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Silver Sulphadiazine- xanthan gum- hyaluronic Acid Composite Hydrogel for Wound Healing: Formulation Development and *in vivo* Evaluation

M. O. ILOMUANYA[1,2 A-F], Z. A. SERIKI[1, BCF], U. N. UBANI-UKOMA[*1 DEF], B. A. OSENI[1, DEF], B. O. SILVA[1, EF]

[1] Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy. University of Lagos, PMB 12003, Surulere, Lagos, Nigeria
[2] Center for Biomedical Research, Population Council, 1230 York Avenue, New York, NY, 10065, USA

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article.

Abstract

Background: Development and modifications of hybrid hydrogels have been done to improve biological properties or to decrease the disadvantages of biomaterials.
Objectives: The efficacy of hyaluronic acid in combination with silver sulphadiazine in wound healing was investigated. The retaining properties of xanthan gum to aid re- epithelialization was also explored.
Materials and Method: Four hybrid hydrogels comprising of different concentrations of xanthan gum, eugenol and antimicrobial agents – hyaluronic acid and silver sulphadiazine were formulated. The physicochemical properties of the gels were assessed, and the antimicrobial effectiveness of the different hydrogel were determined using the extent of wound closure as an index.
Results: The hydrogel samples had approximately 90% moisture content with rate of evaporation between 26- 32% for a 5 h period at 37ºC. The pH of all formulations was between 7.59 - 8.05 considering that the formulation would be applied to underlying tissues of the skin. The swelling index after a 12 h period in distilled water was 10% for HX 1, 27% for HX 2, 29% for HX 3 and 30% for HX 4. There was no new peak observed in the FTIR analysis to indicate formation of new bonds.
Conclusion: Incorporation of silver sulphadiazine at 0.1% and hyaluronic acid at 1.5% in the formulation yielded the best results with regards to least presence of inflammatory cell infiltrates and excellent wound closure at 14 days compared to the control and other formulations. Further investigation may be required for clinical use as an effective wound dressing material.

Keywords: Silver sulphadiazine, Xanthan gum, Hyaluronic acid, Hydrogels, Wound healing.

INTRODUCTION

Wound refers to a breakage or damage to the epithelial lining of the skin which may be due to physical or thermal effect that leads to disruption in structure or function of tissues around the area of impact (Kamoun *et al.*, 2017). They are susceptible to complications from other presenting conditions of the patient like co-morbidity, medication, lifestyle and infection; these can elicit immune response in the body that cause inflammation and tissue damage that delay the process of wound healing (Cartotto, 2017) and cause debilitating pain. A moist environment also aids re-epithelialization and reduces scar formation (Junker *et al.*, 2013)

Although, there are various commercially available wound dressings including silver sulphadiazine creams, limitations to their use pose a greater problem

in terms of conformability of membranes and sheets with wound surfaces, and presence of antimicrobial agents that might elicit cytotoxic effects due to prolonged exposure (Cartotto, 2017; El-Kased *et al*., 2017; Morsi *et al.,* 2014;). The ability to provide moist environment for wound healing and accessibility still pose a serious challenge to some of the available wound dressings. In chronic wound healing, different factors are considered in making wound dressings which includes providing moist environment for healing, preventing infections, reducing bacterial load at the site of healing or content of dressing aiming to aid wound healing. Focusing on hyaluronic acid and xanthan gum as a composite, the individual characteristic of each agent would be explored but conjoined to enhance wound healing as hydrogels to provide a moist environment for the wound healing process, allow the composite to conform with the shape of the wound without wrinkling thereby leaving little or no scar after the healing process.

Previously, efficacy of formulated hyaluronic acid-gelatin hybrid hydrogel in animal wound model was investigated (Higley *et al.,* 2016; Ilomuanya *et al.,* 2018). Though different beneficial effects of xanthan gum and gelatin have been accessed in research works and the effectiveness of gelatin- hyaluronic hydrogels have been elucidated in wound healing, there is no report yet for xanthan gum- hyaluronic acid hydrogel and evaluation of its efficacy in wound healing.

Xanthan gum is a polysaccharide derived from the bacterium *Xanthamonas campestris.* It is a water-soluble polymer that consists of repeated units of D-glucose, D-mannose and D-glucuronic acid units (Saidin *et al.,* 2018). It is 100% natural and biodegradable.

Xanthan gum has been used in colon specific drug delivery systems (CDDS) to target delivery of medicaments to the colon where they are selectively degraded. It has also been used as a thickening, suspending and emulsifying agent in hydrophilic systems (Ramasamy *et al.,* 2012). Xanthan gum solutions are stable in acidic and basic conditions, thermally stable and its pseudoplastic property ensures good pourability of the finished dosage form (Alhalmi et al., 2018). In this study, its suspending and flow properties will be exploited to ensure homogeneity and stability of the formulated hydrogels.

In this study, the ability of hyaluronic acid to regulate inflammation and trigger building of blood vessels in the cascade of wound healing and moisture absorption, antimicrobial properties of silver sulphadiazine (Venkataraman and Nagarsenker, 2013) and retaining properties of xanthan gum to aid re- epithelialization were evaluated in an *in vivo* model.

METHODOLOGY

Materials

Xanthan gum powder (CAS: 11138-66-2, Zhejiang Taizhou, China), Silver sulphadiazine powder (Xi'an Pino Biotech Co., Ltd), Eugenol (Dharma research Miami, FL USA), Hyaluronic acid (Jinan Shangyang Medical Technology Co., Ltd), Sodium periodate solution (Sigma–Aldrich St. Louis, USA), Glutaraldehyde (Agar Scientific), Milli-Q water (Millipore, USA). All other chemical reagents and solvents were of analytical grade and were used for this research without further purification.

Method

Formulation of the hydrogels

Hyaluronic acid sodium salt powder (1 g), was dissolved at 1% (w/v) in double-distilled water (50 mL). Sodium periodate solution (2.67% w/v) was gradually added to HA at a molar ratio of 1:1. The oxidation reaction was left to proceed for 24 h at 25^{o}C after which it was dissolved with varying portions of silver sulphadiazine, xanthan gum and eugenol already dispersed in 50 mL purified water. Xanthan-based hydrogels were prepared by mixing a 5 g/ L xanthan gum aqueous solution in the presence of eugenol a weak acid phenolic compound at 0.6 g/L (Mohammad *et al.,* 2019). The solutions were homogenized with a magnetic stirrer at 500 rpm for 30 min at 65 ^{o}C, and centrifuged for 5 min at 700 rpm, to remove air bubbles. The xanthan gum and hyaluronic acid hydrogels were then mixed in a closed system (Table 1).

Table 1: Composition of Silver sulphadiazine- xanthan gum- hyaluronic acid composite hydrogel

Formulations	Xanthan gum (% w/w)	Hyaluronic acid (% w/w)	Silver sulphadiazine (% w/w)	Eugenol (ml) (% w/w)
HX 1	0.6	5	-	0.5
HX 2	0.6	2.5	-	0.5
HX 3	0.6	5	0.1	0.5
HX 4	0.6	1.5	0.1	0.5

Physicochemical characterization of hydrogel

The hydrogels were evaluated for viscosity using a Brookfield AMETEK SC4-28 High-Range Viscometer. The rheological properties of the varying hydrogels were assessed in triplicate at 40 rpm. Using a pH 700 Benchtop Meter, double-junction refillable glass pH electrode, ATC probe and probe stand the pH of the samples were measured in triplicate. The Scanning electron microscopy (SEM) was utilized to assess the structure of the gels using a JEOL JSM-840 scanning electron microscope (Jeol USA, Inc., MA, USA) after coating the samples with gold using a Hummer Sputter Coater (Technics, Ltd.). Infrared transmission spectra were also obtained using a BOMEM MB 104 FTIR spectrophotometer. The samples were dispersed in potassium chloride (6% w/w), ground to fine powder using an agate mortar and then compressed into a KBr disc at 10000 psi, which was then scanned with a resolution of 4 cm^{-1} in the wave-number range of 400-4000 cm^{-1}.

Determination of moisture content of hydrogels

Using the standard IUPAC method for the determination of moisture content; 2 g of sample was heated in a porcelain crucible in a temperature-controlled water bath for about six hours at 105 ºC. It was then cooled in desiccators and weighed again. The moisture percentage (MP) in the HX hydrogels was calculated using Equation 1

$$MP = 100 \times \left(\frac{W_1 - W_2}{W_1}\right) \text{.....Eq. 1}$$

where, W_1= original weight of the sample before drying and W_2 = weight of the sample after drying.

Rate of water evaporation from hydrogels

The rate of evaporation of water from biological dressings plays a vital role in maintaining wound moisture by retaining the water within the dressings. These composite hydrogels in different ratios were put in dishes and were kept at 37 ºC and 35% relative humidity. At regular intervals (1 hour) for a period of 12 h the weight was noted in triplicate and results reported ± SD.

Gel content and degree of swelling at equilibrium

Gel content was evaluated using Equation 2 to determine the total concentration of the polymer present in the formulation that was to undergo gelation. To evaluate the rate at which the formulation would swell at equilibrium (Q) Equation 3 was utilized.

$$Gel\ Content\ \% = \left[1 - \left(\frac{M_{pp} - M_{dg}}{M_{pp}}\right)\right] \times 100 \text{... Eq. 2}$$

$$Q = \frac{M_W}{M_{dg}} = \frac{M_s - M_{dg}}{M_{dg}} \quad \text{..... Eq. 3}$$

where M_{pp} is the initial mass of all polymer present in the hydrogel, M_{dg} is the mass of dried hydrogel, M_W is the amount of water absorbed by the gel and M_s is the mass of swollen hydrogel.

***In vivo* wound healing study**

Twenty-four male rats aged 12 weeks old weighing 185 - 210 g purchased from Joss Rattery® breeds Ibadan Oyo State were used in this study. The animals were kept in polycarbonate cages housed in well-aerated rooms, maintained under controlled temperature (30 ± 2 °C), relative humidity (45 ± 10%) and a 12 h light and dark cycle. They had access to a standard rodent chow diet, and clean drinking water ad libitum. This study followed the National Institutes of Health guide for the care and use of laboratory animals (National Institute of Health, 2011). All the experiments accorded with the Institution Guidelines and were approved by College of Medicine University of Lagos Health Research Ethical Committee CMUL/HREC/09/19/616. Wounds incised on the rats' dorsal surface with diameter 10 mm were covered with varying hydrogel formulations HX 1, HX 2, HX 3, and HX 4. Each wound was then covered with semi-occlusive polyurethane dressings. Excision wound margin was measured with a Vernier caliper. Wound contraction was measured in each 2 days interval, until complete wound healing and expressed in percentage of healed wound area. The evaluated surface area was then employed to calculate the percentage of wound contraction; initial size of wound is 10 mm^2 (Equation 4)

$$\%\ Wound\ Contraction = \frac{Initial\ Wound\ Size - Specific\ Day\ Wound\ size}{Initial\ Wound\ Size} \times 100 \text{ -----Eq. 4}$$

At day 14, the animals were euthanized, and the wounded area was sampled by trimming to include the dermis and hypodermis. The trimmed skin layers were fixed in 10% Neutral Buffered Formalin (NBF). Representative sections were then stained with hematoxylin and eosin (H&E) for histology.

STATISTICAL ANALYSIS

The data was presented as mean ± standard deviation of more than three experimental values for every variable and analyzed by one-way ANOVA. p-value ≤ 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Physicochemical characterization of hydrogel

The hydrogels prepared were all clear and had a slight odour. The consistency of the formulations varied depending on the concentration of hyaluronic acid incorporated into the hydrogel. The higher the concentration of hyaluronic acid in the formulation the higher the viscosity of the formulation

Moisture content of hydrogels

The values for the moisture content in the hydrogel samples as presented in Table 2, - HX 1, HX 2, HX 3, HX 4 are expressed as percentages 90, 95, 90 and 92, respectively. This evidently states that all the hydrogel samples do not contain less than 90% of water and would ensure adequate provision of moist environment to wound site and facilitate faster healing process. The moisture content of the composite hydrogels can also be attributed to the presence of hydrophilic groups.

Rate of water evaporation from hydrogels

The water retaining ability of hydrogels within wound dressings was evaluated by the rate of evaporation of water from the hydrogel. A notable characteristic of an ideal dressing is to provide adequate moisture to the wounded area. After an hour of exposure at 37^{o}C, there was negligible loss of water through evaporation but after the 5 hours, about 30% of the initial weight was lost via evaporation of water with HX 1, HX 2 and HX 3 having similar rate of 31%, 31% and 32% respectively and HX 4 had 26% loss via evaporation, this indicates that with respect to progression in time the hydrogels would lose their water content and be able to absorb exudates from wound thereby maintaining moisture balance on wound surface (Figure 1a) . Generally, the pH of a normal skin is found to be slightly acidic around 4- 6. However, in wounds, there is a loss of this pH value due to the exposure of the underlying tissues with internal pH of about 7.4. In chronic wound management, the pH of the wound tends towards the alkaline except when re-epithelization occurs, and pH tends towards being acidic at about 5.6. In modern standard care, wound dressings with pH around a mean of 7.4 has been employed (Schneider *et al.*, 2007). HX 1, HX 2 and HX 3 had pH of 7.45, 7.48, 7.36 respectively while HX 4 had 7.29, because only HX 3 and HX 4 had silver sulphadiazine incorporated into the composite hydrogel.

The aim of the FTIR study is to assess compatibility of all the ingredients used in the formulation development. The technique is used as a pre-formulation study for the development of products. The FTIR spectra of the composite hydrogels are represented in Figure 1b, to evaluate or identify any changes in peaks or peak shifts indicating interactions in the formulation. For all the hydrogel samples, the FTIR spectra shows two main peaks at-; 1632- 1637 cm^{-1} due to the bound water present in the xanthan gum and a broad band due to hydrogen bonded hydroxyl group (O-H) at 3420- 3434 cm^{-1} and is attributed to the complex vibrational stretching associated with free, intra and inter molecular bound hydroxyl group. There are multiple peaks between two spectra with almost similar absorption peaks in these spectra for all hydrogel samples, indicating that each compound incorporated in the hydrogel is not undergoing any major chemical interaction, hence all individual properties of each chemical compound is retained.

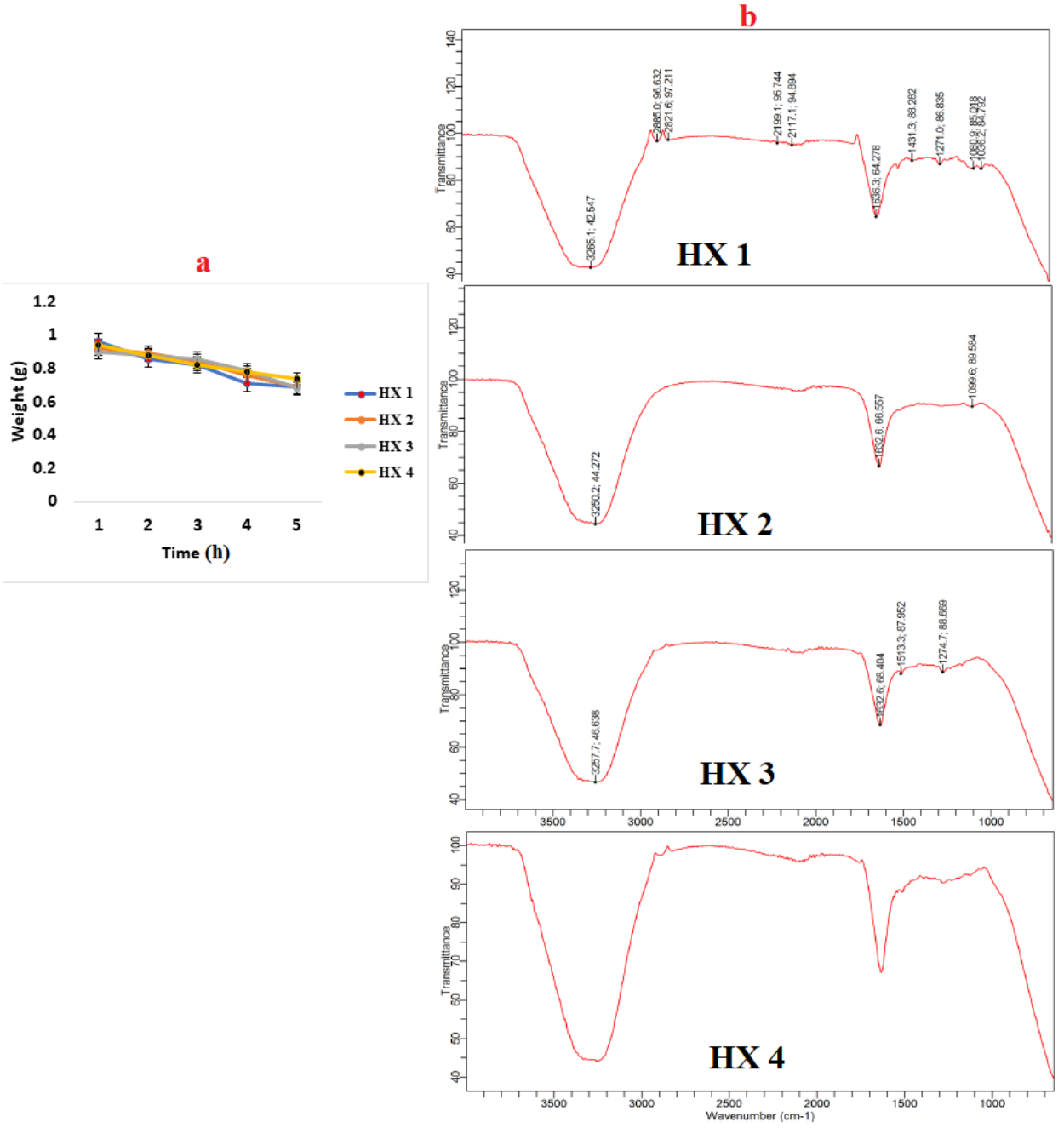

Figure 1. (a) Rate of evaporation of water from the hydrogel formulation at 25ºC after a 12 h period (b) FTIR spectra of hydrogel samples

Formulations	pH	Viscosity (MPa)	% Gel content	Swelling degree (Q)	% Moisture content
HX 1	7.45 ± 0.33	1120 ± 2.12	68.3 ±0.45	22 ± 3	90
HX 2	7.48 ± 0.29	1080 ± 3.12	61.3 ±0.94	17 ± 2	95
HX 3	7.36 ± 0.17	1290 ± 1.54	69.1 ± 0.34	25 ± 2	90
HX 4	7.29 ± 0.46	1160 ± 3.14	58.7 ±0.33	17 ± 1	92

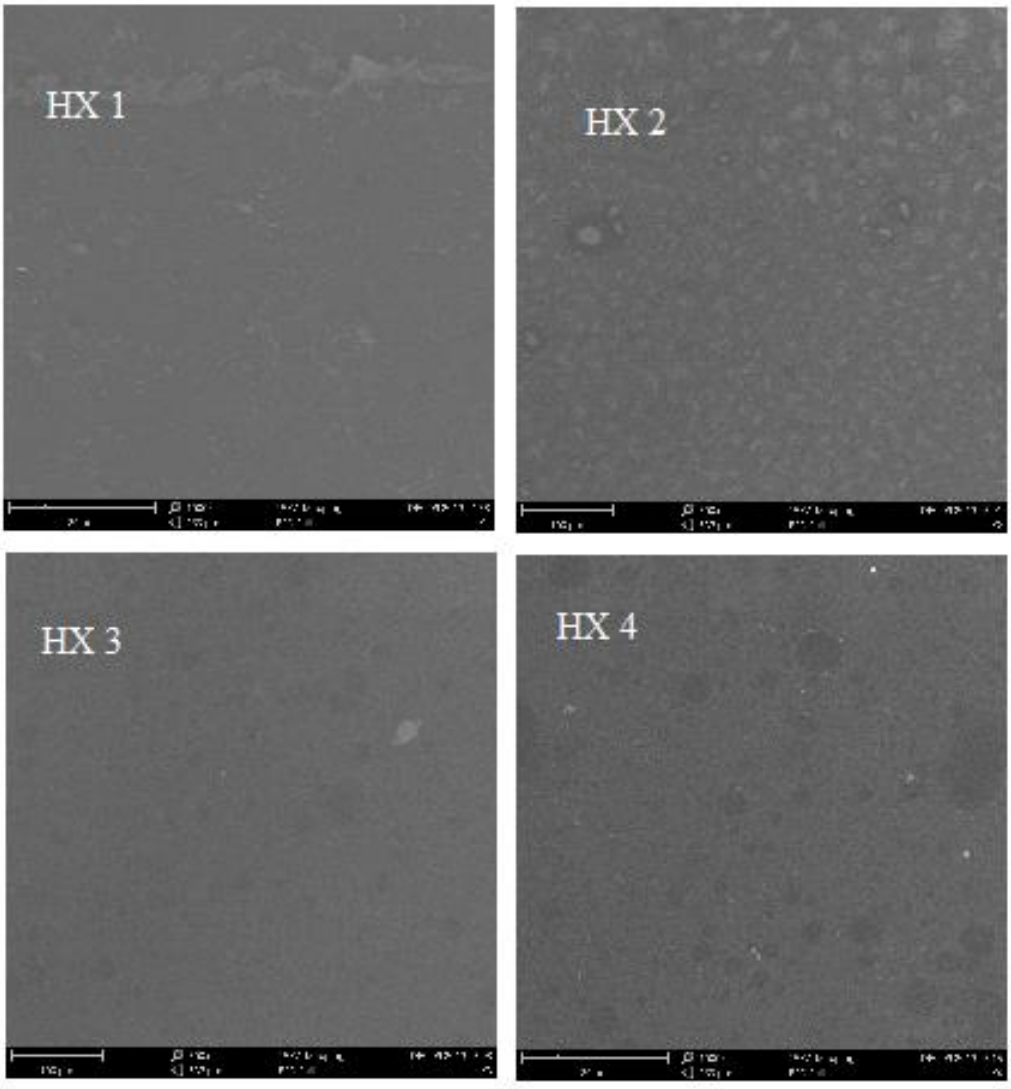

Figure 2: Surface morphology of composite hydrogel as determined by SEM

Table 2: Physicochemical characterization of the hydrogels

Gel content and degree of swelling at equilibrium

The gel content of the formulation was appreciable and in tandem with the concentration of polymer contained in the formulation. HX 3 had the highest gel content of 69.1 ± 0.34 (Table 2), this can be attributed to the 5% hyaluronic acid gel concentration in its formulation and this also led to its increased viscosity of 1290 ± 1.54 MPa.

***In vivo* wound healing study**

For the animal study using wound contraction rate as method of evaluation, all the rats utilized for the study survived throughout the postoperative process until euthanisation. During the period of treatment, there was no visible inflammation and no evidence of tissue necrosis observed on the wounds in all the rats due to the antioxidant effect of eugenol and this was presented pictorially in Figure 3. After the 10-Day treatment period, there was 45.34% wound contraction in the negative control, 70.16% in HX 1, 71.47% in HX 2 and HX 3, 71.75% in HX 4 and 72.57% in the positive control as presented in Figure 3. HX 4 had the highest wound contraction rate compared to all other hydrogel sample while the negative untreated control had the least wound contraction with presence of hemorrhage. HX3 had the highest viscosity as a result of its high hyaluronic acid content and the presence of the PAI silver sulphadiazine. Increased concentration of HA led to a higher water retention capacity of the formulated hydrogels, ensuring that the formulations were retained on the surface of the wound there by increasing the rate of wound contraction (Figure 3a) for HX3 and HX 4.

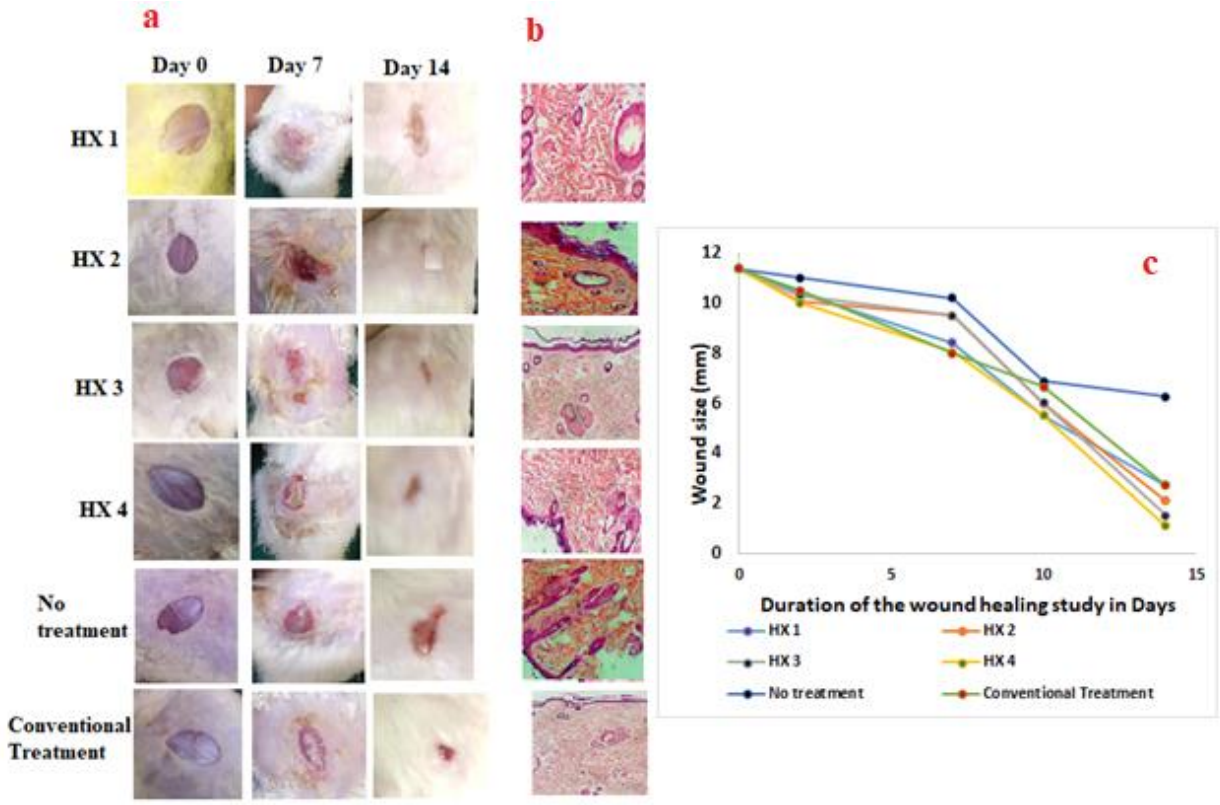

Figure 3. (a)Representative images of wounds as days elapsed showing marked difference between varying hydrogel HX 1, HX 2, HX 3 and HX 4, no treatment group cover with gauze and conventional treatment Sofratulle gauze containing Framycetin sulphate BP 1%, (b) Representative sections stained with hematoxylin and eosin 14 days post treatment (H&E) (c) wound contraction in the animals treated with varying hydrogels and control.

Hydrogels generally are expected to have high moisture content to maintain their dimensional stability and integrity. The solubility and diffusion of the active ingredients in hydrogels for biomedical application is essentially enhanced by the moisture content of the hydrogels (Bueno *et al.,* 2013; Vladimir *et al*., 2017). The swelling index is a very important characteristic of hydrogels, because the relationship between the nature of the swelling medium and swelling of the polymer is fundamental (Kim *et al.,* 2015). The hydrophobically -modified cross-linked hyaluronic acid polymer effectively imparts uniformity to the hydrogel formulations. The water content of hydrogels may be responsible for swelling or shrinking when exposed to external conditions and may be influenced by pH, temperature and solvent nature or nature of biological fluid. After a 12 h period in distilled water, HX 1 containing 5% of hyaluronic acid had the *Q* of 22 which was the highest swelling degree due to the total polymer content of this formulation. The pores of the hydrogel allowed

significant uptake possibly due to the hydrophilic properties and other bonds of the hyaluronic acid.

The surface of the hydrogel samples as indicated in Figure 2 from the SEM analysis is predominantly homogeneous indicating good porosity. Porosity of the composite hydrogel affects the diffusion of oxygen and nutrients especially in the absence of a functional vascular system (Ilomuanya, 2020). Thus, porosity observed in the hydrogel samples indicate ability to elicit beneficial effects on wound healing. The animals that were treated with HX3 and HX 4 composite hydrogels had better wound presentation due to the synergistic antioxidant and antibacterial properties of eugenol and silver sulphadiazine, the control drug and the formulated hydrogels were all superior to the untreated control which showed a dense wound area with blood. The hydrogel samples did not cause haemorrhage or increase its incidence as observed with the untreated negative control. Relative wound size reduction was almost similar in all hydrogel samples - HX 1, HX 2, HX 3 and HX 4 compared to the control drug and negative control. The presence of silver sulphadiazine and high amount of hyaluronic acid in HX 3 enhanced the physical appearance of the wound compared to all other samples of hydrogel but HX 4 with the least amount of hyaluronic acid 1.5% and silver sulphadiazine had a better histological presentation compared to all other hydrogel samples. The presence of silver sulphadiazine and hyaluronic acid in HX 3 and HX 4 facilitated removal of products of inflammation through its antioxidant activity thus facilitating wound healing.

In undamaged skin, the epidermis (surface layer) and dermis (deeper layer) form a protective barrier against the external environment. A distortion or impact on the structure activates the repair process of both multiple cellular and extra-cellular pathways in a tightly regulated and coordinated fashion, with the aim of restoring tissue integrity through four distinct phases: haemostasis, inflammation which involves epithelization, proliferation and tissue re-modelling.

The hydrogels showed comparable results with the conventional product (Framycetin Sulphate 1% - Sofra-Tulle®) but the number of infiltrated inflammatory cells was significantly higher in HX 1 than any of the formulations (Figure 3b).The wounded skin area was considerably reduced in the hydrogel formulations because the hydrogels facilitated the re-epithelization and reconstruction of skin tissues on the full-thickness wounds better than the control. They contained more collagen tissues and less inflammatory cells compared to the control. This is also evident by the percentage of collagen in the granulation tissue which was higher for the hydrogel formulations when compared with the control and conventional product. As seen in the histological examination (Figure 3b), carried out after a 14-day treatment period, all hydrogel samples were able to aid formation of fibro collagenous stroma (dermis) containing sebaceous gland and hair follicle. The hydrogel sample containing the least amount of hyaluronic acid and 0.1% silver sulphadiazine had the most significant physical healing and the most dense dermis than the other formulations. Only the HX 4 samples had a defined thickness of central region from epidermis to dermis that is similar to the positive control and this can be due to the fact that it had the least but optimal amount of hyaluronic acid that aided tissue regeneration in conjunction with the antioxidant properties of eugenol and antibacterial properties of silver sulphadiazine and its high swelling index that indicated adequate moisture availability for the healing region.

CONCLUSION

In conclusion, silver sulphadiazine, xanthan gum, hyaluronic acid, eugenol and purified water were used to fabricate a series of composite hydrogels. All hydrogels displayed good effect on wound healing but HX 4 sample containing 0.1% silver sulphadiazine and 1.5% hyaluronic acid is the best with regards to least presence of inflammatory cell infiltrates compared to control and excellent wound closure at 14 days.

Further investigation may be required for clinical use as an effective wound dressing material.

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*Address for correspondence: Uloma N. Ubani-Ukoma
Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy
University of Lagos
PMB 12003, Surulere
Lagos, Nigeria
Telephone: +234 813 135 4110
E-mails: uubani-ukoma@unilag.edu.ng

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