Synthesis of Polymeric (Self-Disappearing) Nano Medical Patches Loaded with a Long-Acting Pharmacological Substance by Electrospinning Method

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\textbf{ABSTRACT}

Nano-polymer (self-disappearing) medical patches loaded with a long-acting drug were manufactured by co-spinning method of synthetic polymers PVA and PVP at a rate of 10%W for each polymer and with the addition of different medicinal substances, namely diclofenac de ethylamine, gentamicin, in concentration 5%w (each substance separately). And studying the morphological structure of the prepared samples by scanning electron microscope (SEM) and X-Ray diffraction (XRD), then converted into a medical adhesive form, and then tested on the human hand directly, as it has proven its effectiveness in delivering the drug to the affected area directly. It is very easy to use, medically safe and economic, as it does not need huge industrial equipment for its production.

\textbf{Keywords}

Electrospinning, Nanofibers, PVA, PVP.

\textbf{Introduction}

Instruments based on electrospinning technology to obtain nanofibers are beginning to gain the attention of scientific research around the world, providing fast, efficient and highly specific economic solutions to most medical issues. As a result, the global demand for nanomaterials is expanding very rapidly. It is estimated that the market for nanomaterials was about $2.6 trillion in 2015. In medicine, various applications of nanotechnology have proven to revolutionize medical diagnosis, immunization, treatment and even healthcare products. Loading materials can be coupled to a wide range of nanoparticles (NPs) by many means: chemically (coupling), physically (encapsulation), or by adsorption. The use of suitable nanomaterial for loading depends on the purpose of the application. It can be used to deliver different chemicals (drugs, imaging materials, or chemotherapeutic agents), or biological materials (antigens or antibodies) through cell fusion. They can even be used to deliver heat and light to target cells when needed [1,2].

Electrospinning is a technology for fabricating fibers with extremely small diameters due to its ability to produce nanomaterials and structures of an outstanding level in their properties. As a drug delivery system [3], where nanofiber networks offer a high percentage of porosity and high surface area, bioactive materials/drugs can be encapsulated in polymeric nanofibers by coaxial or un coaxial electrospinning or by some other method that includes adding medicinal materials and linking them as nanoparticles to the nanofiber network, of antimicrobial/antioxidant substances [4,5]. Electrospinning is the only technique that uses electrostatic force to produce nanofibers from solutions or smelters of polymers. The electrospinning technique is unique and unconventional as it relies on producing nanofibers from a polymeric solution at low temperatures.

The ability to easily control the diameters of the nanofibers resulting when changing some working conditions, such as controlling the
velocity of the flow of the solution over time, controlling the applied electrical tension, or controlling the chemical composition of the spun solution gave it wide applications in different fields as any change in one of the working conditions changes the composition. The resulting fiber. Figure 1 shows the mechanism of action of the electrospinning device and the formation of nanofibers [5,6].

Figure 1: The electrospinning Machen and the resulted nanofibers [6].

The skin is the largest organ in the body and acts as a barrier and protector against bacteria and organisms. However, the skin can be damaged or cut (ruptured) due to various factors, certain surgery, or certain diseases (including diabetes). It is expected that the condition and spread of the wound will worsen, especially in the elderly and diabetics, and wound healing is a complex process, which aims to restore the normal anatomical structure and function of the skin, and wound healing mainly consists of three stages called the inflammatory stage, the proliferative stage (including protein synthesis and wound contraction). And the reconstruction phase wounds are treated to prevent infections with a strict regimen of antibiotics, which imposes a significant economic burden on the patient. Therefore, the urgent need to prevent the growth of microbes, and reduce the possibility of its increase by using antibiotics, which are safe for human use or using herbal extracts to speed up the healing process of wounds and reduce the need to use pharmaceutical chemicals such as antibiotics, and thus prevent the side effects of their use., were wound dressings. It initially consists of natural materials such as plants, plant fibers and animal fats. With the development of science, it contains medicinal materials that speed up the healing process [6,7]. Nanofibers are a type of nanostructure structure, which because of their unique properties can be used in wound dressings and medical plasters, and electrospinning is a good way to produce them. The benefits of electrically spun nanofiber wound dressings include a large area (area to volume ratio), high absorption of wound exudate, high air permeability, mimicry of extracellular matrix (ECM) morphology for tissue damage and the possibility of gradual release of nanofiber-laden drugs [8-10].

Due to the bad side effects and the spread of antibiotic resistance, the interest is growing in the use of drugs and their combination with natural and synthetic medical polymers to obtain nanofibers, which is a method of integrating the physical properties of the nanofiber structure and the chemical and antibacterial properties of drugs. In recent years, many plant extracts and antibiotics have appeared in the form of active extracts, essential and pure oils. These materials have been used with some medical polymers in electrospinning and production of therapeutic nanofibers [11,12].

The bad side effects of some drugs taken through the gastrointestinal tract prompted researchers to develop a drug delivery technology through drug-laden nanofibers with long-term release, through electrospinning of various polymeric solutions with different drugs according to the application to be obtained [13-16]. This leads to enhancing the ability to heal wounds as well as treating the burn area on the skin. Through a number of substances such as proteins, fats, amino acids, vitamins and enzymes [17]. Research in this field is still few and scattered [18,19].

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID), one of the derivatives of acetic acid and benzene and one of the best NSAIDs in the treatment of acute and chronic painful injuries and inflammations. Encapsulation of drugs with polymeric nanofibers can enhance its clinical efficacy and specificity. tolerance, therapeutic indication, Polymer nanofibers can protect drugs from degradation and reduce toxicity or side effects. Although diclofenac is considered a powerful anti-inflammatory, and has analgesic and antipyretic properties, it also has negative toxicological effects, it has been suggested to add it to polymeric nanofibers for local postoperative pain relief, and a 10-day continuous release of diclofenac has been recorded while maintaining the mechanical strength of the wound closure [8,20].

Also, gentamicin is an antibiotic [18] that fights bacteria, and is used to treat severe or serious bacterial infections and it helps in eliminating the bacteria that cause acne and in the treatment of bacterial skin dissections and eczema. [10,21,22]. Figure 1 shows the Chemical structure of (a) Diclofenac Sodium DS and (b) Gentamicin GM.

Figure 1: Chemical structure of (a) Diclofenac Sodium DS and (b) Gentamicin GM.

Several polymers have also been used for medical purposes to produce drug-laden polymeric nanofibers by electrospinning method, including natural and synthetic polymers and mixtures of several polymers at the same time. Among the most important polymers used in the medical field to obtain nanofibers (medical plasters) are polyvinyl alcohol and polyvinyl pyrrolidone [23].
Figure 2 shows the chemical structure of (a) polyvinyl pyrrolidone (PVP) and (b) polyvinyl alcohol (PVA).

![Chemical structure of (a) polyvinyl pyrrolidone (PVP) and (b) polyvinyl alcohol (PVA)](image)

**Materials and Methods**

**Materials**

Polyvinyl alcohol (PVA) (Mw, 30,000–70,000) was obtained from Sigma–Aldrich (St. Louis, USA). Polyvinyl pyrrolidone (PVP) (Mw 360,000) was obtained from Sigma–Aldrich (St. Louis, USA), Gentamicin (GM) 80, Exir Pharmaceutical Co. [IRAN] was added to the liquid component in drug loaded samples, Diclofenac Sodium Salt (DS) was purchased from Sigma Aldrich (St. Louis, MO, USA). distilled water was used as the cement liquid with pure Ethanol in equal proportions (50:50).

All chemicals were used as received without any further purification.

**Sample Preparation**

20 g of PVA powder was dissolved into (45 ml of distilled Water and 45 ml of Absolute Ethanol at 20 % w/v concentration. The solution was stirred at 80 °C for 3 h using electromagnetic stirrer to get homogenous and crystal-clear solution.

20 g of PVP powder was dissolved into (45 ml of distilled Water and 45 ml of Absolute Ethanol at 20 % w/v concentration. The solution was stirred at 60 °C for 3 h using electromagnetic stirrer to get homogenous and crystal-clear solution. Then mix the two solutions together, and thus we have obtained a polymeric solution that contains PVA/PVP 10%w/v of each polymer separately.

Meanwhile, Diclofenac 5% powder was mixed with PVA/PVP at 10%v/w. And Gentamicin 5% was mixed with PVA/PVP at 10%v/w. All solutions were cooled down at room temperature for several hours before electrospinning.

**Electrospinning Process**

We used an electrospinning device designed by the work team during the research. The designed device consists of three main sections [16], which are the voltage booster, the injection pump, and the rotating cylindrical collector. Electrospinning solutions were fed into two syringes 5 ml equipped (Thus, we get a double number of nanofibers and shorten the time) with a 0.5 mm needle. A high voltage of 20 kV was applied across the needle and the cylindrical collector covered with aluminum foil for easy taking of the fibers from the collector and at a rotation speed of 100 rpm. Adjusted feed rate at 0.5 ml/hr., the distance between the injector head and the collector was 100 mm. All samples were spun for 10 hours to obtain nanofibers of the same thickness. The figure (3) shows a picture of the device designed by the work team with its three main sections.

![The device designed by the work team](image)

Figure 3: The device designed by the work team.

Figure 4 also shows the process of droplet extrusion and the formation of the Taylor cone, without which electrospinning does not occur., leads to the accumulation of charges on top of the formed droplet and it stretches at an angle of 49.3°, and the so-called Taylor Cone is formed where tangential electrical stress causes the polymeric solution to move, which generates hydrodynamic pressure on the surface of the droplet, and the mutual effects between electrical and hydrodynamic stresses cause deformation Droplet [24,25].

![Taylor cone](image)

Figure 4: Taylor cone.

Figure 5 also shows the extrusion of the fibers and their assembly on the rotating cylindrical collector, where the injector head is connected to the positive electrode and the collector is connected to the negative electrode. Figure 5a also shows the extrusion of the fibers and their assembly on the rotating cylindrical collector, where the injector head is connected to the positive electrode and the collector is connected to the negative electrode, and figure 5b shows the shape of the resulting fiber after the end of the electrospinning process on an aluminum sheet.
Figure 5a: The extrusion of the fibers, b; the shape of the resulting fiber.

**Surface Morphology Characterizations (SEM)**

The surface morphology of Nanofibers was evaluated by using scanning electron microscopy (Scanning Electron Microscopy” SEM, American-made Tuscan Veqa 2 model) with an accelerating voltage of 12 kV. The average diameter distribution of nanofibers was calculated by image analysis software (Image, version 1.49). The nanofiber specimen was sputter coated with platinum before subjecting to the SEM imagery.

**Physicochemical Characterizations**

A Fourier transform infrared (FTIR) spectroscopy (FT/IR-4100, Jasco, Japan) was used to determine the nanofiber chemical composition. FTIR spectra were scanned over the wavelength range 4000–600 cm\(^{-1}\) at temperature of 25°C.

**Result and Discussions**

**Nano Fiber Characterization**

SEM micrographs (Figure 6) were evaluated to analyze any surface difference the morphology and diameter of the PVP/PVA loaded DS, GM nanofibers compared to the original nanofibers. SEM micrographs confirm that continuous is uniform and bead-free, Nanofibers were obtained in all cases. Figure 6(P1) shows a picture of the formation of fine and homogeneous fibers and continuous fibers of pure PVP nanofibers, there is no bead formation within the PVP nanofibers, the average diameter of the PVP nanofibers was 85 nm. As the Figure 6(P2) shows a picture of the formation of fine and homogeneous fibers and continuous fibers of pure PVA nanofibers, there is no bead formation within the PVA nanofibers, the average diameter of the PVA nanofibers was 110 nm [26,27].

The figure 6 (P3) also shows the nanofibers resulting from a mixture of polyvinyl alcohol) PVA (and polyvinyl pyrrolidene (PVP (at a ratio of (50:50), where we notice an increase in the average diameter of the resulting nanofibers due to the forces of attraction between the molecules of one type of polymer, which leads to a noticeable increase in the average diameter of the fibers, but it remains the same. Smooth surface, fine, continuous fibers without beads the average diameter of the PVA/PVP nanofibers was 190 nm [2,28]. The addition of diclofenac sodium salt DS, which is highly soluble in water, to the polymeric mixture of polyvinyl alcohol PVA and polyvinyl pyrrolidene PVP led to a slight increase in the average diameter of the resulting nanofibers while maintaining the smooth, fine- structured mats the average diameter of the PVA/PVP/DS nanofibers was 225 nm [17].

The addition of the highly water-soluble antibiotic gentamicin to the polymeric mixture of polyvinyl alcohol and polyvinyl pyrrolidene led to a slight increase in the average diameter of the resulting nanofibers while maintaining smooth and fine-structured mats the average diameter of the PVA/PVP/GM nanofibers was 265 nm [20].

![Image](image1.png)

**Table 1:** The average diameter of the nanofibers for each sample.

<table>
<thead>
<tr>
<th>samples</th>
<th>Composition</th>
<th>Diameter(nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>PVP</td>
<td>85</td>
</tr>
<tr>
<td>P2</td>
<td>PVA</td>
<td>110</td>
</tr>
<tr>
<td>P3</td>
<td>PVP+PVA</td>
<td>190</td>
</tr>
<tr>
<td>P4</td>
<td>PVP+PVA+ Diclofenac</td>
<td>225</td>
</tr>
<tr>
<td>P5</td>
<td>PVP+PVA+ Gentamicin</td>
<td>265</td>
</tr>
</tbody>
</table>

**Infrared spectrophotometer (FT/IR)**

FTIR spectroscopy was performed to verify the interaction between the two PVA/PVP synthesized polymers by comparing the single and previously prepared virgin polymers. Figure 7 represents the FTIR spectra (1) PVA nanofibers, (2) PVP nanofibers, PVA/PVP nanofibers, (4) Gentamicin GM, (5) Diclofenac Sodium DS, (6) PVA/PVP/GM, (6) PVA/PVP/DS.

The FT-IR spectrum Figure 7(1) of PVA electro spun nanofibers showed the characteristic absorption bands of PVA: Broad(C–H) alkyl stretching band (2950 cm\(^{-1}\)) and the Stretching hydroxyl...
bands (O-H) 3370 cm\(^{-1}\), 1045 cm\(^{-1}\) (C–C), 1260 cm\(^{-1}\) (C–O), 1480 cm\(^{-1}\) (CH\(_2\) bend) [29].

Figure 7(2) The FT-IR spectra of the PVP electro spun fibers are depicted in Figure 7(2). The absorption bands at 3450 (O-H stretching), 2900 (aliphatic C-H), 1640 (amide C=O), and 1284 cm\(^{-1}\) related to (C–N) respectively, are the characteristic peaks of PVP [30]. The FT-IR spectrum of PVA/PVP nanofibers is shown in Figure 7(3). The peaks at 1050, 1250, 1365, 1590, 1650, 2900 and 3400 cm\(^{-1}\) were assigned to the vibrations of C– N, C–O, C–O–C, amide C=O, acetate C=O, (aliphatic C-H) and OH, respectively [31].

By comparison, the FT-IR spectrum of PVA/PVP nanofibers with PVA and PVP nanofibers, the presence of both PVA and PVP structure in blend nanofibers was Analyzed, as shown in Figure 7(3), the characteristic absorption bands of PVA/PVP.

The FT-IR spectrum Figure 7(4) of Gentamycin Sulfate (GM) showed the characteristic absorption bands of (GM): 3490, and 1250 cm\(^{-1}\) were assigned to the vibrations of -O-H Stretch, and

-C-O-C Stretch respectively.

The FT-IR spectrum Figure 7(5) of Diclofenac Sodium (DS) showed the characteristic absorption bands of (DS): 3480, 2950, 1550, and 700 cm\(^{-1}\) were assigned to the vibrations of -N-H Stretch, -C-H alkyl, -C=C Aromatic, and -C-Cl respectively.

The FT-IR spectrum Figure 7(6) of PVA/PVP/GM showed the characteristic absorption bands of PVA/PVP/GM: 3500, 3050, 1650, 1590, 1550, 1250, and 1050 were assigned to the vibrations of -O-H Stretch, -C–H Stretch, -C=O acetate, -C=O amide, -CH2 Bend, -C=O-C Stretch, and -C-N respectively.

The FT-IR spectrum Figure 7(7) PVA/PVP/DS showed the characteristic absorption bands of PVA/PVP/DS: 3500, 3050, 1650, 1590, 1550, 1500, 1050, and 700 were assigned to the vibrations of -N-H Stretch, -C–H Stretch, -C=O acetate, -C=O amide, -C=C Aromatic, -CH2 Bend, -C-N, and -C-Cl respectively [32,33,34,35].

The table (2) shows FTIR spectroscopy for each bend of material.

**Figure 7:** (FT-IR) spectra of (1) PVA nanofibers, (2) PVP nanofibers, (3) PVA/PVP nanofibers, Gentamicin GM, (5) Diclofenac Sodium DS, (6) PVA/PVP/GM, (6) PVA/PVP/DS.
Table 2: FTIR spectroscopy for each kind of material.

<table>
<thead>
<tr>
<th>NO.</th>
<th>Effective Material</th>
<th>Wavenumber (cm⁻¹)</th>
<th>Functional Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PVA</td>
<td>3370, 2950, 1480, 1260, 1045</td>
<td>O–H Stretch, -C-H alkyl, -CH₂ Bend C–O Stretch C–C</td>
</tr>
<tr>
<td>2</td>
<td>PVP</td>
<td>3450, 2900, 1480, 1640, 1284</td>
<td>O–H Stretch, -C-H alkyl, -CH₂ Bend, -C=O, -C=N</td>
</tr>
<tr>
<td>3</td>
<td>PVA/PVP</td>
<td>3400, 2900, 1650, 1590, 1365, 1250, 1050</td>
<td>O–H Stretch, -C=O acetate, -C=O amide, -C=O-C, -C–O, -C–N</td>
</tr>
<tr>
<td>4</td>
<td>Gentamycin Sulfate (GM)</td>
<td>3490, 1250, 700</td>
<td>-O-H Stretch, -C-O-C Stretch</td>
</tr>
<tr>
<td>5</td>
<td>Diclofenac Sodium (DS)</td>
<td>3480, 2950, 1550, 700</td>
<td>-N-H Stretch, -C-H alkyl, -C=O Aromatic, -C-Cl</td>
</tr>
<tr>
<td>6</td>
<td>PVA/PVP/GM</td>
<td>3500, 3050, 1650, 1590, 1550, 1250, 1050</td>
<td>-O-H Stretch, -C=O acetate, -C=O amide, -CH₂ Bend, -C-O-C Stretch, -C-N</td>
</tr>
<tr>
<td>7</td>
<td>PVA/PVP/DS</td>
<td>3500, 3050, 1650, 1590, 1550, 1500, 1050, 700</td>
<td>-N-H Stretch, -C-H Stretch, -C=O acetate, -C=O amide, -C=O amide, -C=C Aromatic, -CH₂ Bend, -C-N, -C-Cl</td>
</tr>
</tbody>
</table>

Test of self-disappearing for produced patches
In order to investigate the self-disappearing Feature for the medical patches prepared, the patches were applied on human skin directly, we see in figure 8 the steps of patches disappearing ability.

Conclusion
Self-disappearing medical labels (dissolved in living tissue) were obtained by co-electro-spinning method of polymers (PVP/PVA) at a rate of 10%W for each polymer and in the presence of two medicinal substances separately: diclofenac sodium DS and gentamicin sulfate GM.

The scanning electron microscope SEM images showed a smooth, fine and porous structure without any adhesion or knotting of all samples, where the addition of diclofenac and gentamicin led to a slight increase in the average diameter of the Nanofibers than it was, while the IR spectrum showed strong interactions between the two copolymers (PVP/PVA) And the two additives (DS, GM) by forming clear and powerful function peaks, and these results herald a new generation long-acting topical medications medicines.

When testing the self-disappearing ability of the medical patches we noticed a good ability for the batches to disappear which helps in absorption of the drug loaded with it.

References
6. Ayça Aydoğdu. development of nanofiber based active packaging materials by electrospinning technique and food validation. a thesis Submitted to the Graduate School of Natural and Applied Sciences of Middle East Technical University. 2019.


