Fabrication of Nanocomposite Scaffolds Including Metal Nanoparticles for Tissue Engineering Applications

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Abstract: This study presents the findings of a research on fabricating composite nanofibrous mats including silver and copper nanoparticles for tissue engineering applications. For this purpose, two different types of silver nanoparticles (soluble starch capped silver nanoparticles, sodium alginate capped silver nanoparticles) and two different types of copper nanoparticles (soluble starch capped copper nanoparticles, sodium alginate capped copper nanoparticles) were successfully incorporated into polyvinyl alcohol (PVA) fibers through electrospinning process. Characterization studies with x-ray diffraction (XRD), scanning electron microscope (SEM) and Fourier transform infrared spectroscopy (FTIR), inductively coupled plasma spectrometer (ICP) were conducted to determine physical and structural properties of the obtained nanofiber mats. According to SEM analysis it was observed that interconnected and randomly-oriented nanofibers were successfully generated. Additionally, XRD and FTIR studies proved the existence of silver nanoparticles and hydroxapatite on the nanofiber mats immersed in simulated body fluid (SBF) for 7 days. The results indicated that long term silver ion release was achieved. Overall results showed that these nanofibrous mats can be good candidates as multifunctional scaffolds for tissue engineering applications.

Keywords: Polyvinyl alcohol, electrospinning, nanocomposite, silver nanoparticles, copper nanoparticles.

1. INTRODUCTION

In recent years, organ transplantation request is ascending because of the increase in population in the world. This necessity can be achieved more effectively by the aid of tissue engineering applications. Tissue engineering is very interesting in the light of the fact that it is a developing and rapidly growing field. One of the most important goals in tissue engineering is to develop biosimilar structures to repair, replace or recover harmed or missing tissues or organs [1-3]. It is an interdisciplinary field that applies principles of engineering and life sciences to create natural substitutes like cartilage, skin and bladder, aiming to restore, maintain and improve tissue function or an entire organ [4]. The designed tissue can be grown both inside the patient like cartilage tissue or outside the patient like liver tissue. With the assistance of these primary strategies, tissues or organs of patients are recovered in a biocompatible, biofunctional, immunologically compatible and easily favorable manner [4, 5].

Due to their size, surface area and morphology, nanomaterials show unique thermal, optical, and electrical properties in comparison with their macroscopic and bulk counterparts [6, 7]. Therefore, they have been used in many technological and environmental applications such as water treatment, energy conversion, physics, chemistry, catalysis, sensors, materials science, and bioanalytical medicine [6-8]. Especially, nanotechnology has a crucial part in biotechnology and medication with purpose to create portable, relatively inexpensive, reliable, and available technologies [9]. One of these technologies involves three-dimensional biomimetic nanofiber preparation with utilizing electrospinning, phase separation, freeze drying, and self-assembly. The architecture of unique extracellular matrix at nano-scale dimension can be copied by these scaffolds [10]. Among the production methods of nanofibers, electrospinning is the most widely used method. With this strategy, it is a conceivable to produce nanofibers with various diameters ranging from a few microns to 100 nm or less [11].

In a typical electrospinning process, polymer solution is placed in a syringe and electrically charged jet, which is generated by high voltage differences between the syringe needle and a grounded collector, is used to fabricate fibers [6,12]. As the polymer solution is exposed on the tip of needle, the electrical charges on the polymer solution promotes its stretching, which eventually forms ultrafine fibers. During this process, the solvent associated with polymer evaporates immediately and forms a dry polymer fiber that travels in a chaotic pattern and gets deposited on the grounded collector [12]. Additionally, natural polymers, synthetic polymers and polymers containing nanoparticles, metals and ceramics are suitable for this method [13].

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Nanofiber composites produced by using nanoparticles are more effective than larger scale modification of materials and in biomedical field nanoparticles are preferred to produce excellent medical products [14]. The addition of antimicrobial agents to electrospun nanofibers brings advantage to prevent bacterial colonization and infection [15]. In the last decade, metal nanoparticles have drawn attention as antimicrobial agents due to their low toxicity, chemical stability and long lasting period thermal resistance [12,16-18]. Among metal nanoparticles, silver (Ag) and copper (Cu) nanoparticles are very attractive in nowadays [19]. The strongest antibacterial activity is seen in silver within all metal nanoparticles. For this reason, silver nanoparticle covered surfaces can be utilized in cosmetics, textiles, and medicines [20]. As in Ag nanoparticles, Cu nanoparticles have also exhibited dimensional-dependent antibacterial action with low toxicity and good stability that can be used to improve the quality of biomaterials [21]. On the other hand, this metal, which is one of the trace components found in various cells and tissues, works as a cofactor for the structural and catalytic properties of enzymes. Specifically, copper takes a key part in improving bone formation and healing and it functions as a cofactor in metabolic processes including bone, articular tissues and immune system processes. Noteworthy visible cell copper distributions have been found in human endothetial cells, when they have undergone angiogenesis showing this ion as a significant angiogenic agent. For this reason, new bioactive multifunctional materials can be created by using copper [22].

Polymeric fibers including Ag nanoparticles have been widely utilized for biomedical applications with the use of different polymers such as cellulose acetate, poly (acrylonitrile) poly (Ɛ-caprolactone), polymethyl methacrylate), poly (vinyl alcohol), and polyimide [12, 16, 23]. In comparison with Ag nanoparticles, Cu nanoparticles have been less studied because of its ease oxidation, although they show a significant promise as a bactericidal agent [24].

Polyvinyl alcohol (PVA) is a semi-crystalline, hydrophilic polymer with chemical and heat resistance. This polymer is biodegradable in physiological environments and its mechanical properties are comparable with soft tissues [13, 25]. The hydrolysis products of PVA are harmless to animals which make it a good polymeric material for tissue engineering applications [13]. Electrospinning of PVA solution and preparation of tissue engineering applications including wound dressing, bone tissue, muscle tissue, cardiac tissue, vascular tissue and nerve tissue have been reported by many researchers [26-34]. In this context, emphasis has been placed on investigation the incorporation of biopolimer capped silver and copper nanoparticles in PVA nanofibrous mat. To the best of our knowledge, this study is the first report that introduces biopolimer capped silver and copper nanoparticles into polyvinyl alcohol matrix to develop a composite material by electrospinning technique.

2. MATERIALS AND METHODS

2.1. Materials

Polyvinyl alcohol (PVA, 95.5-96.5 % hydrolyzed, 85000-124000) was obtained from Acros. Glutaraldehyde (GA, 50 wt % in H_20) was supplied from Sigma Aldrich. Acetone was purchased from Merck. All chemicals were used as provided without further purification. Other than these materials, deionized water was used in order to prepare solutions

2.2. Preparation of Electrospinning Solutions

PVA (8 % wt/vol) was prepared in deionized water at 85°C with constant stirring for 4 h. Two different electrospinning solutions were prepared separately. Firstly, the soluble starch capped silver nanoparticles (S-Ag) and the soluble starch capped copper nanoparticles (S-Cu) with particle sizes of 21 nm and 62 nm, respectively were added to 1 wt% of PVA solution. The second solution contains the sodium alginate capped silver nanoparticles (A-Ag) and the sodium alginate capped copper nanoparticles (A-Cu) with sizes of 24 nm and 51 nm, respectively at 1 wt% of PVA solution.

2.3. Electrospinning

As prepared solutions were loaded into a syringe and, they were fed from the syringe to a needle tip at a controlled flow rate of 1.5 ml/h by a syringe pump. Electrospinning process was performed using an electrospinning device (Nanospinner 24 Touch, Inovenso Co.) under ambient conditions. Applied voltage was 31 kV. Electrospun fibers were accumulated on an aluminum foil wrapped around the grounded collector placed at a distance of 12.5 cm. After electrospinning process, the obtained nanofiber mats were placed in an incubator at 37 °C for overnight.

2.4. Cross-Linking Treatment

The nanofiber mats scratched from the aluminum foil were immersed in 5 wt % GA/acetone solution. Then the nanofiber mats were dried at 120 °C for 2 h to remove residual GA. The success of cross-linking treatment was checked by immersing cross-linked nanofibers in simulated body fluid (SBF) at 37 °C for 7 days.

2.5. Metallic Ion Release and Bioactivity Investigations

Briefly, small pieces of the cross-linked fibrous mats (around 10 mg) were soaked into the freshly prepared SBF (15 mL) in sterile polyethylene containers and were stored in an incubator at 37 °C for 7 days. The concentrations of silver and copper ions released into SBF were measured by using ICP.

2.6. Characterization of Nanocomposite Fiber Mats

The surface morphology and microstructure of the nanocomposite fiber mats before and after immersion in SBF were observed by using a scanning electron microscope (SEM, JSM-5410) operated at 20 kV. Prior to the SEM measurements, all of the samples cut from the fibrous mats were coated with platinum under vacuum for 120 s by using a SC7620 sputter coater (Quorum Technologies Ltd) in order to reduce electron charging effects. The mean fiber diameter of the electrospun fibers was measured by using Image J software (National Institute of Health, USA). The characteristic phases and possible crystallinity of the nanocomposite fiber mats before and after immersion in SBF were identified using an X-ray diffraction analyzer (XRD, Bruker™ D8 Advance) with Cu–Kα radiation. XRD patterns were acquired over a 2θ range from 10° to 60° with a step size of 0.01°. The functional groups of the nanocomposite fiber mats before and after immersion in SBF were investigated by Fourier-transform infrared (FT-IR) spectroscopy. FT-IR spectra were collected using a Perkin Elmer Spectrum 100 Model spectrometer in transmittance mode in the mid-IR region (4000–650 cm^{-1}). The release of therapeutic ions were measured as a function of immersion time in SBF with the aid of inductively coupled plasma–mass spectrometer (ICP-MS, Perkin Elmer Elan DRC-e).

3. RESULTS AND DISCUSSION

3.1. Surface Morphology of Fibrous Mats

The structural integrity of a scaffold is an important aspect for the determination of the proliferation, differentation, and long term survival of the cells in the scaffolds. PVA is a water soluble polymer, and electrospun fibers can partially dissolve or lose its fibrous form upon exposure to a high humidity ambient for a certain period of time. To overcome this issue, a cross-linking treatment by using GA was chosen. Figure **1** shows the microstructures of S-Ag/S-Cu containing nanocomposites before/after crosslinking and after immersion of cross-linked sample in SBF for 7 days. The mean fiber diameter of S-Ag/S-Cu containing nanofibrous mat was 119±34 nm **(**Figure **1a)**. After cross-linking treatment the mean diameter of nanocomposite mat was 130±36 **(**Figure **1b)**, showing that there is a slight tendency to increase at the mean diameter after GA treatment. However, it seems that the integrity of the structure was preserved after GA treatment. It can be observed that after 7 days immersion, crosslinked nanofiber structure was still protected proving the success of the crosslinking. Nevertheless, the fibers were swelled after 7 days immersion in SBF. The mean fiber diameter of this nanofibrous mat after 7 days SBF immersion was 182±54 nm. As in the S-Ag/S-Cu containing nanofibrous mat, the mean diameter of A-Ag/A-Cu

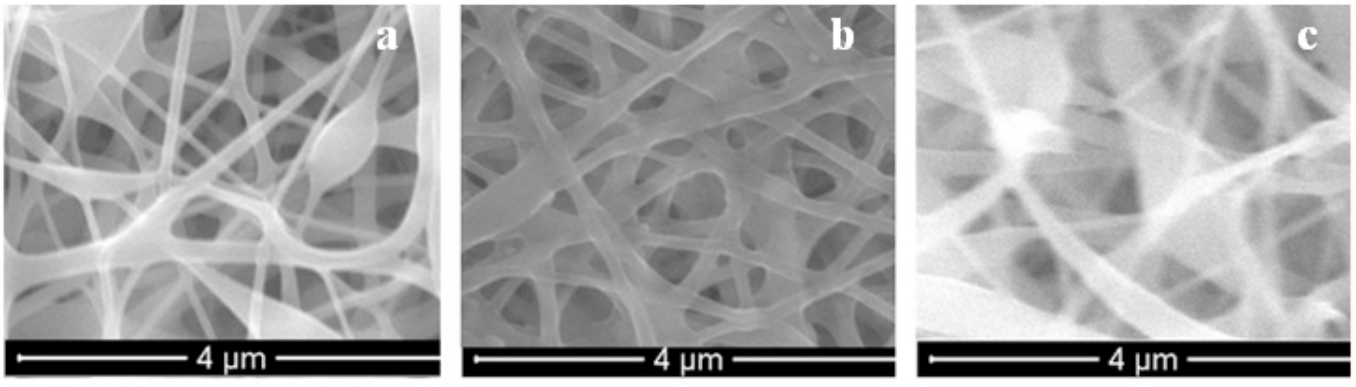

Figure 1: SEM images of S-Ag/S-Cu containing nanofiber composite mat: (**a**) before crosslinking, (**b**) after crosslinking, and (**c**) after immersion in SBF for 7 days.

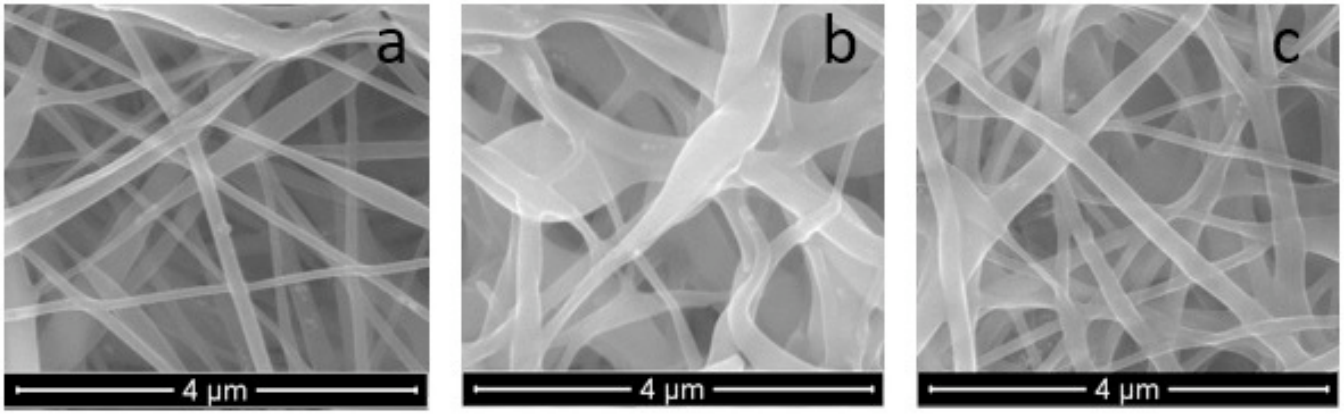

Figure 2: SEM images of A-Ag/A-Cu containing nanofiber composite mat: (**a**) before crosslinking, (**b**) after crosslinking, and (**c**) after immersion in SBF for 7 days.

containing nanofiber mat was found as 119±36 nm (Figure **2a**). However, after the glutaraldehyde treatment the mean diameter of the nanofiber mat was 213±91 nm (Figure **2b**). This significant increase in the nanofiber diameter indicates that the fiber diameter is influenced by cross-linking treatment as it was observed in starch capped metal nanoparticle containing mats. Additionally, some morphological defects at this nanofiber mat were observed due to the partial polymer dissolution. After being soaked in SBF for 7 days, this nanofiber mats' topography has been almost completely maintained. On the other hand, after soaking in SBF the mean fiber diameter was decreased. It was measured as 124±37 nm (Figure **2c**). The reason of shrinkage at the nanofiber mats may be due to the release of sodium alginate, which is water soluble polymer, from the nanofiber structure.

3.2. The Structure Analysis

XRD studies were conducted on nanocomposite mats to confirm the presence of metallic nanoparticles and the presence of hydroxyapatite phase after immersion of both nanofiber mats in SBF for 7 days (Figure **3** and Figure **4**). XRD patterns revealed strong

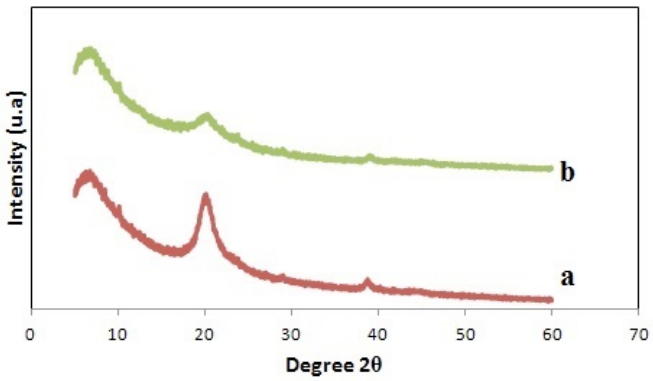

Figure 3: XRD patterns of S-Ag/S-Cu containing nanofiber composite mat: (**a**) before crosslinking, and (**b**) after immersion in SBF for 7 days.

crystalline reflections at around 2θ=19°-21°, which is the particular crystalline peak of PVA [35]. It was observed that after immersion in SBF the semi-

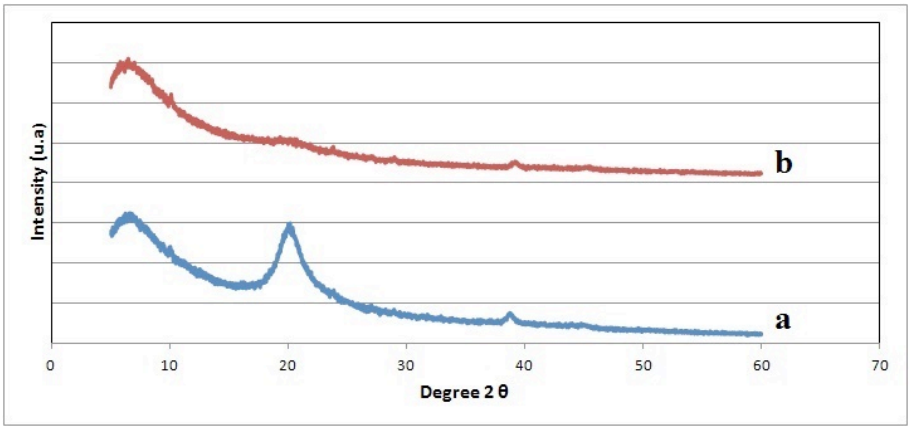

Figure 4: XRD patterns of A-Ag/A-Cu containing nanofiber composite mat: (**a**) before crosslinking, and (**b**) after immersion in SBF for 7 days.

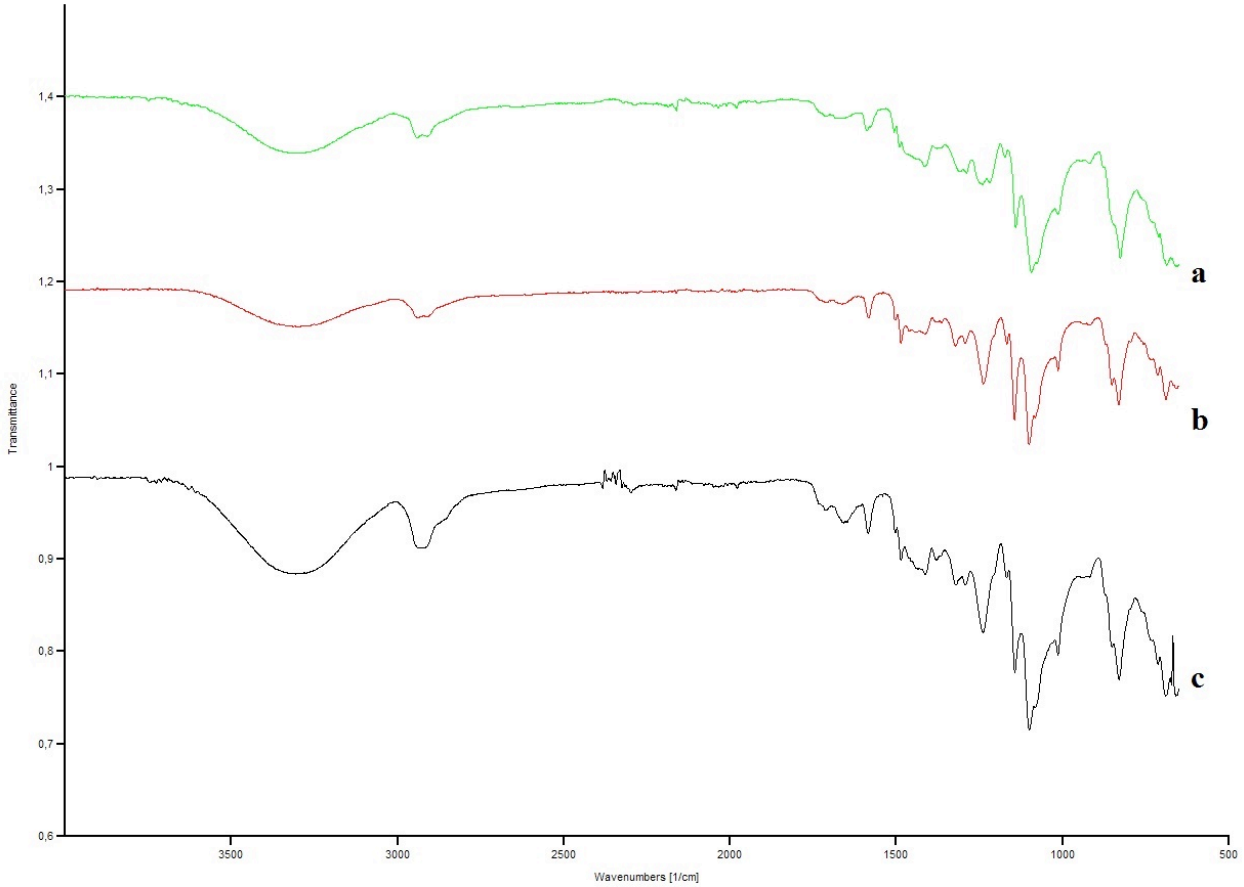

Figure 5: FTIR spectra of S-Ag/S-Cu containing nanofiber composite mat: (**a**) before crosslinking, (**b**) after crosslinking, and (**c**) after immersion in SBF for 7 days.

crystalline structure of PVA has changed considerably. The broad reflection peak in the range of $2\theta=38.5^{o}$ corresponding to the characteristic peak of silver, was detected in both nanofiber mats before and after immersion in SBF for 7 days [36]. This results also showed that these nanofiber mats had long effective silver ion release. However, as seen from Figure **3** and Figure **4**, the formation of hydroxyapatite did not occur within 7 days after immersion in SBF. Taken together, the relatively low hydroxyapatite formation occurred on the sample because of relatively low immersion time in SBF. It was concluded that the immersion time in SBF was not sufficient for the formation of hydroxyapatite. This period should be extended to detect hydroxyapatite formation on the sample.

In addition, FTIR experiments of both nanofiber mats shown in Figure **5** and Figure **6** were also conducted for the structural change before/after crosslinking and after immersion of cross-linked samples for 7 days. The large band at around 3300-3600cm^{-1}, which are identified with the stretching vibration of hydroxyl group, show the presence of intermolecular and intramolecular hydrogen bonds, and the decrease in the band intensity after cross-linking demonstrates the formation of the acetal bridge of -OH groups [37]. In addition to that the band observed between 1000 and 1140 cm^{-1} is assigned to O-C-O vibration of the acetal group [38]. According to the FTIR results of both nanofiber mats, it can be concluded that the cross-linking treatment by GA was successfully achieved.

With respect to FTIR results, the changes in the chemical structure of the nanocomposite mats were determined after 7 days SBF immersion. After 7 days, no chemical changes have been observed in the A-Ag/A-Cu containing sample. But the change in the 1650 cm^{-1} in the S-Ag/S-Cu containing nanofiber, which proves the presence of OH group of hydroxapatite, is the sign of hydroxyapatite occurrence [39]. It can be concluded that hydroxyapatite formation occurred on the surface of the S-Ag/S-Cu containing nanofiber mats. This results also showed that the bioactive behavior of the S-Ag/S-Cu containing nanofiber mats is better than that of the A-Ag/A-Cu containing nanofiber mats.

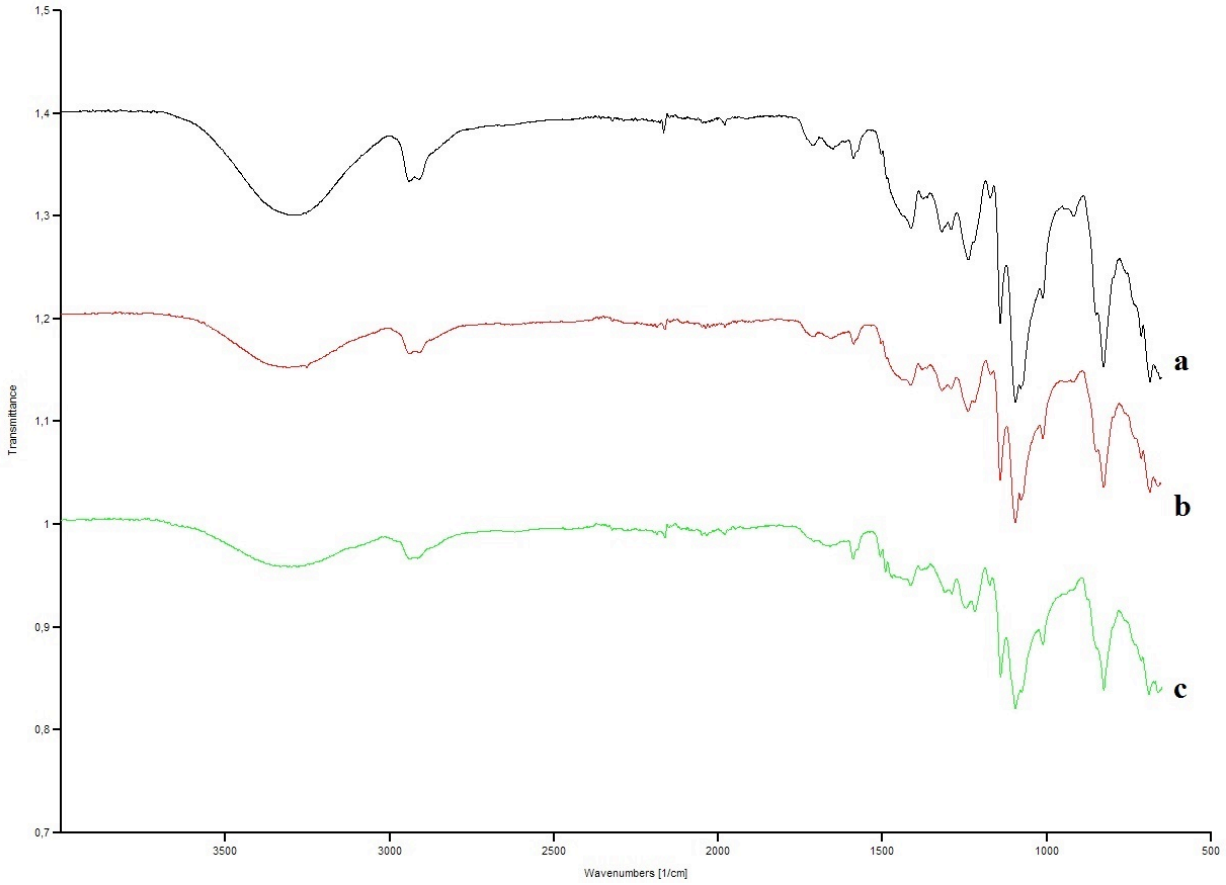

Figure 6: FTIR spectra of A-Ag/A-Cu containing nanofiber composite mat: (**a**) before crosslinking, (**b**) after crosslinking, and (**c**) after immersion in SBF for 7 days.

3.3. Determination of Metallic Ion Release

The copper and silver release of nanofiber mats was measured in order to determine the antibacterial and angiogenic potential of the nanofiber mats. Sen et al, reported that $CuSO_4$ values from 1.6 ppm to 8 ppm significantly increase VEGF expression in keratinocytes [40]. Erol M. M. *et al,* showed upper toxic level of copper as 58 ppm [41]. The copper ion release of S-Ag/S-Cu containing nanofiber mat was 1.306 ppm and the copper ion release of A-Ag/A-Cu containing nanofiber mat was 0.876 ppm showing that these nanocomposite material may have the potential for angiogenic purposes by increasing copper nanoparticle content. In addition to that, Zhao, Y *et al*. reported that the Ag^+ concentration above 0.1 ppb has the ability to prevent bacteria growth. Moreover, it was reported that the Ag^+ concentrations below 2.3 ppm and 1.7 ppm show no toxic effect [42]. The Ag^+ ion release from S-Ag/S-Cu and A-Ag/A-Cu containing nanofiber mats were found 0.535 ppm and 0.750 ppm. These results show that both nanofiber mats have the antibacterial potential and the Ag^+ ions were under the toxic levels.

CONCLUSION

In the present study, two different types of nanofiber mats containing both silver and copper nanoparticles (S-Ag/S-Cu or A-Ag/A-Cu) were successfully incorporated into the PVA fibrous mat by means of electrospinning process. The findings indicated that the currently described S-Ag/S-Cu containing nanofibrous mat was a very promising scaffold as it has the potential to form hydroxapatite on it. Besides, Ag ve Cu ion release in 7 days show that this nanocomposite may be a promising candidate having angiogenic and antibacterial activity. It was concluded that this study provides an insight for future researchers who aim to use composite materials as multifunctional scaffolds in tissue engineering applications.

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