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Preparation of non-woven fabric wound dressings containing layer - by - layer deposited Na-alginate blends and chitosan

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Abstract

Recently, developing of the biomedical materials to maintain optimum functionality has become extremely important. From that point of view, non-woven viscose (NWV) fabric based wound dressings containing Na-alginate (Alg) or its blends with poly aspartic acid (Pas), carboxymethyl cellulose (CMC) or carrageenan (CG), as an anionic layer, and chitosan (CS), as a cationic layer, were prepared via layer - by - layer technique. In addition, nano silver particles (Ag-NPs) were included during processing the last coating layer of the dressings. Factors influencing the building up of these dressings like Pas/Alg weight ratio, coating layers number and the anionic coating layer formulation were studied. The outcomes obtained revealed that: i) the ratio 50/50 of Pas/Alg is the proper ratio to attain high swellability along with remarkable antibacterial activities, ii) increasing of coating layers leads to an improvement in swellability, gel fraction, stiffness, and antibacterial activities in addition to a decreasing in air permeability of treated fabric, and iii) replacing the Pas by CMC or CG in building up of such dressings gave rise to arranging the aforementioned characteristics as: the gel fraction (CG/Alg-CS > Pas/Alg-CS > CMC/Alg-CS), the stiffness (Pas/Alg-CS > CG/Alg-CS > CMC/Alg-CS), the air permeability (CMC/Alg-CS > Pas/Alg-CS > CG/Alg-CS), and the antibacterial activity (Pas/Alg-CS > CG/Alg-CS > CMC/Alg-CS). Among the aforementioned prepared dressings, the Pas/Alg-CS dressing were characterized via SEM and EDX analysis which clearly showed the dressing morphology and confirmed loading of that dressing with the nominated bio-polymers and Ag-NPs.

***Key words*:** Wound dressing; Na-alginate; Poly aspartic acid; Carboxymethyl cellulose; Carrageenan; Chitosan.

1. Introduction

Superabsorbent hydrogels are polymers having three-dimensional cross linked hydrophilic structures. Due to their bearing of strongly hydrophilic groups, such as amino, sulphonic, and carboxyl groups along their molecular chains, they can absorb and retain large water quantities [1-3].

Polysaccharides are considered the most abundant natural polymers as they are obtained from renewable sources like plants, algae, and microorganisms like bacteria and fungi. Due to the polysaccharides merits such as the biodegradability, biocompatibility, and significant solubility and stability, they are commonly used in many biomedical and pharmaceutical applications. However, carbohydrates suffer from some limitations in the pharmaceutical and biological areas, such as the variations from batch-to-batch, thickening, reduced viscosity during storage, microbial attack, and uncontrolled hydration rate. These limitations could be minimized through chemical modifcations such as cross-linking, grafting, and blending with other natural, synthetic, and semi-synthetic polymers [4-7]

Chitosan is a cationic bio-polymer obtained by the alkaline deacetylation of chitin extracted from crabs and shrimps shells. Due to the unique

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characteristics of chitosan including the porous structure, low immunogenicity, haemostatic characteristics, biodegradability, non-toxicity, biocompatibility, hydrophilicity, anti-bacterial activity and anti-tumor characteristics, it is widely used in many pharmaceutical as well as biomedical applications [8-10].

Alginates are copolymers composed mainly of α-L-guluronic acid (G-units) and β-D-mannuronic acid (M-units) residues linked via 1,4-glycosidic bond in an in an irregular structure manner [11,12]. Alginates are commonly used in wound healing because of their unique characteristics like non-toxicity, non-immunogenicity, biocompatibility, affordability, as well as high absorptivity. Alginates based wound dressings have been prepared in various forms including nanofibers, films, hydrogels, and topical preparations. They can absorb the excess wound fluid, providing a moist environment, minimizing bacterial infections and consequently promote the wound healing. Unfortunately, the one component alginate material suffers from poor mechanical characteristics; the matter that renders blending of alginates with the other polymers, natural or synthetic, is necessary [12].

Carboxymethyl cellulose (CMC) is a water-soluble cellulose derivative bearing carboxyl groups. CMC has characteristic characteristics including the strong hydrophilicity, low cytotoxicity, cell adhesion, biodegradability, biocompatibility, and cell viability [13]. Due to that merits of CMC, it has been used commonly in the drug delivery, tissue engineering, bio-sensing, wound dressing, and bone regeneration [14,15]. CMC-based hydrogels as wound dressing materials have excellent ability to preserve a moist medium around the wound which in turn promotes the cell growth as well as supports the enzymes and hormones functioning resulting in the enhancement in the cell growth factors [16-21].

Blending of CMC with sodium alginate (Alg) enhances its solution viscosity as well as improves its bio-printability. Previous studies reported that the Alg/CMC blends based hydrogels have been used as beads in the drug delivery [22,23].

Carrageenans (CGs) are nontoxic gums found in the red seaweed families particular types. CGs are composed of sulfated linear polysaccharides of D-galactose as well as 3,6-anhydro-D-galactose. Owing to the CGs the thickening as well as suspending characteristics, they are used in diverse applications like food, pharmaceutical, coatings, ceramics, etc [24-28]. Despite of the carrageenans usefulness, they show a limitation in their processability and reactivity. To overcome such limitations, carrageenans are modified chemically and physically. Blending carrageenans with other polymers like poly (vinyl alcohol) and alginates, improves significantly their processability [28].

Most of the anionic polymers like poly (acrylic acid) are effective as hydrogels but not readily degradable [29]. Alternatively, poly aspartic acid is a synthetic biocompatible, biodegradable and nontoxic polymer having protein-like backbone structure and widely used in many biomedical applications [30,31]. Due to the strong affinity of poly aspartic acid to calcium ions, it forms poly aspartic acid-Ca complexes that have been exploited for bio-mineralization and bone targeting [32,33]. Moreover, the anionic groups over the poly aspartic acid chains form complexes with the cationic polymers such as chitosan [34].

The important challenges to obtain ideal wound dressings are attaining excellent mechanical characteristics, appropriate pore sizes, a proper water-vapor transmittance, as well as compatibility with the wound tissue sites through an easy preparation technology [35]. Recently, polymers blending are used in the polymer industry to realize vaster range of characteristics compared to the individual polymers [36-43].

This research work was under taken with a view to prepare optimum functionality nonwoven wound dressings containing Na-alginate blends and chitosan using the layer - by - layer technique.

1. Experimental

1.1. Materials

The following materials were used:

- Non-woven 100% viscose (NWV) fabric (supplied by Hebitex Co., Egypt).
- Sodium alginate (Alg) (supplied by Sigma-Aldrich).
- Chitosan (CS) of average molecular weight 480,000 Da and degree of deacetylation of 79% (supplied by Fluca).
- Carboxymethyl cellulose (CMC) of MW = 4000 Dalton, (supplied by Sigma)
- Iota carrageenan (CG), (supplied by Sigma)
- Poly aspartic acid (Pas), (supplied by Bayer).

- Laboratory grades of acetic acid, sodium hydroxide, and tri-sodium citrate.

1.2. Methods

1.2.1. Wound dressing preparation

Solutions of Alg blends with Pas, CMC, or CG were prepared via dissolution in distilled water at 80 ^{O}C/45 min with stirring to get solutions of 2% as a net concentration. Afterwards, NWV wound dressing containing Alg blends and CS was prepared via layer - by - layer technique with procedures of one, two, three or four steps. The first step comprises padding of a NWV fabric sample in 1% CS solution using 1% acetic acid as a solvent followed by squeezing and then drying at 80 °C/10min. In the second step, the CS loaded NWV fabric is padded in solutions of 2% Alg blends, squeezed, dried at 80 ^{O}C/10 min, steeped in 1% acetic acid for 5 min, dried at 80 ^{O}C/10 min, to regenerate the carboxyl groups of Alg, Pas, or CMC in a free hydrogen form, washed with distilled water, and finally dried at 80 ^{O}C/10 min. The third step is padding of the dressing later form in 1% CS solution followed by squeezing, drying at 80 ^{O}C/10 min. The fourth step proceeds via padding of the third step sample in a similar procedure of the second step. In all the aforementioned procedures, the last step includes padding treated samples in solutions containing 1% Ag-NPs, to upgrade the antibacterial activities of such dressings, and then the step is proceeded as usual. The wet pick up of all padded samples was 100%.

2.2.2. Silver nano-particles (Ag-NPs) preparation

The Ag-NPs were prepared by tri-sodium citrate, as a reducing agent, as reported elsewhere [44].

2.3. Testing and analysis

- The swelling degree (% SW) of the dressing was determined by steeping the dressing in distilled water of specific pH at 37 ^{O}C/24 h, followed by removing, wiping gently using a filter paper and finally weighed [27,28]:

  SW% = $(W_a - W_b)/W_b$ X100, where W_a and W_b are the hydrated dressing weight and the dry dressing weight respectively.
- The percentage of Gel fraction (%GF) of the dressing was determined as follows [21,27,28]:

  GF % = $(W_a\text{-}W_b)/$ X 100, where W_b is the dressing initial weight and W_a is the dressing dry weight after leaving it to swell in phosphate-buffered saline (PBS) at 37 ^{O}C/24 h.
- Stiffness (S) was assessed according to ASTM Test Method D 1388-96 in the warp direction using Jika (Toyaseiki) apparatus.
- Air permeability (AP) was assessed according to ATSM (D 737-96).
- Antimicrobial characteristics of untreated and the prepared dressing was evaluated via the count method of bacterial cells [27,28] against the bacteria strains: Gram-positive bacteria: Staphylococcus aureus (SA) and Gram-negative bacteria: Escherichia coli (EC).
- Infra-Red (FTIR) spectroscopy was carried out using Bruker IR Spectrometer.
- Scanning electron microscope (SEM) images of untreated blank NWV fabric and a prepared dressing were obtained using SEM Model Quanta 250 FEG (Field Emission Gun) attached with EDX Unit (Energy Dispersive X-ray Analyses), with accelerating voltage 30 kV, magnification 14× up to 1,000,000 and resolution for Gun, FEI Company, Netherlands.

3. Results and discussion

3.1. Factors affecting performance and antibacterial characteristics of the prepared wound dressings

Recently, developing of the biomedical materials to maintain optimum functionality has become extremely important [18,28]. From that point of view, NWV fabric samples were treated with 1% CS solution as a cationic layer and different Alg blends with Pas, CMC, or CG as an anionic layer to form layer - by - layer wound dressings. Needless to say that using CS soluble in acetic acid as a layer would cause these bio-polymers Na-salts to be in free acid form, i.e. carboxyl or sulphate groups, that indeed stabilize the overall such dressings structure, through H-bonds, in addition to the electrostatic attraction among the oppositely charged groups of CS and Alg blends. Factors influencing preparation of these dressings like Pas/Alg weight ratio, coating layers number and the anionic coating layer formulation were studied.

3.1.1. PA/SA ratio

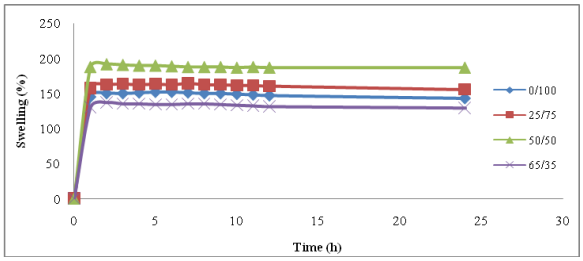

Figure 1: Effect of Pas/Alg ratio on swellability of the Pas/Alg -CS dressing. [Polymers], 2%; [CS], 1%; No. of layers, 2.

The impact of the PA/SA weight ratio increasing on percent swelling of the prepared Pas/Alg-CS dressing as a function of impregnation time of such dressings in distilled water is shown by Figure 1. It is well seen that increasing of Pas/Alg ratio from 0/100 to 50/50 is accompanied by a progressive increasing in swelling degree of the dressing which can be attributed to the increasing in the accessibility and number of the hydrophilic active sites, carboxylic and amino groups. Moreover, increasing of that ratio to 56/35 causes a reduction in such dressings swellability. Furthermore, increasing of the impregnation time causes a slight reduction in the swellability of such dressings, regardless of their structure. It seems that increasing of either the Pas/Alg ratio to 65/35 or the steeping time of the prepared dressings to 24 h causes dissolution of tiny soluble fraction from such dressing's surfaces [45-47]. However, the swelling degree of the nominated dressings can be arranged according to Pas/Alg ratio as follows: 50/50 > 25/75 > 0/100 > 65/35.

PA/SA ratio (%)	GF (%)	S (mg)	AP $cm^3/cm^2.sec$	Reduction (%)	
				SA	*EC*
0	99.3	819	346	94.13	94.4
25/75	98.5	1958	368	99.25	97.6
50/50	98.1	1531	383	100	100
65/35	95.3	1068	399	100	100

Table 1: Effect of PA/SA ratio on some performance and antibacterial characteristics of the PA/SA-CS dressing. [Polymers], 2%; [CS], 1%; No. of layers, 2.

On the other hand, as far the variation in the prepared Pas/Alg-CS dressing physico-mechanical characteristics as a function in Pas/Alg ratio. Table 1 demonstrates that: i) incorporation of Pas in building up of the above mentioned dressings structure leads to an enhancement in SW, S, AP and antibacterial activities along with a lowering in GF characteristics of such dressings reflecting the chemical structure of polymers constituting such dressings as well as the ionic interactions among that polymers [45-47], ii) increasing of the Pas/Alg ratio in the dressing structure from 25/75 to 50/50 results in an enhancement in extents of AP and antibacterial activity accompanied with a reduction in GF and S extents of the prepared dressing, which may be a direct consequence for a partial solubility of Pas in the aqueous medium [45], iii) Beyond the ratio of 50/50 and up to 65/35, a further solubility of the Pas component occurs leading to a significant reduction in extents of the above mentioned characteristics but keeps the antibacterial activities of the prepared dressing unchanged, and iv) inclusion of Ag-NPs in the dressing last coating layer, significantly improves the aforementioned dressings antibacterial activities via formation of Ag-ions, in the presence of moisture, which bind to the bacterial DNA causing its inactivation as seen by equation (1):

$$O_2 + 4H_3O^+ + 4Ag \rightarrow 4Ag^+ + 6H_2O \quad \ldots\ldots (1)$$

and/or formation of oxygen radicals which oxidize the bacterial molecular structure as seen by equation (2) [48-50]:

$$H_2O + (1/2)O_2 \xrightarrow{Ag^+} H_2O_2 \rightarrow H_2O + (O) \quad \ldots\ldots (2)$$

Nevertheless, incorporation of Pas in the coating formulation of dressing's structure would significantly enhance the antibacterial characteristics extent of such dressings due to the higher ability of Pas with respect to Alg to form complex bonds with Ag-NPs [51-54]. However, it seems that the Pas/Alg ratio of 50/50 of the prepared dressing is a convenient option from the antibacterial and physico-mechanical characteristics points of view.

3.1.2. Number of layers

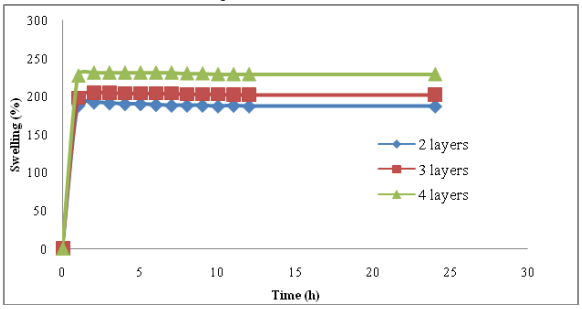

Figure 2: Effect of layers number on swellability of the Pas/Alg-CS dressings. [Polymers], 2%; [CS], 1%; Pas/Alg ratio, 50/50.

Number of coating layers	GF (%)	S (mg)	AP $cm^3/cm^2.sec$	Reduction (%)	
				SA	*EC*
2	98.1	1531	383	100	100
3	99.1	1566	322	100	100
4	99.5	1602	275	100	100

Table 2: The impact of coating layers number on performance and antibacterial characteristics of the PA/SA-CS dressing. [Polymers], 2%; [CS], 1%; PA/SA ratio, 50/50.

The impact of coating layers number on performance and antibacterial characteristics of the aforementioned dressing is shown by Figure 2 and Table 2. It is well seen that increasing of the NWV fabric coating layers results in an improvement in swellability of the treated NWV fabric samples (Figure 2) and gives rise to an enhancement in extents of GF and S along with a reduction in AP but preserve the full antibacterial activity of the treated fabric samples against both the nominated bacterial strains (Table 2). This can be attributed to increasing of such hydrophilic biopolymers ingredients deposition inside the fabric samples structure by increasing of coating layers which logically enhances swellability and alters extents of the above mentioned properties [45]. Indeed, beside the antibacterial properties of chitosan [8-10], inclusion of Ag-NPs in the last coating layer containing CS would promote the antibacterial characteristics of such dressings.

3.1.3. Coating layer formulation

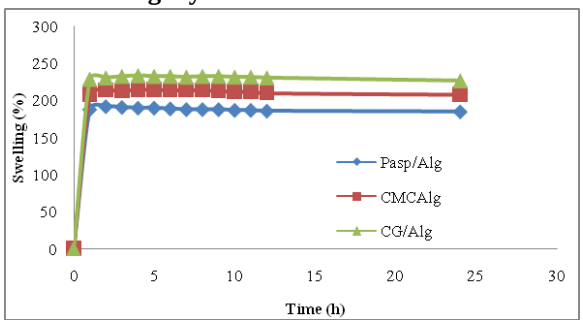

Figure 3: Effect of anionic coating layer formulation on swellability of the prepared dressings. [Polymers], 2%; [CS], 1%; Pas, CMC or CG/Alg ratio, 50/50; No. of layers, 2.

Anionic coating layer formulation	GF (%)	S (mg)	AP $cm^3/cm^2.sec$	Reduction (%)	
				SA	*EC*
Pas/Alg	98.1	1531	383	100	100
CMC/Alg	97.3	1424	386	95.7	98.5
CG/Alg	99.2	1460	309	95.6	100

Table 3: Effect of anionic coating layer formulation on some performance and antibacterial characteristics of the prepared dressings. [Polymers], 2%; [CS], 1%; No. of layers, 2; PA, CMC or CG/SA ratio, 50/50.

Figure 3 shows the percent swelling of CMC/Alg-CS, Pas/Alg-CS, and CG/Alg-CS dressings. It is clear that the swellability of such dressings can be arranged in the following descending order: CG/Alg-CS > CMC/Alg-CS > Pas/Alg-CS. Furthermore, Table 3 reveals the impact of the anionic coating layer formulation on the performance and antibacterial characteristics of the CMC/Alg-CS, Pas/Alg-CS, and CG/Alg-CS dressings. It is well seen that extents of the performance and antibacterial properties of the prepared dressings can be arranged in the following orders:

- the gel fraction: CG/Alg-CS > Pas/Alg-CS > CMC/Alg-CS
- the stiffness: Pas/Alg -CS > CG/Alg -CS > CMC/Alg-CS
- the air permeability: CMC/Alg-CS > Pas/Alg-CS > CG/Alg-CS, and
- the antibacterial activity: Pas/Alg-CS > CG/Alg-CS > CMC/Alg-CS.

This could be explained in terms of the differences among these anionic polymers with respect to their chemical structure, molecular weight, orientation and configuration of the molecules, polarity, chain branching, degree of solubility, rheological characteristics, film-forming characteristics, compatibility and ionic interaction with each other, location and extent of penetration, cohesive and adhesive characteristics, as well as the polymer degree of substitution [55,56].

3.2. SEM and EDX analysis

3.2.1. FTIR

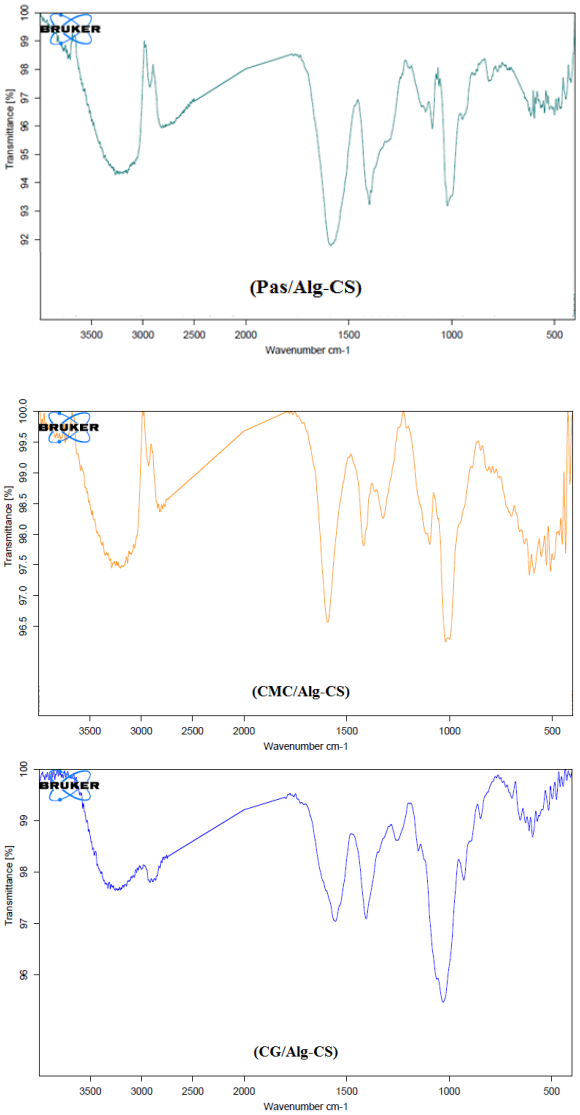

Figure 4: FTIR of the Pas/alg-CS, CMC/Alg-CS, and CG/Alg-CS films.

The FTIR spectrum of Pas/alg-CS, CMC/Alg-CS, and CG/Alg-CS films are represented by Figure 4. Actually, all that prepared films contain Alg and CS as components in their chemical structures. Thus, it is expected that the only differences among these films will be in their third component, i.e. Pas, CMC, and CG, chemical structure. It is clear that the CG/Alg-CS film spectrum includes peaks belonging to CG, Alg, and CS such as a broad peak at 3672 cm^{-1} due to OH stretching vibrations present in CG, Alg, and CS, two peaks at 1029 -1084 cm^{-1} of the C-O-C group stretching vibration, and a peak at around 1742 cm^{-1} belonging to COOH groups. Moreover, other peaks are also present that are two peaks at 846 and 928 cm^{-1} corresponding to a d-galactose-4-sulfate and 3,6-anhydridegalactose stretching vibrations, respectively, a peak at 2917 cm^{-1} of C-H stretching, peaks at 1600 and 1404 cm^{-1} corresponding to unbalanced and symmetric stretching vibrations of COO^- groups of alginate, a peak at 3483 cm^{-1} corresponding to the -NH_2 stretching vibration of CS and a peak at 1557 cm^{-1} corresponding to N–H bending of the primary amine of CS [26-28,44,45]. On the other hand, the spectrum of Pas/Alg-CS film shows, beside the common peaks of Alg and CS that mentioned before, peaks belonging to Pas such as a peak at 3519 cm^{-1} which is attributed to N–H bonding vibration and special peak at 1585 cm^{-1} that is ascribed to -COOH and/or –CONH [57]. Besides, the CMC/Alg-CS film spectrum shows peaks similar to so what to that of the Pas/Alg-CS film beside the common peaks of Alg and CS which listed before.

3.2.2. SEM and EDX analysis

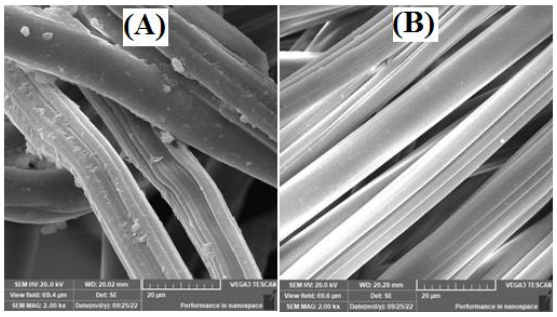

Fig. 4. SEM images of PA/SA-CS dressing (A) and untreated NWV fabric (B).

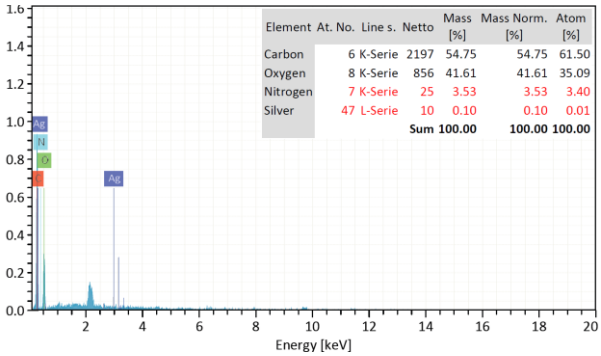

Fig. 5. The EDX image of the PA/SA-CS dressing.

Among the aforementioned prepared dressings, the Pas/Alg-CS dressing was selected to be characterized via SEM and EDX analysis. Figure 5(A and B) respectively. Figure 5A clearly shows a

deposition of a thin layer onto the dressing surface which is not present onto that of the untreated NWV fabric (Figure 5B). Moreover, Figure 6 confirms containing of that dressing on carbon, oxygen, and nitrogen elements of the nominated polymers in addition to Ag-NPs.

Conclusions

- The ratio 50/50 of Pas/Alg is the proper ratio to attain high swellability and antibacterial characteristics.
- Increasing of the coating layers of the NWV fabric results in an increasing of extents of swelling degree, gel fraction, stiffness, and antibacterial activities in addition to a decreasing in air permeability of that fabric.
- Inclusion of Ag-NPs in formulation of the final coating layer of the NWV fabric enhances remarkably the antibacterial activities of such fabric.
- Replacing Pas with CMC or CG in formulation of the NWV fabric coating layers alter the aforementioned performance characteristics resulting in arranging of that characteristics as follows: the gel fraction (CG/Alg-CS > Pas/Alg-CS > CMC/Alg-CS), the stiffness (Pas/Alg-CS > CG/Alg-CS > CMC/Alg-CS), the air permeability (CMC/Alg-CS > Pas/Alg-CS > CG/Alg-CS), and the antibacterial activity (Pas/Alg-CS > CG/Alg-CS > CMC/Alg-CS).
- The SEM analysis of shows the Pas/Alg-CS dressing morphology whereas the EDX analysis confirms containing of that dressing on the nominated polymers as well as Ag-NPs.

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