of electrospun products and nanomaterials.<sup>1</sup> These electrospun products and nanomaterials are gaining more interest and attention due to their versatility and applications in different fields. The most important applications of electrospinning can be observed in the field of tissue engineering<sup>2</sup> and drug delivery.<sup>3,4</sup>

Both natural and synthetic polymers can be used to make polymer blends and composites for the successful electrospinning of nanofibers. Different electrospinning parameters can be manipulated to regulate the morphological and physicochemical properties of nanofibers to fulfill the requirement of a specific application.<sup>5</sup> So, the determination of appropriate experimental parameters for electrospinning of polymer blends and single biopolymers utilized for multifunctional membranes and biomedical structural elements (scaffolds used in tissue engineering, wound dressing, drug delivery, artificial organs, vascular grafts) is the current emphasis of advanced research.<sup>6</sup> The most important parameters responsible for the appearance of electrospun fibers include: (i) the solvent utilized for making solutions, (ii) viscoelastic forces, which depend on solution concentration, (iii) the average molecular weight and ratio of polymers used for making blends, (iv) polymer concentration, (v) applied voltage, (vi) distance to the collector and (vii) the type of collector used to collect the fibers.<sup>7</sup> These experimental parameters are very important to understand not only the nature of electrospinning, but also the conversion of polymer solutions into nanofibers through electrospinning.

Specifically, the voltage applied is a crucial factor and is strongly correlated with the originating droplet shape of the solution jet and higher voltage may result in a greater tendency to form beaded fibers.<sup>8-10</sup> Meanwhile, fine fiber formation with an increase in voltage for poly(vinyl alcohol) (PVA) nanofibers has been also reported.<sup>11</sup> It has been established that higher voltages can increase the electrostatic repulsive force on the charged jet, favoring the narrowing of fiber diameter. For example,

Yuan *et al.* investigated the effect of voltage on the morphology and fiber alignment with polysulfone (PSF)/DMAC/acetone as model.<sup>12</sup>

In this study, cellulose acetate (CA) has been selected as a model polymer for making polymer blend solutions. The polymer fibers of CA have gained much attention in recent years and remained an important research subject, especially when addressing several industrial applications, including in the textile and biomedical fields. Cellulose acetate has a wide range of applications ranging from cigarette filters to highly absorbent diapers, semi-permeable membranes for separation processes, as well as fibers and films for biomedical functions.<sup>13</sup> Studies on the effect of different parameters on fiber diameters and morphologies of CA polymer and its blends with different polymers have been reported.<sup>14</sup>

Ethyl cellulose (EC) has been also chosen as a model polymer in this study for making polymer blends. It is a semisynthetic material and has biocompatible and biodegradable characteristics. Due to these features, it is used for making water-insoluble microparticle drug delivery systems.<sup>15</sup> The size and morphology of these drug delivery systems can be controlled by adjusting the spinning parameters.<sup>16</sup> The reason for making polymer blends is to provide an efficient way to fulfill new requirements for materials. Subsequently, it is also important to predict how blending conditions will influence fiber morphology, especially the weight ratios of the two polymers used for making polymer blends.<sup>17</sup> In our previous study, we prepared sustained release drug loaded nanofibers of CA and EC polymer blends by electrospinning and analyzed them by XRD, FTIR and TGA analysis techniques. Also, the *in vitro* drug release profiles were studied.<sup>18</sup> By these analysis techniques, it was found that an efficient polymer blend can be prepared and used as a suitable candidate for novel fabrication of sustained release matrices. In the present study, different parameters have been studied in order to investigate their effects on the morphology and diameter distribution of the resulting electrospun nanofiber mats. Also, the selection of a suitable solvent system has been conventionally made on trial and error basis to study its effect on electrospun products, compared with similar systems or solubility models limited by physico-chemical records.<sup>19</sup> Related studies on the effect of different single and mixed solvent systems on fiber diameters and morphologies have been also reported previously.<sup>14,20</sup>

This study focused on the effects of solvent system, applied voltage and ratio of polymers used for making polymer blends on the fiber morphology and diameters of electrospun CA+EC polymer blend nanofibers. The single solvent systems were acetone, N,N-dimethyl acetamide (N,N-DMAC) and N, N-dimethyl formamide (N,N-DMF). The mixed solvent systems were acetone+N,N-DMAC, acetone+N,N-DMF and acetone+N,N-DMAC+ethanol. The selection of the single and mixed solvent systems was based their suitability for better electrospinning of CA+EC polymer blends. This study clearly states that different solvents resulted in different morphologies of CA+EC polymer blends. Also, the voltage applied and the polymer ratio have a significant effect on fiber morphology and diameters of CA+EC polymer blends. Furthermore, the high boiling point of different solvent systems is also responsible for better electrospinnability of CA+EC polymer blends, while low boiling points result in clogging during electrospinning. Finally, mixed solvent systems proved to be a better option for electrospinning CA+EC polymer blends, as compared to single solvents.

## EXPERIMENTAL

### Materials

Cellulose acetate (white powder; Mw = 100,000 Da) was purchased from Acros (NJ, USA) and used as received. Ethyl cellulose (9.0 cPa s) was obtained from Shanghai Yunhong Pharmaceutical Aids and Technology Co., Ltd. (Shanghai, China). Acetone, acetic acid, N,N-dimethylacetamide (DMAC), N,N-dimethyl formamide (DMF) and anhydrous ethanol were purchased from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China). All other chemicals used were of analytical grade. Water was doubly distilled immediately before use.

### Preparation of spinning solution

To study the effect of different solvents, polymer blends of CA and EC solutions with a concentration of 10% (8:2, w/w) were prepared by dissolving their appropriate amounts into four different solvent systems of acetone (F1), N,N-DMAC (F2), N,N-DMF (F3) and acetic acid (F4), respectively (Table 1). Also, eight solutions of polymer blends of CA+EC were prepared with binary solvent mixtures of acetone+N,N-DMAC (F5-F8) and acetone+N,N-DMF (F9-F12) to investigate the effect of voltage variation on fiber diameters and morphologies (Table 2). In addition, four ratios of polymer blends were prepared in a binary solvent mixture of acetone+N,N-DMAC+ethanol (F13-F16) to study the effect of polymer ratios used in making blends (Table 3). Mechanical

stirring and persistent heating ( $50 \pm 1.8$  h) were applied for at least 12 h to obtain homogeneous co-dissolved spraying solutions. The solutions were degassed with a SK5200H ultrasonicator (350W, Shanghai Jinghong Instrument Co., Ltd. Shanghai, China) for 10 min before electrospinning.

### Electrospinning process

A high voltage power supply (Shanghai Sute Electrical Co., Ltd.) was used to provide high voltages in the range of 0-60 kV. To avoid air bubbles, electrospinning solutions were carefully loaded in a 5 mL syringe to which a stainless steel capillary metal-hub needle was attached. The inside diameter of the metal needle was 0.5 mm. The positive electrode of the high voltage power supply was connected to the needle tip and the grounded electrode was linked to a metal collector wrapped with aluminum foil. The electrospinning process was carried out under ambient conditions ( $21 \pm 2$  °C) and relative humidity  $57 \pm 3\%$ ). Electrical potential was applied across a fixed distance of 15 cm between the tip and the collector. The feed rate of the solutions was controlled at 0.5-1.0 mL/h by means of a single syringe pump (KDS100 Cole-Parmer®, USA). The formed fiber meshes were dried for over 24 h at 40 °C under vacuum (320 Pa) in a DZF-6050 Electric Vacuum Drying Oven (Shanghai Laboratory Instrument Work Co. Ltd., Shanghai, China). This facilitated the removal of residual organic solvent and moisture.

### Characterization

#### Morphological analysis

The morphology of the nanofibers was assessed using an S-4800 field emission scanning electron microscope (FESEM) (Hitachi, Japan). Prior to the examination, the samples were platinum sputter-coated under a nitrogen atmosphere to render them electrically conductive. Images were recorded at an excitation voltage of 10 kV. The average fiber diameter was determined by measuring the diameters of the fibers at over 100 points from FESEM images using NIH Image J software (National Institutes of Health, MD, USA).

#### Swelling and weight loss behavior

To measure the potential use of the prepared polymer blends as carriers for sustained release of drugs, electrospun CA+EC polymer blend nanofiber mats were selected and further characterized by determining their swelling and weight loss behavior in distilled water. The electrospun fiber mats were cut into  $2.5 \times 2.5$  cm<sup>2</sup> squares and placed in closed bottles containing 50 mL distilled water and incubated at room temperature. To measure the swelling behavior, after immersion in water for 24 h the samples were weighed, then dried in a vacuum oven at 50 °C for 1 day, and reweighed to determine the dry weight. The percentage swelling of these specimens was calculated using the equation:

$$\text{Swelling (\%)} = \frac{W - W_d}{W_d} \times 100 \quad (1)$$

where  $W$  is the weight of each specimen after immersion in water and  $W_d$  is the dry weight of the specimen after drying in the oven. To determine the weight loss behavior, after immersion in water for 24 h the specimens were dried in a vacuum oven at 50 °C for 1 day and weighed. The percentage weight loss of these specimens was then calculated by the equation:

$$\text{Weight Loss (\%)} = \frac{W_i - W_d}{W_i} \times 100 \quad (2)$$

where  $W_i$  is the initial weight of each sample in its dry state and  $W_d$  is the dry weight of the specimen after being immersed in water and then dried in the oven.

#### Viscosity and conductivity measurements

The relative viscosities, surface tension and conductivities of pure acetone, acetic acid, N,N-dimethyl acetamide, N,N dimethyl formamide and different polymer blend solutions of CA and EC polymers (F1-F16) were measured by a Brookfield DV-III programmable rheometer, a CSC Scientific tensiometer, and a Jenway 4130 conductivity meter, respectively.

## RESULTS AND DISCUSSION

### Effect of solvents

To study the effects of different solvents on the electrospinnability of the cellulose acetate and ethyl cellulose polymer blends, acetone, N,N-DMAc, N,N-DMF and acetic acid were chosen. Each solution was prepared at a fixed concentration of 10% and the applied electric field strength was fixed at 12 KV/15 cm (Table 1). Although polymer blends of CA and EC form clear solutions with acetone, N,N-DMAc, N,N-DMF and acetic acid, numerous discrete beads were obtained on the collector. Similar consequences were also found previously,<sup>14,21</sup> when acetone was used to dissolve CA polymer

alone, forming clear solutions, but the resulting CA solution was difficult to electrospin because of solution clogging at the tip of the nozzle, and when CA solutions were electrospun in acetic acid/water solvent mixture.<sup>20</sup> The reason for solution clogging was the low boiling point of the solvents (56.3 °C; Table 1), which resulted in rapid evaporation of the solution and was also explained previously.<sup>22</sup>

Electrospinning of the 10% (w/v) (2:1) CA and EC polymer blend solution in acetone (10 ml, v/v) resulted in the formation of short and beaded fibers (Fig. 1a). Similar short and beaded fibers were also obtained when Son *et al.*<sup>23</sup> electrospun 9% (w/v), 13% (w/v), 17% (w/v) and 21% (w/v) CA solutions alone in acetone solvent. However, clogging remains the main problem in electrospinning of CA solutions alone or with polymer blends of CA and EC polymers in acetone solvent. To avoid clogging and improve the electrospinning of CA and EC polymer blends, a co-solvent or a modified liquid was added to the acetone solvent system. In past research, it was found that the addition of DMAc helped improve the electrospinnability of the CA polymer in acetone-DMAc,<sup>21</sup> and the presence of water also helped improve the electrospinnability of the CA solution in acetone-water.<sup>23</sup> The reason for improved electrospinnability of resulting CA solutions in the mixed solvent systems could be that the boiling points of DMAc and DMF are greater than that of acetone (Table 1), as explained below.

The electrospinning of the 10% (w/v) (2:1) CA and EC polymer blend solution in N,N-DMAc (10 ml, v/v) alone results in irregularly shaped diffused microcapsules, as shown in the SEM images in Figure 1b. Due to the high boiling point of DMAc, evaporation cannot occur and proper fibers could not be formed. As a result, a diffused beaded structure can be observed. This morphology is very different from the one obtained while mixing the same polymer blend solution with a mixed solvent of acetone and N,N-DMAc (2:1) (as discussed in the next section). Another solvent, N,N-DMF (10 ml v/v), was also chosen to electrospin the 10% (w/v) (2:1) CA+EC polymer blend solution. The SEM images show regularly shaped beaded hollow microcapsules (Fig. 1c). The high boiling point of N,N-DMF is responsible for the formation of the beaded microcapsule-like structure and regular nanofibers could not be formed.

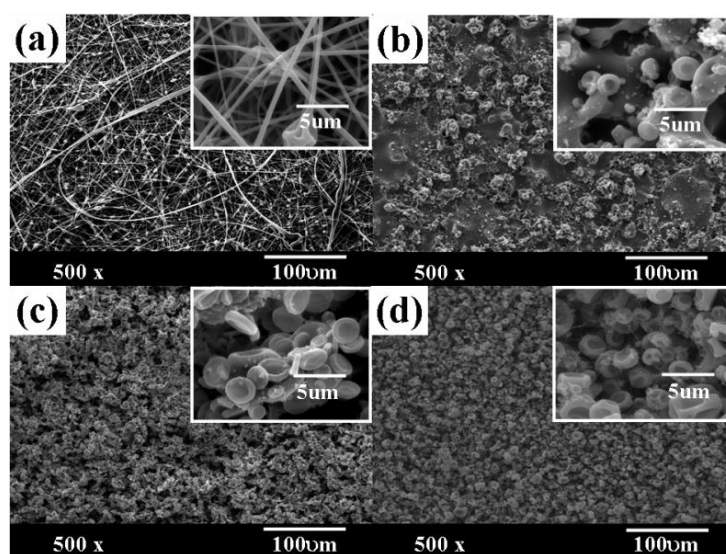


Figure 1: Selected SEM images of nanofibers from 10% (2:1, w/v) CA+EC polymer blend solutions at X500 magnification in (a) acetone (F1), (b) N,N-DMAc (F2), (c) N,N-DMF (F3) and (d) acetic acid (F4). The fibers were spun under an applied electrostatic field strength of 10 kV/10 cm (the inset in each picture is a SEM image of the same nanofibers taken at a magnification of 10,000X)

Table 1

Density, boiling point, shear viscosity, amount of solvent system and ratio of polymer blend CA+EC solutions in different solvents and their morphologies

Fiber mats	Solvents	Density (g cm <sup>-1</sup> )	Boiling point (°C)	Amount of solvent (ml)	Ratio of polymer blends (w/v)	Morphology
F1	Acetone	0.786	56.3	10	2:1 (CA:EC)	Nanofibers with beads
F2	N,N-DMAc	0.937	166	10	2:1 (CA:EC)	Diffused microcapsules
F3	N,N-DMF	0.945	153	10	2:1 (CA:EC)	Round, hollow microcapsules
F4	Acetic acid	1.049	119	10	2:1 (CA:EC)	Round, hollow microcapsules

Table 2

Voltage, ratio of mixed solvent and ratio of polymer blends of CA+EC solutions in 2:1 (v/v) acetone+N,N-DMAc and acetone+N,N-DMF and their effect on diameters and morphology of the resulting electrospun fibers as a function of solution concentration

Fiber mats	Solvents	Voltage (kV)	Ratio of mixed solvent (v/v)	Ratio of polymer blends (w/v)	Morphology
F5	Acetone+N,N-DMAc	9	2:1	2:1 (CA:EC)	Long, thin nanofibers
F6	Acetone+N,N-DMAc	10	2:1	2:1 (CA:EC)	Long, thin nanofibers
F7	Acetone+N,N-DMAc	11	2:1	2:1 (CA:EC)	Long, thin nanofibers
F8	Acetone+N,N-DMAc	12	2:1	2:1 (CA:EC)	Long, thin nanofibers
F9	Acetone+N,N-DMF	9	2:1	2:1 (CA:EC)	Nanofibers+spindle beads
F10	Acetone+N,N-DMF	10	2:1	2:1 (CA:EC)	Nanofibers+spindle beads
F11	Acetone+N,N-DMF	11	2:1	2:1 (CA:EC)	Nanofibers+spindle beads
F12	Acetone+N,N-DMF	12	2:1	2:1 (CA:EC)	Nanofibers+spindle beads

Table 3

Ratio of mixed solvent system and ratio of polymer blends of CA+EC solutions in 3:1:1 (v/v) acetone+N,N-DMAc+ethanol and their effect on diameters and morphology of the resulting electrospun fibers as a function of solution concentration

Fiber mats	Solvents	Ratio of mixed solvent (v/v)	Ratio of polymer blends (w/v)	Morphology
F13	Acetone+N,N-DMAc+Ethanol	3:1:1	1:0	Nanoballs
F14	Acetone+N,N-DMAc+Ethanol	3:1:1	5:5	Microcapsules with few nanofibers
F15	Acetone+N,N-DMAc+Ethanol	3:1:1	6:4	Long, thin nanofibers
F16	Acetone+N,N-DMAc+Ethanol	3:1:1	8:2	Long, thin nanofibers

Acetic acid (10 ml v/v) was also chosen to electrospin the 10% (w/v) (2:1) CA+EC polymer blend solution. The SEM images show regularly shaped big and small hollow microcapsule-like structures, as given in Figure 1d. The high boiling point of acetic acid is responsible for the formation of such structures and regular nanofibers could not be formed. Similar microcapsules were also obtained in our previous research, when a binary solvent mixture of acetic acid+ triple distilled water was used to electrospin a similar CA+EC polymer blend solution.<sup>18</sup> Such microcapsules were also observed when EC polymer was electrospun at different polymer concentrations and it was found that as the EC polymer concentration increased the microcapsules collapsed and became dispersed.<sup>16</sup>

## Effect of voltage

### Acetone and N,N-DMAc

The polymer blend solutions at a fixed concentration of 10% CA+EC (2:1, w/v) were prepared in 2:1 (v/v) acetone+N,N-DMAc solvent mixture (F5-F8) (Table 2). The mixed solvent system of acetone+N,N-DMAc has been used previously in many research works.<sup>22,24</sup> The values of some parameters, such as voltage, concentration of the mixed solvent, the ratio of the polymer blends of CA+EC solutions in 2:1 (v/v) acetone+N,N-DMAc and acetone+N,N-DMF, as well as the diameters and morphology of the resulting electrospun fibers as a function of solution concentration, are summarized in Table 2. The voltage for F5 fiber mat was set at 9 KV, while for F6, F7 and F8 fiber mats, it was set at 10 KV, 11 KV and 12 KV, respectively, as shown in Table 2.

Figure 2 shows selected SEM images of the electrospun fibers after electrospinning the 10% CA+EC (2:1, w/v) polymer blend solution in the 2:1 (v/v) acetone+N,N-DMAc solvent mixture at different voltages. Clearly, only smooth, long and thin nanofibers were obtained at this concentration, despite the difference in voltage. On the basis of these SEM images, the diameters of the electrospun fibers were found to increase with the increase in the voltage applied to each polymer blend solution. Specifically, the average fiber diameter increased from  $717.4 \pm 24$  nm for F4 fiber mat to  $1030.08 \pm 42$  nm for F8 fiber mat. This can be also explained as an increase in the frequency of voltage, or correspondingly a change in the frequency of drop formation accompanying the variation of the mode of spray initiation. As the voltage applied to the polymer solution is increased gradually, the measured current undergoes a step-wise increase, which corresponds to the observed changes in the jet initiation modes. The flow of the polymer from the tip to the collector target is the only mechanism for charge transport.<sup>8</sup> Thus, an increase in the electrospinning current generally reflects an increase in the mass flow rate from the capillary tip to the grounded target when all other variables (conductivity, dielectric constant, and flow rate of solution to the capillary tip) are kept constant.<sup>25,26</sup>

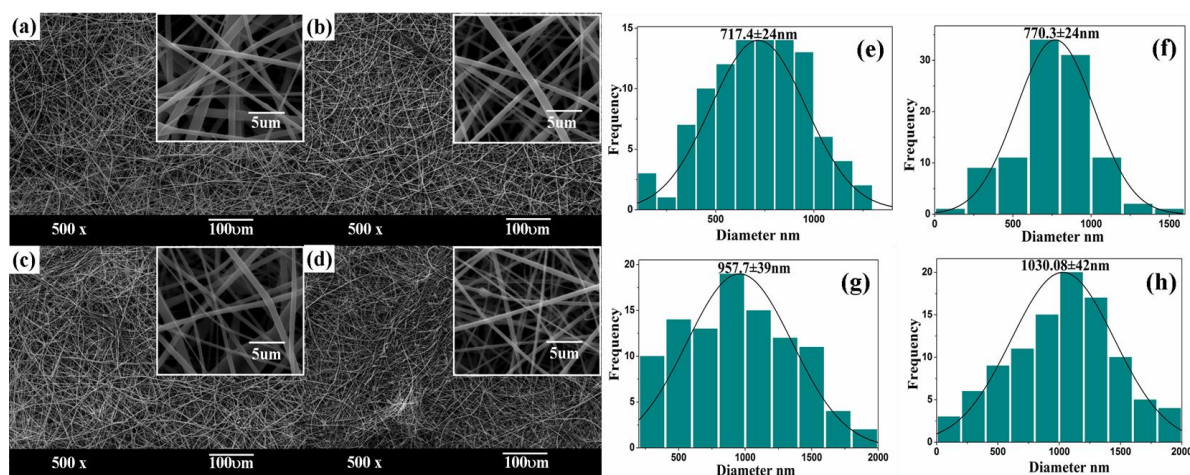


Figure 2: Left panel: Selected SEM images of nanofibers from 10% (2:1, w/v) CA+EC polymer blend solutions at X500 magnification (a) F5, (b) F6, (c) F7 and (d) F8 in solvent mixture of acetone+N,N-DMAc (the inset in each picture is a SEM image of the same nanofibers taken at a magnification of 10,000X). Right panel: Graphs showing fiber diameter distribution measured from each SEM image (e) F5, (f) F6, (g) F7 and (h) F8



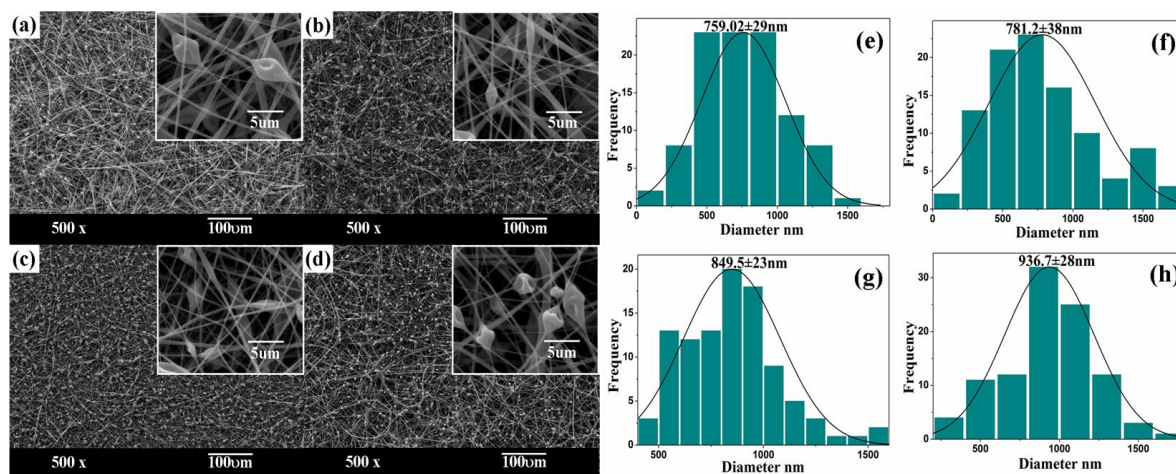


Figure 3: Left panel: Selected SEM images of nanofibers from 10% (2:1, w/v) CA+EC polymer blend solutions at X500 magnification (a) F9, (b) F10, (c) F11 and (d) F12 in solvent mixture of acetone+N,N-DMF (the inset in each picture is a SEM image of the same nanofibers taken at a magnification of 10,000X). Right panel: Graphs showing fiber diameter distribution measured from each SEM image (e) F9, (f) F10, (g) F11 and (h) F12

### Acetone+N,N-DMF

The polymer blend solutions at a fixed concentration of 10% CA+EC (2:1, w/v) were prepared in 2:1 (v/v) acetone+N,N-DMF solvent mixture (F9-F12) (Table 2). The voltage for F9 fiber mat was kept at 9 KV, while for F10, F11 and F12 fiber mats, voltage was kept at 10, 11 and 12 KV respectively, as shown in Table 2.

Figure 3 shows selected SEM images of the as-spun fibers after electrospinning of the 10% CA+EC (2:1, w/v) polymer blend solution in 2:1 (v/v) acetone+N,N-DMF solvent mixture at different voltages. Nanofibers with numerous discrete beads on their surfaces were obtained. On the basis of the SEM images, the diameters of the as-spun fibers were found to increase with the increase in the voltage applied to each polymer blend solution. Specifically, the average fiber diameter increased from 759.02±29 nm for F9 fiber mat to 936.7±28 nm for F12 fiber mat. The increase in the average fiber diameter with increasing applied voltage has been also established previously,<sup>27</sup> although contradictory results have been reported as well.<sup>28</sup>

The main differences, as observed from Figures 2 and 3, are the nanofibers with simple smooth, long and cylindrical morphology, with a trend of increase in fiber diameter with the increase in voltage, and the nanofibers with numerous discrete beads with the same increasing trend.

When the 10% CA+EC (2:1, w/v) polymer blend solution was electrospun with N,N-DMAc (10 ml, v/v) solvent alone (Fig. 1b), it was observed that irregularly shaped diffused microcapsules were formed. However, when the same polymer blend was electrospun with acetone+N,N-DMAc (2:1, v/v), no diffused and irregularly shaped microcapsules were remarked any more. Instead, long, smooth and thin nanofibers were observed (Fig. 2). This improved electrospinnability of the resulting CA+EC (2:1, w/v) polymer blend solution in this mixed solvent system could be due to the high boiling point of N,N-DMAc (166 °C), as compared to that of acetone (56.3 °C).

Almost similar results were observed when the 10% CA+EC (2:1, w/v) polymer blend solution was electrospun with the N,N-DMF (10 ml, v/v) solvent alone. Regularly shaped beaded hollow microcapsules were formed (Fig. 1c). However, when the same polymer blend was electrospun with the acetone+N,N-DMF (2:1, v/v) solvent mixture, no beaded hollow microcapsules were observed, and smooth, long and thin nanofibers with numerous discrete beads were obtained (Fig. 3). The reason for this improved electrospinnability of the CA+EC (2:1, w/v) polymer blend solution in this mixed solvent system was the same, *i.e.* due to the high boiling point of N,N-DMF (153 °C), as compared to that of acetone (56.3 °C). In the same way, this polymer blend solution can be electrospun with a wider selection of mixed solvent systems in order to explore the release of other therapeutic agents.

### Effect of ratio of polymers used in polymer blend solutions

Similar polymer blends of CA and EC solutions with a concentration of 10% with 4 different polymer blend ratios (1:0, 5:5, 6:4, 8:2) were also prepared by dissolving their appropriate amounts into a mixture of another binary solvent system of acetone+N,N-DMAc+ethanol (3:1:1 v/v/v) (Table 3). This solvent mixture has been also used previously for the electrospinning of CA+EC polymer blends.<sup>18</sup>

The fabrication of CA nanofibers with a mixture solvent of acetone+N,N-DMAc with a volume ratio of 2:1 and 1:2 and a mixture solvent of acetone+N,N-DMAc+anhydrous ethanol has been also studied previously.<sup>22,29</sup> Likewise, they found that the mixture of acetone+N,N-DMAc was the most flexible solvent system for successful fabrication of CA nanofibers.

Representative scanning electron microscopy (SEM) images of the nanofibers with different weight ratios of CA and EC are shown in Figure 4 (left panel). When the ratio of the polymer blend solution is 1:0 (w/w) (F13), electrospraying takes place, which results in the formation of round, globular, non-porous and smooth nanoballs, as shown in SEM images (Fig. 4a). When using the CA and EC in the ratio of 5:5 (w/w) (F14), the polymer blend solution yields irregularly shaped, hollow microcapsules with very few nanofibers, as shown in Figure 4b. Further increasing the CA content in the ratio of 6:4 (w/w) (F15) leads to long, thin, non-porous and smooth nanofibers, as may be remarked in the SEM images in Figure 4c. When the CA content is increased even more, while decreasing the EC content to 8:2 (w/w) (F16), long and thin, non-porous, smooth nanofibers are obtained (Fig. 4d). It may be thus concluded that as the concentration of CA is increased in the solution, bead-free nanofibers are achieved. Similar results were attained in our earlier research, namely, when increasing the CA content in the polymer blend solution, bead-free long cylindrical smooth nanofibers were obtained.<sup>18</sup>

Interestingly, it was observed that the composition of the mixed solvent system and polymer blend solutions determined the average fiber diameters of the CA nanofibers. The diameter distribution of fiber mats F15 and F16 are given in Figure 4 (right panel). It was observed that the average diameters of the fabricated nanofibers increased when increasing the CA+EC weight ratio, from about 927.1±29 nm in the case of F15 (Fig. 4e) and 952.6±30 nm in the case of F16 (Fig. 4f). Also, the average diameters of the nanofibers increased as the CA polymer content increased and the EC polymer content decreased in the polymer blend solutions, when electrospinning took place in the solvent mixture of acetone+N,N-DMAc+ethanol solvents. Thus, the average fiber diameter can be adjusted by controlling the CA and EC polymer content when preparing polymer blend solutions.

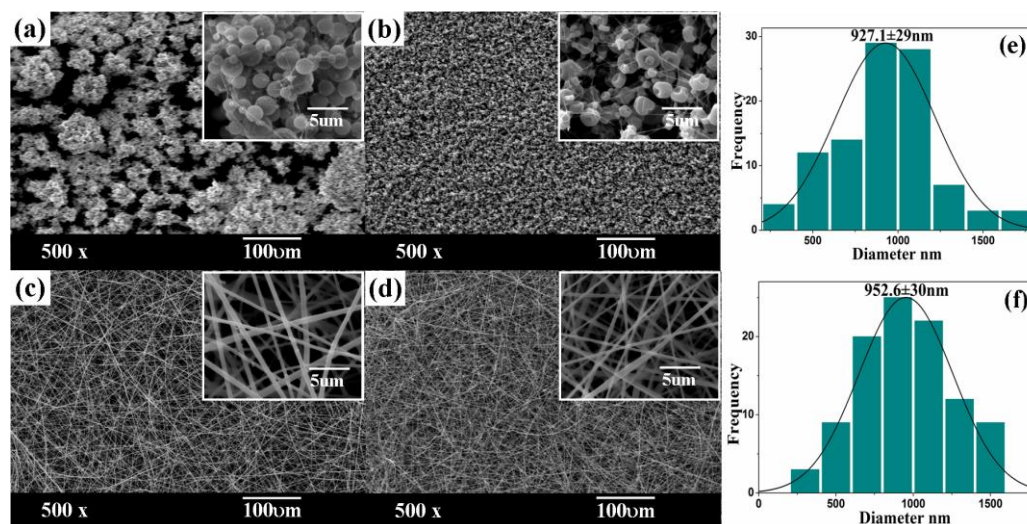


Figure 4: Left panel: Selected SEM images of nanofibers from 10% (2:1, w/v) CA+EC polymer blend solutions at X500 magnification (a) F13, (b) F14, (c) F15 and (d) F16 in solvent mixture of acetone+N,N-DMAc+ethanol (3:1:1, v/v/v) (the inset in each picture is an SEM image of the same nanofibers taken at a magnification of 10,000X). Right panel: Graphs showing fiber diameter distribution measured from SEM images of (e) F15, (f) F16



Table 4

Swelling and weight loss behavior of electrospun fibrous membranes from F13, F14, F15 and F16 (1:0, 5:5, 6:4 and 8:2 w/v, respectively) CA+EC polymer blend solutions in 3:1:1 (v/v) acetone+N,N-DMAc+ethanol after immersion in distilled water for 24 h

Ratio of polymer blends (w/v)	Swelling (%)	Weight loss (%)
1:0	702	1.6
5:5	818	1.3
6:4	890	1.2
8:2	1250	1.2

Table 5

Conductivity, viscosity, surface tension and fiber diameter of CA and EC polymer blends electrospun in single and mixed solvent systems

No.	Solvents	Conductivities (S/cm)	Viscosities (mPa s)	Surface tension (mN m <sup>-1</sup> )	Fiber diameters (nm)
F1	Acetone	20	0.36	22.7	-
F2	N,N-DMAc	25	1.020	34.0	-
F3	N,N-DMF	10.90	0.796	36.3	-
F4	Acetic acid	$1.12 \times 10^{-8}$	1.31	27.6	-
F5	Acetone+N,N-DMAc	22	0.57	24.6	717.4±24
F6	Acetone+N,N-DMAc	24	0.46	24.5	770.3±24
F7	Acetone+N,N-DMAc	26	0.39	22.3	957.7±39
F8	Acetone+N,N-DMAc	28	0.34	22.9	1030.08±42
F9	Acetone+N,N-DMF	20	0.78	26.2	759.02±29
F10	Acetone+N,N-DMF	21	0.66	24.11	781.2±38
F11	Acetone+N,N-DMF	22	0.57	23.7	849.5±23
F12	Acetone+N,N-DMF	23	0.42	21.9	936.7±28
F13	Acetone+N,N-DMAc+Ethanol	26	0.47	27.1	-
F14	Acetone+N,N-DMAc+Ethanol	27	0.68	29.56	-
F15	Acetone+N,N-DMAc+Ethanol	28	0.92	34.39	927.1±29nm
F16	Acetone+N,N-DMAc+Ethanol	28	1.78	37.58	952.6±30nm

### Swelling and weight loss behavior

Electrospun nanofibers obtained from F13, F14, F15 and F16 (1:0, 5:5, 6:4 and 8:2 w/w, respectively) CA+EC polymer blend solutions in 3:1:1 (v/v) acetone+N,N-DMAc+ethanol were further investigated to determine their swelling and weight loss behavior in distilled water, as these are important characteristics for the use of these nanofibers for sustained release of drugs (Table 3). The nanofibers were electrospun from solutions at an applied voltage of 12 kV/15 cm for a collection period of approximately 4 h. The electrospun nanofibers were cut into squares, which were immersed in distilled water for 24 h to determine their swelling and weight loss behavior by the procedure described above. Approximately five specimens for each fiber mat sample were characterized; the average results are summarized in Table 4. As previously discussed, the average fiber diameters of the nanofibers increased as the CA polymer content increased and the EC polymer content decreased in the polymer blend solutions when electrospun in the solvent mixture of acetone+N,N-DMAc+ethanol solvents (Fig. 4). The larger the fiber diameter, the larger the volume per unit length of the fibers in which water molecules can be fixed. It is evident from Table 4 that, after immersion in distilled water for 24 h, swelling of the fibrous membranes increased regularly with the increasing ratio of CA polymer concentration of the spinning solutions (hence, increasing fiber diameter). Specifically, the swelling increased from approximately 702% for the nanofiber mat obtained from F13 (1:0, w/w) CA+EC solution in 3:1:1 (v/v) acetone+N,N-dimethyl acetamide (DMAc)+ethanol to approximately 1250% for the nanofiber mat obtained from F16 (8:2, w/w) solution. The loss of weight of these nanofiber mats was low (approx. 1.6-1.2%) and seemed to be independent of the ratio of polymer concentration of the spinning solutions. The small weight loss observed was obviously the result of the insolubility of CA and EC in water.

### Viscosities and conductivity trends for different polymer blend solutions

The most important and critical parameter that determines the key fiber morphology is solution viscosity. The viscosity of a solution should be optimum for successful ejection of the electrospinning solution. It is directly linked with polymer concentration and conductivity. Solution conductivity is generally determined by the polymer content used, the solvent mixture and salts. Generally, natural polymers are polyelectrolytic in nature and their ions increase the charge carrying ability of the polymer jet subjecting to higher tension under the electric field, resulting in poor fiber formation. The addition of ionic salts, such as  $\text{KH}_2\text{PO}_4$ ,  $\text{NaCl}$  and others, results in the formation of smaller diameter nanofibers. The addition of organic acid as solvent results in high solution conductivity. In short, if solution conductivity increases, it favors the formation of thin fibers.

Specifically, the average fiber diameter of the nanofibers prepared from polymer blends in the mixture of acetone+N,N-DMAc (2:1, v/v) increased from  $717.4 \pm 24$  nm to  $1030.08 \pm 42$  nm (Table 5). Apparently, the solution conductivity also increased with the increase in applied voltage. This could be possibly explained by the fact that, as the electrostatic forces on the jet increased due to an increase in the applied voltage, this caused an increased speed of the jet, which ultimately resulted in higher conductivity of the solution. This gave rise to fibers with greater diameter. Similar results were also found and explained in previous studies.<sup>14</sup> Several other research groups also suggested that greater fiber diameters could be obtained by applying higher voltages.<sup>30</sup>

The increasing trend of fiber diameter remained the same for the polymer blends prepared in the solvent mixture of acetone+N,N-DMF, *i.e.* from  $759.02 \pm 29$  nm to  $936.7 \pm 28$  nm (Table 5). For F9-F12 nanofibers, spindle-shaped, large and small beads also appeared in the fiber mats. The number of beads increased as the applied voltage increased in spinning the solutions. These facts were also observed in previous studies.<sup>31,32</sup> Likewise, the fiber diameter for nanofibers prepared from the polymer blends in the solvent mixture of acetone+N,N-DMAc+ethanol displayed an increasing trend from  $927.1 \pm 29$  nm to  $952.6 \pm 30$  nm (Table 5). The viscosities and surface tension of all the relative polymer blend solutions decreased as the conductivity increased. The general trend of decrease in viscosity and increase in solution conductivity of the polymer blend solutions is shown in Figure 5.

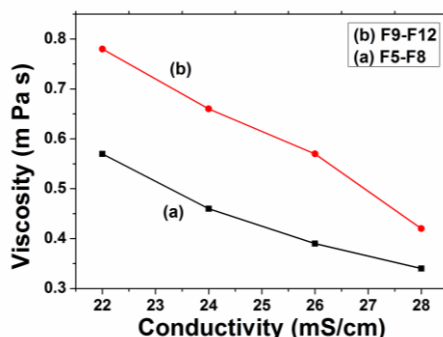


Figure 5: Conductivity vs. viscosity trend for (a) F5-F8 and (b) F9-F12 nanofiber mats

### CONCLUSION

In this work, the effects of solvent system, applied voltage and ratio of polymer blends on the morphological appearance and fiber diameter distribution of electrospun cellulose acetate (CA) and ethyl cellulose (EC) polymer blend products were thoroughly investigated. Polymer blend solutions of CA+EC were prepared in a range of single-solvent systems (acetone, N,N-dimethylacetamide (DMAc), N,N-dimethylformamide (DMF), acetic acid) and mixed solvent systems (acetone+N,N-dimethylacetamide (DMAc), acetone+N,N-dimethylformamide (DMF) and acetone+N,N-dimethylacetamide (DMAc)+ethanol). The morphological appearance and fiber diameter distribution of the electrospun products were investigated using scanning electron microscopy (SEM). Despite the solubility of CA+EC polymer blend in acetone, N,N-dimethylacetamide (DMAc), N,N-dimethylformamide (DMF) and acetic acid, the electrospinning of 10% (w/v) solutions resulted in the formation of discrete beads with a string appearance when electrospun in acetone only, whereas electrospinning of the 10% (w/v) solution of CA+EC polymer blend in N,N-dimethylacetamide (DMAc), N,N-dimethylformamide (DMF) and acetic acid produced round, hollow and diffused

microcapsules, respectively. In particular, for the mixed solvent system of acetone+N,N-DMAc at 2:1 (v/v), a large amount of cylindrical fibers were obtained, while for acetone+N,N-DMF at 2:1 (v/v), nanofibers with spindle-shaped beads were observed. The average diameter of the fibers obtained from the polymer blend solutions in the mixed solvent system was in the range from 717.4±24 to 1030.08±42 and from 759.02±29 to 936.7±28, respectively. Thus, it is concluded that, as the spinning voltage is increased, nanofibers with larger diameters are obtained. Also, it has been determined that, as the ratio of the polymer blend is increased for the mixed solvent system of acetone+N,N-DMAc+ethanol, nanoball morphology disappears, and smooth, long and cylindrical nanofibers are obtained. The average diameter of the fibers also increased from 927.1±29 nm to 952.6±30 nm with the rise in the ratio of polymers. After immersion in distilled water for 24 h, the electrospun CA+EC polymer blend fibers swelled considerably (by 702-1250%) with minor weight loss (1.6-1.2%). Also, it has been observed that the viscosity and surface tension of CA and EC polymer blends decrease upon increasing the conductivity and the applied voltage on spinning solutions. Particularly, it can be concluded that by varying the experimental parameters for CA+EC polymer blend solutions, better morphological and physical characteristics of nanofibers can be achieved.

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