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Fabrication of Dual Layer Polyvinyl Alcohol Transdermal Patch: Effect of Freezing-Thawing Cycles on Morphological and Swelling Ability

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Abstract

The transdermal patch is polymeric-based patches containing a dispersed bioactive ingredient that deliver therapeutic agents at a constant rate through the human skin surface. In this study, the dual layer PVA patch was prepared using a combination of freezing-thawing (F-T) and electrospinning techniques to study the effect of F-T cycles on morphology structure and swelling ratio of the fabricated patch. The effect of F-T cycles on swelling ability as well as the morphological study of the patch was employed and characterized using Scanning Electron Microscopy (SEM) and immersion of dual layer PVA patch for 24 hours in distilled water was calculated. Morphological structure of dual layer PVA patch has proved the correlation between the PVA cryogel and PVA electrospun nanofiber membrane. The results revealed that the dual layer PVA patch was successfully fabricated as the under layer PVA electrospun nanofiber membrane does not fully dissolve throughout the F-T process. Furthermore, in this study, it is shown that increasing of F-T cycles has decreased the swelling ability of the dual layer PVA patch. It also found that the presence of PVA electrospun nanofiber has also affected the swelling ability of the dual layer PVA patch due to the high surface ratio of the electrospun nanofiber membrane. The highest percentage of swelling ratio was found approaching 66% for dual layer PVA with 3 cycles (2L-3C), as for dual layer PVA with 5 cycles (2L-5C) the percentage found significantly lower (33%). The improvement of dual layer PVA patch can be utilized for drug release assessment and also could be good potential for transdermal drug delivery.

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Keywords: Poly-vinyl Alcohol (PVA); Electrospun Nanofibers; Freezing-thawing; Swelling Ratio

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1. Introduction

PVA is a biocompatible water-soluble polymer of increasing interest due to its large-scale applications as a biomaterial and for drug-delivery systems, for building sensors and membranes with selective permittivity [1-4]. Among the existing PVA-based systems, the chemical and physical hydrogels with controlled macroscopic properties are of particular interest, as successfully shown in biotechnological and biomedical applications. Electrospinning is the most cost-effective with simple tooling that utilizes electrostatic forces to produce nanofibers from polymer solution with unique characteristics including a large surface area to volume ratio, ultrafine structure and high porosity with pore sizes ranging from submicron to nanometer [5]. In addition, the nonwoven, ultrathin, and super porous structures of electrospun fibrous films allow sufficient air and water vapor to permeate through. Development of electrospun nanofibers have been widely used for skin tissue scaffolds, wound dressings as well as drug delivery applications including Alzheimer drugs, antimicrobial and antifungal drugs, proteins, cosmeceuticals and genes [6-8].

Extensively, properties of PVA cryogel prepared by cyclic F-T been studied and depend upon a variety of factors, most important of which are molecular weight, concentration of polymer and number of F-T cycles [9]. Previous research by Butylina et al., [10] has shown that as the number of F-T cycles increase from three to five adversely affected the compressive properties of hydrogels. The final properties of the cryogels can be changed by different variables such as time, temperature and number of cycles in the F-T process, as well as by the polymer fraction content. Many studied has found that equilibrium-swelling ratio of PVA cryogels decreases with increasing number of F-T cycle. A study by Peppas et al., [11] stated that the crosslinks in cryogel hindered the mobility of polymer chain and resulted in lower swelling ratio. The highly swollen cryogel represents a less compact structure and a lesser degree of crosslinking when compared with the cryogels with the lower swelling rate. Increasing the number of F-T cycles leads to the further formation of crystals that act as crosslinking sites, therefore, indicating a more stable network structure, which behaves like a less swollen structure [12].

2. Materials and Methods

2.1. Materials

Poly (vinyl alcohol) (PVA, molecular weight ~ 89,000-98,000, 99+% hydrolyzed) was purchased from Sigma-Aldrich and distilled water as a solvent.

2.2. Fabrication of Dual Layer PVA patch

A weighed amount of PVA powder was dissolved in distilled water at 80o C for 3 h to prepare a PVA solution at a fixed concentration of 10% w/v. After that, the solution was cooled down to room temperature (25o C). Electrospinning of the as-prepared solutions was carried out by connecting the emitting electrode of positive polarity from a Gamma High-Voltage Research ES30PN/M692 high voltage DC power supply to the solutions contained in a standard 5-ml syringe. The open end of which was attached to a blunt gauge-23 stainless steel needle (outer diameter = 0.91 mm), used as the nozzle, and the collection plate laminated with aluminium foil (dimension = 15 cm x 15 cm), used as the fiber-collection device. A fixed electrical potential of 20 kV was applied across a fixed distance of 15 cm between the tip of the nozzle and the outer surface of the collector plate (i.e., the electrostatic field strength of (20 kV /15 cm). The feed rate of the solutions was controlled to about 1 ml h-1 utilizing a syringe pump.

The aqueous PVA solutions were then poured on the surface of the electrospun nanofibers membrane that has been placed inside the specifically designed mold with dimensions: length x width x thickness: 100 mm x 100 mm x 1.5mm. F-T of dual layer PVA patch was obtained by subjecting the PVA aqueous solutions with corresponding concentrations to repeated F-T cycles (3 and 5 cycles), consisting a 24 h freezing step at -20 oC followed by a 2 h thawing step at room temperature. The choice of numbers of F-T cycles was based on previous studies [13]. Figure 3.2 shows the schematic diagram of the combine process of dual layer PVA patch.

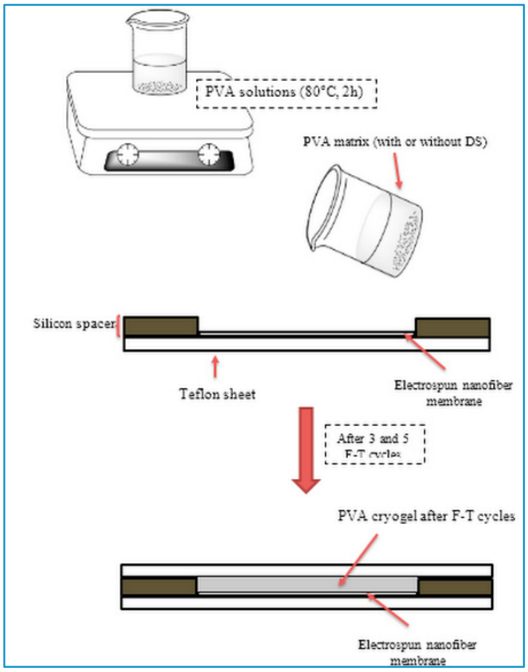

Fig. 1. Schematic diagram of combine electrospun nanofiber membrane and F-T cryogel for 3 and 5 cycles.

2.3. *Scanning Electron Microscopy (SEM)*

The freeze-dried dual layer PVA samples were cut into small dimension (5 mm x 5 mm), and the samples were directly sent to Auto Fine Coater Machine for a sputtered thin layer of gold on its surface at 25 mA plasma current and 2 Pa of chamber pressure to make them conducting samples. The function of the coating is to make sure the insulating freeze-dried Dual layer PVA samples are electrically conductive during high-resolution electron imaging applications. The Dual layer PVA samples were then examined by using SEM of JEOL-JSM6380LA (Japan) operates at 15 kV at 10 and 50 µm magnifier under high vacuum.

2.4. *Swelling property*

The pre-weighed dry samples were immersed in distilled water for different times at room temperature until an equilibrium state of absorption was achieved. After the excessive surface water was removed with filter paper, the weight of the swollen gel was measured at various time intervals. The procedure was repeated until there was no further weight increase. The swelling ratio can be determined as a function of time.

$$\text{SR}(\%) = \frac{W_t/W_0}{W_0}\, x\, 100 \tag{1}$$

Where, W_t = Wet weight, W_o = Original dry weight.

3. Results and Discussions

3.1. PVA electrospun nanofiber membrane

Scanning Electron Microscopy, SEM is an excellent technique for examining the surface morphology of electrospun nanofibers and cryogels. Photomicrographs of electrospun nanofiber and average fiber diameter are shown in Fig.2. (a) and (b).

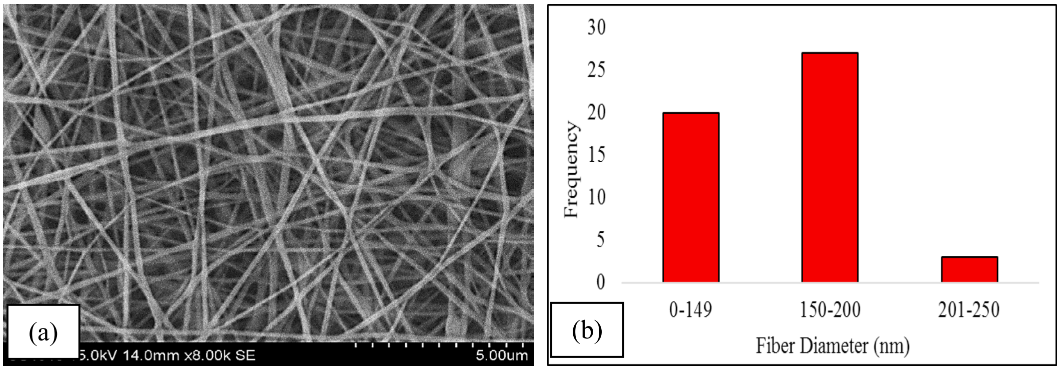

Fig. 2. SEM micrographs of average fiber diameter electrospun fibers from 10% PVA solutions (voltage = 20kV, tip–to nozzle distance =15 cm, flow rate = 1 ml/h). PVA magnification 8000x.

PVA Electrospun nanofiber with smooth and uniform the suitable electrospinning obtained. The nanofiber has successfully electrospinned, and the selected parameters were used for electrospinning are consistent throughout the experiment. The resulting fibers showed cylindrical morphology fibers diameters ranged from 90 to 250 nm (Fig. 2(b)). The obtained PVA electrospun nanofiber has been further to develop dual layer PVA patch.

3.2. Composition of Dual Layer PVA patch

For the preparation of dual layer PVA patch, the process was mentioned in section 2.2. An average thickness of PVA electrospun nanofiber membrane after running 2 ml of electrospinning technique was calculated at 5 different points. Table 1 shows the composition of the dual layer PVA patch.

Table 1. Composition of Dual Layer PVA patch

Cryogel samples	Concentration of PVA (%w/v)	Thickness of electrospun nanofiber membrane (mm)	No. of cycles
2L-3C	10	0.062 ± 0.005	3
2L-5C		0.059 ± 0.009	5

3.3. Morphological of Dual Layer PVA Patch

The combined technique (F-T and electrospinning) has been successfully conducted. Fig. 3. (a) and (b) shows the morphological structures of the 2L-3C and 2L-5C. PVA Cryogel (upper layer) and PVA electrospun nanofiber (bottom layer) after finishing each F-T cycles.

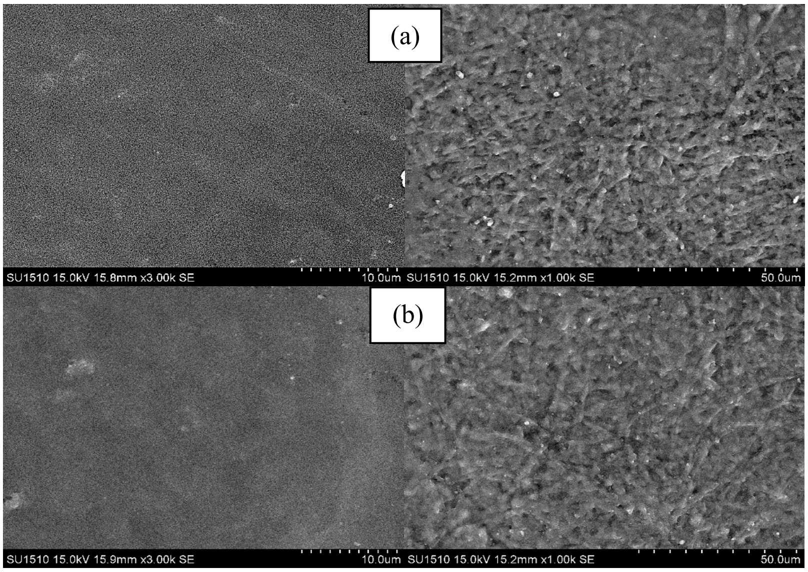

Fig. 3. Surface morphological (top and bottom) of (a) 2L-3C and (b) 2L-5C.

The combination of PVA cryogel and PVA electrospun nanofiber after F-T cycles does not demolish the nanofiber even though both structures were hydrophilic. However, during the pouring process of PVA solution on top of nanofiber, it does affect the diameter of the nanofiber as the nanofiber observed swollen in shape. On physical observation, the dual layer PVA patch has a phase distinction between gel and nanofiber. This claim can be supported by a cross-section of the dual layer PVA patch showed in Fig. 4.

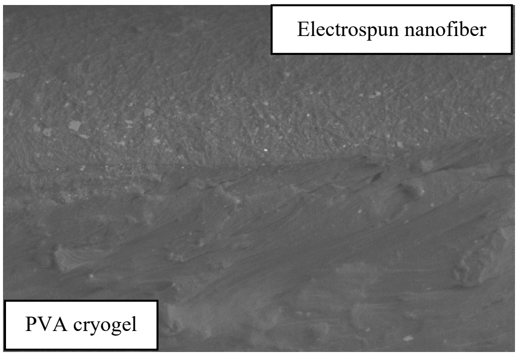

Fig. 4. SEM micrograph for cross-section of dual layer PVA patch

3.4. Swelling Ratio

Refer to Fig. 5, swelling ratio for both dual layer PVA patch immersed in distilled water as a medium for 24 hours are shown. Fig. 5 represent the swelling ratio for 2L-3C and 2L-5C patches.

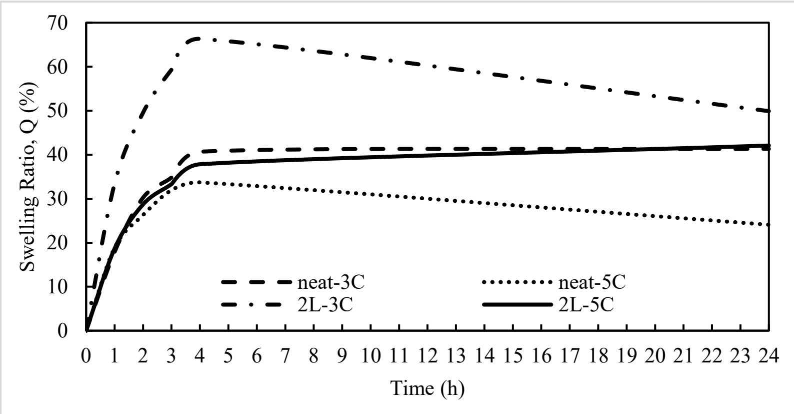

Fig. 5. Swelling ratio of 3 cycles-dual layer PVA patch and (b) 5C-dual layer PVA patch.

Fig. 5 revealed that 2L-3C has the largest swelling ratio compared to 2L-5C which up to 66% compared to 2L-5C (33%) for the first four hours of immersion. These results confirm that the swelling behavior is notably influenced by the number of F-T cycles and incorporation nanofiber membrane in PVA cryogel. Essentially, as the number of freezing and thawing cycles increased, more PVA chains participated in the formation of a stable crystal of 2L-5C which lead to strong hydrogen bonding, and associated physical crosslinking resulting less dissolution of sample occurred [9], [14].

To further understand the swelling properties of the dual layer PVA patch, the samples of PVA cryogel namely neat-3C and neat-5C also been examined. In comparison to PVA cryogel (neat-3C and neat-5C), the dual layer PVA patch graph exhibited greater swelling ability. The 2L-3C samples show the highest rates of a swelling percentage while the lowest in neat-5C. However, the swelling ratio for 2L-5C and neat-3C is almost comparable with each other. This phenomenon occurred due to the presence of the nanofiber membrane which increases its swelling percentage. As mentioned by the previous researcher, the swelling ability of electrospun nanofiber is higher compared to cast film due to high surface area and porosity nature of the electrospun nanofiber [15].

4. Conclusions

In this work, the dual layer PVA patch was fabricated using a combination of F-T and electrospinning method to assess the effect of F-T cycles on its morphological structures and swelling properties. Results shows that increase in F-T cycles has decreased its swelling ability. As for the dual layer PVA patch, the results demonstrate that the presence of nanofiber has increased the swelling percentage due to the high surface area of the nanofiber resulting in the water uptake by the nanofibers. In a nutshell, the fabricated dual layer PVA patch evidently improved in swelling properties for further drug release assessment.

Acknowledgements

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