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RESEARCH PAPER

Various parameters in the preparation of chitosan/polyethylene oxide electrospun nanofibers containing Aloe vera extract for medical applications

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ABSTRACT

Objective(s): The present study aimed to fabricate chitosan/polyethylene oxide (CS/PEO) electrospun nanofibers loaded with Aloe vera extract for biomedical applications. The polymer-to-extract ratio and electrospinning parameters (applied voltage and nozzle-to-collector distance) were evaluated in order to optimize the process of nanofiber fabrication.

Materials and Methods: The characterizations were performed using scanning electron microscopy (SEM), ImageJ software, attenuated total reflectance Fourier-transform infrared spectroscopy (ATR-FTIR), tensile strength test, and UV-Vis spectroscopy.

Results: The obtained results indicated that the fabrication of nanofibers from pure Aloe vera extract was unsuccessful, and reducing the extract concentration from 100% to 92% resulted in the formation of the nanofibers. Moreover, further reduction in the extract from 92% to 50% led to the production of fine nanofibers (mean diameters: 204±42 and 398±51 nm, respectively). Therefore, it was concluded that the reduced concentration of the herbal extract increased the diameters of the prepared nanofibers. In addition, the results of the optimization process indicated a direct correlation between the applied voltage and nanofiber diameters, as well as an inverse correlation between the nozzle-to-collector distance and nanofiber diameters. The FTIR spectroscopy also confirmed the presence of CS, PEO, and Aloe vera in the final prepared scaffold. The release measurement revealed a burst effect within the first five hours, followed by a sustain release within 30 hours. Moreover, the biocompatibility assay confirmed the proliferative potential of Aloe vera within seven days.

Conclusion: According to the results, a nanofibrous scaffold composed of CS and PEO could be fabricated as the carrier of Aloe vera extract, which is a suitable platform for biomedical applications.

Keywords: *Aloe Vera, Chitosan, Electrospinning, Nanofibers, Polyethylene oxide*

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INTRODUCTION

Aloe vera is known as the immortality herb, 'drug vegetable, and queen of herbs in some areas and is widely used in medical treatments and food industry owing to its remarkable properties and composition [1]. The health benefits of *Aloe vera* include wound healing [2], alleviation of menstrual pains, strengthening of the immune system, curing dermatitis, and reducing arthritis pain [3]. Furthermore, this plant could lower cholesterol and blood sugar levels, inhibit the growth of cancerous tumors, cure nausea, reduce oxidative stress, promote hair growth, and eliminate ulcers [4].

Aloe vera is composed of gel (obtainable from the cells at the center of the leaves) and latex (obtainable from the cells beneath the leaf skin). The gel consists of 98% water and only 2% of the original composition, and *Aloe vera* extract contains approximately 200 compounds [5, 6]. In addition, the dry matter of *Aloe vera* contains 50% polysaccharides, 17% sugars, 16% minerals, 7% proteins, 4% lipids, and 1% phenolic compounds (Fig 1).

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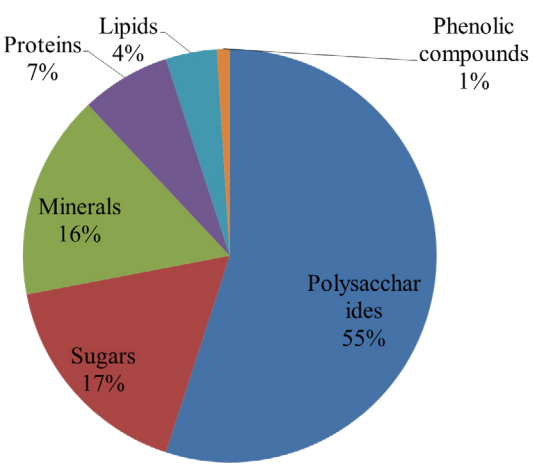

Fig 1. Compositions of Aloe vera Extract (Data extracted from study by Abid Aslam et al. [2])

Among the other beneficial compounds found in *Aloe vera* are vitamins B1, B2, B12, E, A, and C, choline, niacin, and folic acid. This plant also contains hydroxyanthracene derivatives (e.g., aloins A2-B), oxidase enzymes, amylase, and catalase [7-9].

Aloe vera is widely used for medical applications owing to its remarkable antimicrobial, anticancer, and anti-inflammatory properties. Various formulations containing *Aloe vera* extract (e.g., hydrogels, ointments, capsules, and bandages) are also available to deliver the effective materials of the extract [10, 11].

Nanofibers have attracted significant attention owing to their large surface-to-mass ratio, high drug loading efficacy, extremely small pore dimensions, and mimicking the extracellular matrix of tissues. Several methods have been proposed to produce nanofibers with variable morphology, structure, and diameters; such examples are self-assembly, template synthesis, phase separation, drawing, and electrospinning [12, 13].

Electrospinning is an enabling, sophisticated, simple, flexible, and cost-efficient method to fabricate microfibers and nanofibers. It is able to produce nanofibers from various materials with different morphologies within a wide range of diameters. The basic principle of electrospinning is the interaction between the applied electric field and polymer changes. The interaction results in the stretching of the polymer molecules and formation of fibers with micrometric and nanometric diameters [14-16]. Electrospun nanofibers have been extensively used in drug delivery, filtration, food packaging, tissue engineering, and wound dressing [17, 18].

Various biopolymers have been investigated in terms of medical applications. Chitosan (CS) has remarkable properties, including biocompatibility, biodegradability, and nontoxicity, which render this biopolymer ideal for medical applications. Polyethylene oxide (PEO) is another commonly used polymer in pharmaceutical industries owing to its high water solubility, non-toxicity, and ease of production [12].

The present study aimed to fabricate CS/PEO nanofibers containing *Aloe vera* extract for medical applications.

MATERIALS AND METHODS

Experimental materials

In this study, CS with low molecular weight and deacetylation degree of 91.2% was purchased from Easter Groups (Dong Chen Co. Ltd., China). Dry *Aloe vera* extract was obtained from Ginovera Co. Ltd., Iran, and PEO (MW 900KD) was purchased from Acros Organics Co. Ltd., USA. Glacial acetic acid was purchased from Merck, Darmstadt, Germany.

Preparation of the solution

Initially, 20.0% (v/v) acetic acid solution (pH: 3.5) was prepared to dissolve the polymers and herbal extract. The stock solutions of 3.0% (w/v) CS, 3.0% PEO, and 20.0% Aloe vera were prepared in 20.0% acetic acid, and 80/20% solution of CS/PEO was used as the carrier polymer of the *Aloe vera* extract. Various concentrations of *Aloe vera* were prepared in CS/PEO and subjected to electrospinning, including 100% (pure *Aloe vera*), 98%, 96%, 94%, 92%, 90%, 85%, 80%, 70%, 60%, and 50%

Electrospinning

The electrospinning of the solutions was performed using an electrospinning device (Fanavaran Nano Meghyas Co. Ltd., Tehran, Iran). In each experiment, the solution was added to a 5-cc syringe, which was attached to an 18-gauge blunted needle as the nozzle. The syringe was mounted onto the device, and electrospinning was performed based on various parameters. Following that, the nanofibers were collected on a collector wrapped in aluminum foil. The effects of various parameters on the size and morphology of the nanofibers were evaluated, such as the voltage

and distance between the nozzle and drum.

Evaluation of the morphology and diameters of the nanofibers

Scanning electron microscopy (SEM) (Philips XL-30, at 20 kV) was used to observe the morphology of the prepared nanofibers. Small pieces of the electrospun nanofibers were cut, and after sputtering with a thin layer of gold, SEM imaging was performed. The mean diameters of the nanofibers were calculated using the ImageJ software (1.47v, National Institute of Health, USA) based on a 30-point calculation.

Surface functional groups

The surface functional groups of the prepared nanofibers were determined using attenuated total reflectance Fourier-transform infrared (ATR-FTIR) spectroscopy (Mark EQUIONOX55. BRUKER) and evaluated with the resolution of 4 cm^{-1}.

Mechanical measurement

The mechanical properties of the nanofibers were evaluated based on their tensile strength in the dry and soaked forms. The measurements were based on ISO5270:1999 standard test methods using the uniaxial tensile test device (Santam, Karaj, Iran) at the extension rate of one millimeter per minute.

Release of Aloe vera

UV-visible spectroscopy was used to measure the *in-vitro* release of Aloe vera from the nanofibers. To do so, one milligram of the nanofibers (containing 80% *Aloe vera* extract) was incubated in phosphate buffered saline (PBS) at the temperature of 37ºC. At the predetermined intervals, one milliliter of the solution was removed and replaced with fresh PBS. The concentration of *Aloe vera* in one milliliter of the solution was measured using UV-Vis spectroscopy, and Equation 1 was used to calculate the released *Aloe vera*, as follows:

$$Drug\ release\ (100)\frac{Amount\ of\ released\ drug}{Amount\ of\ loaded\ drug\ into\ nanofibers}\times 100$$

Cell viability measurement

The viability of L929 murine fibroblastic cells on the fabricated nanofibers was measured using the 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) assay kit on days one, three, and seven after the seeding of the cells. The cells were purchased from Pasteur Institute (Tehran, Iran). At this stage, 1×10^4 of cells were suspended on the DMEM/F12 culture medium, which was supplemented with 10% (v/v) fetal bovine serum, 100 unit/ml of penicillin, and 100 µg/ml of streptomycin, and seeded on the nanofibers. After one, three, and seven days, the viability of the cells was measured using the MTT assay. The positive control was defined as the tissue properly cultured without the nanofibers.

Statistical analyses

Data analysis was performed using the Minitab software version 17 (Minitab Inc., State College, USA). Data were expressed as mean and standard deviation (SD), and P-value of less than 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Effects of the polymer and extract concentration on the nanofibers

According to the information in Table 1, various volume ratios of the *Aloe vera* extract and carrier polymer (CS/PEO) were electrospun, and the morphology and diameters of the nanofibers were evaluated. The obtained results indicated that the electrospinning of the polymer blend containing 100%, 98%, 96%, and 94% of the *Aloe vera* extract was not successful and produced no nanofibers.

Table 1. Electrospinning Experiments of CS/PEO/Aloe vera (Nozzle-to-collector distance: 80 cm, applied voltage: 22 kV, feeding rate: 0.5 ml/h)

Aloe vera Concentration in Final Nanofibers (%)	CS/PEO (%)	Mean Diameter (nm)
100	0	No fibers formed.
98	2	No fibers formed.
96	4	No fibers formed.
94	6	No fibers formed.
92	8	Beaded fibers formed.
90	10	204±42
85	15	276±52
80	20	344±62
70	30	355±43
60	40	390±69
50	50	398±51

According to the obtained results, decreasing the volume ratio of the *Aloe vera* extract to 92% resulted in the formation of beaded nanofibers, and fine nanofibers without beads were formed below this ratio. On the other hand, increasing the volume ratio of the carrier polymer increased the nanofiber diameters, leading to the production of fine nanofibers. According to the findings, increasing the volume ratio of the carrier polymer

from 10 to 12 and 14 increased the mean diameter of the nanofibers to 204±42, 276±52, and 344±62 nanometers, respectively.

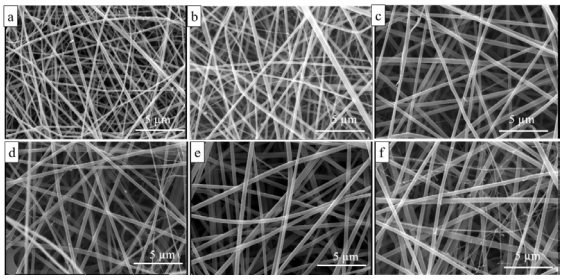

Fig 2. SEM Micrograph of Nanofibers with Various Volume Ratios: a) 90%, b) 85%, c) 80%, d) 70%, e) 60% and f), 50% of Aloe vera Extract (Applied voltage: 20 kV, feeding rate: 0.5 ml/h, nozzle-to-collector distance: 9 cm)

Moreover, a further increment in the carrier polymers (CS/PEO) resulted in the production nanofibers with larger diameters.

These phenomena could be attributed to the viscosity of the polymer solution and interaction between the polymer chains. The obtained results also indicated that increasing the carrier polymer ratio made the polymer solution more viscous, thereby inhibiting the flexibility and movement of the polymer chains, leading to the formation of nanofibers with larger diameters.

Effect of the nozzle-to-collector distance on the diameters of the nanofibers

The nozzle-to-collector distance was considered to be an influential factor in the electrospinning process, and three distances were evaluated so as to optimize this critical parameter.

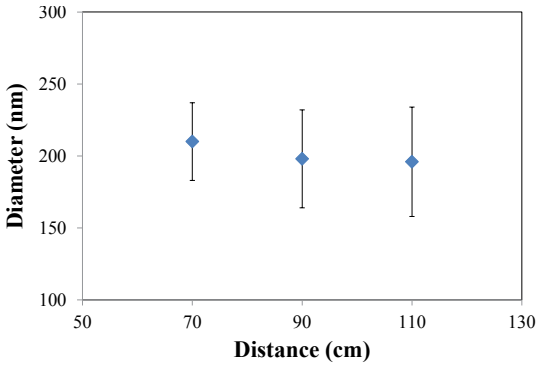

Fig 3. Effects of Nozzle-to-collector Distance on Nanofiber Diameters
Polymer Solution Concentration (Fixed applied voltage and feeding rate)

The obtained results indicated an inverse correlation between the nozzle-to-collector distance and diameter. According to the obtained results, increasing the nozzle-to-collector distance from seven to nine and 11 decreased the mean nanofiber diameter to 286±24, 276±52, and 270±45 nanometers, respectively. As is depicted in Fig 3, the effect of the nozzle-to-collector distance on the nanofiber diameters was not considered statistically significant. The effect of the nozzle-to-collector distance on the nanofiber morphology is shown in Fig 4. As can be seen in Fig 4, the nanofibers had fine, uniform structures at the distances of 70 and 90 centimeters. However, increasing the nozzle-to-collector distance resulted in the formation of multiform nanofibers. This observation is consistent with the previous findings in this regard, indicating that the increased nozzle-to-collector distance could cause the formation of nanofibers with smaller diameters due to providing more time for the evaporation of the solvent.

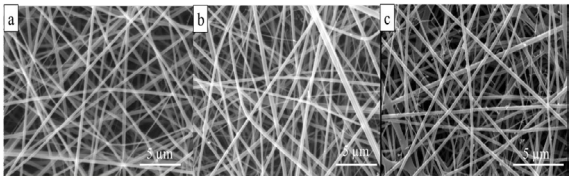

Fig 4. Effect of Nozzle-to-collector Distance on Nanofiber Morphology: a) 70 cm, b) 90 cm, and c) 110 cm (applied voltage: 20 kV, feeding rate: 0.5 ml/h)

Effect of the applied voltage on the diameters of the nanofibers

The applied electric field is the main driving force in the electrospinning process. During electrospinning, the applied electric field interacts with the polymer solution, and the polymer chains stretch due to this interaction, thereby leading to the formation of nanofibers.

The effects of the applied voltage on the diameters and morphology of the nanofibers are shown in Figs 5 and 6.

As is depicted in Fig 5, there was a direct correlation between the applied voltage and diameters of the nanofibers, so that increasing the applied voltage to 18, 20, and 22 kV increased the mean diameter of the nanofibers to 197±32, 276±52, and 323±20 nanometers, respectively.

The direct correlation between the applied voltage and nanofiber diameters could be

attributed to the effect of the applied electric field on the movement of the polymer chains from the nozzle tip toward the collector.

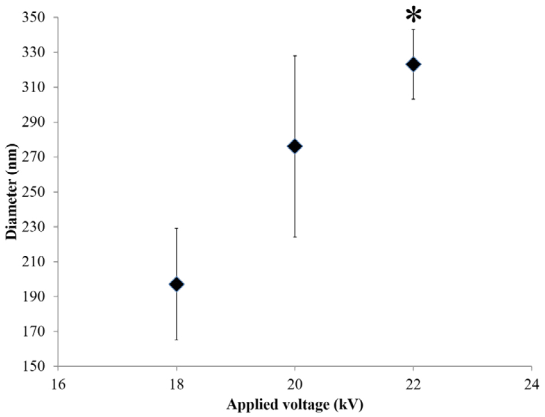

Fig 5. Effect of Applied Voltage on Nanofiber Diameters (*P<0.05)

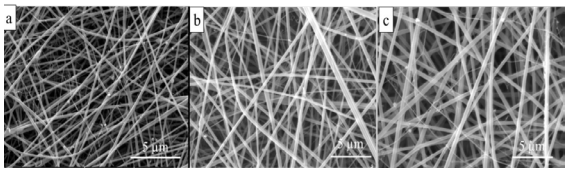

Fig 6. Effect of Applied Voltage on Nanofiber Morphology: a) 18 kV, b) 20 kV, and c) 22 kV

Furthermore, increasing the applied voltage caused the movement to become faster, so that the polymer solvent took shorter to be evaporated, thereby resulting in the formation of nanofibers with larger diameters.

Fig 6 shows the effect of the applied voltage on the morphology of the nanofibers. Accordingly, the applied voltage of 20 kV resulted in the formation of uniform nanofibers with a smooth surface, while the voltage of 22 kV led to the production of multiform nanofibers. Therefore, it could be concluded that the voltage of 20 kV was more effective than the applied voltages of 18 and 22 kV in the production of fine, uniform nanofibers.

ATR-FTIR spectroscopy

ATR-FTIR spectroscopy is a practical method to determine the presence of every component in a composite system containing various materials. In the present study, the FTIR spectra of the *Aloe* vera extract and CS/PEO polymer blend were obtained separately at wave numbers within the range of 500-4,000 cm^{-1} (Figs 7 and 8, respectively).

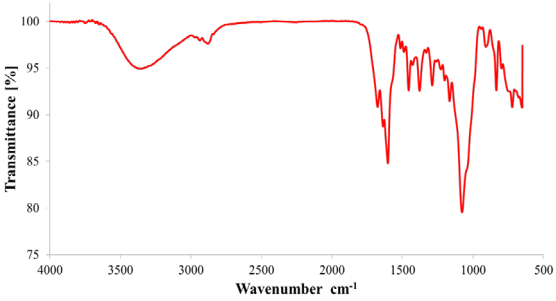

Fig 7. FTIR Spectra of Pure Aloe vera in Wave Numbers within Range of 500-4,000 cm-1

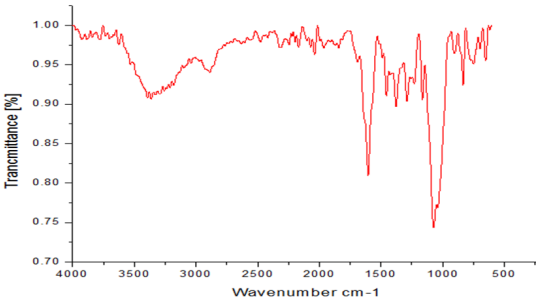

Fig 8. ATR-FTIR Spectra of Prepared CS/PEO/Aloe vera Scaffold in Wave Numbers within Range of 500-4,000 cm-1

As is shown in Fig 7, the intense peak around 1,600 cm^{-1} assigned to amino groups was the characteristic peak of pure *Aloe vera* [19]. On the other hand, the broad peak at 3,394 cm^{-1} was attributed to the N-H group from the peptide linkage present in the *Aloe vera* extract [20]. The peaks around 1,620-1,676 cm^{-1} were attributed to the carbonyl groups from polyphenols such as epicatechin gallate, epigallocatechin, catechin gallate, epigallocatechin gallate, theaflavin, and gallocatechin gallate [21]. According to the findings, the peaks around 909 and 1,166 cm^{-1} corresponded to the saccharide structures in CS. Moreover, the observed peaks at 1,650 and 1,322 cm^{-1} characterized chitin and CS, reported as the amide I and III peaks, respectively [22]. As is depicted in Fig 8, the peaks were located within the range of 2,500-3,000 cm^{-1}, arising from methylene stretching in the PEO polymer. Moreover, the peaks around 1,100 cm^{-1} corresponded to the combination of the ether and stretching methylene groups [23]. The results of the FTIR spectroscopy clearly indicated the presence of each component in the final structure of the CS/PEO/*Aloe vera* scaffold, so that they could have their structural and biological functions.

UV-Vis absorption

UV-Vis spectroscopy is an applicable method to measure the concentration of a specific substance in a medium. As can be seen in Fig 9, the maximum absorption of *Aloe vera* was approximately 300 nanometers, and the data suited further studies on drug release. UV-Vis spectroscopy was used to evaluate the absorption intensity of *Aloe vera* in the UV-Vis area, and the results are depicted in Fig 8.

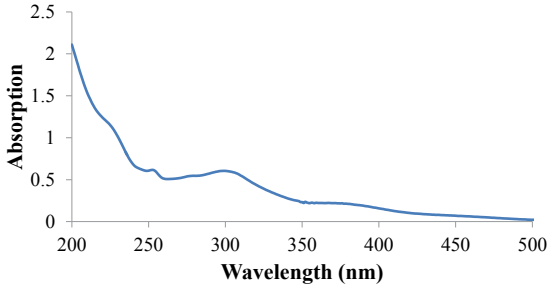

Fig 9. UV-Vis Spectrum of Aloe Vera

Release data

The release of *Aloe vera* from the fabricated nanofibers was measured in the PBS solution within 30 hours under sink conditions, and the results are shown in Fig 10.

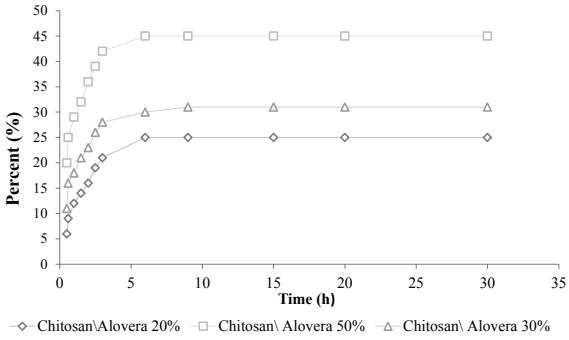

Fig 10. Release of Aloe vera from Produced Nanofibers in PBS Solution within 30 Hours under Sink Conditions

According to the obtained results, 42% of the loaded *Aloe vera* was released after five hours of measurement. In addition, the burst effect was followed by a sustain release within 30 hours. Increasing the concentration of *Aloe vera* was observed to enhance the release from the nanofibers, which could be due to the fact that *Aloe vera* was encapsulated in the nanofiber matrix. On the other hand, increasing the concentration of Aloe vera reduced the polymer ratio, thereby leading to the faster and higher release of the encapsulated *Aloe vera*.

Results of mechanical measurement

Mechanical strength is a determinant of the nanostructures developed for biomedical applications. For biomedical applications, nanofibers should be soaked in order to apply the desired effects. In the present study, the tensile strength of the fabricated nanofibers was measured in the dry and soaked forms (Fig 11).

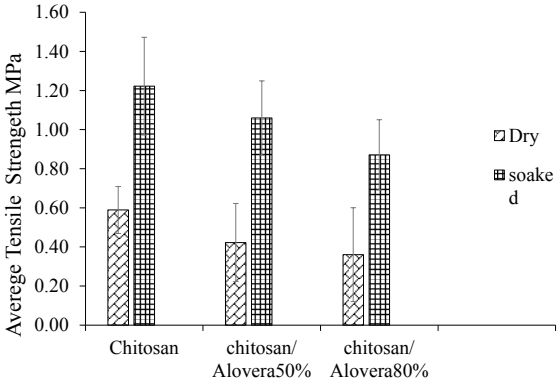

Fig 11. Tensile Strength of Fabricated Nanofibers in Dry and Soaked Forms

As is depicted in Fig 11, increasing the concentration of *Aloe vera* reduced the average tensile strength of the nanofibers, so that the highest tensile strength was obtained with pure CS, while 80% *Aloe vera* exhibited the lowest tensile strength. Moreover, the obtained data indicated that the soaking of the nanofibers in water increased the tensile strength in every nanofibrous mat.

The increment in the tensile strength could be attributed to the enhanced fibril-fibril bond in the soaked nanofibers [24]. This finding is consistent with the study by Rigumula Wu et al. [25], which demonstrated that the maximum stress for wetted mesh increased by more than 1.0 MPa. In another study, Kasinee Prakobna et al. [24] concluded that the soaking condition enhanced the mechanical properties of nanofibers.

Cell viability findings

The cell viability of the fibroblast cells that were seeded on the nanofibers was measured using the MTT assay on days one, three, and seven after the seeding of the cells (Fig 12).The proliferation of the cells on the fabricated nanofibers was measured, and the obtained results indicated that the nanofibers loaded with the *Aloe vera* extract had higher growth rates at three intervals compared to

the control and pure polymer groups. As is shown in Fig 12, the highest cell growth rate was observed in CS/PEO/80% *Aloe vera*, which indicted positive effect of the extract on cell proliferation.

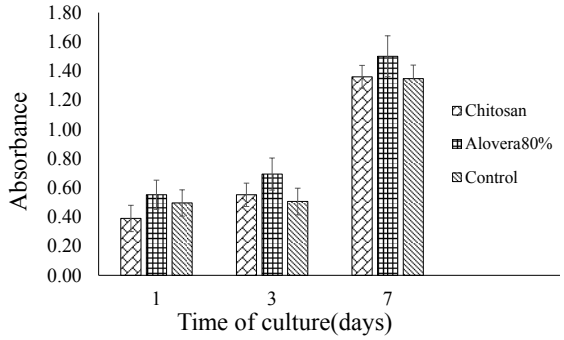

Fig 12. Cell Proliferation Assay Histogram Measured by MTT Assay after One, Three, and Seven Days Cell Seeding (Values expressed as mean±SD; n=3; *P<0.005)

This finding is in line with the previous studies in this regard. For instance, Elahe Zahedi et al. [26] fabricated core-shell nanofibers containing *Aloe vera* extract, reporting the positive effects of the herbal extract on cell attachment and proliferation. In another study, Princeton Carter et al. [27] fabricated PCL nanofibers loaded with *Aloe vera* extract for guided tissue regeneration, denoting the proliferative potential of the extract-loaded nanofibers.

CONCLUSION

In the current research, an electrospun nanofibrous platform of CS/PEO containing *Aloe vera* extract was fabricated for biomedical applications. The CS/PEO nanofibers were successfully fabricated, and the *Aloe vera* extract was incorporated into the prepared nanofibers. In addition, electrospinning was used to fabricate the scaffold, and the involved parameters (applied voltage and nozzle-to-collector distance) were optimized.

According to the results, the pure *Aloe vera* extract could not produce nanofibers, while reducing the concentration of the extract to 92% resulted in the formation of nanofibers. Moreover, decreasing the concentration of the extract increased the diameters of the nanofibers. The results of the optimization of the parameters indicated that increasing the applied voltage from 18 to 22 kV increased the diameters of the nanofibers and vice versa, while increasing the nozzle-to-collector distance reduced the diameters.

The results of FTIR spectroscopy confirmed the presence of each component in the prepared scaffold. Furthermore, the obtained data on release demonstrated a burst release, followed by a sustain release within 30 hours. The cell proliferation evaluation also confirmed the positive effect of the *Aloe vera* extract on the growth of the sutured cells. In conclusion, the nanofibrous scaffold containing the *Aloe vera* extract could be successfully fabricated and could be used for various biomedical applications, such as wound dressing materials, skin tissue engineering, and topical drug delivery.

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