Poly(vinyl alcohol) (PVA) is a water-soluble polymer that has been widely used in medical and pharmaceutical applications [1]. PVA has exceptional biodegradability, water solubility, non-toxic, high elasticity, non-carcinogenic, and hydrophilic characteristics [2]. Therefore, it has been widely used by biomedical and pharmaceutical practitioners [3]. PVA has a simple chemical structure with a polar hydroxyl group (-OH), which tends to form intermolecular and intramolecular hydrogen bonds [1]. The solubility of PVA in water usually depends on its degree of polymerization and, in particular, hydrolysis. Therefore, for the same polymerization degree (1700), 88% hydrolyzed PVA can dissolve in water at 40 °C, whereas 99% hydrolyzed PVA cannot do so at a temperature below 80 °C, due to the differences in intramolecular and intermolecular hydrogen bonds. At 99% hydrolysis, PVA contains large numbers of hydrogen bonds, which restrict the dissolution of many PVA macromolecules in water. With less hydrolysis (88%), PVA still has many residual acetate groups on its macromolecular chains, decreasing the number of hydrogen bonds and increasing its water solubility [4].

Grafting can modify and improve the properties of polymers, by covalently bonding a second polymer’s monomers as branches onto the backbone of the first polymer [5]. Grafting with urea can improve the water solubility of PVA which, in turn, improves its degradability for more effective performance in tissue engineering and drug delivery applications [4]. This is because urea can break hydrophobic and hydrogen bonds. Therefore, many researchers have studied the configuration changes induced by urea in water-soluble non-ionic synthetic polymers, including poly(methyl acrylamide), poly(vinyl alcohol), poly(ethylene glycol), and poly(vinyl pyrrolidone) [6]. For biomedical applications, the hydrophilic properties and structure of the scaffold are important, as the scaffold structure should mimic the body’s extracellular matrix. To obtain these characteristics, the scaffold should provide a structure with high open porosity, adequate pore size, and a high surface area, in order to improve cell attachment, proliferation, and penetration [7]. Electrospinning is one of the simplest and most efficient methods to produce fibers with diameters from several micrometers down to less than 100 nm. Electrospun fibers have a very high surface area to mass ratio and high porosity [8]. Electrospinning is an electrically driven method, forming fibers from polymer solution or melt that is fed through a capillary tube into a region with a high electric field, generated by a high-voltage power supply connected to the capillary tip [9].

To improve the wound-healing ability of PVA, Mwiiri F.K. et al. have prepared electrospun PVA nanofibers containing triterpenes from the outer bark of birch, which is known for its pharmacological effects [10]. Mano F. et al. have produced new functionalized PVA fibers, using a eutectic mixture of...
choline chloride and citric acid in a molar ratio of 1:1, for drug delivery systems and to overcome the poor solubility of PVA in water [11]. To add an antimicrobial agent to PVA, Vilamova Z. et al. have prepared a composite from silver nanoparticles encapsulated inside electrospun PVA nanofibers [12]. For this study, we aimed to find the best electrospinning parameters (including capillary–collector distance, voltage, and flow rate) for the newly prepared material graft urethanized poly(vinyl alcohol) (U-PVA) and comparing the results of wettability and drug release rates between pure PVA and graft U-PVA specimens for pharmaceutical applications.

2. Materials and methods

2.1. Materials

Our starting materials were poly(vinyl alcohol) (PVA) with molecular weight \( \approx 72,000 \text{ g/mol} \) (Fluka, U.K.), 99.8% pure urea (Sigma Aldrich), dimethyl sulfoxide (DMSO; Sinopharm Chemical reagent Co. Ltd. China), 95% pure ethanol (Tomas Baker, India), phosphate buffered saline PBS (Sigma Aldrich) PH 7.4, and Insulin human (rDNA 100 IU/ml a solution for injection that contains the active substance human insulin from Actrapid, Charters, France. Actrapid is a replacement insulin that is very similar to the insulin made by the pancreas).

2.2. Methods

2.2.1. Preparation of graft U-PVA

We added 10 g PVA, 13.6 g urea, and 50 mL DMSO into a two-necked flat-bottomed flask equipped with a condenser, thermometer, and magnetic stirrer. We heated the contents of the flask under reflux for 3 h. Finally, we allowed the stirred mixture to cool to room temperature while adding ethanol and then dried it [13, 14].

2.2.2. Preparation pure PVA solution

We prepared a solution of pure PVA and distilled water at a concentration of 10% w/v for comparison with the best prepared specimen of Graft U-PVA. We dissolved pure PVA using a hot magnetic stirrer at a temperature of 80 \({}^\circ\text{C}\) for 6–7 h until it formed a homogeneous solution.

2.2.3. Preparation of graft U-PVA solution

We prepared a solution of the prepared graft U-PVA and distilled water at a concentration of 10% w/v. We dissolved the graft U-PVA using a hot magnetic stirrer at a temperature of 80 \({}^\circ\text{C}\) for 3–4 h until it formed a homogeneous solution.

2.2.4. Preparation of graft U-PVA nanofiber mats

We prepared graft U-PVA nanofiber mats using a bio-electrospinning/electrospray system (ESB-200 Nano NC). We altered the electrospinning conditions (capillary–collector distance, voltage, and flow rate) in order to choose the best properties of the nanofiber mats. First, we fixed the applied voltage at 20 kV and the flow rate at 1.5 mL/h, and changed the capillary–collector distance first, starting with 15, 18, and 20 cm. We fixed the distance at 20 cm, as the scanning electron microscope (SEM) images showed a suitable structure at this distance. Second, we changed the voltage: we applied 20, 18, and 25 kV, then fixed the voltage at 25 kV, according to the structure shown by SEM. Finally, we changed the flow rate by testing the results at 1.5, 0.5, and 1 mL/h. Table 1 summarizes the applied electrospinning parameters.

2.2.5. Scanning electron microscope (SEM) characterization with statistical analysis

We characterized the graft U-PVA nanofiber mats and compared them with pure PVA using SEM. First, we coated the samples with gold by sputtering and then investigated them under SEM with an accelerating voltage of 5 kV.

2.2.6. Statistical analysis

We measured the diameter in 50 fiber/SEM images using the AutoCAD 2010 software. Then, we calculated the average fiber diameter and standard deviation using Microsoft Excel [15].

2.2.7. Contact angle measurements

We measured the contact angle at room temperature according to the ASTM standard D 5946-04. We measured two specimens: Graft U-PVA, with the best structure based on the SEM results, and a reference pure PVA specimen, prepared using the same parameters as the first specimen (concentration = 10% w/v, capillary–collector distance = 20 cm, applied voltage = 25 kV, and flow rate = 1 mL/h). We measured the static contact angle of distilled water using the optical contact angle and an interface tensiometer (Creating Nano Technologies Inc. Tainan, Taiwan) on dry and clean specimens tightened onto a glass slide (Figure 1).

2.2.8. Fourier transform infra-red spectroscopy FTIR characterization

We used Fourier transform infra-red spectroscopy (FTIR) to characterize any change occurred in pure PVA spectrum after grafting urea to PVA. We characterized two specimens: Graft U-PVA with the best structure based on SEM results, and a reference pure PVA specimen, prepared using the same parameters as the first specimen (concentration = 10% w/v, capillary–collector distance = 20 cm, applied voltage = 25 kV).

Table 1. Applied electrospinning parameters.

| Electrospinning Parameter | Specification |
|---------------------------|---------------|
| Concentration w/w%        | 10% graft U-PVA|
| Orifice size              | 22 G (0.7 mm) |
| Collector type            | Stainless steel flat plate |
| Capillary–collector distance | 15, 18, 20 cm |
| Applied voltage           | 18, 20, 25 kV |
| Flow rate                 | 0.5, 1, 1.5 mL/h |

Figure 1. The fixation of specimens on a glass slide: F, graft U-PVA specimen; H, pure PVA specimen.
kV, and flow rate = 1 mL/h). The spectra were accomplished in absorption using Bruker Optik system, (Type of spectrometer, Tensor 27, Germany). This spectrometer is equipped with a mid-IR source 4000–400 cm\(^{-1}\) and a KBr beam splitter.

2.2.9. In vitro drug release study

Specimens of 30 mg weight of best graft U-PVA and pure PVA electrospun mats were immersed in 10 mL insulin (human insulin rDNA) for 12 h. Insulin solutions were then withdrawn and 50 mL of phosphate buffered saline PBS PH 7.4 was added to each specimen and these specimens were incubated at 37\(^\circ\)C to study insulin release rate with time. After 10 h, 10 mL of the solution was withdrawn from each specimen and it was replaced with 10 mL of fresh PBS, and this procedure was repeated after 20, 30, 40, and 50 h of in vitro incubation. Ultra-Violet UV-Visible spectrometry was used to determine the concentration of released insulin at wave number \(\lambda\) equal to 276 nm. The cumulative insulin released was calculated after preparing different known concentrations of insulin solutions to determine the standard calibration curve. The experiments were achieved in triplicate and the insulin concentration was taken as an average [16, 17].

3. Results and discussion

3.1. Electrospinning parameters characterization

Determining the best parameters for graft U-PVA spinning depends on the resultant structure after SEM characterization. The capillary–collector distance is one of the most important process parameters affecting the fiber morphology and properties [11]. We applied three distances (15, 18, and 20 cm). Figures 2, 3, and 4 show the fiber

![Figure 2](image1.png)

**Figure 2.** (a) Fiber diameter distribution; (b) SEM image (magnification = 10,000x) for graft U-PVA specimen prepared under the following conditions: Concentration = 10% w/v, voltage = 20 kV, flow rate = 1.5 mL/h, and capillary–collector distance = 15 cm.

![Figure 3](image2.png)

**Figure 3.** (a) Fiber diameter distribution; (b) SEM image (magnification = 10,000x) for graft U-PVA specimen prepared under the following conditions: Concentration = 10% w/v, voltage = 20 kV, flow rate = 1.5 mL/h, and capillary–collector distance = 18 cm.
morphology and diameter distributions, along with the calculated average fiber diameter and standard deviation, for the graft U-PVA specimens prepared using different capillary collector distances.

The highest average fiber diameter (345.4 ± 102 nm) was obtained when we applied a 15 cm capillary–collector distance (as shown in Figure 2a). We also observed some fiber adhesion (Figure 2b), which may be attributed to residual solvent that did not evaporate. Other researchers have made similar observations [11]: Mwiiri F.K. et al. observed that, at distances lower than 11 cm, particles formed, instead of fibers; meanwhile, at distances higher than 16 cm, more homogeneous fibers formed. When we increased the capillary–collector distance to 18 and 20 cm, the average fiber diameter decreased to 287.4 ± 105 nm and 218.4 ± 78 nm, respectively (as shown in Figures 3a and 4a). Applying a 20 cm distance lowered the deviation in fiber diameter, which meant more uniformity in the fiber structure. The reason behind this finding is the elongation in fiber diameter, resulting from the distance between the needle and collector increasing, which allowed the solvent to evaporate and reduced the fiber adhesion and bead formation as noticed in Figures 3b and 4b. The formation of beads may also be a result of the increased field strength when the capillary–collector distance is small, which has a similar effect as the high applied voltage increases jet instability and encourages bead formation [18]. Considering the previous results, a capillary–collector distance of 20 cm was considered the best, compared with 15 and 18 cm.

The second parameter we characterized was the applied voltage. After applying 20 kV, we applied 18 and 25 kV to compare the resulting graft U-PVA structures and to decide which one is most suitable for application in the biomedical and pharmaceutical fields. Figures 5a, 5b, 6a and 6b show the fiber morphology and diameter distributions, along with the calculated average fiber diameter and standard deviation, for graft U-PVA specimens prepared with applied voltages of 18 and 25 kV, respectively.

As previously mentioned, the average fiber diameter with a 20 kV applied voltage was 218.4 ± 78 nm. Reducing the applied voltage to 18 kV increased the average fiber diameter to 221.8 ± 62 nm, while increasing the applied voltage to 25 kV resulted in the lowest average fiber diameter (149.8 ± 58) and the lowest deviation as shown in Figures 5a and 6a respectively. Vilanova Z. et al. have also observed this behavior [12]. Generally, increasing the applied voltage leads to a stable
Taylor cone, and the columbic repulsive forces within the spinning jet force the viscoelastic solution to extend. However, if the applied voltage is higher than the critical limit, this causes some drop from the tip of the needle, due to jet instability resulting from the high field strength, which may cause some bead formation [18] (as shown in Figure 6b).

Finally, we characterized the flow rate to obtain a more suitable structure for biomedical and pharmaceutical applications. After applying a flow rate of 1.5 mL/h, we applied rates of 0.5 and 1 mL/h. Figures 7a, 7b, 8a, and 8b show the fiber morphology and diameter distribution, along with the calculated average fiber diameter and standard deviation, for graft U-PVA specimens prepared with flow rates of 1 and 0.5 mL/h, respectively.

When we decreased the flow rate to 1 mL/h, the specimen formed a homogeneous structure that was free of beads and had a small deviation in diameter, as shown in Figure 7b. The average fiber diameter was 159 ± 59.32 nm (Figure 7a), and this specimen was the best among the prepared specimens. Lowering the flow rate slowed the ejection of solution from the needle, such that the solvent more efficiently evaporated and did not cause bead formation. Jabur A.R. et al. have also observed this phenomenon [3]. Decreasing the flow rate to 0.5 mL/h also resulted in a homogeneous structure that was free of beads, as shown in Figure 8b, but the average fiber diameter increased to 211.4 ± 79.1 nm (Figure 8a). A high flow rate results in a higher solvent to polymer ratio, which increases the probability of beads forming in the resultant structure. However, decreasing the flow rate below the optimum value may cause the polymer to solidify between the needle and collector, which lowers fiber elongation and increases the fiber diameter, as shown in Figure 8b.

We prepared a control specimen from 10% w/v pure PVA under the same electrospinning conditions used for the optimum specimen, in order to observe the differences in structure after grafting with urea to form graft U-PVA, which may be used as a drug delivery system. Figures 9a and 9b show the fiber morphology and diameter distributions, along with the calculated average fiber diameter and standard deviation, for the pure PVA specimen. The structure was free of beads and had homogeneous fiber diameters as noticed in Figure 9b, but the average fiber diameter (289.52 ± 47.11 nm) was much higher than that of the best graft U-PVA specimen. In a drug delivery system, thicker fibers mean that the drug molecules have to travel further through the polymeric matrix, leading to...
Figure 8. (a) Fiber diameter distribution; (b) SEM image (magnification = 10,000×) for graft U-PVA specimen prepared under the following conditions: Concentration = 10%w/v, voltage = 25 kV, flow rate = 0.5 mL/h and capillary-collector distance = 20 cm.

Figure 9. (a) Fiber diameter distribution; (b) SEM image (magnification = 10,000×) for pure PVA specimen prepared under the following conditions: Concentration = 10%w/v, voltage = 25 kV, flow rate = 1 mL/h, and capillary-collector distance = 20 cm.

Figure 10. Contact angle measurements for (a) pure PVA specimen (55 ± 6.08°) and (b) best graft U-PVA specimen (36 ± 3.85°).
a slower release, whereas thinner fibers result in high and rapid drug release. Hence, we can control the drug-release rate by adjusting the thickness of the electrospun fibers [10]. For tissue engineering applications, grafting with urea is more effective than using pure PVA as, in a scaffold, thinner fibers increase the surface area onto which cells can attach; therefore, cell attachment improves, causing higher penetration and the formation of three-dimensional tissue [8].

3.2. Contact angle measurements

Being hydrophilic with a low contact angle or hydrophobic with a high contact angle determines the applications of the prepared tissue. Hydrophilicity is more effective in tissue engineering applications, as it causes faster scaffold degradation to match fast cell-growth rates, whereas hydrophobicity causes the scaffold to degrade slower, which matches with slow cell-growth rates. In polymer matrix drug delivery systems, drug release rate depends on common mechanisms which are: diffusion, erosion and swelling. For hydrophilic drug delivery systems, the release occurs through water penetration, so the responsible mechanisms are swelling and diffusion. While, for hydrophobic polymer matrices the mechanisms responsible for drug release are diffusion or erosion [19]. Therefore, for graft U-PVA as a hydrophilic drug delivery system, increasing the hydrophilicity leads to higher drug release rates. Figure 10a, b shows the contact angle measurements for the pure PVA and the best graft U-PVA specimens. Grafting with urea enhanced the wettability of the PVA, making the specimen more effective for tissue engineering applications and increased the released drug rates as a drug delivery system. The contact angle decreased in the urea-grafted specimen from 55° to 36°. The increased wettability occurred due to the ability of urea to break the hydrophobic and hydrogen bonds in PVA [4].

3.3. Characterization by FTIR spectroscopy

Figure 11 shows the FTIR spectra of pure PVA and graft U-PVA specimens, and all major peaks were observed. Pure PVA revealed broad peak at 3302 cm⁻¹ for O-H stretching, peaks at 2920 cm⁻¹ and 2856 cm⁻¹ are for C-H asymmetric stretching and C-H symmetric stretching of Figure 11. FTIR spectra for (a) pure PVA specimen and (b) optimum graft U-PVA specimen.

Figure 12. In vitro insulin release profiles from graft U-PVA and pure PVA specimens.
In vitro drug release study

Insulin release profiles of graft U-PVA and pure PVA electrospun mats are shown in Figure 12. Graft U-PVA specimen revealed much higher insulin release rates than pure PVA. Generally, the concentration of insulin released after 50 h from both specimens was low and this may be attributed to the small weight of the specimens used (specimens with higher weight and thickness can be used in future studies). After 50 h of incubation in PBS solution, only 30% and 10% of loaded insulin was released from graft U-PVA and pure PVA respectively. However, much higher insulin release rates were recorded in graft U-PVA than pure PVA after 10 h of incubation. The reason behind this finding is attributed to two points; the first point is the higher wettability of graft U-PVA which increased the swelling of the specimen when immersed in the drug and increased its content of insulin. The second point is the improved degradation of PVA by grafting with urea which makes the degradation occurs in faster rates accompanied with higher insulin% released within the same time and this was consistent with Taepaiboon et al. who observed that the high degradation rates resulted in burst release of the drug loaded [20].

4. Conclusions

In this study, we characterized some electrospinning conditions for graft U-PVA. We analyzed the electrospun fibers using SEM and concluded that the best conditions were as follows: Capillary–collector distance = 20 cm, applied voltage = 25 kV, and flow rate = 1 mL/h. We also found that grafting urea with PVA enhanced the wettability of the PVA, which favors cell attachment and scaffold degradation in tissue engineering applications; whereas, when considered as a drug delivery system, the low average fiber diameter and enhanced wettability of graft U-PVA released drugs in higher rates than pure PVA and the burst release occurs after 10 h of incubation.

5. Further studies

1. Investigating the preference of graft U-PVA over pure PVA as a scaffold in tissue engineering applications.
2. Characterizing other electrospinning parameters like concentration to determine the effect of concentration on graft U-PVA structure.
3. Apply response surface methodology (RSM) to determine the optimum electrospinning parameters used for graft U-PVA preparation.

Declarations

Author contribution statement

Manar A. Najim: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.
Bassam I. Khalil: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.
Ali A. Hameed: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

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Data availability statement

The data that has been used is confidential.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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