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Influence of Diclofenac Sodium Loading on Physicochemical and Mechanical Properties of Dual Layer Polyvinyl Alcohol Transdermal Patch

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Abstract. Transdermal drugs delivery offers many advantages over conventional routes of drug delivery that led to this burgeoning interest in this route in recent years. The aim of this work is to investigate the influence of diclofenac sodium (DS) loaded dual layer PVA patch on physicochemical and mechanical properties. The influence of DS-loaded dual layer PVA patch was employed and characterized using Scanning Electron Microscopy (SEM) to observe the polymeric interaction between PVA cryogel and electrospun nanofiber, the FTIR were used to study the interaction of DS in dual layer PVA patch and tensile strength were tested to study the mechanical properties of the DS-loaded dual layer PVA patch. The results show the polymer interaction between PVA cryogel and electrospun nanofiber were observed. The DS spectra were found separately from PVA matrix. As for mechanical strength the curves of DS-loaded were decreased as the percentage of DS loading increases. These results shows that the dual layer PVA patch can be used as the carrier for transdermal DS delivery.

1. Introduction

Transdermal drug delivery system (TDDS) is adhesive drug-containing devices of defined surface area that delivers the specific amount of active drug across the skin, into the systemic circulation [1]. TDDS have an advantages over conventional pharmaceutical dosage formulations, such as circumventing gut and hepatic first-pass metabolism, improving drug bioavailability, reducing administration frequency, and stabilizing drug delivery profiles [2]. For the past few years, transdermal drug delivery systems has gain great interest with the development of various types of transdermal therapeutic systems for several drugs such as, Estradiol for steroidal delivery [3], combination patches containing Gestodene and Levonorgestrel for contraception and hormone replacement [4], Mafenide Acetate for antimicrobial delivery [5], Carvedilol for anti-hypertensive[6], Titanocene Dichloride for antitumor [7]. Insulin for anti-diabetic delivery [8] and Meloxicam delivery systems for anti-inflammatory [9].

Polyvinyl Alcohol (PVA) is one of the polymeric drug carriers that are a semi-crystalline polymer with excellent chemical and thermal stability and demonstrated great interest because of its biocompatibility, non-toxic; non-carcinogenic and water permeable polymer with great electrospinnability [10]. According to Baker *et al.*, [11], PVA shows higher tensile strength and elongation before breaking than hydrogels such as polyhydroxy ethyl methacrylate, making PVA a suitable hydrogel for soft contact lenses, extending wearing time without inducing hypoxia to the cornea. Furthermore, High mechanical strength, rubber-like elasticity and no adhesion to surrounding



tissue make PVA gels potential materials for soft tissue replacements, artificial cartilage and other artificial organs [11-15]. PVA hydrogels have been investigated for replacement of damaged cartilage due to their high water content, as well as their elastic and compressive mechanical properties.

Recently, electrospinning techniques gain interest in transdermal drug delivery. This supported by Rives *et al.*, [16] in their studies emphasized that one of the apparent advantages of the electrospinning process compared to conventional film-casting techniques is the highly porous structure of electrospun nanofiber membrane, which exhibits a much higher surface area that could potentially allow drug molecules to diffuse from the matrix more effectively.

Diclofenac sodium (DS) is nonsteroidal anti-inflammatory drugs used to relieve the inflammation, swelling, stiffness and joint pain associated with rheumatoid arthritis, osteoarthritis (the most common form of arthritis) and ankylosing spondylitis (arthritis and stiffness of the spine), toothache, trauma, wound, burn and dysmenorrhea treatment because of their analgesic, antipyretic, and anti-inflammatory roles [17]. According to Satyabrata *et al.*, [18] when DS administered orally, only about 50% of the dose is biologically available because of the first-pass hepatic metabolism, and it possesses short biological half-life.

To the author's knowledge, the combination cryogel and electrospun nanofiber with improved properties as a carrier for DS for TDDS have not been done yet. The aim of this work is to investigate the influence of DS loading on physical and mechanical properties of dual layer PVA for potential prolonged transdermal DS delivery.

2. Methodology

2.1 Fabrication of DS-loaded dual layer PVA patch

2.1.1 Preparation of PVA electrospun nanofibers membrane

A weighed amount of PVA powder was dissolved in distilled water at 80° 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 (25° 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.

2.1.2 Preparation of PVA solution loaded with DS

The fabrication of freezing-thawing PVA solution was prepared based on the procedure referred in section 2.1.1. The polymer was entirely dissolved, and the obtained transparent solutions were slowly cooled to room temperature. Same methods were applied for DS loaded in PVA solution. Different mass% of DS (i.e., 1.0, 1.5 and 2.0 wt% of PVA) was loaded by dissolving in 5 ml ethanol in a separate beaker and then, adding it slowly to the above polymer solution by heating gently to avoid re-precipitation.

2.1.3 Combined techniques of dual layer PVA patch

The aqueous PVA solutions (from section 2.1.2) were then poured on the surface of the electrospun nanofibers membrane (from section 2.1.1) that has been placed inside the specifically designed mould with dimensions: length x width x thickness: 10cm x 10 cm x 1.5cm. Freezing-thawing of dual layer PVA patch was obtained by subjecting the unloaded and DS loaded PVA aqueous solutions with corresponding DS concentrations to repeated 5 cycles of freezing-thawing, consisting a 24 h freezing step at -20 °C followed by a 2 h thawing step at room temperature.

2.2 Scanning Electron Microscopy (SEM) of dual layer PVA patch

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 50 and 100 μm magnifier under high vacuum.

2.3 Fourier-Transform Infrared Red (FTIR) spectroscopy of dual layer PVA patch

DS-loaded dual layer PVA samples were cut into a small cube (10 x 10x 10 mm) and place it at FTIR sample holder. FTIR spectra were recorded in the range of 400 to 4000 cm^{-1} collecting 35 scans with 4 cm^{-1} resolution, in the transmittance mode. It is used to study the interaction between DS and dual layer PVA patch.

2.4 Mechanical testing of dual layer PVA patch

Tensile strength, elongation at break and strain at break of both (unloaded and DS loaded) dual layer PVA patch were measured by Universal Testing Machine (LLOYD Instruments LR30K), with load range; 10N. Each specimen was cut according to ASTM D 412. The crosshead speed and the gauge length were 50 mm/min and 33 mm respectively. A minimum of four samples was analyzed to obtain an average result, and all specimens were tested at room temperature.

3. Results and discussions

3.1 Morphological structure of dual layer PVA patch

For fabrication of DS-loaded dual layer PVA patch process mentioned on section 2.1.3. The combined methods (freezing-thawing cryogel and electrospun nanofiber) has been successfully conducted. As for Figure 1 (a) and (b), represent the surface of unloaded PVA patch and DS-loaded dual layer PVA patch with 5 cycles of freezing-thawing respectively.

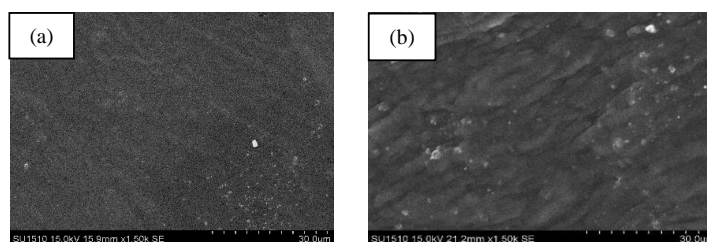


Figure 1. Surface morphology of 5 cycles of (a) Unloaded dual layer PVA patch and (b) DS-loaded dual layer PVA patch.

The micrograph shows rough surface of cryogel after finishing freezing-thawing cycles. This might be due to the presence of the drug's molecule incorporate with cryogel that slightly altered the linkage during freezing-thawing process. DS is partially insoluble in nature, therefore small particles of DS can be observed scattered on the surface of cryogel and nanofibers. Though the presences of DS slightly effect the polymeric structure, number of cycles somehow does not show significant different. On physically observation, the dual layer PVA patch have phase distinction between gel and nanofiber. This claim can be supported by cross-section of the dual layer PVA patch showed in Figure 2.

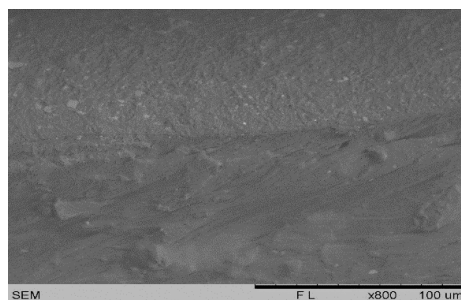


Figure 2. SEM micrograph for cross-section of dual layer PVA patch.

3.2 FTIR spectroscopy of dual layer PVA patch

It is well known that the infrared spectrometer is a powerful instrument for the investigation of the bonding behavior. The FT-IR absorption spectra of unloaded and DS-loaded dual layer PVA patch are shown in Figure 3. 2L-3ml-5C represents the 5 cycles freezing-thawing of dual layer with 3 ml (volume of PVA spinning) thickness of electrospun nanofiber. While 1.0, 1.5 and 2.0 DS represent the percentages of the drug loading in the dual layer PVA patch.

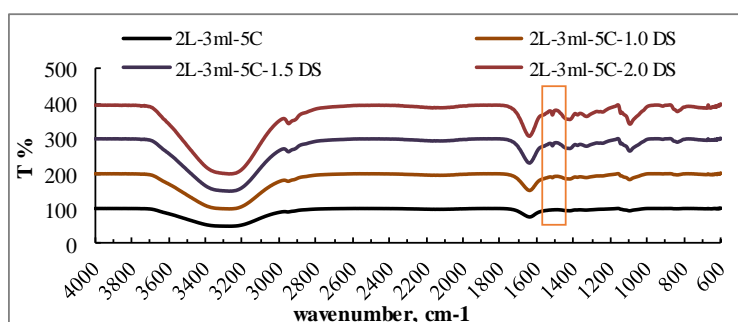


Figure 3. FTIR spectra for unloaded and DS-loaded dual layer PVA patch with different percentage drug loading.

The most characteristic bands of PVA and their respective assignments are observed between range of 3500 and 3100 cm^{-1} and are ascribed to the O-H stretching from the intermolecular and intra molecular hydrogen bonds. The absorption band at 2944 cm^{-1} and a shoulder at 2900 cm^{-1} correspond to the stretching of -CH₂- and -CH-, respectively. Further, the band at 1750 cm^{-1} and the shoulder at 1641 cm^{-1} correspond to the unhydrolyzed acetate groups. The band at 1420 cm^{-1} is attributed to -CH₂- bending. The band at 1091 cm^{-1} corresponds to C-O unbounded and it could be associated with PVA crystallinity.

Furthermore, the presence of DS in dual layer PVA patch (Figure 3), the spectra shows the distinctive peaks at 1566 cm^{-1} (carboxylate COO- asymmetric stretching) and 1515 cm^{-1} (dichlorophenyl ring) [19]. It also can be observed that the intensity of DS peak was increased when the percentage of DS loading increases. Therefore, presence of drug was confirmed in samples as their respective spectra revealed characteristic peaks of DS. These peaks appeared either in separate form, or fused with the characteristic peaks of dual layer PVA patch, confirmed the presence of the drug in the cryogel that did not interact with any of the components in polymer matrix [20].

3.3 Mechanical properties of dual layer PVA patch

The freezing-thawing cycles and DS loading percentage are an important factor determining physical properties, so the mechanical properties of dual layer PVA patch with different percentage were compared Figure 4, the curve represent the stress strain curve for 2L-3ml-5C with 3 different percentage of DS loading.

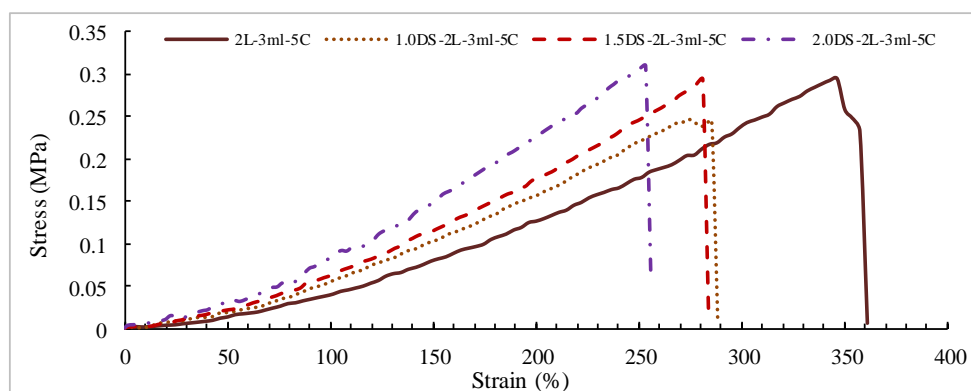


Figure 4. Typical stress-strain curves for unloaded and DS-loaded dual layer PVA patch for 5 cycles.

As shown in Figure 4, the tensile strength were improved as the percentage of DS-loaded in dual layer PVA patch increases (Table 1). However, when comparing with unloaded dual layer PVA patch, the strain percentage of unloaded dual layer PVA shows greater than DS-loaded dual layer PVA patch. This might be due to hydrogen bonding or intermolecular interaction between the drug model and PVA molecules, resulting in its relatively reduced crosslinking density, thus lowering the elongation at break [21].

Table 1. Mechanical Properties of 5 cycles of unloaded and DS-loaded PVA patch with different DS percentages loading.

Cryogel samples	Tensile strength, σ (MPa)	Elongation at break (%)	Young Modulus, E
2L-3ml-5C	0.30 \pm 0.06	360.92 \pm 30.99	0.23 \pm 0.06
1.0DS-2L-3ml-5C	0.26 \pm 0.02	288.01 \pm 41.66	0.29 \pm 0.04
1.5DS-2L-3ml-5C	0.30 \pm 0.04	283.89 \pm 21.44	0.23 \pm 0.06
2.0DS-2L-3ml-5C	0.32 \pm 0.04	255.70 \pm 28.31	0.31 \pm 0.06

4. Conclusions

The influence of DS loading in the dual layer PVA structures as well as its physicochemical properties and mechanical strength of the dual layer PVA patch were conducted. It can be observed that after the DS-loaded dual layer PVA patch freezing-thawing cycles is ended, the surface of dual layer cryogel was found uneven compared to control dual layer PVA patch. While the FTIR spectra of DS-loaded dual layer PVA patch, DS peak were observed separately in the spectra indicates that the DS does not interact in PVA matrix during freezing-thawing cycles. The intensity of DS peak also found increases with increasing percentage loading. While for the tensile strength and the young modulus, the result shows that the expansion and elongation at break was found to decrease when the percentage DS loading increases. Overall, the fabrication of dual layer PVA patch using combined methods has improved the physicochemical as well as mechanical properties for further drug release assessment.

Acknowledgments

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