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Research Article

Production, characterization and antioxidant activity evaluation of quercetin loaded PLGA nanofibers

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ABSTRACT

Quercetin is a flavonoid which is known to have antioxidant, anticancer and antimicrobial activities and found high ratio in many plants and nutrients. As quercetin has a superior ability to scavenging of reactive oxygen species, its use in wound dressing studies is increasing. Electrospun membranes are seen to be advantageous in terms of controlled and continuous drug release, water absorption and mimicry to intercellular matrix elements. In this study, PLGA nanofibers are produced by electrospinning method. In their SEM images, it is observed that PLGA nanofibers are successfully produced with average diameter of 500±20 nm and they are bead-free and randomly. Quercetin was loaded onto the PLGA membrane by spraying method to ensure that the fibers were physically attached onto the surface. FTIR spectroscopy analysis showed that quercetin was successfully loaded onto the nanofibers. In the swelling study, it was found that water absorption capability of PLGA membrane is 300±30%. Drug release studies were performed with quercetin-loaded PLGA nanofibers and it was determined that quercetin was completely released in 7 days. Antioxidant activity of quercetin loaded PLGA nanofibers was tested by DPPH method and it was showed 85.1±0.8% antioxidant activity.

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INTRODUCTION

Wound healing is a physiological process that consists of hemostasis, inflammation, proliferation, and remodeling phases [1]. The hemostasis phase immediately starts after being injured and platelets are activated by the vascular sub-endothelial matrix. The inflammation phase is an immune response in which macrophages and neutrophils phagocyte necrotic tissue and pathogens. In the proliferation, fibroblasts, keratinocytes and growth factors arrange wound closure, epithelialization and vascularization. The wound bed is filled with granulation tissue which is rich in collagen type III. The remodeling phase involves replacing collagen type III with collagen type I, formation of new connective

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and epithelial tissues [2, 3]. Healing takes a long time (more than 8-12 weeks) in chronic wounds such as leg ulcers, diabetic ulcers, vascular ulcers [4, 5], and full-thickness burns. Bacterial infection is responsible for delayed healing in chronic wounds. Wound dressings should limit bacterial colonization and promote cell migration and proliferation [6].

Under normal conditions, endogenous antioxidants provide oxidative stability by taking precautions against reactive oxygen species (ROS) increase [7]. In the case of injury, the endogenous antioxidant mechanism is inadequate against the level of ROS produced due to increased signal transduction, cell migration and cell proliferation. Therefore, the development and production of wound dressings with antioxidant activity becomes very important [8-10]. Oxidative stress occurs with disruption of the balance between free radical increase and antioxidant mechanism during wound healing. In the process of oxidative stress tissues are damaged and this damage significantly slows healing. In this respect, the antioxidant substances also have the property of accelerating wound healing [11]. Quercetin (Figure 1.) is a well-known drug molecule for scavenging free radicals. In a study on this subject in the literature [12], it was observed that the wound treated with quercetin was significantly reduced compared to the control on day 7 and completely closed on day 14.

Quercetin is flavonoid compound found in many plants and nutrients such as red grapes, green tea, onions, apples, St. John's wort [9]. As well as quercetin is known for its antioxidant activity [13] in the literature, there are many studies on its anticancer [14], antimicrobial [15] and antiviral [16] properties. As quercetin one of the most powerful agents in scavenging reactive oxygen species, its use in wound healing and wound dressing studies are increasing [17]. Togay et al. [18] reported that quercetin, hydrophobic drug molecule, exhibits more effective activity through controlled release when used in combination with nanofiber structures.

There are three main approaches in drug loading mechanisms into nanofibers: *i)* blending polymer and drug, *ii)* surface functionalization, and *iii)* immersion (dipping). The blending technique is simple but requires caution as it changes the electrospinning parameters [19]. In the study of Kataria et al. [20] metronidazole, an antibiotic, is loaded onto PVA (polyvinyl alcohol) nanofibers by dipping method. In this study, 1 cm^2 PVA membranes were dipped in saturated metronidazole solution for 10 minutes. It is mentioned that the dipping method is simple and repeatable. Since the drug and polymer do not need to be dissolved in the same solvent, the dipping method was found to be more advantageous than passive loading. In this study, quercetin solution was added in a spray bottle and sprayed onto the electrospun PLGA membrane (Figure 2).

In the present study, a membrane was produced by electrospinning of PLGA solution. Quercetin, an antioxidant molecule, was loaded onto the membrane by spraying method. Drug release profile and antioxidant activity of quercetin loaded PLGA nanofibers were studied.

MATERİALS

PLGA (LA:GA ratio is 75:25, molecular weight: 76-115 kDa), quercetin, N-N-dimethylformamide (DMF), dichloromethane (DCM), 2,2-diphenyl-1-picrylhydrazyl (DPPH) and ethyl alcohol were obtained from Sigma&Aldrich. Distilled water and ultra-pure water were obtained with Milli-Q, Millipore.

METHODS

Production Of Quercetin Loaded PLGA Nanofibers

In this study, the method of Meng et al. [21] was used for the production of nanofiber by electrospinning. Briefly,

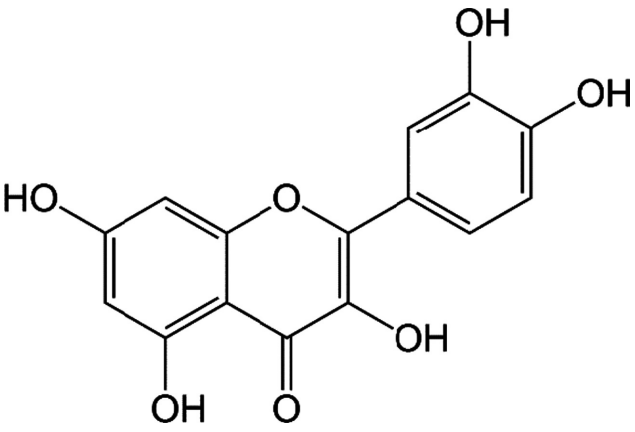

Figure 1. Chemical structure of quercetin molecule.

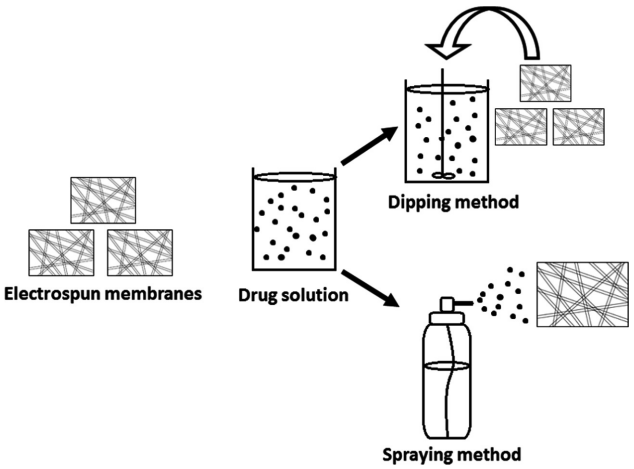

Figure 2. Schematic representation of dipping and spraying methods.

DMF:DCM (2:1) solution was prepared and PLGA (25% w/v) was dissolved in this solution for 8 h at room temperature. Electrospinning parameters were adjusted to be electrical field is 14 kV, flow rate is 0.5 mL/h and distance needle-collector is 150 mm (Inovenso Ltd. Co., NE300). 26 Gauge (0.404 mm) stainless steel needle and cylindrical collector rotating at 200 rpm were used.

In the drug loading step, firstly, solution was prepared by dissolving 20 mg of quercetin in 10 mL of EtOH:dH_2O (1:1). Then, the quercetin solution was filled into a spray bottle and sprayed onto the 40 cm^2 PLGA nanofibers (PLGA-NFs). Quercetin loaded PLGA nanofibers (QPLGA-NFs) were dried overnight in a vacuum oven at room temperature, stored at 4°C and dark condition.

FTIR Assay

In the FTIR assay, vibrational frequencies of functional bonds in the structure of the molecules on surface of samples were measured [22]. PLGA-NFs, QPLGA-NFs and quercetin molecule were analyzed by FTIR spectrophotometer (Shimadzu, Pretige-2100). First, the air was taken as background. Then, the sample was placed and measured with 16 scans per sample in the 600–4000 cm^{-1} wavenumber.

Morphology Analysis

In this study, scanning electron microscope (SEM) was used to examine general view, continuity and diameter distribution of PLGA-NFs [23]. Samples cut to the appropriate size were coated with Au-Pd alloy for 15 min. SEM images were taken at 500, 1000 and 10000 times magnifications and fiber diameter was analyzed from 3 randomly selected regions (Inovenso Ltd. Co., SEMoscope).

Drug Loading Efficiency And Loading Capacity

In this study, 2×2 cm^2 quercetin loaded PLGA membrane was dipped into 1 mL ethanol and shaked. The absorbance of membrane-treated ethanol was measured by UV-Vis spectrophotometer (Shimadzu, UV-1700 PharmaSpec) at 367 nm wavelength. The quercetin concentration was calculated using the calibration curve prepared beforehand (y = 8.111x, R^2 = 0.998). Equation (1) and equation (2) were used to calculate the drug loading efficiency and drug loading capacity, respectively [24]:

$$\text{Drug loading efficiency (\%)} = \frac{M}{M_0} \times 100 \quad (1)$$

$$\text{Drug loading capacity (\%)} = \frac{M\ (\text{drug})}{M\ (\text{drug + membrane})} \times 100 \quad (2)$$

M_0 indicates the mass of quercetin used for loading onto 2×2 cm^2 membrane initially, and M indicates the mass of quercetin loaded to 2×2 cm^2 membrane. The test was performed in 3 replicates and the results obtained were averaged.

***In Vitro* Drug Release**

Drug release of QPLGA-NFs was performed in PBS buffer (pH: 7.4) at 37°C [4]. The spectrophotometric (Shimadzu, UV-1700 PharmaSpec) measurements of the samples taken from the release medium were made and the mass of quercetin in the medium was calculated with the calibration curve prepared beforehand. The procedures were performed in 3 replicates and the results were averaged.

Swelling Study

Electrospun membrane was cut into 3 pieces that same weight. These pieces were dipped into PBS buffer (pH: 7.4) at 37°C. They were removed from the buffer solution at certain time intervals and pressed onto blotter to absorb excess liquid [25]. They were weighed and their swelling rates were determined using equation (3).

$$\text{Swelling ratio (\%)} = \frac{W - W_0}{W_0} \times 100 \quad (3)$$

W indicates weight of membrane removed from PBS buffer, W_0 indicates weight of dry membrane.

Antioxidant Activity

Antioxidant activity of PLGA-NFs and QPLGA-NFs were determined by DPPH assay. In the study, samples were dipped into 1.5 mL of 100 µM DPPH ethanolic solution at the room temperature and dark conditions. After 30 minutes of reaction, spectrophotometric measurements of DPPH solutions treated with samples were performed at 517 nm [26]. Antioxidant activities of PLGA-NFs and QPLGA-NFs were calculated using equation (4).

$$\text{Antioxidant activity (\%)} = \frac{A_0 - A}{A_0} \times 100 \quad (4)$$

A_0 and A indicate absorbance of free DPPH solution and absorbance of DPPH solution treated with each sample, respectively.

RESULTS AND DISCUSSION

Production of Quercetin Loaded PLGA Nanofibers

In the study, quercetin was loaded onto electrospun PLGA membrane by spraying method. During the electrospinning, it was observed that polymer solution became a stable jet under high voltage. Electrospinning parameters were fixed throughout the process. The produced electrospun membrane was dried at room temperature. Drug loading method used in this study, spraying, was found more advantageous than passive method. In the passive method,

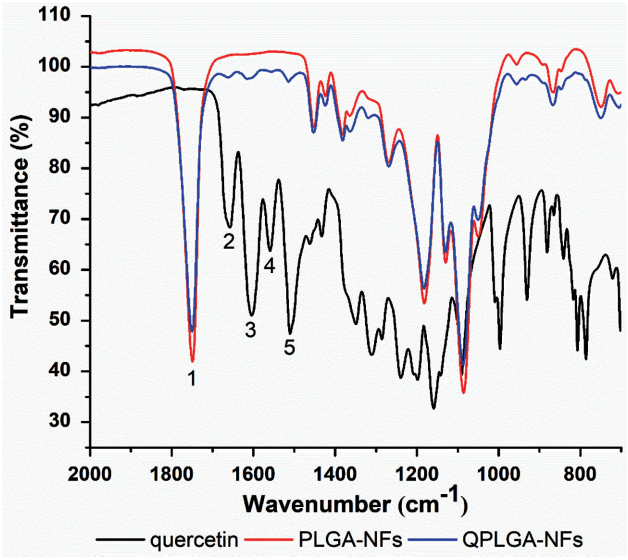

Figure 3. FTIR spectra of quercetin molecule, PLGA-NFs and QPLGA.

the polymer and the drug are dissolved in the same solvent and electrospinning process is performed [18, 27]. Thus, at the end of the process, a completely drug loaded membrane is obtained. In this study, the desired size of membrane was cut and loaded onto the drug molecules. It is believed that the spraying method is easier for the preparation of different nanofiber-drug combinations. In addition, since a different substance is not added to the polymer solution, important parameters for electrospinning such as surface tension, density, and electrical charge are not interfered. On the other hand, drug loss is higher in spraying method.

In the dipping method, which is another active loading mechanism, a concentrated solution of the drug molecule is prepared and the nanofiber membrane is dipped in this solution [28]. The remaining solution after drug loading can be considered as waste. In this study, the required amount of solution was prepared and therefore no waste occurred during drug loading. For this reason, it was decided that the spraying method is more economic and ecofriendly. In short, the spraying process is considered to be simple,

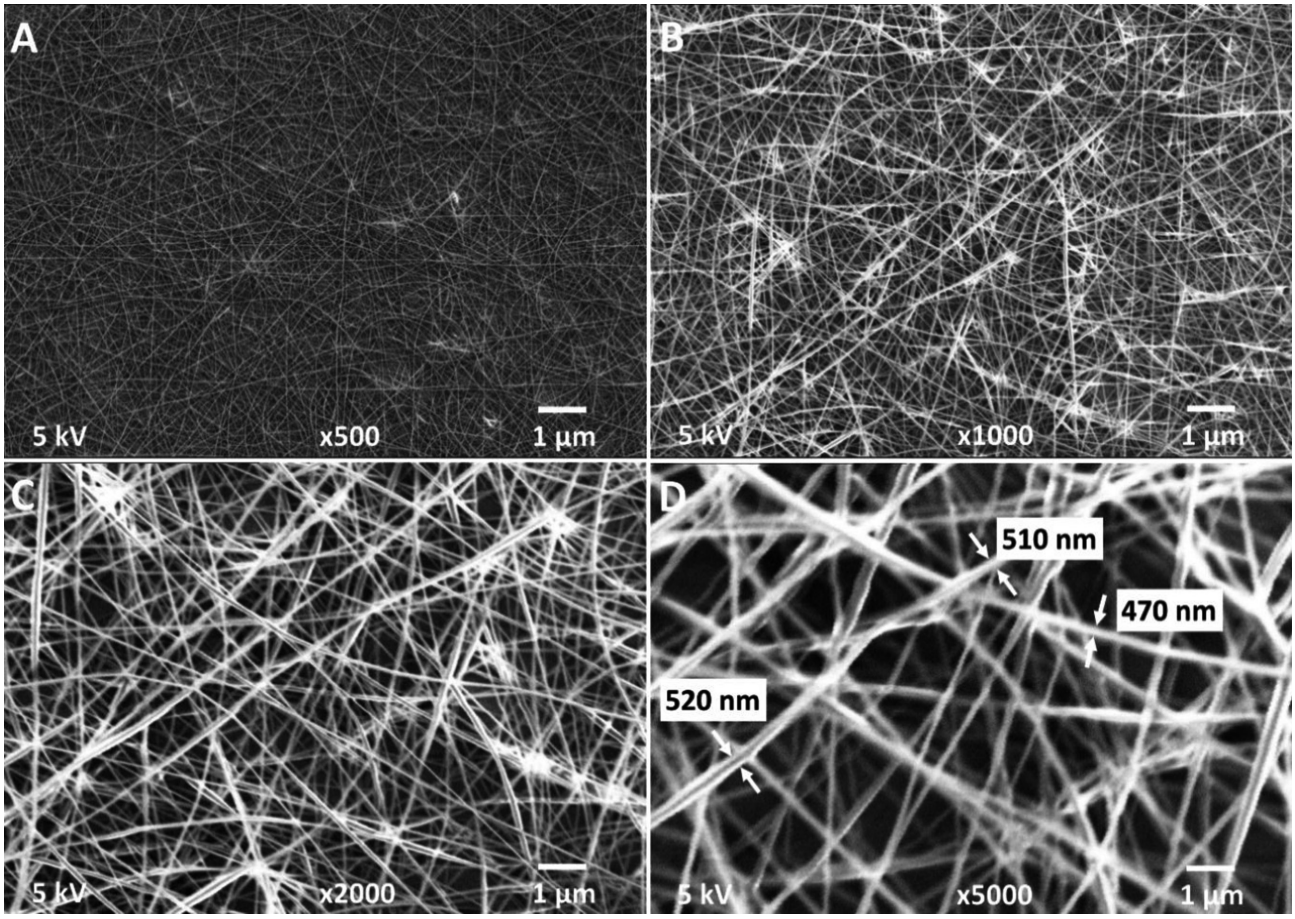

Figure 4. A) ×500, B) ×1000, C) ×2000 and D) ×5000 SEM images and fiber diameters of PLGA nanofibers.

accessible and economic in that the desired drug formulations can be loaded onto the same membrane without requiring a new electrospinning process.

FTIR Assay

FTIR analysis is one of the most preferred technique for determination of surface chemistry of nanostructures [29]. In the present study, spectra of samples were given in Figure 3. The major IR bands were shown with numbers from 1 to 5 in the figure and explained. Band 1 (1750 cm^{-1}) comes from C = O stretching of –COOH groups present PLGA structure [30]. This band also present of QPLGA-NFs spectrum. Band 2 (about 1670 cm^{-1}) comes from aromatic ketone groups in the structure of quercetin. This band is common in the spectra of quercetin and QPLGA-NFs but have very low intensity in QPLGA-NFs. Bands 3 (1650 cm^{-1}), 4 (1610 cm^{-1}) and 5 (1560 cm^{-1}) come from aromatic C=C stretching in the quercetin. Although bands 2, 3, 4 and 5 unavailable in spectrum of PLGA-NFs, these bands are common in quercetin and QPLGA-NFs. It directly show that quercetin is successfully loaded onto PLGA nanofibers. Vashisth et al. [31] have observed that there were characteristic peaks of quercetin in the spectrum of quercetin loaded poly (lactide-*co*-glycolide)–polycaprolactone nanofibers. This was presented as proof that quercetin was successfully loaded on nanofibers. In this respect, the results in present FTIR assay seem consistent with literature.

Morphology Analysis

In the study, SEM images of produced electrospun membrane are taken purpose of morphological analyzes. According to the SEM images in Figure 4, randomly oriented and bead-free PLGA nanofibers were produced. In a similar study [32], it is concluded that PLGA nanofibers are aligned when a cylindrical collector rotating at 3000 rpm was used, and random when a stationary collector was used. Although a rotating collector was used in the present study nanofibers were random. It is thought to be due to the low speed (300 rpm) of collector rotation.

The diameter of the randomly selected fibers was averaged and the fiber diameter was determined to be 500±20 nm (Figure 4D). It is reported that the diameter of the nanofibers correlated with the solvent, molecular weight of polymer, applied voltage, flow rate, and distance between the needle and the collector [33]. The average diameter of PLGA nanofibers produced by Luo et al. [33] is about 700 nm. In the present study, it was produced ultra-thin nanofibers. Thin nanofibers have a great surface area that provide high drug loading capacity and controlled release property [34]. PLGA nanofibers produced by Liu et al. [35] were 412±355 nm in diameter when applied voltage was same as in our study (14 kV). In our study, PLGA nanofibers with too narrow diameter distribution were successfully produced. Fiber diameter distribution is an important factor affecting the porosity and surface area of electrospun membranes. It also shows that the electrospinning parameters are well optimized [36].

Drug Loading Efficiency and Drug Loading Capacity

The loading efficiency study was carried out in order to determine how much of the quercetin loaded on the electrospun membrane. It was found that quercetin loading efficiency and loading capacity are 42.65±4.45%, 10.7±0.97%. In a study [31] where different amounts of quercetin were loaded onto the nanofibers by passive mechanism, it was concluded that the loading efficiency was in the range of

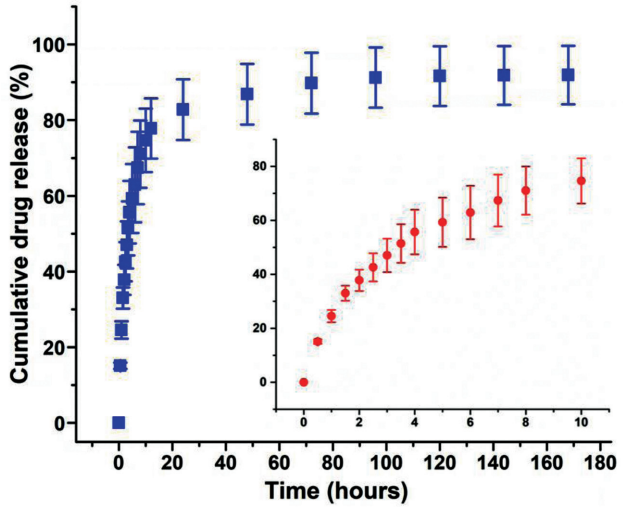

Figure 5. The cumulative release of quercetin from nanofibers: A) 7 days and B) 10 hours.

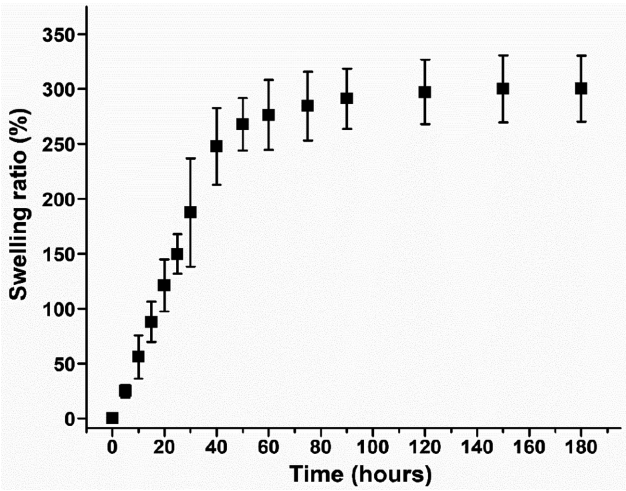

Figure 6. Swelling ratios (%) of the PLGA.

45-67%. The loading efficiency found in our study is very close to the lowest value in this study. Qi et al. [37] have investigated the effect of different pH conditions on drug loading efficiency. They obtained higher loading efficiency in alkaline pH (80%) than in neutral pH (20%). Although the high loss of drug in the spraying method reduces the loading efficiency, similar results were obtained in the literature. This makes the spraying method usable for the loading of drug molecules onto electrospun membranes.

***In Vitro* Drug Release**

In vitro release of quercetin loaded onto PLGA membrane was performed and the obtained values were plotted over time based cumulative percentage of release graphs (Figure 5). It was observed that quercetin was release from membranes in 91.9±7.8% for 7 days. A rapid release occurred during the first 10 hours (74.6±8.4%), but later became a continuous release. It was dedicated by Sun et al. [38] that the rapid release in the first hours was due to the release of drug molecules attached to the surface. The slowing of the release in the following hours was caused by drug molecules attached to the fibers in the inner parts of membrane. When the release profile of this study is examined, it is understood that quercetin is not only attached to the surface but reaches the inner fibers and pores. In the study of Xing et al. [39] was used passive loading mechanism, quercetin release was continue for 16 days. The spraying method allowed quercetin to diffuse more rapidly.

Swelling Study

In order to understand the liquid absorption capacity of PLGA nanofibers, swelling test was performed in PBS medium. Figure 6 shows the time dependent swelling percentages of electrospun PLGA membrane. According to the swelling test results, PLGA membrane absorbed 300.3±30% liquid in 3 hours. In a study, Meng et al. [21] reported that PLGA nanofibers with randomly oriented and diameters of about 1000 nm swell by 141%. In our study, nanofibers have higher surface/volume ratio because of their ultra-low diameter. The high surface/volume ratio enabled nanofibers to interact more with water, positively affecting swelling.

Antioxidant Activity

The quercetin molecule, which is known in the literature [9] for its antioxidant activity, was loaded onto PLGA nanofibers produced by electrospinning. The DPPH method was used to determine the antioxidant activity of QPLGA-NFs and PLGA-NFs. It was observed that the purple DPPH solution turned light yellow after adding QPLGA-NFs. The purple color of the DPPH solution is due to unpaired electrons in the structure. If an antioxidant molecule enters the medium, a hydrogen is bound to the DPPH molecule instead of the free electron. As a result, the color of the solution changes from purple to yellow or colorless while absorbance decreases [40]. When the ratio of decrease in absorbance was calculated, antioxidant activity

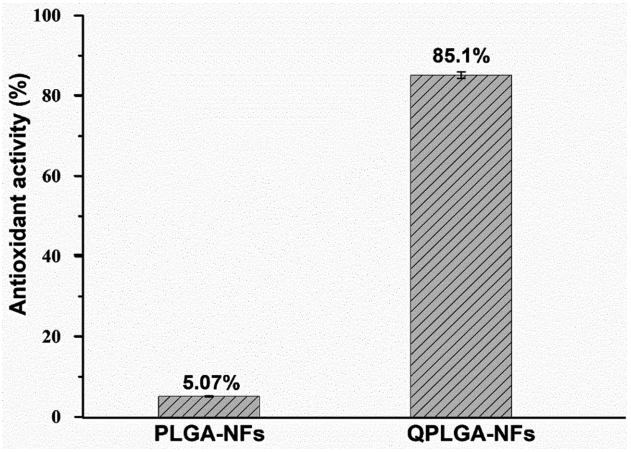

Figure 7. Antioxidant activity of QPLGA-NFs and PLGA-NFs.

of QPLGA-NFs was found as 85.1±0.8%. Antioxidant activity graphs were given in Figure 7. Antioxidant activity of PLGA-NFs was 5.07±0.17%. It was reported that cause of this low antioxidant activity is lactic acid [26].

In a study [41] in which DPPH method was applied, the antioxidant activity of green tea loaded polyvinyl prolidone (PVP) nanofibers was found to be 62.95±0.4%. Green tea is a plant that contains high quercetin. In this study, effect fiber diameter on antioxidant activity was investigated. It was reported that drug loaded ultra thin nanofibers have higher antioxidant activity depending on their high surface area. QPLGA-NFs have higher antioxidant activity than green tea loaded PVP nanofibers because pure quercetin is used. In addition, a rapid release was achieved thanks to the spraying method, thus a high antioxidant activity was observed in 30 minutes.

CONCLUSIONS

In this study, a membrane consisting of PLGA fibers with a thickness of 500±20 nm was produced by electrospinning technique. The antioxidant quercetin molecule was loaded onto the produced membrane by spraying method. It was tested by FTIR spectroscopy that quercetin was successfully loaded onto the PLGA membrane. The swelling rate of this electrospun membrane was found to be 300.3±30%. It was thought that PLGA gained high swelling capacity thanks to nano-thick fibers and pores. In the release study, almost all quercetin was released from the fibers for 7 days. Finally, antioxidant activity of quercetin loaded PLGA nanofibers was tested by DPPH method. It was found that QPLGA-NFs have 85.1±0.8% radical scavenging activity.

The importance of this study is the production of quercetin loaded PLGA nanofibers by the spraying method for the first time in the literature and the evaluation of their

antioxidant activity. The availability of a different loading method in the production of a potential wound dressing was investigated. QPLGA-NFs produced with high antioxidant activity may scavenge free radicals that delay healing in the wound area. It may accelerate wound healing by absorbing wound exudate, which causes infections to increase. Ultra thin nanofibers provide advantages in terms of exudate absorption with their high surface area. In addition, the effectiveness of quercetin in wound healing may be increased with the rapid release observed in the spraying method. With its economical, environmentally friendly and easy-to-apply features, the spraying method is a potential production method in drug loaded wound dressing production.

In future studies, it is planned to determine the antimicrobial activity of QPLGA-NFs by disc diffusion method and time-killing assay. It is thought that this study is important in terms of the spraying method cause positive differences in release and antioxidant activity."

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AUTHORSHIP CONTRIBUTIONS

Authors equally contributed to this work.

DATA AVAILABILITY STATEMENT

The authors confirm that the data that supports the findings of this study are available within the article. Raw data that support the finding of this study are available from the corresponding author, upon reasonable request.

CONFLICT OF INTEREST

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

ETHICS

There are no ethical issues with the publication of this manuscript.

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