

Environmental-Friendly Hydrogels from Hydroxyethyl Cellulose (HEC)/ Sodium Alginate (SA)/ Hyaluronic Acid (HA) for Wound Healing Applications

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Abstract: The aim of the study is to obtain a new hydrogel using HEC/SA/HA via a green chemistry approach for wound healing applications. The properties of the hydrogel have been tested which include: swelling ratio, in vitro degradation, and wound healing test. It was also characterized via UV-Vis, FTIR, TEM, and TGA. The characteristic peak of UV-Vis spectra revealed the formation of AgNPs in the compound at 411 nm. The results from these studies showed that the hydrogel has an excellent performance in swelling ratio and in vitro degradation. Furthermore, the wound healing activity of the hydrogel was tested by measuring the closure of the wound and the hydrogel used in the treated group revealed a significant healing activity compared to the control group. These results suggested that the cross-linked hydrogel based on (HEC/HA/SA) with AgNPs will be a promising dressing for wounds.

Keywords: Hyaluronic acid (HA), Sodium alginate (SA), Hydroxyethyl cellulose (HEC), Silver nano-particles (AgNPs), Tissue engineering (TE).

I. Introduction

The idea of using scaffolds in wound healing applications is that they have essential features, which include excellent mechanical and physical properties as well as excellent background for physiological activities, which enable cell adhesion, proliferation, or differentiation [1]. In addition, The scaffold should be biodegradable and biocompatible, with a degradation profile that reflects the time duration of wound healing. It should also maintain a moist wound environment to facilitate basic cellular signals, angiogenesis, granulation tissue creation, and re-epithelialization [2].

The materials used in tissue engineering (TE) should stimulate the cell response at the molecular level. Also, it must stimulate specific interactions in the cell and thus the cell will work on proliferation, differentiation, production, and organization of the extracellular matrix [3]. Therefore, biomaterials are selected in TE and constitute a successful focal point for this process. The properties that distinguish biomaterials, as basic materials in TE are their biocompatible surfaces and their mechanical properties. Indeed, a conventional single-component polymer cannot meet these requirements. Although many different polymers have been examined for use in TE, no single biodegradable polymer can meet all the requirements of biomedical scaffolds. Therefore, multi-component polymer systems are always prepared and designed that represent a viable multifunctional structured strategy [4]. Many biopolymers have been studied in this field, including Hyaluronic Acid, Sodium Alginate as well as Hydroxyethyl cellulose.

Hyaluronic acid is an acidic linear polysaccharide with repeating disaccharide units of N-acetyl glucosamine and D-glucuronic acid connected by -1,4 glycosidic bonds. [5]. The molecular weight of HA ranges between 10 and 10000 kDa, depending on the extraction, source, and the purification method employed. Increasing the concentration and molecular weight of HA causes its viscosity to increase [6]. Due to the presence of a hydroxyl group in its structure, it is considered a highly hydrophilic polysaccharide with an emollient effect [7], as this group can form hydrogen bonds with water molecules on the polymer chain. Through this process, HA accumulates a large quantity of water, as it can hold up to 1,000 times its own volume [8].

Sodium alginate is a naturally occurring linear polysaccharide composed of units of (1-4)-D- mannuronic acid (M) and (1-4)-L- guluronic acid (G) [9]. The polymer chains are composed of a random sequence of M and G blocks interspersed with regions of alternating MG blocks. In general, alginates are regarded as rigid molecules due to their rigid six membranes of sugar rings and restricted rotation around the glycosidic linkage. Electrostatic repulsion exists between the charged groups of the polymer chain, contributing to the rigidity of the chains. The chain's rigidity depends not only on the ionic strength, but also on the composition of alginate, in the order MG MM GG. Therefore, the mechanical and physical properties of alginates are heavily dependent on the sequence of blocks [10,11]. Alginate has the ability to form a uniform hydrogel that is insoluble in water and thermally irreversible at room temperature by crosslinking with divalent or trivalent ions. Calcium chloride solution is the most commonly used cross-linking agent [12]. This hydrogel is commonly referred to as "egg-box" hydrogel. The divalent ions such as Ca^{2+} form a strong bond with the carboxyl group in the G-block of SA [13].

Cellulose is one of the most widely accessible polysaccharides in the world, and its biodegradability, biocompatibility, and renewability have garnered the attention of researchers. [14] Cellulose is a linear polysaccharide composed of repeating units of D-glucopyranosyl connected by -1,4 glycosidic bonds. It is difficult to dissolve in solvents and cannot be liquefied, limiting its application in various contexts [15]. Hydroxyethyl cellulose is a cellulose derivative and a water-soluble non-ionic compound. It is produced through the reaction of purified cellulose and ethylene oxide. This compound's structure contains a large number of

hydroxyl groups (-OH), which can be linked to other functional groups. As a result, it has outstanding properties and is suitable for numerous biotechnology, biophysical, and industrial applications. In addition to its use in protective colloids during the polymerization process, HEC is frequently incorporated into cosmetics, foods, and pigments as a thickener [16,17].

Antibacterial dressings for the treatment of ulcers were devised in response to the emergence of drug-resistant bacteria. AgNPs have been utilized as a potent antibacterial agent with a significant and enduring effect on microorganisms and drug-resistant pathogens. Several techniques, including chemical reduction, irradiation, electrochemical, thermal, and biological, have been developed to synthesize AgNPs. Alginate-based hydrogel, cellulose, collagen, and clay minerals prevents agglomeration and precipitation of nanoparticles and acts as a capping, reducing, and stabilizing agents. [18].

II. Materials and Methods

Materials

All the materials used in this work are commercially available. HA (50 kDa) was purchased from Merck. HEC was purchased from SIGMA-ALDRICH, Germany. SA, sodium hydroxide, calcium chloride, silver nitrate were purchased from S. D FINE-CHEM Limited, India. All the solutions, sodium hydroxide (NaOH) 0.1 M, CaCl_2 (0.1 M), AgNO_3 (0.1 M), phosphate buffer solution (PBS) were prepared using distilled water. All the chemicals used in this study were with high purity and without further purification.

Preparing HEC/AgNPs solution

1.25 g of HEC was dissolved in 63 mL of distilled water and stirred for two hours at room temperature to ensure complete dissolution and obtain a clear solution. After preparing the solution, it was divided into two beakers (Beaker 1 = 23 mL, Beaker 2 = 40 mL). The second beaker (40 mL) was used to produce AgNPs by adjusting the solution's pH to 10 by introducing sodium hydroxide solution (0.1M). This solution was transferred to a magnetic stirrer with a heating element and its temperature was progressively increased until it attained the desired 90 °C. During the heating procedure, approximately 300 μL of a diluted AgNO_3 (0.1 M) was introduced to the mixture. The reaction mixture (Ag^+ -HEC) was heated and stirred continuously for 30 minutes. (Ag^0). The color of the reaction changed from a clear yellow to a dark brown after the heating indicating the formation of nanoparticles of silver.

Preparation of SA / HA solution

0.2 g of SA powder was mixed with 0.1 g HA (50 kDa). This mixture of powder (HA-SA) was dissolved with 7 mL of distilled water in a glass of 100 mL. Then, the solution was transferred to magnetic stirring for 1 hour until the mixture became a homogenous and clear solution.

Preparation hydrogel / AgNPs composites

The hydrogel was prepared by taking 3 mL of HEC solution, 5 mL of HEC-AgNPs solution and was mixed with HA-SA solution. The final solution was stirred for 5 minutes until the solution became homogenous. The polymer mixture was split into well-plate, each one containing 1.5 mL of the polymer mixture. Finally, 1 mL of CaCl_2 (0.1 M) was added to each one until the hydrogel started cross-linked and conglomerated.

Characterization of Hydrogel

UV-Visible Spectroscopy

The UV-vis spectra of AgNPs in the hydrogel were detected using a Spectrophotometer (UV-1800, Shimadzu, Japan) in the wavelength range of (300-700) nm. All spectra were collected in the absorbance mode, and optical spectra were gathered using quartz cuvettes with a 1 cm path length.

Fourier transform infrared spectroscopy (FTIR)

To assess the structural changes of the hydrogel, the Fourier Transform Infrared (FTIR) spectra of SA, HA, HEC, and a mixture of (SA-HA-HEC) with calcium chloride and AgNPs were recorded and compared using an FTIR IRPrestige-21 (Shimadzu) spectrometer. All samples were freeze-dried before being ground with spectrum-pure KBr and compressed into discs. The analysis was conducted between 400 and 4000 cm^{-1} with 128 images recorded at a resolution of 4 cm^{-1} .

Transmission electron microscopy (TEM)

TEM was used to detect the size and shape of synthesized AgNPs and their distribution in the hydrogel. Images were taken by means of a JEOL-JEM-1400 transmission electron microscope. The sample was prepared by depositing a drop of the hydrogel into Copper grids coated by an amorphous carbon film and dried in oven for 1 hour at 40 °C.

Thermo Gravimetric Analyzer (TGA)

TGA instrument (model SDT Q600) was used to verify the thermal degeneration attribute of the three polymers (HA, SA, HEC) and the hydrogel. The starting weight of analysis was 6 mg sample and the analysis achieved under N_2 and the heating rate was 10 °C/min until 700 °C [19]

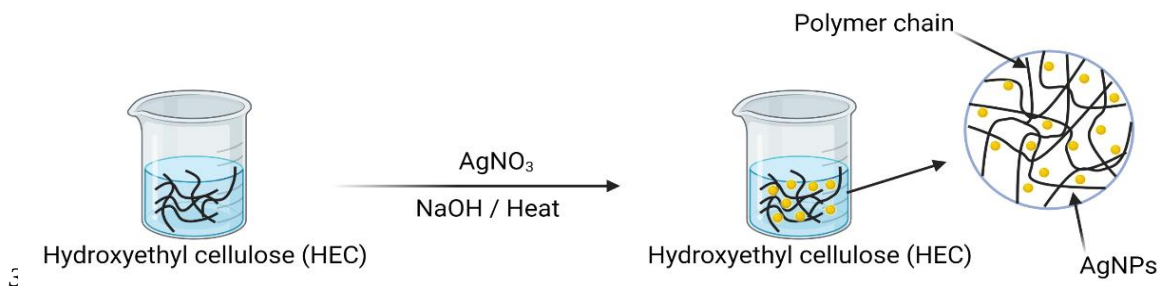
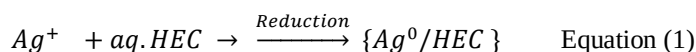
Wounds healing test

Six male mice (CD1) were provided via Animal House in the Research and Natural Science Centre of Nizwa University-Oman (Approval No: VCGSR/AREC/02/2021). The whole mice were anesthetized by injecting them with Ketamine (70 mg/kg) and Xylazine (10 mg/kg) [20]. The skin of the mice was cleaned with a razor and hair removal creams, and then the area was sterilized with alcohol. A 1.5 cm circular wound was created on the back of each mouse with a curved blade and surgical scissors. The wound's depth and diameter in all groups were created to be as similar as possible in all groups of mice. The mice were divided into two groups and each group has three mice as follow, the first group would be as a control, while the second group, the wound was treated with hydrogel [21].

III. Results and Discussion

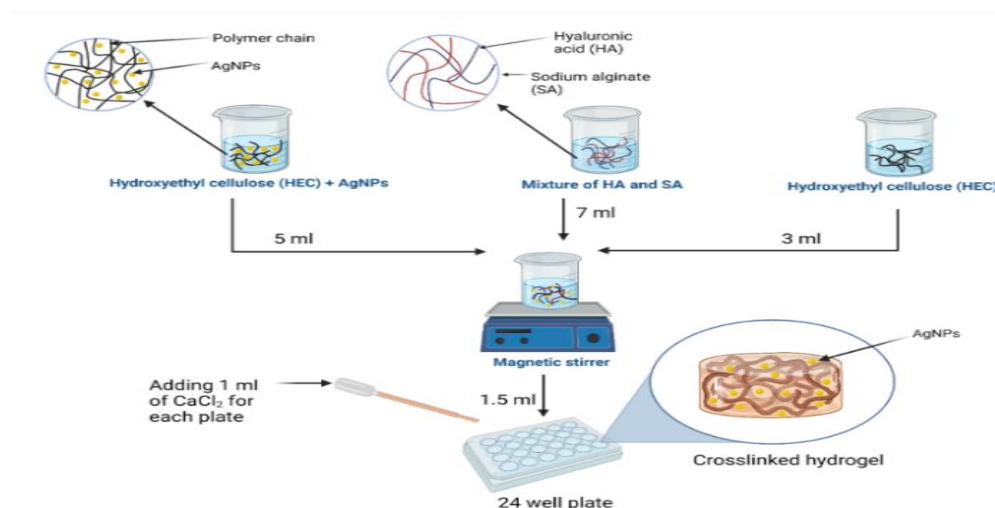
Synthesis of Silver Nano-Particles (AgNPs) Via HEC

AgNPs are synthesized by an environmentally friendly chemical reduction method. Initially, NaOH was introduced to the HEC solution in order to activate the polysaccharide through the alkalization process. Then, 300µl of AgNO₃ was added, and due to the presence of the oxidizing agent (HEC), the silver ions (Ag⁺) were reduced to (Ag⁰) and formed AgNP, as shown in equation (1) [22]. The mechanism of the oxidation-reduction reaction involving silver particles as the oxidizing agent and HEC as the reducing and stabilizing agent is depicted in the scheme (1). Each alcohol group in the structure of HEC was converted into a carboxyl group. Producing these groups allowed the HEC to bind with Ca²⁺ via cross-linking with other polysaccharides.



Scheme 1. the (oxidation-reduction) reaction of hydroxyethyl cellulose (HEC) and silver nitrate (AgNO₃)

The hydrogel was produced by combining three biopolymers, namely HEC-AgNPs, a mixture of HA-SA, and HEC, with the crosslinking agent Ca²⁺ ions. The process of preparing the cross-linked hydrogel is depicted in Scheme (2). First, a HEC solution containing Ag⁰ particles was added to the SA and HA mixture, followed by the addition of a pure HEC solution. The hydrogel was then divided into 24-well plates containing 1.5 mL per well. Finally, 1 mL of calcium chloride was added to each sample to initiate the formation of cross-linked hydrogel. Figure (1) depicts how the three polymers are intertwined and interconnected via crosslinking agent (Ca²⁺) and COO⁻ groups in the three polymers. In addition, it illustrates how the carboxyl groups and unbound OH groups work to stabilize AgNPs.



Scheme2. The process of preparing cross-linked hydrogel

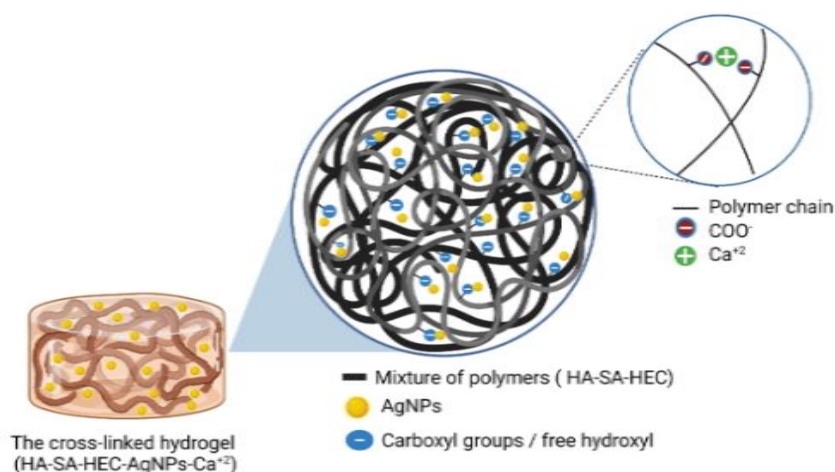


Figure 1. The bonding of the three biopolymers with calcium ions (Ca^{2+}) and silver nanoparticles (AgNPs)

UV-Vis absorbance spectroscopy

The presence of AgNPs in the produced hydrogel was confirmed using UV-Visible spectroscopy. The free oscillating electron contained in metallic AgNPs produce surface plasmon resonance. According to prior research, AgNPs have a Plasmon surface absorbance between 400 and 420 nm [23,24]. The AgNPs displayed Plasmon absorption at 411 nm for AgNO_3 (300 μl), which corresponds to the Ag nanoparticles' plasmon resonance surface and this was mentioned in our previous research paper [25].

FTIR studies

Figure 2 shows the FTIR spectra of HA/HEC/SA/cross-linked hydrogel. There are key common peaks, such as those above 3000 cm^{-1} indicating -OH stretching vibration mode, peaks at 2923 cm^{-1} indicating methylene group (C-H) stretching vibration mode, and the peak at 1108 cm^{-1} indicating C-O group in stretching vibration instance. To examine the probable interactions between the functional groups in the three polymers, calcium ions, and AgNPs, FTIR spectra were obtained.

Pure HEC has a large peak at 3375 cm^{-1} for O-H stretching vibrations and a narrow peak at 2929 cm^{-1} for C-H aliphatic stretching vibrations. HEC absorption spectra exhibit distinct bands at 1456, 1360, 1310, and 933 cm^{-1} [26]. These bands correlate to the possible variability of the amorphous region's distribution of replacement groups in the polymer chain. The C-O was given a band at 1081 cm^{-1} , and there was a band at 1655 cm^{-1} owing to glucose ring stretching cm^{-1} [27]. For pure SA, FTIR spectra show the same distinctive bands at 3430 cm^{-1} ascribed to the absorption of stretching of the O-H and a peak at 2929 cm^{-1} owing to stretching of the C-H in the glucose ring. The spectra also shows a peak at 1412 and 1613 cm^{-1} , which correspond to asymmetric and antisymmetric -COOH (carboxylate groups) that will interact with Ca^{2+} . [28]. The -OH stretching causes a large peak between 3000 and 3600 cm^{-1} in the pure HA spectra. There are furthermore bands at 1605 and 1405 cm^{-1} that are ascribed to carboxylate symmetric and asymmetric stretching vibrations, respectively. C-O-C stretching vibration of the skeleton HA peaks at 1027 and 1145 cm^{-1} . Two minor peaks at 1322 and 1560 are amide bands [29]. There are two absorption peaks in the cross-linked hydrogel at 1420 and 1620 cm^{-1} , reflecting the symmetric and asymmetric carbonyl group (C=O) due to the presence of Ca^{2+} . The signal at 1420 cm^{-1} in the hydrogel is weaker than the comparable peak in pure SA, HA and shifts to a higher frequency in the presence of Ca^{2+} , from 1415 to 1420 cm^{-1} . The asymmetric stretch peak has also been moved up from 1605 to 1620 cm^{-1} . The region between 1150 and 1000 cm^{-1} was a significant indicator of crosslinking produced by C-C and C-O stretching. The signal at 1040 cm^{-1} suggests high-intensity C-C stretching and 1040 cm^{-1} for C-C stretching [28,30]. Moreover, there is an absorption band at 3265 cm^{-1} that corresponds to the O-H stretching in pure SA; this peak grows larger and shifts to a higher frequency in the hydrogel spectra due to reduced intramolecular bonding. The stretching of the -COO asymmetric peak at 1620 cm^{-1} in the hydrogel was clearly seen as a result of the interaction between the -COO group and Ca^{2+} [31].

Thermogravimetric (TGA) studies

TGA is an analytical technique used to determine the thermal stability and volatility of the compound by observing the change in weight during the heating process. The thermal degradation of the HEC/HA/SA /cross-linked hydrogel were tested after freeze-dried via TGA as illustrated in Fig.(3). There were three decomposition steps for all samples, except for HEC, which only had two steps of degradation. These steps in diagrams describe weight loss during heating process (TGA %) as well as the diagram of derivative mass loss (drTGA%). Table (1) shows a summary of the decomposition steps and the percentage of weight loss of the samples.

HA demonstrates three steps of decomposition, where the first step was from 20.86 °C to 171.24 °C and the weight loss was 18.02%, while the second step was somewhat large, as it was 38.78% in the temperature range 171.24 °C to 288.43 °C. The third stage was from 171.24 °C to 519.42 °C and the weight loss was 14.09% for a total weight loss of 70.89%. The TGA curve for HEC showed 7.8% of weight loss in the first stage starting from 25.55 °C to 194.68 °C. More significant loss (74.75%) observed in the second stage begins from 194.68 °C to 513.42 °C. For SA, there was a lower rate of weight loss compared to HEC, HA, where the overall loss rate was about 65.95% divided into three stages starting from 21.34 °C to 515.13 °C. For TGA of the cross-linked hydrogel, it shows three stages of decomposition which start from 25.24 to 198.56 for the first stage with a decomposition percentage of the mass estimated about 16.35%. From the results, it is noted that the cross-linked hydrogel has a slight decrease in the decomposition,

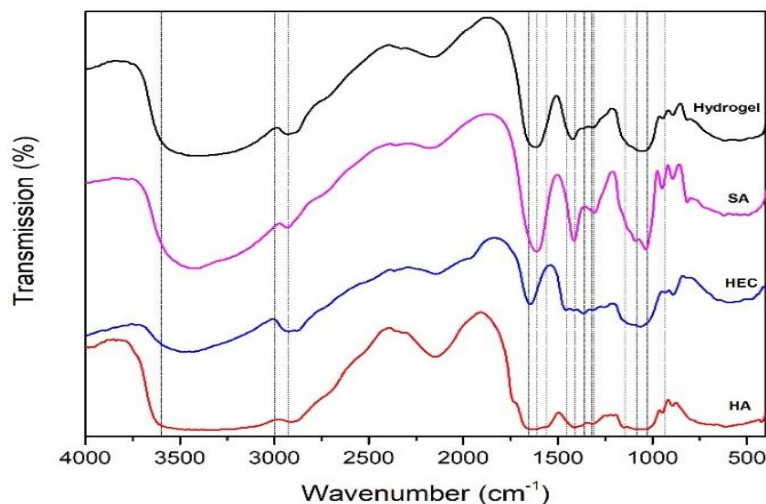


Figure 2. The FTIR studies of the hydrogel, sodium alginate (SA), hydroxyethyl cellulose (HEC), hyaluronic acid (HA)

and this may be due to the presence of SA and HA together in the hydrogel composition, which are characterized by having hydrophilic groups along their main chain that facilitate trapping water molecules in the hydrogel [32,33]. The second step of decomposition was from 198.56 to 344.77, and as it also noted, there is a significant increase in comparison with SA and HA, where the presence of HEC in the hydrogel structure helped to stabilize it for a longer period during the degradation of polymers chain [34]. However, the overall weight loss rate was 66.34%, which is a lower percentage compared to the other three polymers, and this may be due to the presence of calcium ions in the structure and the strong bonding of the polymers with each other [35]. The derivative TGA curve Fig(3) of HA, HEC, SA, cross-linked hydrogel show three endothermic peaks except the HEC polymer, which has only two stages of degradation as mentioned previously. The first peak in all samples is an endothermic peak formed due to the evaporation of water [36]. The second main endothermic peak signed to the decomposition of the organic components (carbon-carbon bond) in the polymers bone [37].

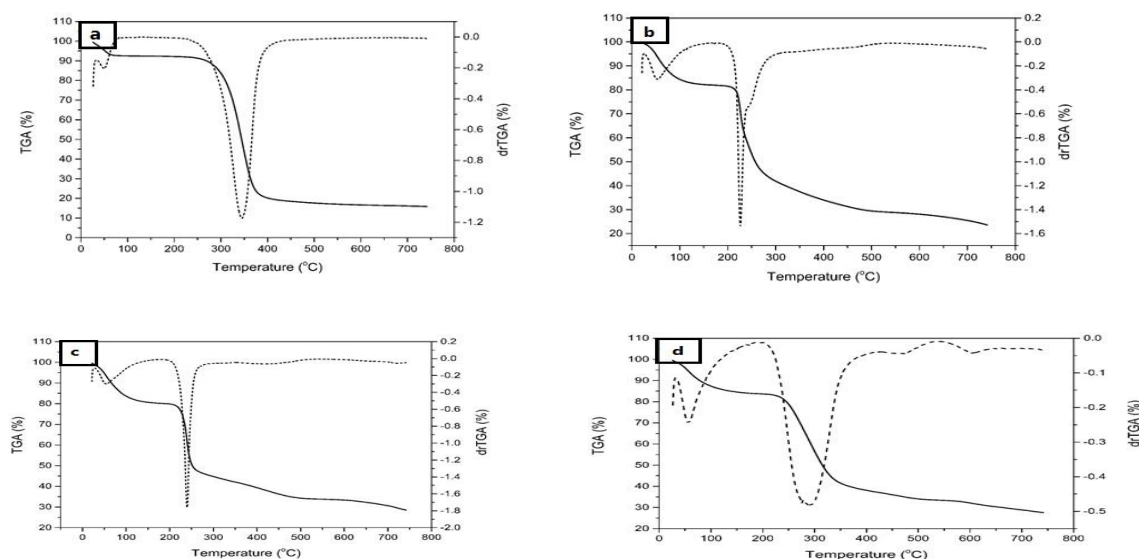


Figure 3. TGA and DrTGA analysis for (a) pure HEC (b) pure HA (c) pure SA (d) Hydrogel

Table 2. TGA and drTGA data for hydrogel, HA, SA, HEC

TGA and drTGA for hydrogel , HA , SA and HEC						
Sample	Region of decomposition	Temperature (°C)			Weight loss (%)	
		T _{start}	T _{end}	T _{peak}	Partial	Total
Hydrogel	1	25.24	198.56	57.68	16.35	66.34
	2	198.56	344.77	286.57	41.48	
	3	344.77	521.36	478.16	8.51	
HA	1	20.87	171.24	53.54	18.02	70.89
	2	171.24	288.43	226.16	38.78	
	3	288.43	519.42	274.11	14.09	
HEC	1	25.55	194.68	51.1	7.8	82.55
	2	194.68	513.42	345.39	74.75	
SA	1	21.43	178.86	54.81	19.84	65.95
	2	178.86	269.62	240.01	33.32	
	3	269.62	515.13	435.27	12.791	

TEM micrographs and size distribution data

Characterization the geometric shape and size of the synthesized AgNPs is a basic parameter to describe the nanostructure. Fig (4) shows TEM images of AgNPs, which confirm what was obtained in UV-Visible spectra [25]. TEM was mainly used to determine the size of particles, dispersion degree, and the aggregation in aqueous environment of the hydrogel with a high resolution. The topographical properties of the synthesized AgNPs were presented via TEM micrographs (Fig.5) for the hydrogel. From the obtained data, it is evident that the prepared sample consists of well dispersed nanostructures. It has also been confirmed that HEC is capable forming nanoparticles through a chemical reduction process as reported in literature [38]. It was also found that the three polymers (HA-HEC-SA) used in the preparation of the hydrogel can act as superior nanocomposite and a surfactant in order to prepare small, stable and spherical AgNPs. The spherical shape of nano-particles is based on the concentration of AgNO_3 . The figures also show the ability of these polymers to stabilize nanoparticles after they have been mixed with each other and bond with Ag^0 well. On the other hand, AgNPs prevent hydrogel degradation either by exposure to light or by oxidation and avoid potential chemical reactions [39]. The Fig.(6.a) shows the particle size distribution of AgNPs and it was found that they are polydispersed in the hydrogel. The graph in Fig(7.a) represents that the majority of nanoparticles have a spherical shape with a very small semi-spherical group. The Fig(7.b) shows the particles area of Ag nanoparticles, the range was from 66.18 to 636.0 nm^2 and the mean was 251.6 nm^2 . From Fig(7.c), it is also clear that the size of the particles ranged between 8.2 to 32 nm, and the average size was 17.6 nm and these data are shown in the table (3). Naturally, after a period of time most minerals tend to agglomerate because of their high surface tension, which results in nanoparticles size with a large surface area.

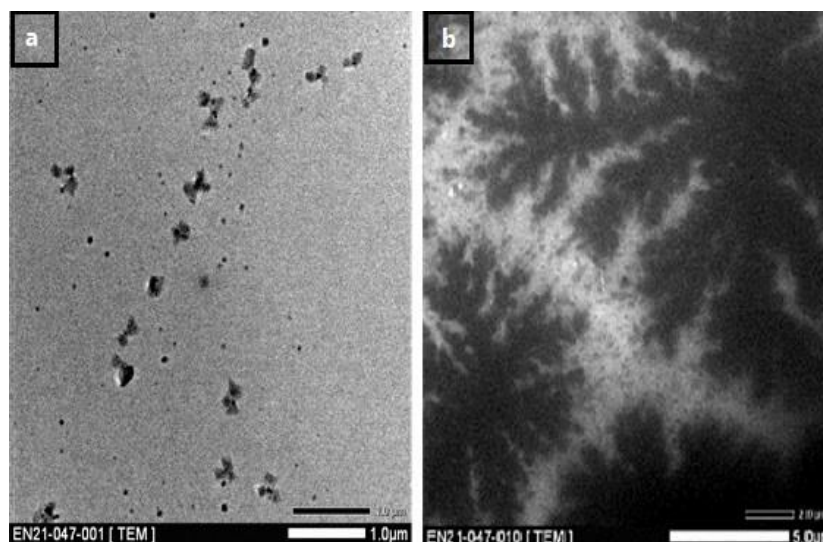


Figure 4. TEM images (a) Nano-particle distribution (1.0 μm) (b) Tree-shape of AgNPs (5.0 μm)

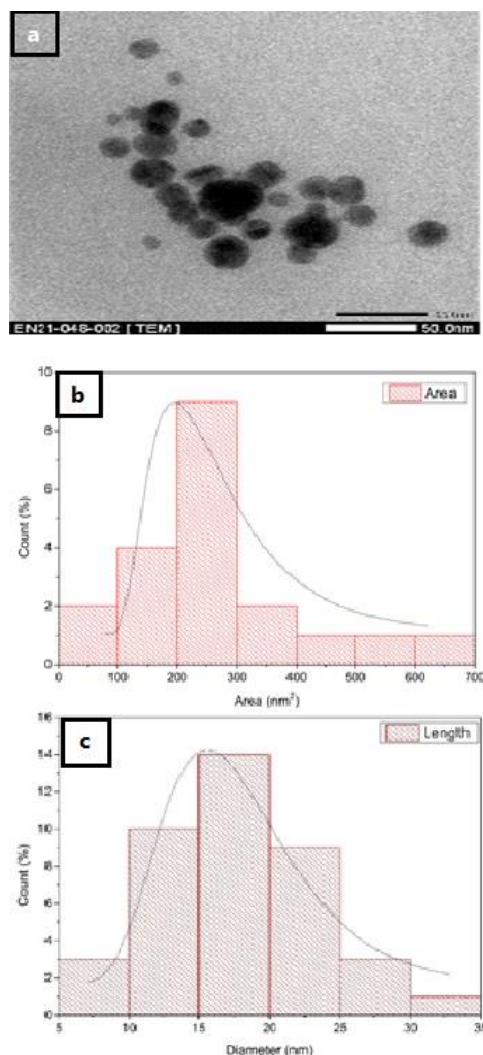


Figure 5. (a) the spherical and semi-spherical shape of AgNPs (b) the area of AgNPs (c) the diameter of AgNPs

Table 3. the diameter and area of AgNPs

	N total	Mean	Standard Deviation	Sum	Minimum	Median	Maximum
Diameter	40	17.61475	5.81052	704.59	8.206	17.1135	32.063

	N total	Mean	Standard Deviation	Sum	Minimum	Median	Maximum
Area	20	251.7696	149.0885	5035.392	66.187	218.5985	636.017

Wounds healing test

To explore the mechanism of action of the cross-linked hydrogel bandage for wound healing, mice were divided into groups, the control group and the hydrogel bandage group. Fig.6 presents the results of wound healing on day 1, 3, 10, 16 and 23. Figures 6 & 7 show that all the wounds presented gradual healing for up to 23 days. On the fourth day, it was clear that the healing rate increased for both groups, but there was a slight increase for the cross-linked hydrogel group where it was 30.97% comparing to the control group 23.81%. These percentages increased with time, but the hydrogel group had a much faster rate of healing. On the 10th day, it was found that the healing rate grew up by 79.86% while the healing rate of the control group was slow, only 49.75%. It is clear from the results and over time that the hydrogel group has the ability to enhance the formation of blood vessels in the wound area during the healing process. On the 23 day, all the wounds of the hydrogel group were healed without scarring and an improvement in tissue quality with hair growth. As for the control group, the wound closure rate was 94.94%, which is due to the natural immunity of the animal [see table 4] [40]. The hydrogel's containment of polymers helped reduce inflammation, scarring,

and speed up the healing process [41,42]. Also, the presence of AgNPs in the hydrogel, worked to kill the microbes that lead to contamination of the wound and disrupt the healing process. Moreover, Ag⁰ particles acted to reduce free radicals in the wound area, such as (OH⁻) group and (O²⁻), which discourage the growth of fungi and bacteria in the wound area [43].

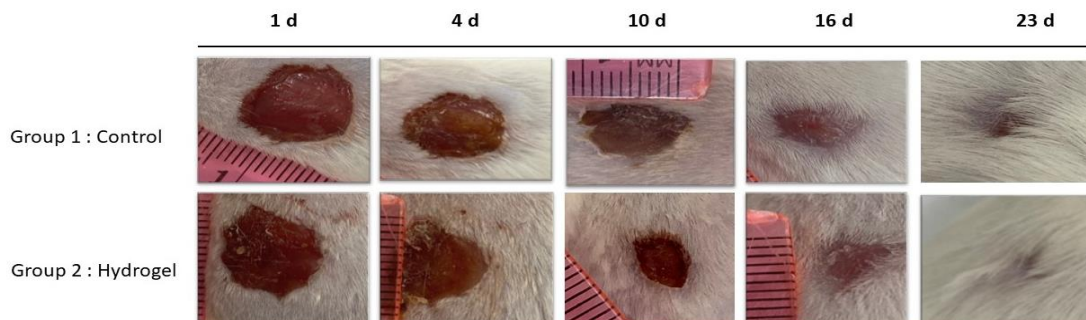


Figure 6. Comparison of wound healing activity of Group 1 (Control group) and Group 2 (Hydrogel)

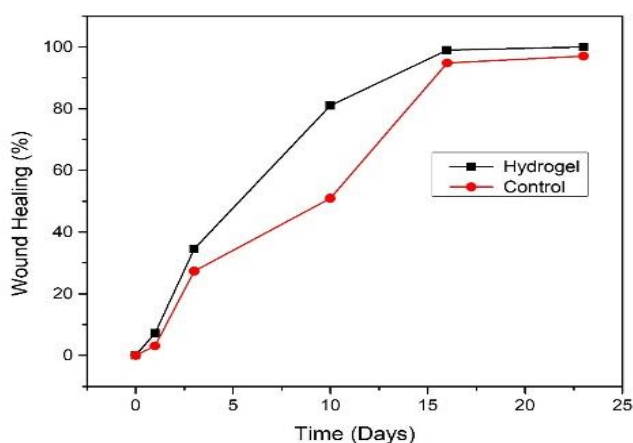


Figure 7. the percentage of wounds healing activity of Group 1 (Control) and Group 2 (Hydrogel)

Table 4. The wound closure rate

Evaluation of wound area mm ² and wound contraction % of two groups over a period of 23 days				
Observation Days	Wound Area (mm ²) and Percentage of Wound Contraction			
	Group 1 : Control		Group 2 : Hydrogel	
	Area (mm) ²	% Contraction	Area (mm) ²	% Contraction
0	146.31 ± 0.21	NIL	103.46 ± 0.06	NIL
1	140.51 ± 0.41	4.22	99.265 ± 0.18	4.05
4	111.467 ± 0.63	23.81	71.417 ± 0.51	30.97
10	73.511 ± 0.31	49.75	20.836 ± 0.32	79.86
16	30.598 ± 0.27	79.08	11.263 ± 0.21	89.11
23	12.55 ± 0.46	91.42	5.23 ± 11	94.94

IV. Conclusions

The development of wound dressings is a hot topic for skin wound care. The wound dressing should provide a moist environment at the site of the wound, cover the wound completely, absorb the secretions of the wound, and facilitate the healing process. In this study, a hydrogel was prepared from three biopolymers, which are HEC, HA and SA loaded with AgNPs via the green chemistry method. The physicochemical properties of the hydrogel were characterized in vitro and in vivo. The results represented that the hydrogel was swollen and deteriorated somewhat well, and also showed the ability of the hydrogel to resist microbes from fungi and bacteria as a result of it containing AgNPs. In addition, the hydrogel showed its ability to promote cell growth and the process of wound healing. A normal growth without scarring compared to the control was observed. In conclusion, the present study showed that the prepared hydrogel loaded with silver nanoparticles could be considered as a functional wound dressing material without scarring.

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Conflicts of Interest

The authors declare no conflict of interest

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