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Fabrication and characterization of electrospun κ-carrageenan based oral dispersible film with vitamin C

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ABSTRACT

Oral dispersible films (ODF) are great alternatives to tablet medications as they will simply dissolve in the mouth. There are several ways to produce ODFs, but electrospinning is emerging as one of the best methods as it increases the surface to volume ratio which allows it to dissolve easily. ODFs are typically formulated using a combination of polymers to produce the necessary film qualities. The use of κ-carrageenan (κ-CAR), a natural polymer in ODFs are yet to be studied in detail. Therefore, this study aims to develop an ODF from a combination of κ-CAR, polyvinyl alcohol (PVA) and vitamin C, where the latter will act as a model drug carrier. 1.5w/v% κ-CAR and 14w/v% PVA at a ratio of 30:70 was added with different concentrations of vitamin C from 2 to 10w/v%, respectively. The resulting nanofibers were then examined for morphology, water contact angle (WCA) and disintegration time. All the solutions formed uniform nanofibers with an average diameter ranging from 190 to 490 nm and showed hydrophilic properties. Sample 4 showed the fastest disintegration time of 3.68 s and the lowest WCA of 38.5°. The results indicated that the best formulation for an ODF was with 8% vitamin C. The findings from this study provide promising groundwork for the use of κ-CAR as the biopolymer in combination with the PVA to develop a biopolymer-based ODF with vitamin C via electrospinning.

1. Introduction

The most common, non-invasive method for taking medicine is by oral intake and usually involves medication in the form of tablets or pills. This usually poses a problem to older and younger patients who have trouble swallowing medicine. Oral dispersible films (ODF) have emerged as one of an easy and convenient alternative as it can simply dissolve in the mouth upon contact with saliva without the need of water. In fact, ODFs have shown to increase patient's compliance for medication intake. The ODF is defined as a thin film dose form that can carry active pharmaceutical ingredients (API), nutrients or vitamins and ingredients for food supplements, where the drug loaded is rapidly released, resulting in a fine suspension or solution in the saliva [1].

ODFs require the presence of a polymer that makes up approximately half of the whole dry film to ensure rapid disintegration of the film to deliver the drug or nutrient [2]. To produce the necessary film qualities, the polymers can be used alone or in combination with other polymers. Non-toxic, non-irritant polymers are essential, as well as the absence of leachable contaminants. Typically, water-soluble polymers from both natural and synthetic sources are used to create a thin film with rapid disintegration, high mechanical strength, and a pleasant mouth feel [3].

Polyvinyl alcohol (PVA) is one of the most widely used synthetic polymers in the biomedical field. It offers good mechanical qualities, a high ability to produce films, nontoxicity, water-solubility, no carcinogenicity, hydrophilicity, good compatibility, and biodegradability in human tissues and fluids [4]. On the other hand, κ-carrageenan (κ-CAR) is a natural biopolymer which is derived from red seaweed. It is abundantly available and has substantial valuable properties, which have made it a recognized biomaterial used in food packaging, wound healing as well as in the pharmaceutical industry. Another important feature of using κ-CAR as a component in the ODF is it has fast disintegration rates which allow efficient release of the drug or nutrient [5]. Besides that, many studies have focused on combining κ-CAR with other polymers to take advantage of κ-CAR's gelling capabilities and

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obtain a suitable controlled-release profile [6] and stable mechanical and thermal properties [7]. Another basic but useful aspect of κ-CAR polymers is their high-water absorption capacity, which promotes medication solubility and, as a result, increases the oral bioavailability of those medicines that are weakly water-soluble. Carrageenan, especially κ-CAR can be covalently linked with other polymers with the aid of natural cross-linking [5,15]. Consequently, the study by Croitoru et al., has shown how the presence of κ-CAR has significantly improved the hydrophilicity and stability of PVA/κ-CAR hydrogels [8]. These criteria show promising results for combining both κ-CAR and PVA to form ODFs [15]. Both polyvinyl alcohol (PVA) and κ-carrageenan (κ-CAR) were used in this study as the main polymers in the ODF due to their favourable properties.

Meanwhile, an ODF requires an active pharmaceutical ingredient (API), which is the active component of a drug product and will usually prefer small molecular weight active ingredients of up to 1000 g/mol [9]. Vitamin C or ascorbic acid is considered a good model API for an ODF as it has a molecular weight of 176.13 g/mol and is also hydrophilic in nature. Its hydrophilic nature will match the properties of κ-CAR and PVA well, making it a suitable API to be studied to understand or demonstrate the ability to develop ODFs using the combination of κ-CAR and PVA.

There are several ways to produce these ODFs, including solvent casting and hot melt extrusion. However, electrospinning has emerged as a preferable method as its product has promising outcomes due to several assuring properties, including the increase of surface-to-volume ratio which allows the ODF to easily dissolve. In fact, electrospinning has proven to be a simple and economical method to produce ODFs using both synthetic and natural polymer [10,15].

There are currently no studies exploring the combination of κ-CAR, PVA with vitamin C via electrospinning method. Therefore, this study aims to develop an ODF from a combination of κ-carrageenan, polyvinyl alcohol (PVA) and vitamin C. Specifically, the vitamin C composition is varied to find the best composition.

2. Methodology

The main steps involved in this study can be broken down into three main phases according to the steps for electrospinning, as specified in the subsections below.

2.1. Materials

There are three main chemical materials used in this study which are κ-carrageenan (κ-CAR), polyvinyl alcohol (PVA) and ascorbic acid (vitamin C) as the nutrient model. The refined κ-CAR, a high molecular weight polysaccharide, was obtained from Tacara Sdn. Bhd. Fully hydrolysed PVA with MW: 145, 000 (Merck KGaA Darmstadt) and L-ascorbic acid (R&M Chemicals). In this study, distilled water will be used as the only solvent to form natural cross-linking.

2.2. Preparation of κ-CAR/PVA/vitamin C solution

In the crosslinking of the PVA with the κ-CAR, 14w/v% PVA and 1.5w/v% κ-CAR aqueous solution was prepared by diluting the materials at 90 ℃ and 50 ℃, respectively on a hot plate. Then the PVA and κ-CAR are mixed at a volume ratio of 70:30 at 300 rpm and 60 ℃ until a homogenous or clear solution was obtained. Then 2w/v%, 4w/v%, 6w/v%, 8w/v% and 10w/v% of vitamin C was added to the solution at a constant temperature of 60 ℃ and 300 rpm for 1 h to produce the five samples. The temperature was set at 60 ℃, to form intermolecular interactions such as van der Waals between the vitamin C and polymers functional groups to allow a physical crosslinking. The solutions were also characterised using Fourier transform infrared spectroscopy (FTIR) to identify the functional groups of the crosslinked solutions.

2.3. Electrospinning of κ-CAR based nanofiber

In order to form the ODFs, 3 ml of each κ-CAR/PVA/vitamin C polymer solution were placed inside a syringe which was connected to a needle. The needle was then connected to a high voltage (16 kV) DC supply at positive polarity. The flowrate of the solution was controlled at 1.5 ml/hr using a syringe pump. The electrospinning parameters used in this study was fixed based on the preliminary work that produced Taylor cone and finally produced consistent nanofibers as specified in Table 1. The performance during electrospinning was recorded and the resulting nanofibers were collected until a thin film is obtained as the ODF. The nanofiber thin films were then cut into 4 × 4 cm as the formulated ODF for further characterization and analysis.

2.4. Characterization of electrospun ODF

The five electrospun ODF samples were then for water contact angle to examine the hydrophilicity of the sample using VCA 3000 Water Surface Analysis System by AST Products Inc. The water contact angle is crucial to ensure that the samples produced are considered soluble in water, as an ODF should be. Next, the nanofiber morphology and size distribution was analyzed under field emission scanning electron microscopy (FESEM), JSM – 7600F by Jeol. This is to observe whether a consistent nanofibre is able to be produced from the combination of the PVA, κ-CAR and vitamin C. Lastly, the disintegration time was recorded by dissolving each of the films in 10 ml of distilled water. Table 2 shows the procedures for the disintegration test.

3. Results and discussions

3.1. Fourier transform infrared spectroscopy (FTIR) of κ-CAR/PVA/vitamin C electrospinning solution

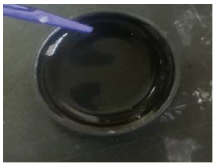
Fig. 1 shows the FTIR spectra of (a) PVA/κ-CAR and vitamin C, (b) PVA/κ-CAR, (c) vitamin C, (d) κ-CAR and (e) PVA.

It is observed that samples (a)–(e) have the same broad peak at range 3270 cm^{-1} to 3309 cm^{-1}. This shows the presence of —OH compound and adsorbed water [8]. The cross-linked spectrum also indicates characteristic bands at range 1634–1654 cm^{-1} which can correlate to the amide I peak. Thus, it can be claimed that the PVA/CAR has been successfully crosslinked. A similar peak is seen at 1506 cm^{-1} which corresponds to aromatic rings. These can be classified as a C—H bending vibration because of the medium peak at range 1600 cm^{-1} to 1500 cm^{-1} [11]. In the FTIR spectra of PVA/CAR in (b) and PVA/CAR vitamin C in (a) mixtures, no new absorption bands could be detected, which could be an indication that the vitamin C is not bound and interacted with the polymers.

Table 1
Electrospinning parameters used in this study to produce the oral dispersible film (ODF) or nanofibers.

Electrospinning Parameter	Value
Syringe pump flowrate	1.5 ml/hr
Applied voltage	16 kV
Distance between collector and syringe	15 cm
Needle size (Terumo)	23 G
Solution volume	3 ml

Table 2
Example of disintegration tests performed on the synthesized electrospun ODF to obtain the disintegration times.

Figure	Explanation
	The sample wascut to 4 cm × 4 cm and put in the 10 ml of distilled water.
	The sample was observed and the time was recorded using the stopwatch.
	The time taken for every sample was recorded.

3.2. Water contact angle of electrospun ODF

A contact angle was used to examine the hydrophilicity of the sample. The degree of the angle was obtained from the angle between the surface and the tangent line to the edge of the water drop. There are 4 factors that influenced the reading which are surface roughness, heterogeneity, particle shape and particle size [12]. The resulting water contact angle measurements are shown in Fig. 2.

Hydrophilic properties were shown in all samples as their water contact angle (WCA) was less than 90°. Also, it can be seen that the angle reading decreases when the concentration is increased. This however was not the case for the sample with 10% vitamin C as the contact angle was larger. Generally, it can be said that an increase in vitamin C content increases hydrophilicity and is expected as vitamin C is also considered hydrophilic. From these results, the sample with 8% vitamin C can be said to have the best hydrophilicity with the lowest contact angle of 38.5 ± 0.20°. The higher contact angle value would reflect to a better surface solid hydrophobicity. A recent study by Mat Yassin et al. (2022) produced a carrageenan-based biofilm with surface hydrophobicity ranging from 81 to 107°. The films were blended with lipid which was extracted from *cholera vulgaris* [13]. Our previous work shows that the electrospun κ-CAR/PVA contact angle was less than 61.7° after reaching the equilibrium time of wetting [15]. In this work, the hydrophobicity reduced with the addition of vitamin C. This is probably due to vitamin C being highly soluble in water.

3.3. Nanofibre morphology and size distribution

The morphology of all the samples were observed using 3 different magnifications which was 1000×, 5000× and 9000× at 2 different locations on the sample. The diameter distribution of the sample was then calculated using ImageJ software by collecting 50 measurements of 5000× magnification fiber diameter. All the images obtained indicated the successful and consistent production of fine fibres. The SEM images of all samples at 5000× magnification is shown in Fig. 3.

After analysis of all the SEM images, it can be seen that the sample with 10% vitamin C had the worst morphology due to the prevalent occurrence of beading in the fibers. Beads formation in electrospinning are often related to the elasticity of the solution. The higher value in vitamin C content has potentially made the electrospinning solution more dilute or less viscous making it more elastic and hard to produce consistent electrospun nanofibers. Nonetheless, the remaining 4 samples had a consistent fiber morphology. Meanwhile, it is obvious that increasing the concentration

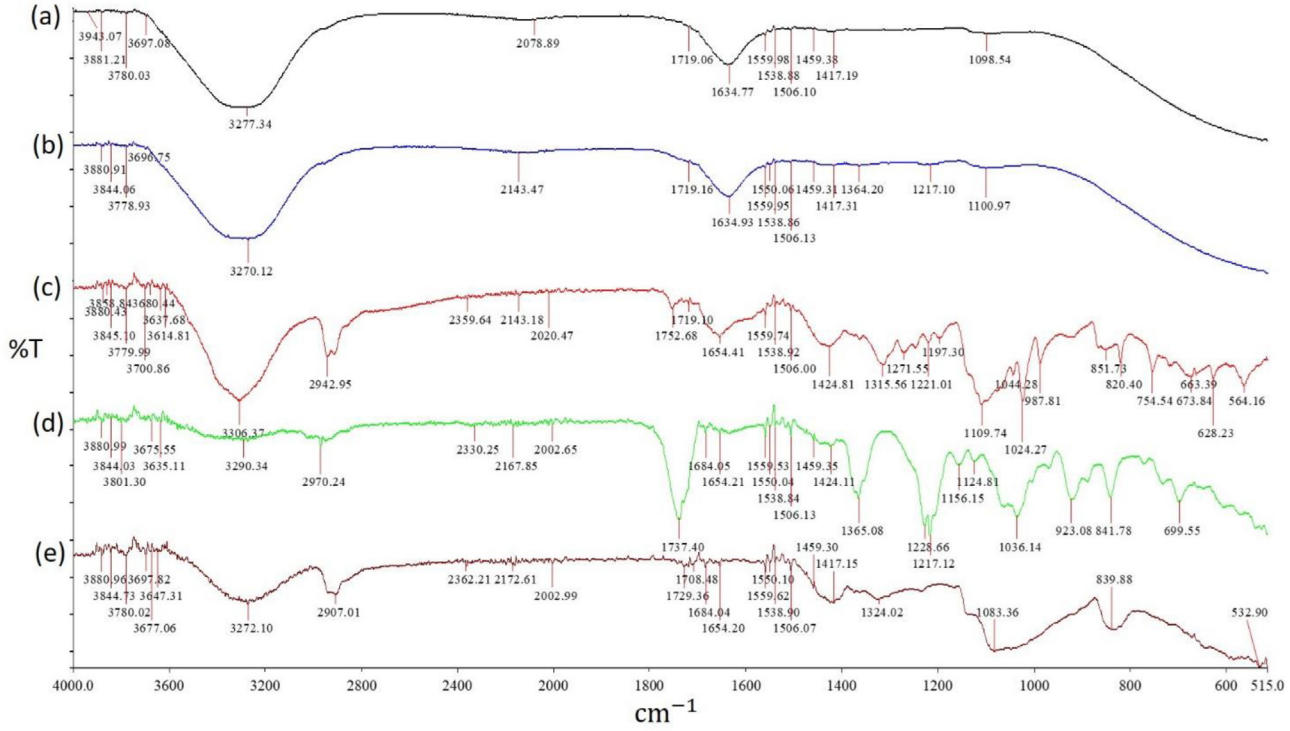


Fig. 1. FTIR spectra readings for five different electrospinning solutions, (a) PVA/κ-CAR/vitamin C, (b) PVA/κ-CAR, (c) vitamin C, (d) κ-CAR and (e) PVA.

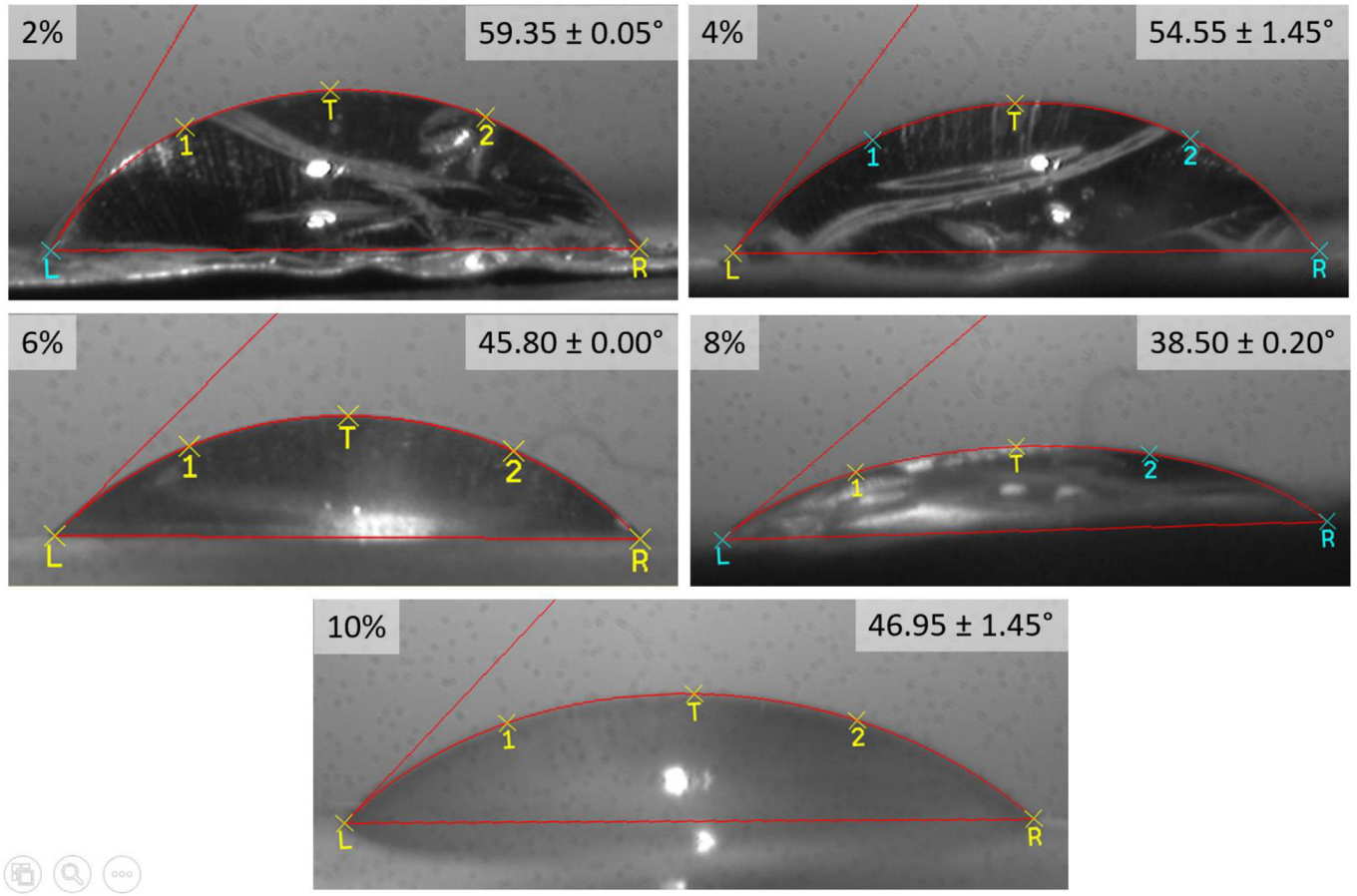


Fig. 2. Water contact angle measurements for all five samples with different concentrations of vitamin C ranging from 2% to 10%, respectively and their corresponding average water contact angle.

of vitamin C lead to . This could probably correlate with the viscosity of the solutions as it has an influence on the morphology as reported by Nuraje et al. [14] and Abu Bakar et al. [15].

To confirm the diameter distribution for all the samples, ImageJ software was used on the 9000× magnification images of each sample. The diameter distribution for each sample is shown cumulatively in Fig. 4. The distribution showed a normal distribution for each sample, hence validated the measurements obtained. The mean diameter for each of the samples are shown in Table 3.

3.4. Disintegration time

The disintegration tests were performed to observe and confirm the dissolution capabilities of the electrospun ODF. In order for it to be considered a viable ODF, it should be able to disintegrate quickly and efficiently upon contact with water. It is important to know the release rate of the sample since the advantage of the ODF is that it is capable to dissolve in water rapidly. A study by Gupta & Kumar reported that the best time for an ODF to dissolve in saliva should be less than 30 s [2]. Table 4 shows the time recorded for every sample to dissolve in water.

All samples had a high release rate due to low surface area as expected from an electrospun product. The sample with 2% vitamin C required the longest time to disintegrate while the sample with 8% vitamin C was the quickest at only 3.68 s. This behaviour corresponded nicely with the morphology and size of the fibres. Similarly, the water contact angle of the sample with 8% vitamin C was also the lowest at 38.5 ± 0.20°, which also supports this finding. The concurrent data indicated that the formulation with 8% vitamin C showed the best properties for an ODF.

4. Conclusions

A κ-carrageenan based ODF with vitamin C has been successfully formulated via electrospinning. The FTIR spectrum from the electrospinning solutions showed no interaction or bond formation between vitamin C and the polymers used. Meanwhile, based on the observations from the SEM images, the sample with 8% vitamin C had the best morphology with the most consistent nanofibers formed. The diameters, water contact angle and disintegration time also favoured the same sample (8% vitamin C) with the smallest water contact angle and quickest disintegration time at 196.4 9 ± 57.47 nm, 38.5 ± 0.20° and 3.68 s, respectively. The compelling data has definitely shown promising groundworks for the use of κ-CAR as the biopolymer in combination with the PVA to develop a biopolymer based ODF with vitamin C via electrospinning. In fact, similar strategies can be developed and utilized to load other APIs with the electropun κ-CAR/PVA thin film for the ease of drug delivery.

CRediT authorship contribution statement

Nurul Haiza Sapiee: Methodology, Validation, Supervision, Writing – original draft. **Muhammad Hasif Mat Saufi:** Investigation, Formal analysis, Writing – original draft. **Noor Fitrah Abu Bakar:** Funding acquisition, Methodology, Resources, Writing -

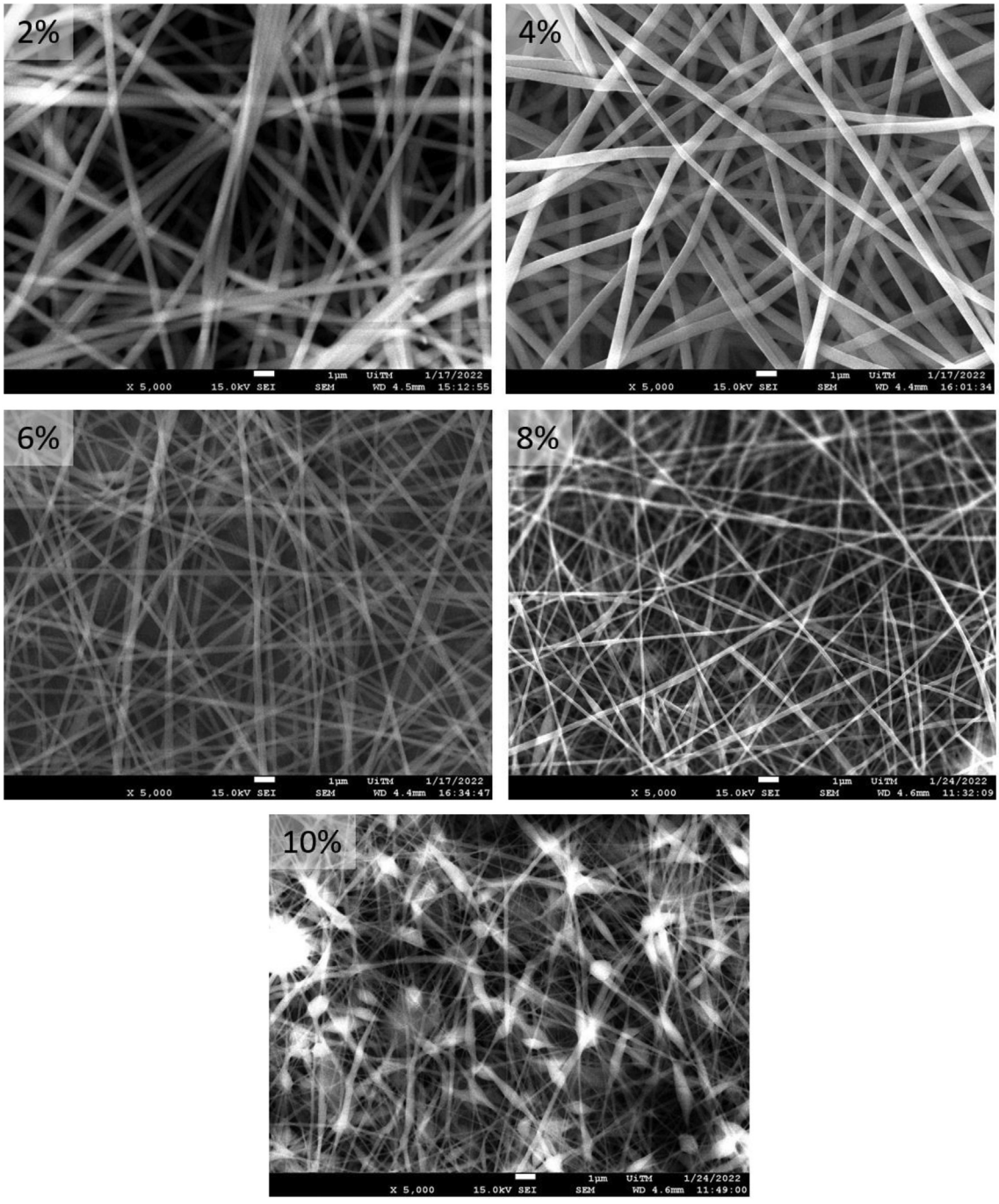


Fig. 3. Scanning electron microscope (SEM) images of all five samples with different vitamin C w/v% ranging from 2% to 10% at 5000x magnification. The images show that a consistent fibre morphology was formed, however with a range of different diameters of the nanofiber.

review & editing. **Fatmawati Adam:** Resources, Writing – review & editing.

Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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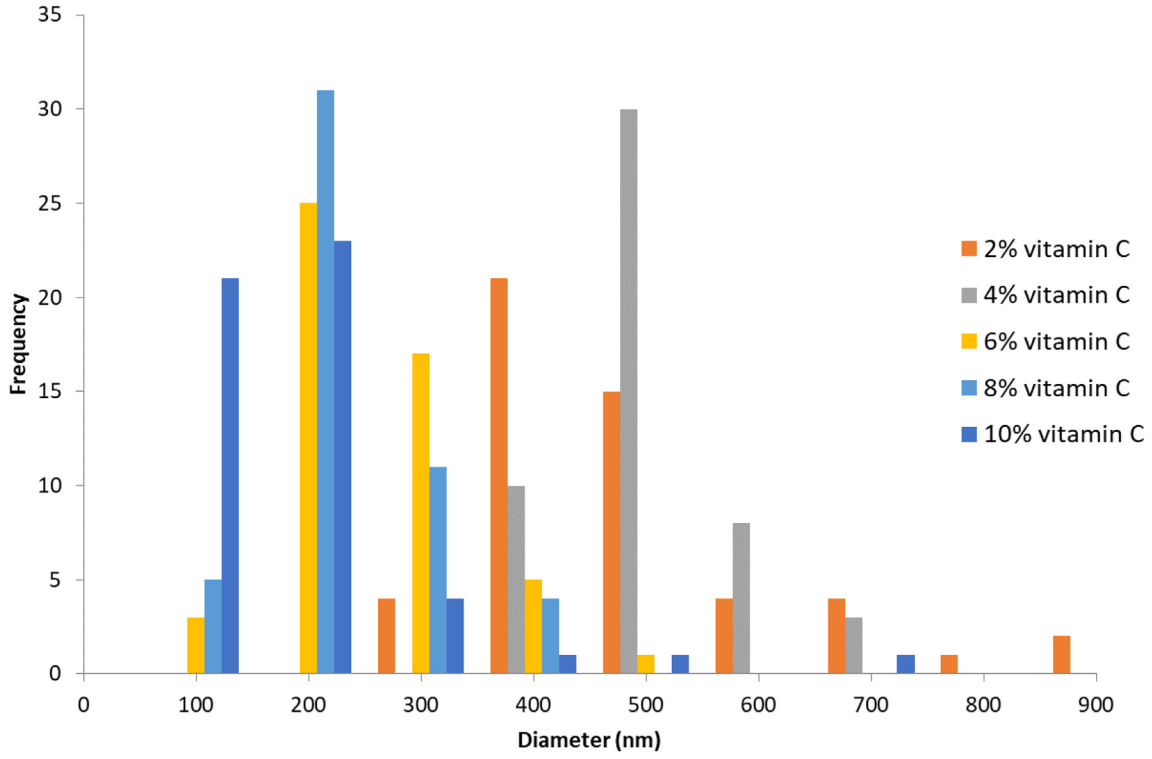

Fig. 4. Diameter distribution of all five samples with different vitamin C content analyzed at 9000x magnification under SEM.

Table 3
The mean diameter of electrospun nanofibres for all five samples with different vitamin C content.

Vitamin C w/v%	Mean Diameter
2%	484.12 ± 105.82 nm
4%	487.75 ± 55.59 nm
6%	237.79 ± 64.35 nm
8%	196.49 ± 57.47 nm
10%	191.69 ± 89.07 nm

Table 4
Recorded disintegration time of all the 4 cm × 4 cm samples in water.

Vitamin C w/v%	Disintegration time (s)
2%	4.87
4%	4.39
6%	4.01
8%	3.68
10%	4.23

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