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ORIGINAL ARTICLE

Development and Optimization of Electrospun Poly(vinyl alcohol) Nanofibers for Vaginal Drug Delivery Using Design of Experiments Approach

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ABSTRACT

Objectives: Vaginal nanofibers with high surface area and tunable porosity are a promising platform for vaginal administration. Poly(vinyl alcohol) (PVA) is a widely used polymer in the pharmaceutical field due to its hydrophilic, biodegradable, non-toxic, and mucoadhesive properties. This study aimed to optimize PVA-based electrospun nanofibers for vaginal drug delivery by evaluating polymer concentration, solvent system, and collector rotation speed using a design of experiments-based approach.

Materials and Methods: PVA was dissolved in distilled water (DW) at 90 °C to prepare polymer solutions; then N, N-dimethylformamide (DMF) or ethanol was added. The surface tension, viscosity, and conductivity of the polymer solutions were evaluated. For the production of nanofibers via electrospinning, the parameters selected were PVA concentrations of 7.5% and 15%, collector rotation speed of 100 and 1000 rpm, and two solvent systems (DMF: DW and ethanol: DW). Mechanical and mucoadhesive properties of nanofibers were evaluated using a texture analyzer.

Results: Viscosity and conductivity increased as polymer concentration increased. An increase in PVA concentration resulted in increased tensile strength of the nanofibers, from 1.41±0.07 to 3.92±0.14 MPa (p<0.0001). Nanofiber diameters ranged from 196±41 nm to 1721±114 nm (p<0.0001). All formulations exhibited complete wettability with contact angles of 0°. *Ex vivo* mucoadhesion studies revealed that collector rotation speed influenced the work of adhesion, with the highest mucoadhesion observed for the R3 formulation produced at 1000 rpm.

Conclusion: The solvent system and collector rotation speed were found to influence the morphological structure of the fibers. R3 (7.5% PVA, ethanol/DW, 1000 rpm) formulation was found to be more suitable than other formulations based on its mechanical and mucoadhesive properties. It was concluded that in the production of PVA nanofibers, the rotating speed of the collector, the polymer concentration, and the solvent system directly affect the mechanical and mucoadhesive properties of the nanofibers.

Keywords: Design of experiments, electrospinning, nanofiber, poly(vinyl alcohol), vaginal drug delivery

INTRODUCTION

The vaginal route offers several advantages, including a large specific surface area with rich vascularization and perfusion; convenient self-administration; suitability for both local and systemic therapy; and circumvention of the hepatic first-pass metabolism, thereby potentially reducing hepatic exposure and limiting adverse effects associated with oral dosing.[1-8] A critical consideration in the development of vaginally administered products is user preference and acceptability. The acceptability of such products depends on multiple factors, including ease of use, mode of administration, therapeutic efficacy, and potential adverse effects.[9] Factors such as formulation design, applicator type, and packaging are also critical to ensuring user adherence. The biocompatibility and tolerability of excipients warrant particular consideration, especially when the vaginal mucosa is compromised or the product is intended to treat mucosal lesions associated with microbial or viral pathologies.[10]

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The pursuit of controlled drug release, targeted delivery, and improved drug stability has intensified interest in nanotechnology-based drug delivery systems.[11] Among various nanocarriers, nanofibers offer unique advantages in multiple applications owing to their porous structure, which closely resembles that of natural biological tissues.[12] Nanofibers have been extensively investigated for use in drug delivery systems, filtration media, face masks, tissue engineering scaffolds, and wound dressings. High surface-area-to-volume ratio, porosity, tunable pore size, adjustable surface characteristics, and favorable mechanical properties of nanofibers provide significant benefits for diverse biomedical applications.[13] Production of nanofibers from synthetic or natural polymers, or their blends, offers versatility in composition, enabling optimization for specific drug delivery applications.[14,15]

Vaginally administered dosage forms include gels, creams, films, rings, tablets, sponges, and suppositories. Semi-solid and liquid vaginal dosage forms, such as gels, creams, and solutions, may suffer from drawbacks including leakage, messiness, and limited residence time at the site of application, which can negatively impact patient compliance and therapeutic efficacy.[16] Nanofibers are a solid dosage form that can mitigate spillage and leakage associated with liquid- or gel-based formulations. Nanofibers can be integrated into composite drug carriers and combined with other dosage forms, such as films, sponges, and 3D-printed scaffolds.[17]

Nanofibers can be produced using various techniques, including electrospinning, template synthesis, phase separation, polymerization, and melt blowing. Among these, electrospinning is the simplest and most suitable method, employing electrostatic forces as the driving mechanism for fiber formation. It is a versatile and scalable technique capable of producing polymeric nanofibers with diameters ranging from nanometers to micrometers.[18] The electrospinning method relies on generating electrostatic charges in a polymer solution by applying a high voltage.[19] Multiple parameters influence the electrospinning process: solution variables (polymer concentration, viscosity, surface tension, conductivity), process variables (applied voltage, flow rate, tip-to-collector distance), collector variables (stationary or rotating collectors, rotation speed), nozzle variables (uniaxial, coaxial, triaxial, needleless), and environmental factors (temperature, humidity). These parameters directly affect the production of smooth, bead-free fibers. By appropriately controlling these factors, fibers with desired morphologies and diameters can be obtained.[20]

Vaginal drug delivery systems are commonly formulated with polymeric carriers to enhance efficacy and prolong absorption and retention in vaginal mucosal cells.[21] Poly(vinyl alcohol) (PVA) is a synthetic, semicrystalline polymer that is highly hydrophilic, non-toxic, and biocompatible with excellent properties, including durability, water solubility, gas permeability, mechanical properties, and thermal stability.[22-24] PVA is a versatile polymer widely employed in oral, buccal, and vaginal drug delivery applications. PVA nanofibers have been reported as fish-oil-encapsulated formulations produced by emulsion electrospinning for oral administration; doxorubicin-loaded PVA/polycaprolactone (PCL) coaxial fibers for cervical cancer treatment; and PEGylated paclitaxel nanocrystal-loaded PVA fibers for cervical cancer treatment via vaginal administration.[25-28] Using PVA as a surface stabilizer or modifying its surface with polyethylene glycol (PEG) chains contributes to vaginal adhesion and enhances binding to the hydrophobic domains of mucin, thereby facilitating rapid diffusion through the cervicovaginal mucus.[29] Sharma et al.[30] developed fluconazole-loaded PVA nanofibers for the treatment of vaginal candidiasis. Beyond pharmaceutical applications, PVA nanofibers have been used in sensors, catalysis, and filtration technologies.[31-33] The properties of PVA-based nanofibers vary markedly with the chosen fabrication technique and associated process parameters.[34]

Despite extensive research on electrospun systems for mucosal delivery, there remains a need for systematically optimized, mechanically robust, and mucoadhesive nanofiber platforms designed for vaginal delivery. Most studies focus on drug-loaded systems without fully characterizing the mechanical integrity, wettability, and bioadhesion of nanofibers; formulation variables are key determinants of the applicability of vaginal products. Quality by Design (QbD) is a systematic approach to product and process development in which objectives are predefined and a comprehensive understanding of critical quality attributes and process parameters is prioritized. This strategy enables the formulation and manufacturing of products in compliance with required safety, efficacy, and quality standards, and the consistent analysis of products with the necessary accuracy and precision.[35] In nanofiber production, testing the influence of every parameter by random selection and measurement would be time-consuming and impractical; therefore, the design of experiments (DoE) approach was employed. In this context, the target product profile of the system was defined to include mechanical strength greater than 1 MPa, elongation at break exceeding 50%, and suitability for vaginal administration. DoE-guided optimization of PVA nanofibers provides a critical foundation for developing next-generation vaginal dosage forms with predictable performance, scalable manufacturing processes, and improved user acceptance.[35]

In this study, we aimed to develop and optimize PVA electrospun nanofiber formulations for vaginal drug delivery using a DoE approach. The effects of polymer concentration, solvent system, and collector rotation speed on the mechanical and mucoadhesive properties of the nanofibers were systematically investigated to identify the optimal formulation for potential vaginal application. This study employs a quantitative approach based on DoE to elucidate the relationships among polymer concentration, solvent system, and process parameters in PVA-based vaginal nanofibers. This evaluation provides a predictive design framework for vaginal PVA nanofibers, representing a quantitative structure-performance relationship that has not previously been demonstrated.

MATERIALS AND METHODS

Material

Polyviol 13/140 (49.000 Da) was purchased from Wacker Chemie AG. N, N-dimethylformamide (DMF) and ethanol were purchased from Sigma-Aldrich. All chemicals were of analytical grade. Distilled water (DW) was used for all studies.

Preparation of the polymer solutions

For solution preparation, PVA was first dispersed in the aqueous phase and heated to 90 °C under magnetic stirring at 500 rpm to ensure complete dissolution. After the polymer was fully solubilized, either ethanol or DMF was added to obtain a homogeneous solution. In all formulations, ethanol/DW and DMF/DW solvent systems were used at a 1:1 ratio. For nanofiber formulations, tensile strength values greater than 1 MPa and elongation at break exceeding 50% are generally desirable. In the present study, polymer concentration, collector rotation speed, and solvent system were selected as independent variables for the DoE model. Considering these parameters, a 2^3 factorial experimental design was applied using Design Expert® 13 software (Stat-Ease Inc., Minneapolis, MN, USA). The Tensile strength and elongation at break of the nanofiber formulations were chosen as dependent variables to determine the optimal formulation. Table 1 summarizes the design parameters and the corresponding nanofiber formulations.

Characterization of electrospinning solutions

Polymer solutions were characterized for electrospinning by measuring viscosity, conductivity, and surface tension. In electrospinning, the transfer of electric charge from the electrode to the polymer droplet requires a minimum electrical conductivity of the solution. Conductivity measurements were performed using a Seven2Go Cond meter S3 (Mettler Toledo, UK) by immersing the probe in the polymer solution. All measurements were carried out at room temperature and were expressed in µS/cm.[36]

Surface tension plays a critical role in the electrospinning process.[37] During nanofiber formation by electrospinning, jet initiation occurs when the polymer solution exhibits sufficient surface tension. In this study, surface tension measurements were performed using the pendant drop method (Attension-Theta Lite, Biolin Scientific, Finland). In this method, an image of a droplet of the polymer mixture suspended from the tip of a syringe needle is captured by the instrument. The droplet remains suspended due to the balance between gravitational forces and the liquid's surface tension; this equilibrium configuration was analyzed to determine the surface tension. Surface tensions were calculated using the Young-Laplace equation.[38]

In the electrospinning process, solution flow and fiber production are impeded when viscosity is high, whereas continuous, uniform fibers from polymer solutions with low viscosity cannot be formed. The viscosities of the polymer solutions were measured using a cone-plate viscometer (Brookfield, DV-III Rheometer with spindle type CPE-41, USA). Experiments were performed using 0.5 mL of the sample. All measurements were conducted at room temperature using spindle 52 at a constant shear rate of $100s^{-1}$.[39]

Electrospinning method

The polymer solutions were electrospun using an NE300 electrospinning apparatus equipped with a rotating drum collector. Electrospinning was carried out using a standard uniaxial stainless-steel needle connected to the high-voltage power supply. The solutions were loaded into 10-mL syringes, and voltages of 15-25 kV were tested for jet formation. The tip-to-collector distance was adjusted between 10 and 20 cm, depending on the solvent system, to ensure adequate solvent evaporation. The collector collector rotation speed was set to between 100 and 1,000 rpm, according to the formulation. After optimizing the distance and collector rotation speed, different feed rates were tested according to polymer concentration to produce fibers (Table 2).

Morphological studies

The fiber morphology of the formulations was characterized by scanning electron microscopy (SEM) (FEI Company, Quanta 400 F, USA). Diameters of the electrospun nanofibers were measured from SEM images using ImageJ software (National Institutes of Health, USA).[40] After importing the images into the software, fiber diameters were measured using the image scale. For each sample, 100 individual fibers were measured

Table 1. DoE parameters and content of nanofiber formulations

Formulations	Polymer concentration (X_1)	Solvent system (X_2)	Collector rotation speed (X_3)
R1	7.5%	Ethanol/DW	100 rpm
R2	7.5%	DMF/DW	100 rpm
R3	7.5%	Ethanol/DW	1000 rpm
R4	15%	DMF/DW	1000 rpm
R5	15%	Ethanol/DW	1000 rpm
R6	15%	DMF/DW	100 rpm
R7	7.5%	DMF/DW	1000 rpm
R8	15%	Ethanol/DW	100 rpm

DoE: Design of experiments, DW: Distilled water, DMF: N,N-dimethylformamide

Table 2. Process parameters used in the electrospinning of nanofiber formulations

Formulation code	Voltage (kV)	Feed rate (mL/h)	Distance (mm)	Rotating speed (rpm)
R1	19.5	1.3	110	100
R2	20	1	100	100
R3	18.5	1	110	1000
R4	19	0.8	130	1000
R5	18	0.8	130	1000
R6	17.5	0.7	110	100
R7	19.5	0.9	105	1000
R8	17.5	0.5	120	100

to calculate the mean diameter and examine the fiber size distribution. Diameter distribution histograms were generated using OriginPro® (Origin Lab, USA). For porosity analyses, SEM images were converted to binary (black-and-white) format, and the percentage of void area relative to the total image area was calculated using ImageJ software.

Mechanical properties of nanofibers

The mechanical properties of the nanofibers were evaluated using a Texture Analyser TA-XT equipped with a mini tensile grip. Nanofiber samples were cut into strips measuring 3×1 cm and clamped between the grips. While the lower grip remained stationary, the upper grip moved upward at a crosshead speed of 5 mm/min. The elongation at break and tensile strength were calculated using the instrument's software. On stress-strain curves, the maximum value on the x-axis represents elongation at break, while the maximum value on the y-axis corresponds to tensile strength. All measurements were performed in triplicate.[41]

Contact angle measurements

An optical tensiometer was used for contact angle measurements (Attension-Theta Lite, Biolin Scientific, Finland). Contact angle measurements were performed by placing a droplet of liquid on the material surface and monitoring changes in droplet shape and dimensions over time using optical imaging systems. During the measurements, a 5 µL droplet of DW was deposited onto the nanofiber surface, and changes in the contact angle were monitored. A convex sample holder was used to ensure a smooth and uniform nanofiber surface for accurate imaging.[42] All measurements were performed in triplicate for each nanofiber formulation.

Ex vivo mucoadhesion studies

The mucoadhesive properties of the nanofibers were evaluated using a Texture Analyser TA-XT. Cow vaginal tissue was selected for experiments because of its large surface area and was stored at -20 °C until use. The mucoadhesion study was conducted under previously validated test conditions.[43] Nanofiber samples were cut and affixed to the upper probe. The cow's vaginal tissue was placed at the bottom. The probe was moved at a predetermined speed to make contact with the vaginal tissue. The software calculated the mucoadhesion work value from the distance-force curve.[44] For each measurement, fresh tissue was used, and all tests were performed in triplicate. The TA.XT.Plus Texture Analyser software calculated the work of adhesion (expressed in N·mm). The work of mucoadhesion was calculated using the following equation:

$$\text{Work of mucoadhesion} = \frac{AUC}{\pi r^2} \quad (1)$$

AUC: Area under the curve

πr^2: Area in contact with the formulation and tissue (1,1304 cm^2)

Statistical analysis

GraphPad Prism version 7.0 (GraphPad Software Inc., San Diego, CA, USA) was used for all statistical analyses. Data were expressed as mean ± standard deviation. Parametric tests were applied throughout the study. Comparisons between two groups were conducted using the unpaired t-test, whereas differences among more than two groups were assessed by one-way analysis of variance (ANOVA). Following ANOVA, Dunnett's T3 test was used for comparisons against a control group, and Tukey's HSD test was employed for pairwise post hoc analyses when appropriate. A 95% confidence interval was adopted, and p-values <0.05 were considered statistically significant. Statistical significance levels were indicated as: ns ($p \geq 0.05$), *p<0.05, **p<0.01, ***p<0.001, and ****p<0.0001).

RESULTS

Characterization of polymer solutions

Characterization results for the polymer solutions prepared for the nanofiber formulations are presented in Table 3. Viscosity values increased with increasing polymer concentration, with the highest viscosity observed in formulations containing 15% PVA. Surface tension values varied with the solvent system; ethanol-DW mixtures exhibited lower values than DMF-DW mixtures. Conductivity was also influenced by solvent composition: DMF-DW systems showed higher conductivity than ethanol-DW systems. These characterization results were used to guide the selection of electrospinning process parameters. R1/R3, R2/R7, R4/R6, and R5/R8 share the same formulation; only the electrospinning processing parameters differ. Consequently, viscosity, conductivity, and surface tension are shared values within each pair.

Table 3. Characterization results of polymer solutions (n=3, mean ± SD)

Formulation code		Viscosity (cP.s)	Conductivity (µS/cm)	Surface tension ($mN.m^{-1}$)
R1	R3	395±26	149.8±1.2	30.98±0.15
R2	R7	219±0	158.4±0.4	42.34±0.10
R4	R6	2497±0	226.2±0.7	41.97±0.07
R5	R8	2672±0	212.2±0.8	32.97±0.15

SD: Standard deviation

Morphological studies

SEM imaging revealed that electrospun PVA nanofiber formulations exhibited continuous, bead-free fiber structures with smooth surfaces (Figure 1). Fiber diameters varied among the formulations, with finer and more uniform fibers observed in formulations containing lower polymer concentrations and a DMF-DW solvent system. In contrast, higher polymer concentrations and ethanol-DW systems tended to produce thicker fibers with a broader diameter distribution. Images at 10,000× magnification confirmed the absence of morphological defects and enabled clear visualization of the fiber surface texture.

The mean fiber diameters obtained from SEM image analysis are presented in Table 4. The smallest average diameter was observed for R2 (196±41 nm), formulated with 7.5% PVA in DMF-DW, whereas the largest diameter was recorded for R5 (1721±114 nm), formulated with 15% PVA in ethanol-DW. Formulations prepared with DMF-DW generally produced finer fibers (196-529 nm) compared to those with ethanol-DW (310-1721 nm). Lower polymer concentration (7.5%) tended to produce more uniform fibers, while higher concentration (15%) resulted in thicker fibers and broader diameter distributions. Porosity values ranged from 57.18% (R5) to 88.01% (R1), with higher porosity generally associated with smaller fiber diameters. These results indicate that both polymer concentration and the solvent system play critical roles in determining fiber morphology and porosity.

Mechanical properties of nanofibers

The tensile strength and elongation at break values of the PVA nanofiber formulations are presented in Figure 2. Tensile strength ranged from 1.41±0.07 MPa (R1) to 3.92±0.14 MPa (R6) ($p<0.0001$). Formulations with higher polymer concentration generally exhibited higher tensile strength than those with lower concentration. Elongation at break values varied widely among the formulations, with the highest values observed in R8 (124.77±9.78%) and R7 (121.73±21.96%), and the lowest in R2 (23.95±2.12%). Higher elongation values were typically associated with higher polymer concentrations. This effect was more evident in formulations prepared with ethanol-DW solvent systems, indicating a relationship between solvent composition and fiber flexibility. These findings indicate that polymer concentration, solvent system, and collector rotation speed collectively influence the mechanical performance of electrospun PVA nanofibers.

The findings determined using the DoE approach on the influence of process parameters on nanofiber properties are presented in Table 5. A 2^3 (two-level, three-factor) factorial design was implemented using Design Expert software to identify the optimal processing parameters, resulting in eight formulations. Tensile strength and elongation at break values obtained from these formulations were statistically analyzed to evaluate the effects of the independent variables on the mechanical properties of the nanofibers. 3D surface plots are presented in Figure 3. Based on the factorial-design analysis, the tensile strength of PVA nanofibers was described by the following equation: tensile strength = 2.563875 + 0.971875 × A (concentration). Similarly, elongation at break was expressed as 0.991000 + 7.20723 × A (concentration). These results demonstrate that polymer concentration (factor A) had a measurable influence on both the tensile strength and the elongation at break of the PVA nanofiber formulations.

Contact angle measurements

In the PVA nanofiber formulations, the contact angles were measured at 0° for all samples. This complete wettability is attributed to the highly hydrophilic nature of PVA, which facilitates immediate spreading of the water droplet upon contact with the fiber surface. The instantaneous absorption of the droplet into the nanofibers indicates strong surface affinity for aqueous media, suggesting that these formulations can rapidly interact with vaginal mucosal fluids, thereby promoting intimate contact and enhancing mucoadhesion.

Ex vivo mucoadhesion studies

The mucoadhesive properties of the PVA nanofiber formulations are presented in Figure 4. The work of mucoadhesion ranged from 0.014±0.010 mJ/cm^2 (R1) to 0.194±0.060 mJ/cm^2 (R3) ($p<0.0001$). Formulations containing a lower polymer concentration of 7.5% PVA and a higher collector rotation speed (1000 rpm) generally exhibited greater mucoadhesion than formulations produced at lower collector rotation speeds. The highest mucoadhesion value was observed in R3, while the lowest was found in R1. These results indicate that, in addition to polymer concentration, processing parameters such as collector rotation speed can markedly influence the mucoadhesive performance of PVA nanofibers.

The influence of processing parameters, particularly the collector rotation speed, on mucoadhesion can be attributed to their effects on fiber alignment and exposed surface area.

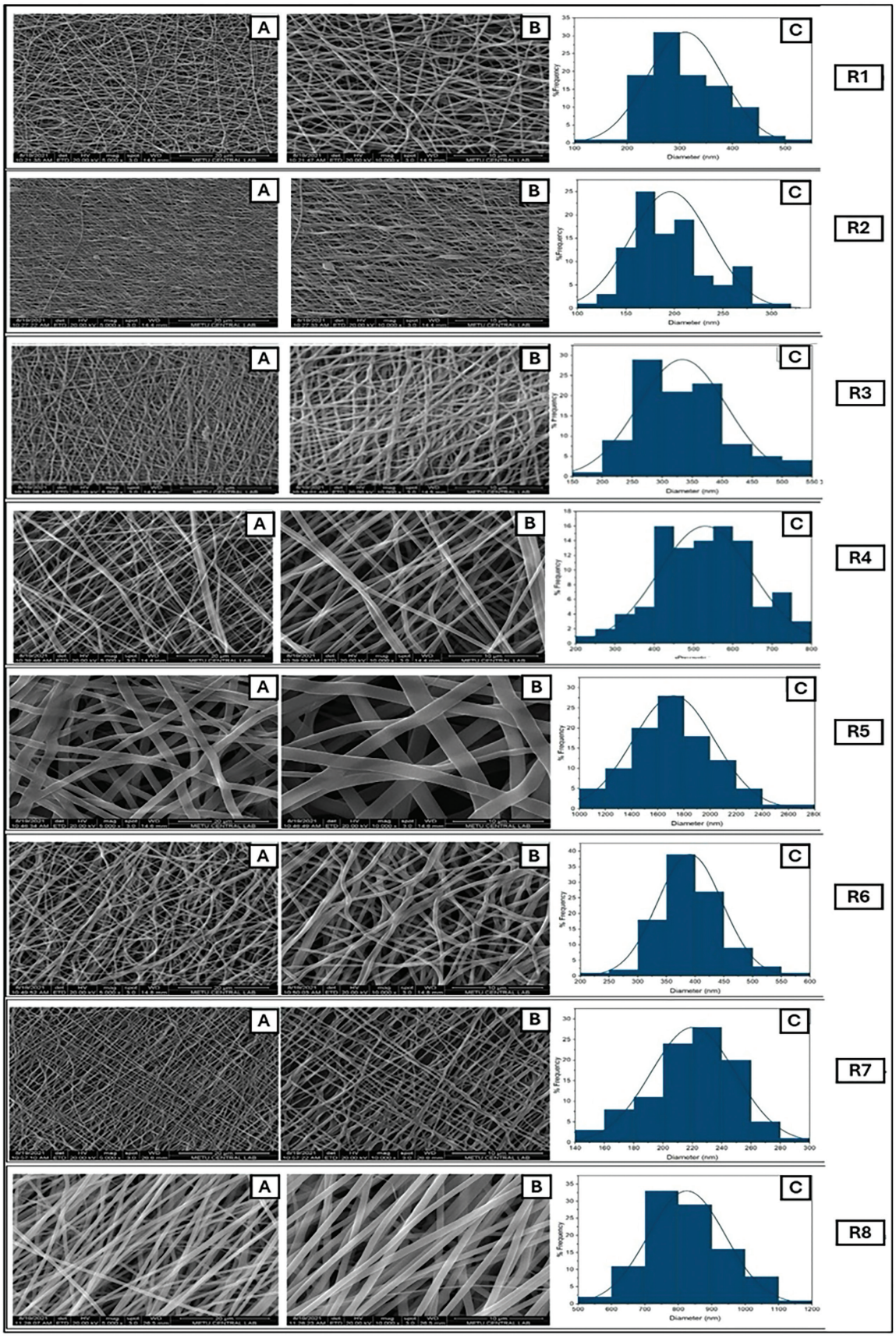

Figure 1. SEM images (a: 5000x magnification, b: 10,000x magnification) and fiber diameter distribution (c) of PVA nanofibers
SEM: Scanning electron microscopy, PVA: Poly(vinyl alcohol)

Higher rotation speeds tend to produce more uniformly aligned fibers, which may enhance the effective contact area with the mucosal surface and facilitate interfacial interactions between the hydrophilic PVA chains and mucin. This improved surface contact likely increases adhesive forces, thereby elevating the measured mucoadhesion work values. Moreover, higher rotation speeds tended to produce finer fibers. Finer fibers increase the specific surface area available for interaction with the mucosal surface.

DISCUSSION

The physicochemical characteristics of polymer solutions are critical determinants of spinnability and the morphological quality of electrospun nanofibers. Viscosity increased significantly with increasing polymer concentration ($p<0.05$). Haider and colleagues reported that increasing the concentration of the polymeric solution would increase the viscosity, which in turn would increase polymer chain entanglement.[19] This chain entanglement overcomes surface tension, resulting in homogeneous, bead-free electrospun nanofibers. In our study, as expected, viscosity increased with PVA concentration. Hameed et al.[45] developed cephalexin-loaded core-shell nanofibers from PVA-based biopolymers using emulsion electrospinning and reported fiber diameters in the range of 270-526 nm. Larger fiber diameters are associated with increased viscosity of the emulsion's oil phase.[45] In our study, the fiber diameters obtained with formulations R1 and R3, for 7.5% (*w/v*) polymer solutions prepared in the ethanol/DMF solvent system, were 310±71 nm and 334±74 nm, respectively ($p\geq0.05$). When the same solvent system was used, larger diameters of 1721±114 nm and 825±116 nm were obtained for formulations R5 and R8, respectively, at 15% concentration ($p<0.0001$). The increase in fiber diameter is due to the higher viscosity of the solution. These findings further confirm that viscosity influences jet stability and fiber thinning during electrospinning, and that solution rheology affects the final nanofiber morphology.

Table 4. Fiber diameter and porosity values of PVA nanofibers

Formulation code	Nanofiber diameter (mean ± SD)	Porosity (%)
R1	310±71	88.01
R2	196±41	73.92
R3	334±74	61.57
R4	529±119	65.45
R5	1721±114	57.18
R6	391±57	68.76
R7	220±29	75.98
R8	825±116	78.61

SD: Standard deviation, PVA: Poly(vinyl alcohol)

Table 5. Comparison of the effect of process parameters on the tensile strength of PVA nanofiber formulations based on ANOVA test.

Tensile strength				
Source	Sum of squares	Mean square	*f* value	*p* value
Model	7.56	7.56	168.5	<0.0001
A- Concentration	7.56	7.56	168.5	
Elongation at break				
Model	5843.72	5843.72	7.65	0.0326
A- Concentration	5843.72	5843.72	7.65	

ANOVA: Analysis of variance, PVA: Poly(vinyl alcohol)

Surface tension varied among formulations; ethanol-DW mixtures exhibited significantly lower surface tension than DMF-DW systems ($p<0.05$). Bonakdar and Rodrigue[46] stated that high surface tension can hinder the electrospinning process, causing instability, an increased tendency for jet breakup, and consequently the formation of beaded fibers. Lower surface tension facilitates electrostatic forces that support jet-based nanofiber formation, preventing bead formation and other defects, and resulting in a smoother, more homogeneous fiber morphology. Conversely, high surface tension in DMF-water mixtures can further inhibit jet formation and lead to defective fiber morphology. In the DMF-water formulation (R2), a few beads were observed, likely due to the higher surface tension, but the low frequency of beads in SEM images indicates that spinning was nearly stable. Khattab et al.[47] measured the surface tension of water-ethanol mixtures prepared by mixing the solvents in volumetric proportions. Varying the solvent composition altered surface tension. In our study, different surface values were obtained for water-ethanol and water-DMF mixtures. Solvent systems with lower surface tension promote more stable Taylor cone formation and continuous jet elongation, thereby improving nanofiber uniformity and reducing morphological defects.

Conductivity measurements revealed significantly higher values for DMF-DW formulations (R2/R7 and R4/R6) than for ethanol-DW formulations ($p<0.05$). Ergin et al.[48] showed that conductivity measurements in DMF-water mixtures increased with increasing DMF weight percentage. Spivey et al.[49] reported

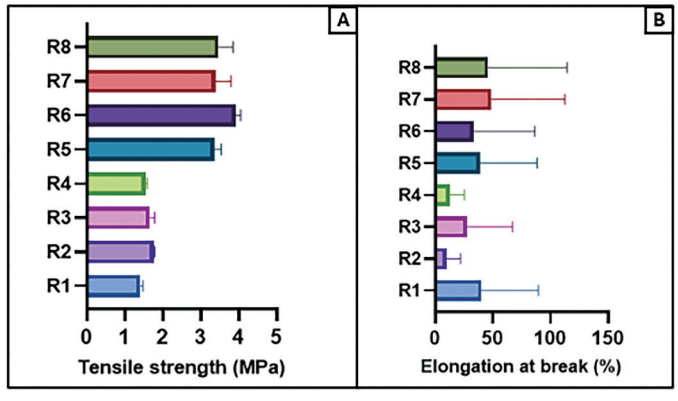

Figure 2. Tensile strength (a) and elongation at break values (b) of PVA nanofiber formulations (n=3, mean ± SD)

SD: Standard deviation, PVA: Poly(vinyl alcohol)

that increasing the ethanol concentration in water decreases the conductivity of various electrolyte solutions. These findings indicate that polymer concentration and solvent system have a measurable effect on the physicochemical properties of the electrospinning solutions. In the study conducted by Ge et al.,[50] increasing the PVA concentration caused an increase in conductivity values. In this study, it was 485.8±1.92 µS/cm at 8% PVA and 663.8±5.89 µS/cm at 15% PVA. Similarly, in our study, for 7.5% concentrations prepared using ethanol and DW, values of 149.8±1.2 µS/cm were obtained for R1 and R3, whereas values of 212.2±0.8 µS/cm were obtained for R5 and R8. At 7.5% concentration, prepared in DMF and DW, values of 158.4±0.4 µS/cm were obtained for R2 and R7, whereas values of 226.2±0.7 µS/cm were obtained for R4 and R6. Increasing concentration led to higher conductivity. These results demonstrate that both the solvent composition and the polymer concentration modulate the charge-carrying capacity of the electrospinning solution, thereby influencing jet stability and fiber formation; higher conductivity mixtures promote more efficient charge transfer.

One of the advantages of SEM is its high depth of field, which provides information on structures at various distances.[51] SEM is a valuable technique for evaluating the fundamental characteristics of nanofibers, such as fiber diameter, and for examining the effects that arise during the electrospinning process and that depend on factors such as polymer concentration and solution conductivity. Analysis of fiber diameter revealed significant differences among the formulations ($p<0.05$). The significant increase in fiber diameter observed with higher PVA concentration is consistent with previous studies, which showed that increased solution viscosity reduces jet stretching and produces thicker fibers. Zhang et al.[52] showed that increasing the concentration and viscosity of the PVA solution suppressed bead formation but increased fiber diameter. Similarly, the smaller fiber diameters obtained from DMF-DW systems are consistent with reports that higher-conductivity solvents enhance charge-carrying capacity, resulting in greater elongational forces on the jet and, consequently, finer fibers.[53] Electrospun nanofibers with small fiber diameters can be obtained from the solution with the highest conductivity. In contrast, ethanol-DW systems, with lower conductivity and higher surface tension, tend to produce thicker fibers, as observed in our R5 and R8 formulations. These results confirm that optimizing both polymer concentration and solvent system is crucial. The R3 formulation demonstrated improved performance by providing both the optimum fiber diameter and a bead-free morphology. In nanofiber production, fiber morphology varies depending on the applied voltage, flow

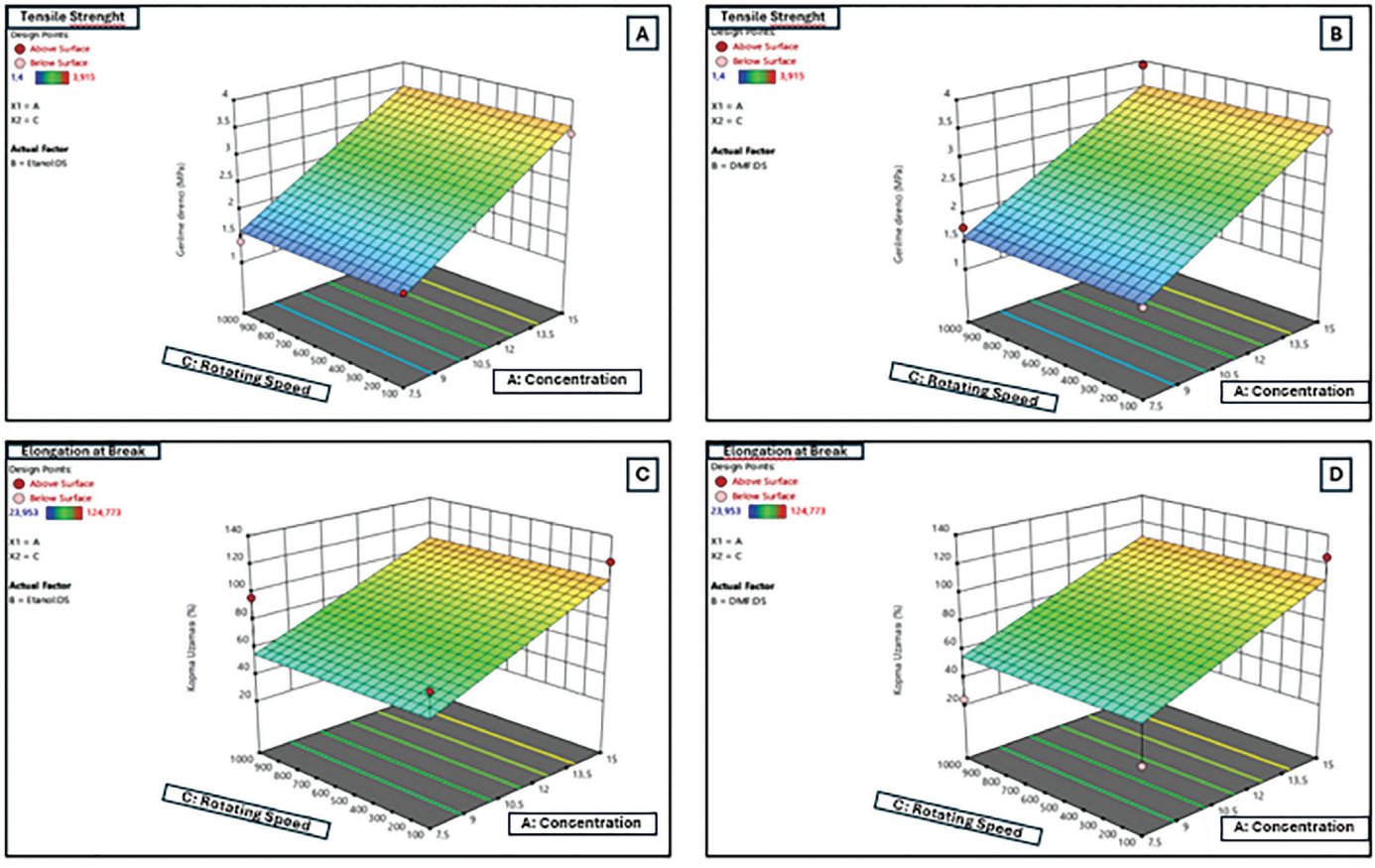

Figure 3. Three-dimensional surface plots illustrating the effect of process parameters on tensile strength and elongation at break of PVA nanofiber formulations prepared with ethanol-DW (a, c) and DMF-DW (b, d) solvent systems

DW: Distilled water, DMF: N,N-dimethylformamide, PVA: Poly(vinyl alcohol)

rate, and tip-to-collector distance. Environmental parameters such as relative humidity and ambient temperature, although not the focus of this study, are known to influence solvent evaporation rates and fiber morphology and may explain minor variations observed among replicate samples.[54]

The production parameters directly influence the morphology and mechanical properties of the nanofibers. The mechanical properties of nanofibers depend on the polymer type, crystallization rate, and crystallinity level.[55] The arrangement of the fibers on the collector during the production process, the interaction between the fibers, and excessive porosity affect the mechanical properties of the nanofibers. Our findings also indicate that collector rotation speed plays a critical role in determining fiber morphology; higher rotation speeds improve fiber alignment and reduce mean fiber diameter through enhanced mechanical stretching during deposition. Collector rotation speed emerged as another critical factor influencing mechanical performance. Higher rotation speeds promote fiber alignment, which is known to improve tensile strength. In the study by Wong et al.,[56] the tensile strength of electrospun PCL nanofiber was increased by decreasing the fiber diameter. They determined that reducing the fiber diameter improves crystallinity and molecular orientation, which explains the enhanced tensile properties of smaller-diameter fibers. In the study by Habeeb et al.,[57] nanofibers collected at high collector rotation speed exhibited greater tensile strength than those collected at low collector rotation speed. Similarly, in our study, formulations spun at 1000 rpm showed markedly higher elongation-at-break values, suggesting that improved fiber alignment not only enhances strength but also increases flexibility. Additionally, the influence of the solvent system on mechanical behavior can be indirectly explained by its effects on fiber morphology. DMF-water systems with higher conductivity likely produced fibers with fewer structural defects, thereby improving tensile properties. Ethanol-water systems, on the other hand, tend to produce thicker and less aligned fibers, explaining the relatively lower tensile strengths despite similar polymer content. Among the tested formulations, R3 demonstrated a favorable balance between tensile strength and elongation-at-break values, attributable to its smaller average fiber diameter and a high degree of fiber alignment achieved at 1000 rpm. For example, R3 exhibited a tensile strength of 1.657±0.133 MPa and an elongation at break of 73.12±6.15% with an average fiber diameter of 334±74 nm, while R1 showed a similar fiber diameter of 310±71 nm but a lower tensile strength of 1.412±0.065 MPa and a higher elongation at break of 96.20±21.50%, suggesting that alignment, rather than diameter alone, influences mechanical performance. These parameters suggest that R3 not only meets the mechanical strength required for the intended application but also maintains flexibility, making it a strong candidate for further development. These relationships emphasize that mechanical optimization in electrospun PVA systems should simultaneously consider solution composition, fiber alignment (*i.e.*, collector rotation speed), and the resulting morphological features.

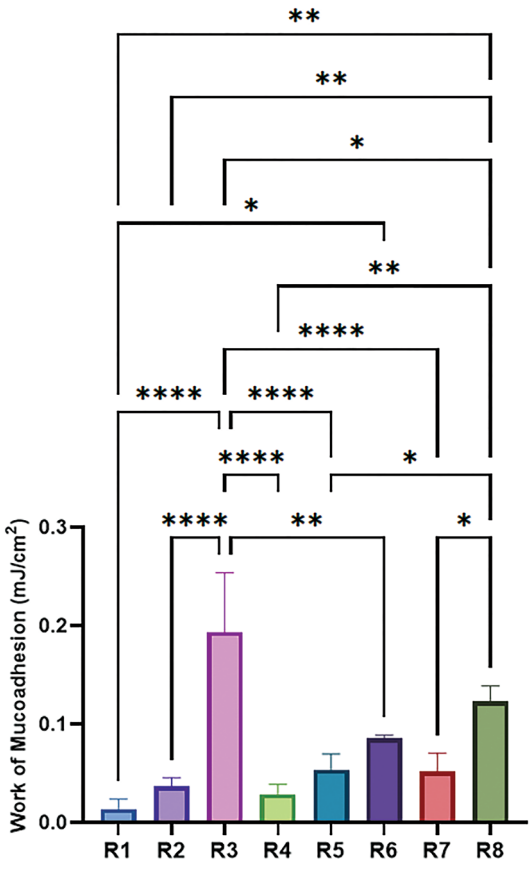

Figure 4. Work of Mucoadhesion of PVA nanofiber formulations measured on cow vaginal tissue (n=3, mean ± SD, p≥0.05, *p<0.05, **p<0.01, ***p<0.001, and ****p<0.0001)

SD: Standard deviation, PVA: Poly(vinyl alcohol)

Production parameters influenced the adhesive performance of PVA nanofibers. Formulations containing 7.5% PVA produced at a higher collector rotation speed (1000 rpm) exhibited significantly higher mucoadhesion compared to their lower-speed counterparts. This may be attributed to the reduced fiber diameter observed in these formulations, which increases the total surface area available for polymer-mucin interactions. Smaller fiber diameters increase the intimate contact with the mucosal surface, thereby supporting stronger adhesive forces. Dehydration theory proposes that the polymer absorbs water from the mucosa, creating a tighter contact with the mucosa and resulting in stronger adhesion. This effect allows the fibers to bond more strongly with the mucosa.[58] Furthermore, the solvent system influenced mucoadhesive strength. DMF-DW systems, which produced thinner fibers due to higher conductivity, generally exhibited superior mucoadhesion compared with ethanol-DW systems. R3 exhibited the highest work of mucoadhesion among all tested formulations, a result linked to its smaller fiber diameter, which increases the available surface area for polymer-mucin interactions. This suggests that solvents with higher conductivity promote electrostatic tension during spinning, creating thinner fibers that can more effectively penetrate the mucus layer. For instance, R3 achieved a work of mucoadhesion of 0.194±0.060 mJ/cm² with an average fiber diameter of 334±74 nm, whereas R1 exhibited only 0.014±0.010

mJ/cm² with an average fiber diameter of 310±71 nm. Similarly, among the 15% PVA formulations, R8 reached 0.123±0.016 mJ/cm² and had fiber diameters of 825±116 nm, compared to R5, which exhibited a lower mucoadhesion of 0.054±0.016 mJ/cm² despite having the thickest fibers. These data clearly demonstrate that finer fiber diameters, regardless of polymer concentration, correlate with enhanced mucoadhesive performance. Tuğcu-Demiröz et al.[59] obtained higher mucoadhesion values at higher concentrations of metronidazole-loaded PVP nanofibers. Similarly, in our study, increasing PVA concentration resulted in higher mucoadhesion values: R1 (7.5%), 0.014±0.010 mJ/cm^2; R8 (15%), 0.123±0.016 mJ/cm^2. Lower values were obtained for R3 (7.5%) were obtained for R3 (7.5%) and R5 (15%): 0.194±0.060 mJ/cm^2 and 0.054±0.016 mJ/cm^2, respectively. This suggests that mucoadhesion values depend not only on concentration but also on fiber diameter, porosity, and other properties that may affect them. These findings suggest that optimizing polymer concentration, collector rotation speed, and solvent conductivity can synergistically enhance the work of mucoadhesion, which is critical for achieving long-term retention in vaginal drug delivery systems. Mucoadhesion results revealed that both polymer concentration and processing parameters affect nanofiber properties.

Thanks to their thin and flexible architecture, nanofiber-based systems facilitate easy insertion, exhibit rapid hydration upon contact with vaginal fluids, and conform effectively to the mucosal surface, thereby reducing friction and irritation while enhancing comfort and overall patient tolerability.

Study limitations

This study focused on optimizing blank PVA-based electrospun nanofibers without active pharmaceutical ingredients; therefore, drug-polymer interactions, drug-loading efficiency, and drug-release profiles were not evaluated. Moreover, the experimental scope was limited to mechanical and mucoadhesive characterization; several critical performance parameters relevant to vaginal application, such as *in vitro* drug release and permeation, stability under simulated vaginal conditions, cytotoxicity, and *in vivo* retention, were not investigated. The absence of permeability studies on *ex vivo* or cell-based vaginal models limits the estimation of mucosal transport, while the lack of cytotoxicity testing prevents an initial assessment of biocompatibility. Stability under simulated vaginal conditions was also not examined, although such data are critical for understanding the behavior of PVA-based systems in the presence of vaginal fluids and under variable pH conditions. In addition, the *in vitro* mucoadhesion results were not supported by *in vivo* retention studies, which would be necessary to confirm prolonged residence under physiological conditions. These evaluations were beyond the scope of the present work. Future studies will incorporate model drugs or clinically relevant active compounds, followed by comprehensive *in vitro* and *in vivo* evaluations to fully characterize the therapeutic performance, safety profile, and biological applicability of the optimized nanofiber formulation.

CONCLUSION

Electrospun nanofibers offer practical advantages for vaginal administration: their thin, flexible, and conformable structure facilitates comfortable insertion and intimate contact with the mucosal surface. Their solid, sheet-like architecture minimizes leakage and improves handling compared with semi-solid formulations, thereby enhancing patient acceptability and adherence. Moreover, the ability to control nanofiber dimensions, mechanical softness, and folding characteristics provides a clinically relevant platform that can be optimized for ease of use and reproducible administration.

This study developed and optimized PVA electrospun nanofiber formulations for vaginal drug delivery using DoE. Polymer concentration, solvent system, and collector rotation speed were identified as critical determinants of both the physicochemical properties of polymer solutions and the mechanical and mucoadhesive performance of the resulting nanofibers. The optimized formulation exhibited desirable tensile strength (>1 MPa), elongation at break (>50%), and mucoadhesive performance, along with uniform, defect-free fiber morphology. These findings underscore the potential of PVA-based electrospun nanofibers as an advanced platform for vaginal drug delivery, offering enhanced retention and improved patient compliance compared to conventional semi-solid and liquid dosage forms. Future work will focus on drug incorporation, release kinetics, and comprehensive *in vitro* and *in vivo* evaluations to assess their translational and clinical applicability.

Ethics

Ethics Committee Approval: Not required.

Informed Consent: Not required.

Footnotes

Authorship Contributions

Concept: S.S., F.T.-D., F.A., Design: S.S., F.T.-D., F.A., Data Collection or Processing: S.S., F.T.-D., F.A., Analysis or Interpretation: S.S., F.T.-D., F.A., Literature Search: S.S., F.T.-D., F.A., Writing: S.S., F.T.-D., F.A.

Conflict of Interest: The authors declare no conflicts of interest.

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