Electrospinning, Preparation and Characterization of Polyvinylidene Fluoride / Pectin Electrospun Loaded with Benzalkonium Chloride as a Drug Reservoirs

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ABSTRACT

Porous nanofiber electrospun of polyvinylidene fluoride (PVDF)/pectin was successfully developed using electrospinning method containing benzalkonium chloride (BAC) as a drug model for the controlled drug delivery system assessment. The electrospun was tested for its mechanical, morphological, and wettability properties. Scanning electron microscope (SEM) micrograph demonstrated that the smooth surfaces of nanofibers morphology had achieved up to 2 wt% pectin inclusion with optimum fiber diameter, 143 ± 1.4 nm. The optimized scaffold PVDF/Pectin showed that the reduction of mechanical integrity and optimum value of tensile strength, modulus strength, and elongation at break were 5.98 ± 0.17 MPa, 16.82 ± 0.10 MPa, and 79.3 ± 1.3% MPa. Water contact angle analysis and degree of swelling suggested that inclusion of pectin had enhanced the wettability properties of hydrophobic PVDF electrospun with highest swelling capacity achieved of 78.9 ± 1.7%. The in vitro drug release tests using BAC, which was released from the hybrid electrospun nanofibers, achieved prolonged release profile due to elimination of the uncontrollable initial burst release.

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Kinetic release study from Higuchi Model and Korsmeyer-Peppas further validates that the drug release mechanism is only influenced by the diffusion factor. The present study indicates the potential of PVDF/pectin electrospun nanofibers to be exploited as a tool for sustainable drug delivery system.

Keywords: *Electrospinning; drug delivery; polyvinylidene fluoride; pectin; benzalkonium chloride.*

Introduction

Sustained release of a drug delivery system (DDS) has gained great attention as an alternative solution to reduce uncontrollable initial burst release of conventional DDS. This system will improve oscillation of the systemic drug concentration and reduce the potential of under or overdosing cases. In this case, sustained release DDS provides high therapeutic efficiency with minimum side effects by prolonged release duration of loaded drug with constant systemic concentration [1]. Electrospun nanofibers membrane has great potential as drug carriers due to its unique characteristics such as a large surface area to volume ratio with control micro to nano-meter sizes of fiber. Besides, studies have shown that a wide range of polymer can be used in electrospinning process and drugs ranging from antibiotics and anticancer agents to proteins, aptamer, DNA, and RNA which have been incorporated into electrospun fibers [2]. These features provide a promising structure for high encapsulation of targeted drugs and potentially achieve controlled loading/release profile [3-4].

Polyvinylidene fluoride (PVDF) is a unique chemically inert thermoplastic fluoropolymer synthesized by the polymerization of vinylidene fluoride that exhibits strong piezoelectric properties, chemical resistance, biocompatibility, transparent, and widely used in biomedical applications as biosensor, smart DDS, and tissue engineering [5-6]. This material also is easily processed to generate well defined nanofibers which can then be used for DDS and tissue engineering studies. However, PVDF has poor reactive side-chain with hydrophobic characteristic which can cause inflammatory effect on host cell/tissue and less capable to act as drug carrier without the aid from bioactive, biomacromolecule, or drugs [7]. For that reason, some modifications and improvement of those particular properties are technically crucial.

Pectin is an underrated polysaccharide based which has been widely used in conjunction with certain polymers or other biomaterials in drug delivery system and tissue engineering. These polysaccharides contain –OH and –COOH chemicals groups at the polymer surface and subject to calcium induced gelation results in the formation of egg box like structures that can

help in modulating the fate of surface-attached bioactive components and cells as illustrated in Figure 1 [8-10]. The correlation between pectin in the polymer backbone has shown that to increase density of active site, surface free energy and water absorption content are more suitable for drug, biomolecule, and cell attachment [11-13].

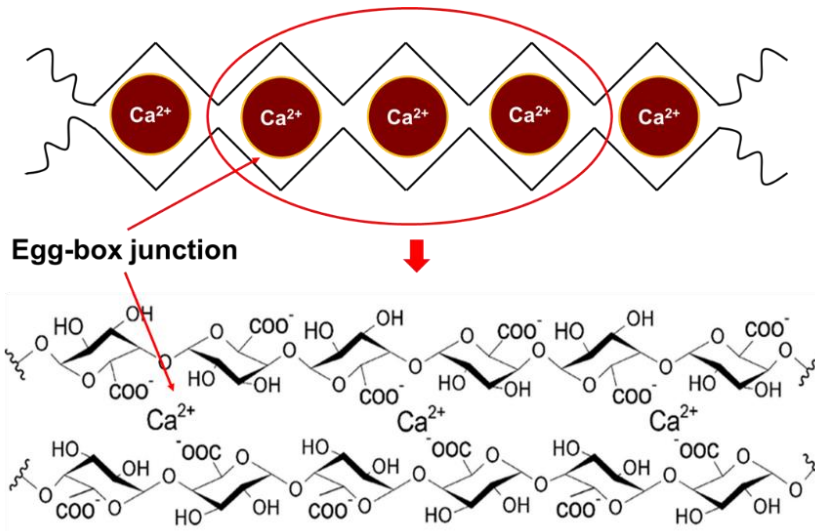

Figure 1: Illustration of 'egg-box' model of pectin.

Currently, no experimental works have utilized PVDF and pectin combination as nanodrug carrier for bioregenerative medicine applications. Few studies reported on the combination of polysaccharide materials into PVDF electrospun. Most existing researches have focused on combining of PVDF with other materials such as hydroxyapatite (HA), fibrin, chitosan, collagen, bio-glass, graphene oxide (GO), polycaprolactone (PCL), polyvinyl alcohol (PVA), and gold (Au) [5,7,14]. Therefore, this study utilizes the electrospinning method to fabricate a hybrid single layer polymeric nanofiber using PVDF-Pectin solution and benzalkonium chloride (BAC) as model drugs. This study aims to address the potential of pectin on improving the wettability and sustainable drug release properties of PVDF electrospun. The polymer blends were characterized via tensile test, morphological analysis, water contact angle (WCA), degree of swelling, and in vitro drug release profiles. This works will provide a new knowledge on the capability of the polymer blend materials application in drug delivery system.

Materials and Methods

Fabrication of PVDF-Pectin Electrospun

10% (w/v) PVDF polymer (Mw=89,000 g/mol, Sigma) solution was prepared in dimethylformamide (DMF) solution at 50 ºC under magnetic stirring until a clear polymer solution was formed. Pectin (apple based, Sigma) solutions (1, 2, and 3 wt% diluted in acetic acid solution) was added slowly into the prepared PVDF solution forming homogenous PVDF/Pectin polymer solution. The copolymer solution was fed into a 5-mL disposable plastic syringe with a gauge needle size 0.7 mm. The syringe was loaded onto an electrospinning device with horizontal set up (eSpinner NF-COEN/II, Birooni Saintifik) that delivered the polymer to a collector panel at a flow rate of 1.5 mL/h with voltage 15 kV. The distance between the syringe tip and the collector was 10 cm. All spinning experiments were conducted at 23±2 ºC as illustrated in Figure 2.

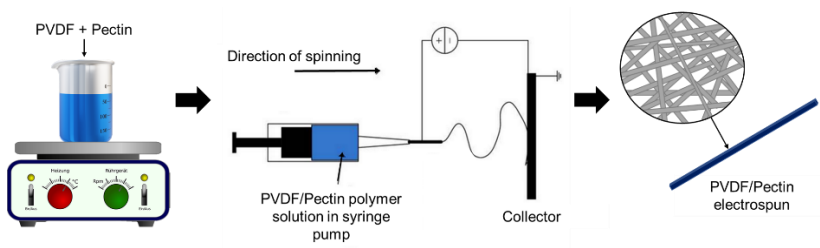

Figure 2: The schematic illustration of fabricating PVDF/Pectin electrospun membranes.

Scanning Electron Microscope

The electrospun produced was subjected to morphology analysis using Variable-Pressure Scanning Electron Microscope (VP-SEM, JEOL, USA) at an accelerating voltage of 10 kV. The SEM micrograph was used to determine the mean diameter of the electrospun nanofibers by using Image-J analysis

Mechanical Testing

The tensile test of the electrospun samples was assessed using a computer controlled Instron machine according to ASTM D882. The test was performed at a strain rate of 10 mm/min with load strength of 5kN at room temperature to determine tensile strength, modulus strength, and elongation at break properties of the samples. The measurement was performed triplicate and the average value was calculated.

Surface Wettability

Surface wettability was determined by measuring water contact angle using contact angle goniometer (VCA Optima system, AST Products USA) with droplets of each medium on the scaffolds. 5 µl of medium was gently dropped on the surface of scaffolds using a micro syringe and released from 1 cm above the surface to minimize the inconsistency between each measurement. The angle between scaffold surface and tangent line was measured. The measurement was performed five times at different locations of the membrane and the average value was calculated.

Degree of Swelling

The samples were dried in an oven at 70 °C for 24 h until constant weight to eliminate water before being placed in a phosphate buffered saline (PBS) for 24 h for degree of swelling studied [14]. The percentage of water adsorption (degree of swelling) was calculated using the formula below:

$$Degree\ of\ swelling = \frac{W_t - W_0}{W_t} x100\% \quad (1)$$

in which w_t represents the weight of swollen nanofiber at predetermined time and w^o is the initial weight of the nanofiber. The measurement was performed triplicate for each samples.

In-vitro Drug Loading and Release Profile

The electrospun samples were loaded with 0.14% benzalkonium chloride (BAC) for 24 h and dried at room temperature [15]. Then, the dried samples were immersed into phosphate buffer saline (PBS) at 37 °C for 24 h. The absorbance of the samples was observed at 272 nm using UV-vis (Thermo Scientific, Genesys 10S UV-VIS) to evaluate the drug release pattern. The mechanism was also studied with several kinetic models [16]:

Zero-Order Kinetics Model:

$$Q_t = Q_0 + K_0 t \quad (2)$$

Higuchi Model:

$$Q = K_H \times t^{1/2} \quad (3)$$

Korsmeyer-Pepas Model:

$$\frac{M_t}{M_o} = Kt^n \quad (4)$$

where Q_t represents the amount of drug dissolved in time (t), Q_o is the initial amount of drug in the solution, and K_o is the zero-order release constant. Meanwhile, Q indicates the amount of drug released in time, K_H is the Higuchi dissolution constant, and $t^{½}$ is the square root of time. Finally, M_t is the amount of drug dissolved as a function of time, M_o is the total amount of drugs being released, and t^n is an account for the log time measured as a result of the dissolution process. The measurement was performed triplicate for each sample.

Results and Discussion

Electrospinning Process

The incorporation of pectin into PVDF electrospinning solution directly influenced the nanofiber structure formation. Figure 3 exhibits the SEM micrographs of different electrospun nanofibers in this study. It was observed that the bead-free nanofibers were obtained for PVDF/pectin solution with slight increase in the average diameter of nanofibers up to 2 wt% pectin inclusion and reduces at 3 wt% as the excess of pectin has increased the viscosity of the polymer solution as shown in Table 1. However, due to ionic functionalities group from the polyanion of pectin, the blended polymer solutions had achieved minimal electrical conductivity for nanofibre formation although PVDF concentration was reduced. The average diameter of electrospun was ascertained to increase in correspondence to the polymer solution concentration [15, 17]. As previously mentioned, the incorporation of more than 3 wt% of pectin to PVDF solution further hindered the electrospinning process as the defective effect can be seen in Figure 3(d). The nanofiber morphology starts to lose its structure integrity and uniformity at higher inclusion of polysaccharides. A possible reason is that the increase of pectin has triggered more repulsive force among negative charge that disrupts the chain entanglement between pectin and PVDF in the polymer solution. The insufficient chain entanglements result in an unstable jet formation during the electrospinning process which causes beaded nanofiber electrospun [18].

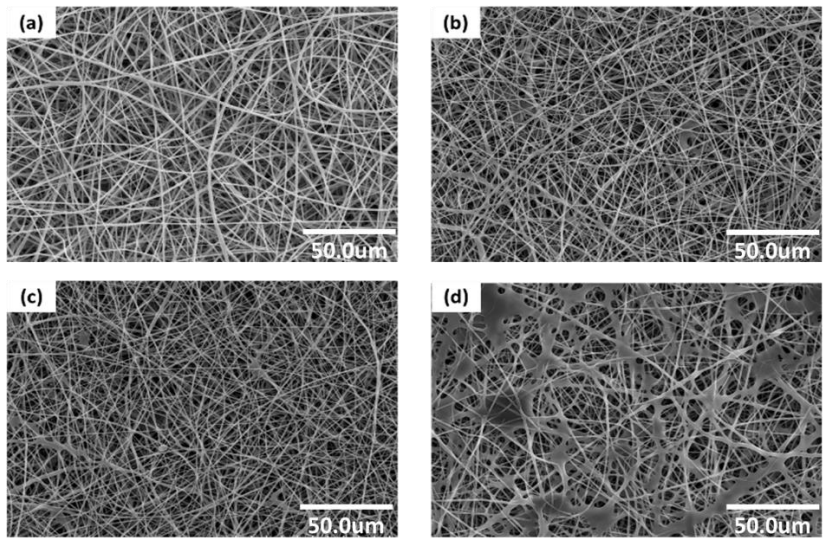

Figure 3: SEM micrograph of; (a) PVDF/0Pectin, (b) PVDF/1Pectin, (c) PVDF/2Pectin and (d) PVDF/3Pectin.

Mechanical Properties: Tensile Test

Table 1 shows the results from the tensile test done onto the PVDF/Pectin electrospun at different percentage. The results show that the incorporation of pectin into the PVDF polymer solution has slightly reduced the mechanical properties of the electrospun. As compared to the neat PVDF eletrospun, the tensile strength of PVDF/1Pectin is reduced by ~2.53% from 6.33 to 6.17 MPa, the modulus strength is reduced by ~7.14% from 19.05 to 17.69 MPa, while the elongation at break is increased by ~25.27% from 63.3% to 79.3%. The inclusion pectin has introduced an egg-box structure on the PVDF monomer which contributes to an increase of interfacial shear stress between both polymers. This likely has reduced the tensile properties [8,18]. On the other hand, introducing the amide side chain from pectin has contributed to stretchable enabled by the interchain hydrogen bond which maximized the tensile stress to 79.3±1.3% for PVDF/2Pectin [19]. Higher inclusion of pectin also has reduced the mechanical properties of PVDF/Pectin electrospun due to loss of structural integrity as shown in Figure 3(d). Overall, the PVDF/Pectin electrospun mechanical properties meets the requirement for soft collagenous tissues application for cartilage, skin, nerve, and cornea treatment at the scaffold tensile strength around 1 to 10 MPa [3,12,15].

Table 1: Mechanical properties and fibre diameter of electrospun

Sample	Tensile Strength (MPa)	Modulus Strength (MPa)	Elongation at break (%)	Diameter (nm)
PVDF/0Pec	6.33±0.12	19.05±0.33	63.3±1.2	133±1.9
PVDF/1Pec	6.17±0.25	17.69±0.19	76.9±1.7	138±2.2
PVDF/2Pec	5.98±0.17	15.82±0.10	79.3±1.3	143±1.4
PVDF/3Pec	4.16±0.19	8.45±0.21	58.9±1.1	129±0.7

Hydrophilicity Properties Analysis

The water contact angle analysis was used to investigate the wetting profile of electrospun surface chemistry on liquid contact. Table 2 demonstrates that the inclusion of pectin in the polymer solution reduces the water contact angle by altering the surface from hydrophobic to hydrophilic condition. Pectin consists of –OH and –COOH (ionized functional groups) transforms the polarity surface of electrospun which gives water interaction. Besides, previous studies also reported that as the size of the nanofibers decreased, the porosity increased as a result from air pocket effects that contribute to higher water contact angle of the electrospun surface [20]. Furthermore, the hydrophobic surfaces properties will greatly affect the swelling potential of electrospun by reducing the free surface energy for liquid interaction with electrospun fibers [21-22] as tabulated in Table 2. Swelling capacity is important in order to allow high loading capacity of drug molecules and migration of new cells during healing process. Swelling of the electrospun increased up to ~208.20% compared to that of neat PVDF electrospun when 2 wt% of pectin was added in the polymer solution. This owes to the hydrophilicity characteristic of pectin forming hydrogen bonds with water molecules spontaneously as the Gibbs free energy is a negative value [18,23].

Reduction of PVDF/3Pectin swelling percentage is subjected to the morphological defect on the nanofiber which probably enhances the surface roughness and leads to low water drop-material contact area. Considering that the purpose of adding pectin to improve the hydrophilicity properties of PVDF electrospun has successfully achieved up to 2 wt%, the PVDF/2Pectin was selected for further testing as it has balanced physical and mechanical properties.

Table 2: Water contact angle and swelling percentage of electrospun samples.

Sample	Water Contact Angle (°)	Degree of Swelling (%)
PVDF/0Pectin	103.9±2.6	25.6±1.9
PVDF/1Pectin	55.6±1.3	67.8±1.5
PVDF/2Pectin	43.2±2.1	78.9±1.7
PVDF/3Pectin	67.1±2.7	50.2±1.4

In-Vitro Controlled Drug Release

Figure 4 illustrates the cumulative drug release profile of PVDF/0Pectin and PVDF/2Pectin electrospun nanofibers. The early burst release pattern at early release for neat PVDF electrospun makes it inconvenient to be used as a delivery device for drugs or biomolecules. The initial bolus released leads to higher initial drug delivery which will reduce the lifetime effectiveness of the device. Besides, the burst release effects will cause systemic toxicity and wounded area, shorten drugs half-life in vivo, not economically friendly, and patient will require more frequent dosing [24-25]. This condition may due to the surface characteristic of the neat PVDF electrospun that does not fully support host-drug interactions. Inclusion of pectin in polymer solution reduces the burst release phenomenon as the charged density holds the target drugs and prolongs the release towards body system. The ability to form 'egg-box' like structure due to gelling effect has prevented direct hydrolytic degradation of host/drug interaction of PVDF/2Pectin [9-10]. Therefore, the carrier systems were significantly improved to maintain sustainable drug delivery system. Kinetic modeling of drug release was calculated using the concentration release of the hydrogel and recorded in Table 3. The PVDF/2Pectin electrospun treated is fitted mostly on the Higuchi Model as compared to Zero-Order. This shows that the release pattern is not at constant release as stated by the perfect theory of Zero-Order. However, referring to the Higuchi Model, the mechanism of drug release from the matrix follows the diffusion-controlled system. Based on the Korsmeyer-Peppas theory, n=0.248, it reveals that the release pattern is following the Fickian's diffusion theory. These theories explain that the drug release from the hybrid electrospun matrix is influenced by the diffusion factor only [16, 26].

Table 3: Kinetic drug release profile of PVDF/0Pectin and PVDF/2Pectin electrospuns

Sample	Zero-order		Higuchi		Koshmeyer-Peppas
	R^2	K_O	r^2	K_H	N
PVDF/0Pectin	0.454	1.303	0.627	8.285	0.319
PVDF/2Pectin	0.817	1.547	0.930	10.100	0.248

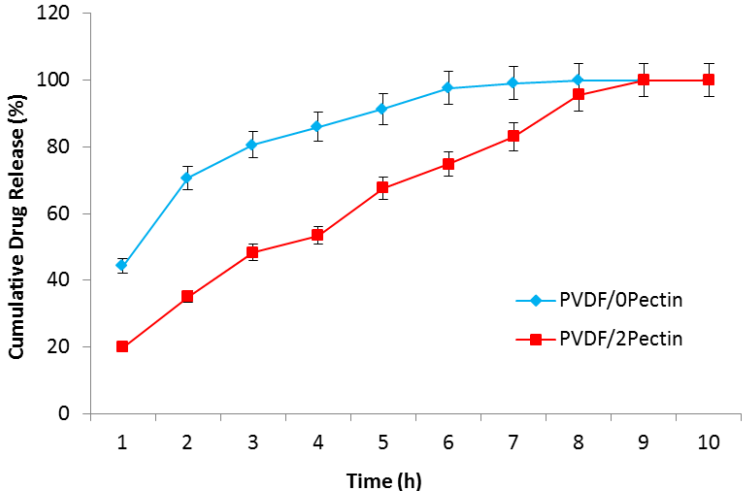

Figure 4: Cumulutative drug release for PVDF/0Pectin and PVDF/2Pectin electrospun samples.

Conclusion

This paper has studied the electrospinning of PVDF/Pectin solutions with different pectin concentration to see its effects on the morphology, mechanical, and wettability of electrospun samples. The PVDF/Pectin electrospun with up to 3 wt% pectin inclusion has successfully produced nanofibers as indicated from the SEM micrograph. However, the increase of pectin concentration of more than 2 wt% leads to bead formations due to the unstable jet formation resulting from viscous polymer solution. The mechanical integrity of the PVDF/Pectin electrospun was slightly reduced at an acceptable amount of tensile strength ranging from 6.17 to 4.16 MPa. Water contact angle and swelling percentage indicate that the inclusion of pectin has improved the hydrophilicity of the electrospun by introducing hydrophilic monomer on the polymer chain such as -OH and -COOH. Based on these findings, PVDF/2Pectin electrospun is suggested to be the best formulation. Further analysis shows that the incorporation of pectin has reduced the burst release effect and prolong drug release capabilities. Over and above, results from the Higuchi Model and Korsmeyer-Peppas Model prove that the factor for drug release is only influenced by the diffusion factor. This gives a decent sign for more upcoming analysis of this composite scaffold especially in vivo drug kinetic release study.

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