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Research Article

Optimization of Dendrimer Polyamidoamin Electrospun Nanofibers: Preparation and Properties

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Background: The most common polymers in the treatment of wounds are natural (e.g., polysaccharides, proteins, and peptides) and synthetic polymers (e.g., poly-glycolic acid, polyacrylic acid, polylactic acid, and polyvinyl alcohol) due to their biodegradability, biocompatibility, and their structural resemblance to the macromolecules known to the human body.
Objectives: The current study aimed to develop an electrospinning method using the nanofibers of polyvinyl alcohol (PVA)/ carboxymethyl cellulose (CMC)/polyamide amine (PAMAM)/tetracycline (Tet) to cover the wound. The antibacterial effect of PAMAM was also tested against *E. coli* and *S. aureus* bacteria.
Materials and Methods: The morphology of the composite nanofiber was studied by a field emission scanning electron microscope. Infrared spectroscopy (FTIR) was used to characterize the nano chemical structure.
Results: Nanofibers were evaluated based on the release of different amounts of the antibiotic tetracycline (1%, 3%, 5%, and 7% by weight) while preventing wound infection. The findings indicated that the highest-profile release of all nanofibers occurred early within 12 hours. It was found that nanofiber membranes loaded with 1%, 3%, and 5% tetracycline released drugs for over 28 days, while those containing 7% tetracycline released drugs for more than 14 days.
Conclusions: According to the findings related to the drug release of PVA/CMC/15% PAMAM/Tet and surface morphology of the nanofibers, the optimal amount of Tet was 5%. The results of FTIR spectroscopy indicated that the tetracycline and polyamidoamine were successfully placed in nanofibers.

Keywords: Dendrimer polyamide amine, Drug release, Nanofibers wound dressing, Polyvinyl alcohol, Tetracycline

1. Background

Wound dressings can be of significant help to promote patients' health and their healing process since unattended wounds could result in the incidence of serious complications ranging from different types of infections to even death. To date, nanomedicine has contributed to great advancements in the areas related to wound healing as its materials are able to imitate the natural dimensions of tissue (1).

Complete wound evaluation involves the extent of the wound, its associated attributes, host factors influencing its status, and environmental factors impacting optimum wound management (2). In this regard, there is a large number of studies addressing different biological and physiological stages involved in wound healing, which can be divided into five sequential phases of hemostasis, inflammation, migration, proliferation, and maturation (3).

Currently, to improve the healing process, various kinds of wound dressings have been developed to create a moist environment and lead to cell adhesion and proliferation. These wound dressings are biodegradable and non-toxic, absorb wound exudates, impede dehydration of the patient, and prevent the formation of eschar.

Wound dressings that consist of electrospun nanofibers have auspicious properties that enhance the healing process (4). Liakos *et al*. employed electrospinning to produce nanofibers made of cellulose acetate (CA) and essential oils (EOs). The results indicated the successful formation of CA electrospun fibers but inadequate biological activity (i.e., antibacterial activity) of such microfibers (5). In another study performed by Zhou *et al*., the successful utilization of the electrospinning of aqueous maleilated chitosan/methacrylated Polyvinyl alcohol (MCS/MPVA) solution and photopolymerization resulted in obtaining photocrosslinked MCS/MPVA bicomponent nanofibrous scaffolds, suitable to enhance the water stability of hydrophilic nanofibers (6). Deling Kong *et al*. combined electrospun poly (ε-caprolactone) (PCL) nonwoven mat with chitosan-based nitric oxide-releasing biomaterials (CS-NO). The findings indicated the good stability of PCL/CS-NO dressing under physiological conditions. The utilization of this dressing demonstrated that the sustained release of NO could speed up wound healing. More importantly, tissue regeneration was optimal at the epidermal-dermal junction and resembled those of native tissues. (7). Furthermore, in a study conducted by Morsy *et al*., novel antibacterial electrospun gelatin-based mats were fabricated for wound dressing application. The obtained results were suggestive of the strong antibacterial capacity of these electrospun gelatin-based fibrous mats against *S. aureus* and *E. coli* bacteria which means that they are suitable wound dressings (8).

2. Objectives

With this background in mind, the current study aimed to delineate the effects of practicing nanofiber wound dressings of polyvinyl alcohol/polyamidoamine dendrimers containing tetracycline and its basic properties. This study was thus motivated to investigate the optimal amount of polyamide amine dendrimer in the combination of polyvinyl alcohol and carboxymethyl cellulose by antibacterial properties as well as the optimal amount and release of tetracycline. The combination of three polymers PVA/CMC/PAMAM can be used in the fields of tissue engineering and drug delivery due to their compatibility with the human body.

3. Materials and Methods

3.1. Materials

Polyvinyl alcohol (PVA) and carboxymethylcellulose (CMC) were obtained from Merck Co., Germany. PAMAM dendrimer (3rd generation, 20% w/w methyl methacrylate and tetracycline antibiotic) was purchased from Sigma-Aldrich, Germany.

3.2. Preparation of PVA/CMC/PAMAM Nanofibers

To begin the study, two solutions were prepared; one from 7% w/w of carboxymethyl cellulose (CMC) in deionized water and the other from 8% w/v of polyvinyl alcohol (PVA) in deionized water. An electroporation solution of composite nanofibers was obtained by mixing the two solutions with a ratio of 20:80 (CMC/PVA) (9). In the next stage, different amounts of polyamide and amine dendrimers (0, 1, 5, 10, 15, 20, and 25, wt%) were added to the electrolytic solutions. To obtain a homogeneous mixture, the mixing process was performed at room temperature for a period of 6 hr by a magnetic stirrer.

With regard to the viscosity of the solution, an electric operation within the voltage range of 16-23kV was performed using a Gamma High Voltage Research RR60 device on an aluminum layer as a collector. The needle gap was adjusted to 16 cm collector and the polymeric feed rate was 1.2 mm/hr. After the fiber was prepared, a thermal phase was carried out for 1 hr at 130 °C to create a cross-linking effect on the nanofibers. In the area, C = O in amide dendrimers and amide bonds in carboxymethyl cellulose made cross-linking bonds in nanofibers.

Electrolyzed PVA/CMC/PAMAM nanoparticles were selected according to the antibacterial properties of the nanoparticles. The PAMAM was selected at its optimal percentage. Afterward, an optimum electroporation solution was prepared. After complete mixing of both the polymer and the dendrimer, different amounts of tetracycline antibody (Tet; 0, 1, 3, 5, 7, and 9% w/w) were added to the solution for 2 hrs. Subsequently, solutions at the voltage range of 16-23 kV were converted to fiber by a resin viscosity using a Gamma High Voltage Research RR60 device on an aluminum layer. The needle gap was adjusted to 16 cm collector and the polymeric feed rate was 1.2 $mm.hr^{-1}$.

3.3. Fourier Transformed-Infrared (FT-IR) Spectroscopy

The FTIR spectra of nanofiber were used to identify functional groups by the Infrared Fourier Transform

spectrometry (ThermoNicolet NEXUS 870 FTIR from Nicolet Instrument Corp., USA).

3.4. Electron Beam Microscope FESEM

The surface morphology of all nanofibers was examined by a field emission scanning electron microscope (FESEM, the Sigma model of Zeiss, Germany). Before the analysis, the sample was coated with a layer of Au under vacuum conditions. Moreover, the nanofiber-forming elements were determined by the X-ray energy dispersive microanalyzer (EDS, Oxford Instruments, UK).

3.5. Antibacterial Test

The antimicrobial activity of nanofiber wound dressing was examined against two bacteria, namely Staphylococcus aureus (*S. aureus*, American Culture No. 6,538) as a gram-positive bacterium and Escherichia coli (an American Culture Culture No. 11303) as a gram-negative.

For this purpose, a colony of bacteria was transferred to a physiological saline solution (9% NaCl in distilled water at pH 6.5) at a concentration of 0.5 (unit) Mc Farland at a temperature of 37-23 °C centrifuging at 220 rpm for 2 hrs. The homogenous suspensions prepared from bacteria were divided into 5 parts (dilution 1:100,000), and a concentration of about 1.5-2 × 103 $CFU.mL^{-1}$ was used for antibacterial examinations. The bacteriological tubes (e.g., 125 × 17 mm glass tubes) that contained PVA/CMC/PAMAM (10 × 10 mm) nanofibers were sterilized using thermocouples (121 °C and 15 Ib) autoclave for 20-15 minutes. In the next stage, 1 cc of the bacteria suspension and 2 ccs of TSB (Tryptic Soy Broth) were added to each tube and the volume of each tube was adjusted to 3 mL.

In order to ensure that any reduction in bacterial volume was due to PVA/CMC/PAMAM nanofibers, two control groups were used. One of them received the salt solution with TSB and the other one received the PVA/CMC nanofibers containing PVA/CMC/PAMAM nanofibers with bacterial suspensions. The investigated bacteria and control tubes were placed at 37 °C for 24 hr. Afterward, 10 µL of the sample was removed from each tube and counted using the method of placement in the plate. Therefore, the samples were melted in agar (which has been reduced to 45 °C) and mixed with suspension bacteria. The plate was placed at 37 °C for 24 hrs, and the colonies of each plate were counted by a colony count to ascertain the reduction of suspension bacteria.

The pre- and post-operation results of nanofibers were analyzed to examine the antibacterial effects and the reduction percent of bacteria using the following equation:

Here, R is the ratio of bacterial reduction, A denotes the number of bacterial colonies of PVA/CMC nanoparticles, and B refers to the number of PVA/CMC/PAMAM nanofibers bacterial colonies.

3.6. Thermogravimetric Analysis

Thermogravimetric analysis (TGA) was performed on a Perkin Elmer thermoanalyzer (Pyris diamond SII). In every case, 5 mg of the sample was tested under N_2 gas at a heating rate of 5 °C/ min from 50-600 °C.

3.7. Studies on Antibiotic Release

The antibiotics of tetracycline were tested in PVA/CMC/PAMAM/Tet nanofibers to evaluate the drug release profile at pH 7.3, phosphate buffer solution (PBS). In this regard, 40 mL of each of the nanowire membranes were moved into a dialysis bag and immersed in 250 mL of PBS at 37 °C with gentle shaking. At pre-planned time points, PBS was removed with a pipette and replaced with PBS. The amount of Tet release in solution was determined by a UV-vis spectrophotometer at 359 nm (10).

4. Results

4.1. Antibacterial Properties of Nanofiber Wound Dressings

The antibacterial activities of PVA/CMC/PAMAM nanofibers against Gram-negative bacteria *E. coli* were investigated in the current study (**Fig. 1A -Table 1**). The obtained results showed that the number of bacteria on the samples containing 1%, 5%, 10%, and 15% of dendrimers significantly reduced after 3 hrs. The same was true for the samples containing 20% and 25% of dendrimers. Although there was no specific mechanism for antibacterial activity on PAMAM dendrimers, this process was probably due to the electrostatic absorption of a negative bacterium by polycation dendrimers, after which the cytoplasmic membrane of the bacterium was disrupted by amine groups (11). Regarding, the antibacterial activity of PVA/CMC membrane, the results indicated that the membrane had an activity of

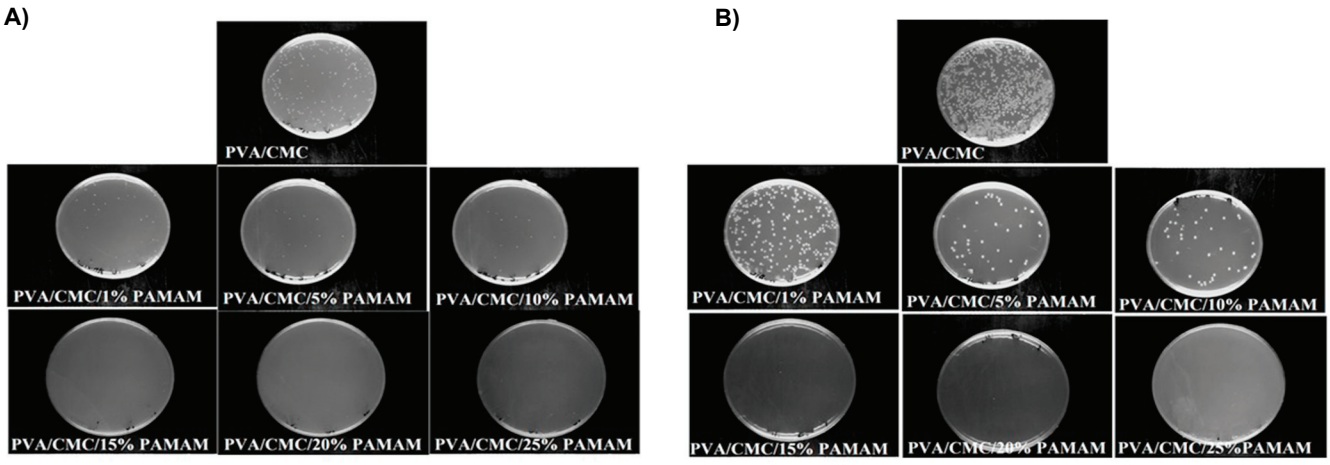

Figure 1. Antibacterial test results of different nanofiber wound dressings against Gram-negative bacteria; **A)** *E. coli*, **B)** *S. aureus*

Table 1. Antibacterial test results related to *E. coli* and *S. aureus* bacteria

	E. coli bacterial	**S. aureus bacterial**
sample	**Reduction Percent**	**Reduction Percent**
PVA/CMC	33.75%	22.10%
PVA/CMC/1% PAMAM	55.53%	38.13%
PVA/CMC/5% PAMAM	62.90%	50.70%
PVA/CMC/10% PAMAM	77.13%	64.53%
PVA/CMC/15% PAMAM	87.40%	79.20%
PVA/CMC/20% PAMAM	87.61%	79.61%
PVA/CMC/25% PAMAM	88.03%	80.23%

33.75% based on the weak antibacterial properties of CMC (10). The CMC is a highly significant derivative of cellulose; it is non-toxic and has high chemical stability. Nevertheless, because of its weak antimicrobial activity and low mechanical strength, it cannot be used as a successful wound dressing agent. Therefore, the mixture of CMC with antimicrobial agents and drugs is necessary for controlling and sustaining the release of antimicrobial agents that impede bacterial growth in wounds and improve the healing process (12).

As shown in Figure 1b and **Table 1**, there was a significant reduction in the number of bacterial colonies although dendrimers can not kill all bacteria. Therefore, with the increase of PAMAM levels after 3 hrs, antibacterial activity increased, compared to the control sample.

Based on the obtained data, PVA/CMC/15% PAMAM nanoparticles were considered desirable, and further analyses were performed on this sample.

4.2. Examination of the Antibiotic Release Performance of Nanofiber Wound Dressings

The tetracycline release profile of fibrous nanofibers was studied in phosphate buffer (pH = 7.3) at 37 °C as an antibiotic in PVA/CMC/PAMAM composite nanofibers. The amount of antibiotic release from nanofibers was measured for 28 days (**Fig.3**) indicating the highest levels of release during the initial 12 hours. Fiber membranes that contained 1%, 3%, and 5% by weight tetracycline released drug for over 28 days, while those containing 7% tetracycline released drug for up to 14 days.

The drug release in the first 12 hours was about 35%, 70%, 85%, and 90% in PVA/CMC/15% PAMAM/1%

Tet, PVA/CMC/15% PAMAM/3% Tet, PVA/CMC/15% PAMAM/5% Tet, and PVA/CMC/15% PAMAM/7% Tet, respectively.

The increase of tetracycline led to the placement of more drug molecules on the surface of the nanofibers and its faster release behavior (**Fig.2**). Due to the dissolution of tetracycline in the environment, brittle nanoparticles were porous and porous, which was faster in samples with higher tetracycline levels. Since its release of tetracycline was controlled by the penetration of water and the drug into the fiber, its release was 28 days in nanofibers that contained 1%, 3%, and 5% by the weight of the drug and over 14 days for the nanofibers that contained 7% w/w (**Fig. 2**).

4.3. Composite Nanofibers Morphology

As can be seen in **Figure 3**, the morphology of composite nanofibers was indicative of uniform and apart patterns, which was supported by other studies as were similar to the pure PVA nanofibers (9).

On the basis of the antibacterial test of different nanofibers, PVA/CMC/15% PAMAM was selected as optimal. According to the nano life image (**Fig. 4**), it had a soft and smooth surface, and the mean diameter of the nanofibers was about 100 nanometers. According to the adhesion images between nanofibers, especially at the intersection of the fiber, cross-coupling between the polymer chains and the dendrimer molecules can be observed.

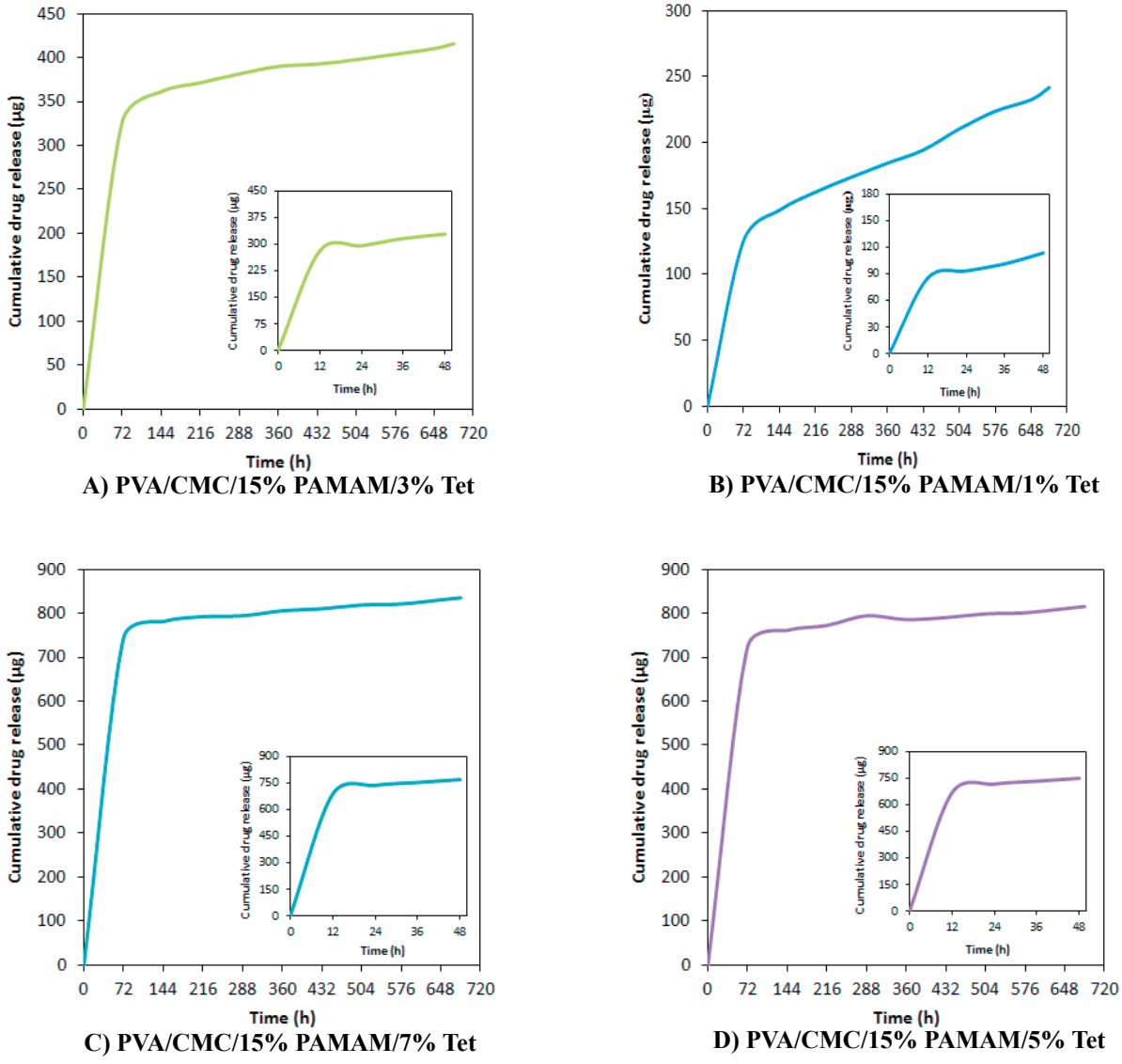

Figure 2. Profile of tetracycline release from various nanofiber wound dressings. **A)** PVA/CMC/15% PAMAM/3% Tet, **B)** PVA/CMC/15% PAMAM/1% Tet, **C)** PVA/CMC/15% PAMAM/7% Tet, **D)** PVA/CMC/15% PAMAM/5% Tet.

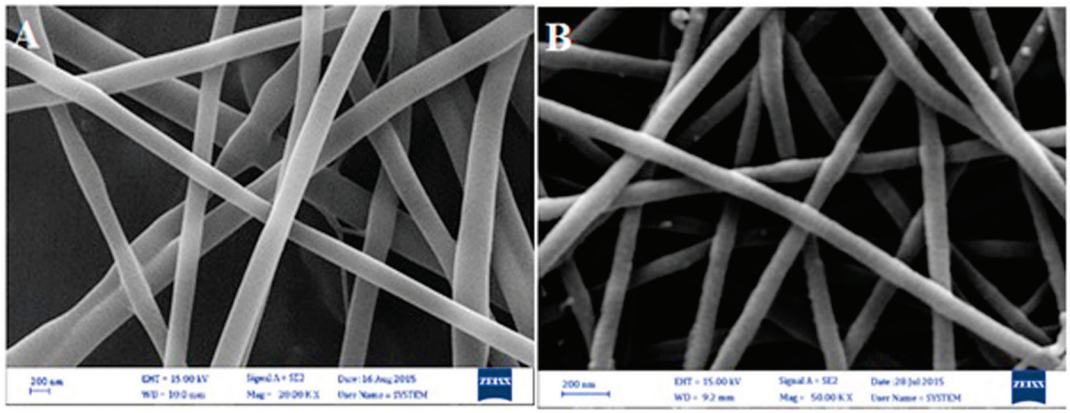

Figure 3. FESEM (A) PVA and (B) PVA/CMC composite nanofibers

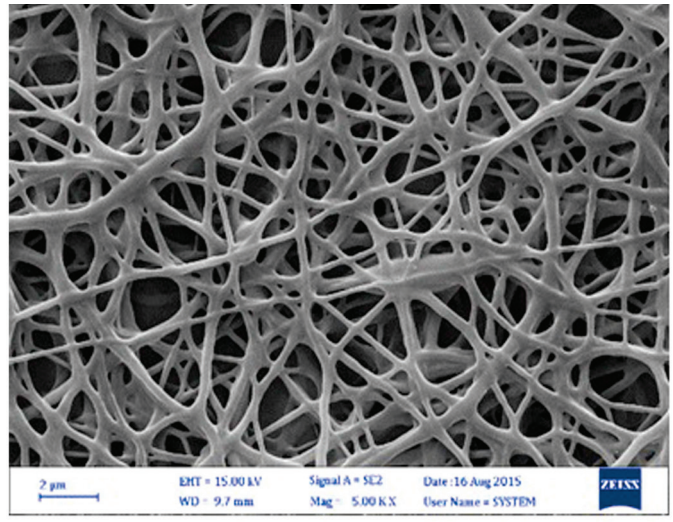

Figure 4. FESEM composite nanofibers PVA/CMC/15% PAMAM

According to **Figure 5**, the observed electrolytic fibers on the nanofiber surface contained 1%, 3%, and 5 wt% Tet without waders with a smooth and soft surface, and no Tet particles, which confirmed a good mixing of Tet with polymer and dendrimer in an electrolytic solution. In a sample of 7% Tet nanofibers, there were defects such as willow and cornice seed. It should be noted that nanofibers containing 9 wt% Tet were not produced due to the lack of uniform spinning solution and high concentrations of solution.

Based on the results of the nanomaterial release of the PAMAM/Tet PVA/CMC/15% and the surface morphology of this nanofiber, the amount of 5% by weight of Tet was optimal.

4.4. FTIR Analysis

Figure 6 shows various produced nanofibers. In the PVA/CMC spectrum, the absorption band of 3413 cm^{-1} was attributed to the vibrational tensile strengths of hydroxyl groups in polyvinyl alcohol and carboxymethyl cellulose. The absorption band of 1735 cm^{-1} was related to the tensile vibrations of C=O in the PVA-static groups. Furthermore, the tensile vibrations of CH in the main chain of polymers appeared in 12940 cm^{-1} (13). The strong absorption bar attributed to cm^{-1}- 1096 and 848 referred to the tensile vibrations of C-O in the main chain and C-O in alcoholic groups, respectively. After depositing a dendrimer in the nanofiber structure, the appearance of two absorption bands at 1676 and 1568 cm^{-1} was observed for the tensile vibrations of C = O in amide dendrimers and amide bonds, respectively, after cross-linking with carboxymethyl cellulose and the bending vibrations of the amine groups (14). After

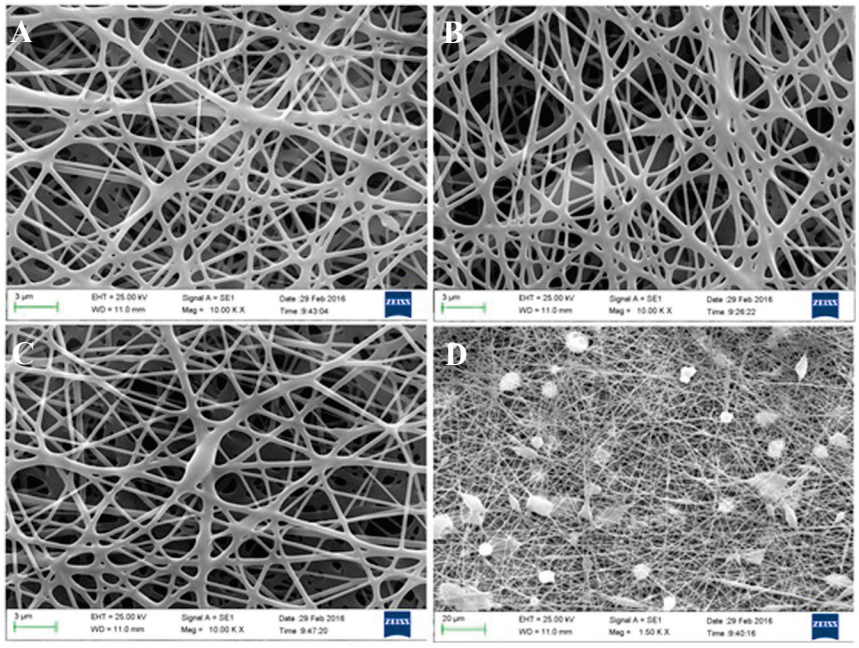

Figure 5. FESEM images of composite nanofibers **A**) PVA/CMC/15% PAMAM/1% Tet, **B**) PVA/CMC/15% PAMAM/ 3% Tet, **C**) PVA/CMC/15% PAMAM/5% Tet, and **D**) PVA/CMC/15% PAMAM/7% Tet

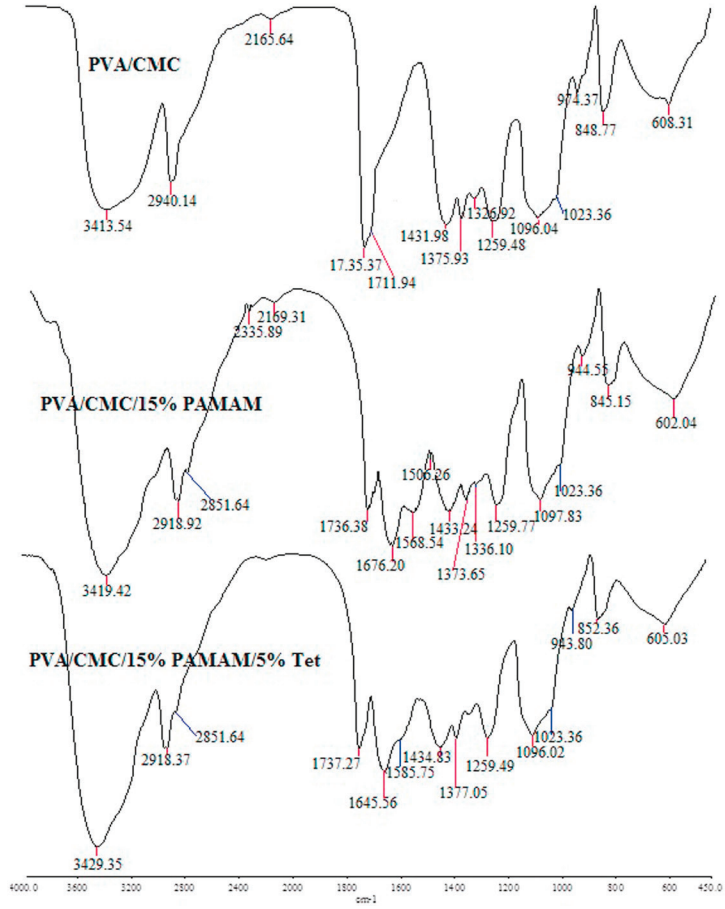

Figure 6. FTIR images of different composite nanofibers

the addition of antibiotics, the infrared spectrum did not change significantly, compared to other spectra, except for an increase in the absorption band intensity of 3429 cm^{-1} resulted from the tensile vibrations of hydroxyl groups.

4.5. Thermal Analysis

The TGA curve for the nanofibers provided is indicated in **Figure 7**. The PVA/CMC nanoparticles demonstrated a decrease of 8.5% up to 100 °C. Weight loss at this stage was caused by the physical elimination of absorbed water molecules in nanofibers. Afterward, the weight loss process continued and the weight loss at 300 °C reached 73%. At this temperature, the amount of weight loss resulted from the chemical removal of water molecules from the structure and the initiation of the polymeric chain destruction. After placing the dendrimer molecules in the nanofiber structure, the weight loss rate was reduced to 300 °C. This reduction was due to the crackling of polymer chains after the presence of PAMAM and thermal treatment. However, after placing antibiotics in the structure, the weight loss dropped to below 300 °C, which was lower than that of PAMAM. This phenomenon was due to the interactions between antibiotics and polymer chains.

5. Discussion

The current study aimed to examine PVA/CMC/PAMAM/Tet laminated nanofibers with a soft and smooth surface using the electrothermal method.

Lower antibacterial activity of nanofiber against *S. aureus* in comparison with *E. coli* bacterium, it can be stated that for the gram-negative *E. coli*, a thin membrane consisting of a thin paraben side plasmid was surrounded by a negative external membrane causing dendrimer attachment and disrupting the cell. In contrast, the gram-positive bacterial membrane of *S. aureus* consisted of a thick and coarse peptidoglycan layer; therefore, its harder activity was impaired by the dendrimer.

Dendrimers are synthetic polymers identified by branched repeating units that appear from a focal point and have a high number of exposed anionic, neutral, or cationic terminal functions on the surface that lead to hydrophilic or hydrophobic compounds. They are radially symmetric, globular, mono-dispersed, and homogenous nanometric molecules. The characteristics of dendrimers vary from the conventional polymers. Nanomedicine research has made use of dendrimers because of their size. They can be used a delivery or carrier systems for medications and genes; however, research has revealed that some dendrimers have medicinal usages of their own, mainly because of their antifungal, antibacterial, and cytotoxic features. The advantages of many drugs can not be used due to their solubility, toxicity, or stability problems. Usage of dendrimers as carriers of these compounds is able to resolve such issues, and thereby enhance their clinical applications (15).

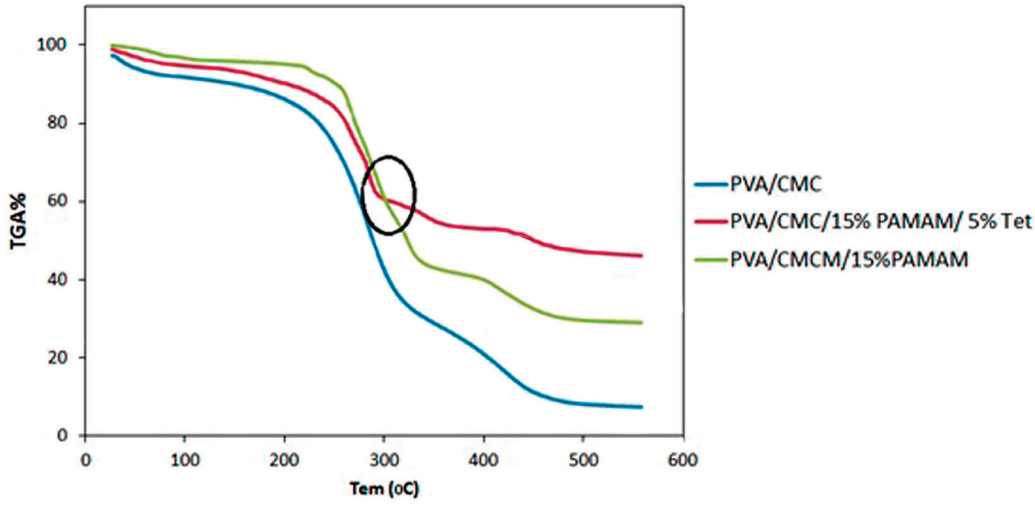

Figure 7. TGA curves of different composite nanofibers

An ideal dressing with effective antimicrobial properties should maintain a long-term controlled drug release to avoid frequent dressing and accelerate the treatment process. The use of tetracycline as an antibiotic in the current study indicated rapid dissolution of tetracycline on the surface of nanofibers leading to its early release. The release of the drug slowed down after its early release, it lasted for a period of time since the nanofibers were not significantly degraded in a month (16). It should be noted that the primary concentration of tetracycline to eliminate invasive bacteria was important prior to the onset of proliferation to prevent postoperative infection, and it was essential to continue antibiotic release in order to prevent accumulation (17). Considering the morphology of composite nanofibers, the findings showed that the amount of adhesion in the nanofibers increased with the addition of antibiotics. Additionally, some parallelism was found in the fiber diameter after the addition of antibiotics (9). Moreover, when the organic matter was dispersed in a suitable solution of a polymer solution, the produced nanofibers are usually smooth with a uniform size (18) which confirmed the soft and smooth morphology of PVA/CMC nanofiber.

The thermal analysis of PVA/CMC nanofibers indicated the weight loss of this nanofiber due to the removal of the physicochemical properties of water. After dendrimer plunging, weight loss was lower than PVA/CMC nanofibers.

6. Conclusion

The current study aimed to examine PVA/CMC/PAMAM/Tet laminated nanofibers with a soft and smooth surface using the electrothermal method. The obtained results showed that dendrimers had a better anti-bacterial property against gram-negative bacteria due to the electrostatic absorption of negative bacteria and positive charge dendrimers. Accordingly, nanofiber PVA/CMC/15% PAMAM was selected as the optimum for performing other analyses. Given the results of the nanomaterial release of the PVA/CMC/15% PAMAM/Tet and the surface morphology of this nanofiber, the amount of 5% by weight of Tet was optimal.

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