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ORIGINAL ARTICLE

Vitamin E incorporated in Carboxymethyl Cellulose-Gelatin Hydrogel Increases Wound Healing

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ABSTRACT

Improving wound care products to facilitate effective skin repair is very important. Hydrogels are promising polymer-based dressings that enhance wound healing. Vitamin E can improve skin injuries by increasing antioxidant capacity. This study aimed to construct an innovative hydrogel from carboxymethyl cellulose (CMC) and gelatin (Gel) containing vitamin E to enhance wound healing.

Five unique hydrogel formulations were constructed by combination of CMC-Gel and 25, 50, 100, and 200 µL/mL of Vitamin E. Structural characteristics of hydrogels were assessed using scanning electron microscopy (SEM) and Fourier-transform infrared spectroscopy (FTIR). Biochemical properties of hydrogels, including swelling, weight loss, pH values, and blood compatibility, were evaluated by specific methods. The cytotoxicity effects of hydrogels on the NIH-3T3 fibroblasts were determined by MTT assay. The therapeutic potential of the hydrogels was investigated using a full-thickness wound model in Wistar rats. The constructed CMC-Gel-Vit E hydrogel had a porous structure characterized by interconnected voids measuring 73.15±9.61 µm, which is favorable for promoting cell migration. The cytotoxicity results showed no toxicity effects of hydrogels with and without VitE 100 µL/mL, also a survival rate of over 120% in cells after 72 h. In vivo data showed the CMC-Gel-Vit E hydrogel (91.36±8.23%) significantly increased the percentage of wound closure and re-epithelialization compared to the control group (68.31±13.59%).

The results highlight the considerable potential of the CMC-Gel-VitE hydrogel as a viable option for skin regeneration and wound healing. This hydrogel exhibits substantial promise for use in clinical and therapeutic interventions.

Keywords: Skin Regeneration, Hydrogel dressing, NIH 3T3 Cells, Tocopherols, Biopolymer

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Introduction

The skin is one of the largest and most essential organs in the body; the skin develops and regenerates itself throughout life (1). It covers the whole exterior surface of the body and acts as the primary protective layer. Extensive research has been performed to better understand the structure and function of the skin, with significant developments in research over the last decade (2). The skin includes numerous functions and objectives, the most fundamental of which is to protect internal organs from external assaults (3). Furthermore, it aids in preventing excessive loss of body water. Through an assortment of nerves related to the central nervous system, the skin responds to fluctuations in temperature (hot and cold), pressure, touch, and pain, making it a crucial sensory organ (4, 5).

A healthy skin structure is composed of three layers: epidermis, dermis, and hypodermis. Cells, fibers, blood vessels, and nerves are all found in these layers. However, the skin is delicate and any injury to it could expose the body to infections, which could cause severe cases of impairment or even death (6). Necrosis is one of the most prevalent skin ailments that can cause considerable costs, reduce performance, and interfere with individual's physical activities (3, 7). An injury known as a wound is caused by the bursting of skin cells as a result of external violence. Numerous variables, including age, the presence of infection, and moisture content, affect how quickly wounds heal. Scars are one of the most important side effects left by wounds. Scar formation is a type of fibrotic tissue response that results from excessive deposition of extracellular matrix (ECM) components such as collagen, combined with an imbalance in fibroblast proliferation and apoptosis. This procedure is not only aesthetically unappealing but also results in functional difficulties.

The increase of various infections caused by bacteria has made wound care more challenging, which is a serious public health issue (8, 9). Several methods such as use of plant extracts and drugs that stimulate skin regeneration, stem cells, biological coatings and hydrogels based on biocompatible polymers, hydrogels, 3D printing, laser therapy, etc. for improving scars and healing wounds have been discovered and suggested in recent years (10-14). Recently, hydrogel-based wound dressing materials have drawn some critical attention due to their biocompatibility, biodegradability, non-toxicity and their cost-effectiveness. Among these, wound dressings derived from Carboxymethyl Cellulose (CMC) have garnered particular attention owing to their advantageous physicochemical properties. Carboxymethyl cellulose (CMC) is a semi-synthetic polymer characterized by its remarkable ability to absorb water and swell. It is considered physiologically safe and exhibits compatibility with various biological tissues, including mucous membranes and skin. Due to these properties, CMC is suitable for use as a scaffold in applications related to wound healing and skin regeneration (15-17).

On the other hand, Gelatin is a naturally occurring polymer that can be obtained from insoluble collagen through the process of hydrolysis. As a derivative of collagen, gelatin shares many of its properties, making it a valuable material in various applications. Research has demonstrated that gelatin is biocompatible with human tissues, exhibiting flexibility and stability, and it can be modified to serve as a foundational scaffold. The amino acid composition of gelatin, which includes Proline, Glycine, and Hydroxyproline, closely resembles that of collagen, effectively mimicking the extracellular matrix. Notably, the presence of glycine in gelatin plays a crucial role in facilitating cell adhesion (18-20).

Therefore, in the structure of CMC-Gel wound dressing, carboxymethyl cellulose plays the role of structural support and exudate absorbent, and gelatin plays the role of cell adhesion and providing conditions similar to the extracellular matrix. In a study by loading Omega-3 in CMC/Gel scaffold by hydrogel-emulsion method, they concluded that increasing the percentage of carboxymethyl cellulose leads to increased exudate absorption in the wound site and improved mechanical strength. Increasing the ratio of gelatin was associated with improving the biocompatibility of 3T3 fibroblast cells (21).

Support of nutrition is one of the most important conditions for wound healing. For wounds to heal effectively, an extensive amount of macronutrients and micronutrients are required. In particular, cellular migration and proliferation are significantly impacted by vitamin insufficiency, making it a major element in the long-term healing of wounds. Ascorbic acid (vitamin C), vitamin A, vitamin E, magnesium, zinc, and iron are some of the micronutrients that are essential for wound healing. These components affect

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the overall quality of the recovered tissue in addition to accelerating the wound healing process (22, 23). Vitamin E is one component that greatly promotes wound healing. An essential fat-soluble antioxidant that protects cells from oxidative damage is vitamin E. Herbert M. Evans initially described it in 1922, and in 1936, it was biochemically determined to be Tocopherol (24, 25).

The most potent and prevalent forms of vitamin E in the body are tocopherols. They may protect against reactive oxygen species (ROS) through stimulating signaling pathways, which is why they are most commonly recognized for their antioxidant capabilities. Although investigation has primarily concentrated on its antioxidant abilities, Vitamin E's involvement is more extensive and diverse (26).

Vitamin E has the potential to alleviate a number of pathological occurrences in the skin due to its important role in enhancing the body's antioxidant capacity. Since managing scars has always been crucial, a lot of investigation has demonstrated that vitamin E-containing therapies can have a beneficial effect on wound healing. As an anti-inflammatory, vitamin E can additionally reduce the production of excessive scar (27, 28). Parichehr Foroughi et al., in a study by loading vitamin E in polyvinyl alcohol/chitosan hydrogel, acknowledged that in the adhesion and cytotoxicity analysis of the samples, the non-toxic nature of the hydrogel was confirmed and it can be effective for wound healing (29).

Therefore, with the mentioned prerequisites of the effectiveness of carboxymethyl cellulose hydrogel and gelatin in creating a biocompatible and suitable bio-polymeric wound dressing for skin repair, this combination can be used to create a scaffold. Adding a repair agent such as Vitamin E can improve the specificity and effectiveness of the scaffold. In this study, it was designed to evaluate and characterize the mechanical, biological, and hemostatic CMC-Gel-Vit E wound dressing and to model a full-thickness wound in rats to provide a deeper insight in this field and to address the existing uncertainties and challenges.

Methods

Materials

Gelatin powder (Gel) (bovine skin, type B), Carboxymethyl cellulose (CMC) (viscosity ≈ 800–1200 mPa.s, Fetal bovine serum (FBS), and Dulbecco's modified Eagle's medium (DMEM) were obtained from Sigma-Aldrich (USA). Penicillin–Streptomycin (Pen-Strep), MTT ((3-(4, 5-dimethylthiazol-2-yl)-2.5-diphenyl-tetrazolium bromide), and Trypsin–EDTA were sourced from Gibco (Germany). Vitamin E was purchased from Daana pharmaceutical company (Tabriz, Iran). NIH/3T3 is a fibroblast cell line was sourced by Pasteur Institute (Tehran, Iran). Animal experiments were approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences, (ethics code: IR.AJUMS.REC.1402.513) and were carried out in accordance with the university's guidelines.

Construction of Hydrogel

The CMC-Gel hydrogel was prepared by dissolving Carboxymethyl cellulose powder (4% w/v) and Gelatin powder (3% w/v) in deionized H_2O for 12 h with 8:1 ratio. Then, different amount of vitamin E was added to the hydrogel from the previous step. It should be noted that Tween 80 surfactant (0.3% of the total volume of the final hydrogel) was added (1µL/10min) and homogenized for 30 minutes. The surfactant was added to the hydrogel gradually and drop by drop. Finally, phenoxyethanol should be added to 0.9% of the final volume of hydrogel for stability and preservative effects (Table 1) (21). Following the synthesis process, the hydrogels were preserved in a glass beaker at a temperature of -80 °C for a duration of 16 h. Subsequently, they were moved to a freeze dryer (Terrace, Spain) set at -54 °C, where they remained for 48 h to facilitate the development of a porous structure (Figure 1).

Characterization of the Scaffolds

Scanning Electron Microscope (SEM)

Surface characteristics (pore size and interconnectivity) of the fabricated lyophilized hydrogels were assessed with Scanning Electron Microscopy (SEM; DSM 960A, Zeiss, Germany). Freeze-dried hydrogels were coated with a thin layer of gold to enhance conductivity (SCD 004, Balzers, Germany) (5kV with 50X and 250X magnification). The assessment of the average pore diameter was conducted utilizing Image J software from the National Institutes of Health in Bethesda, USA, alongside Origin Pro 2024 software developed by Origin Lab in Northampton, USA. This evaluation involved scanning 20 randomly selected points within each image (30).

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Table 1. Formulation of CMC-Gel-Vit E for preparation 1 mL of hydrogels

Hydrogel (Sample)	Ratio CMC:Gel	Polymer (w/v)	Vitamin E (µL)	Tween 80 (µL)	Preparations Information
CMC-Gel	8:1	4:3	0	0	Dissolving CMC in deionized H_2O for 24 h on a stirrer (300 RPM) and Gel in deionized H_2O for 12 h on a heater-stirrer (500 RPM and 40 °C)
CMC-Gel-VitE 25	8:1	4:3	25 µL	3	Dissolving CMC in deionized H_2O for 24 h on a stirrer (300 RPM) and Gel in deionized H_2O for 12 h on a heater-stirrer (500 RPM and 40 °C)
CMC-Gel-VitE 50	8:1	4:3	50 µL	3	Dissolving CMC in deionized H_2O for 24 h on a stirrer (300 RPM) and Gel in deionized H_2O for 12 h on a heater-stirrer (500 RPM and 40 °C)
CMC-Gel-VitE 100	8:1	4:3	100 µL	3	Dissolving CMC in deionized H_2O for 24 h on a stirrer (300 RPM) and Gel in deionized H_2O for 12 h on a heater-stirrer (500 RPM and 40 °C)
CMC-Gel-VitE 200	8:1	4:3	200 µL	3	Dissolving CMC in deionized H_2O for 24 h on a stirrer (300 RPM) and Gel in deionized H_2O for 12 h on a heater-stirrer (500 RPM and 40 °C)

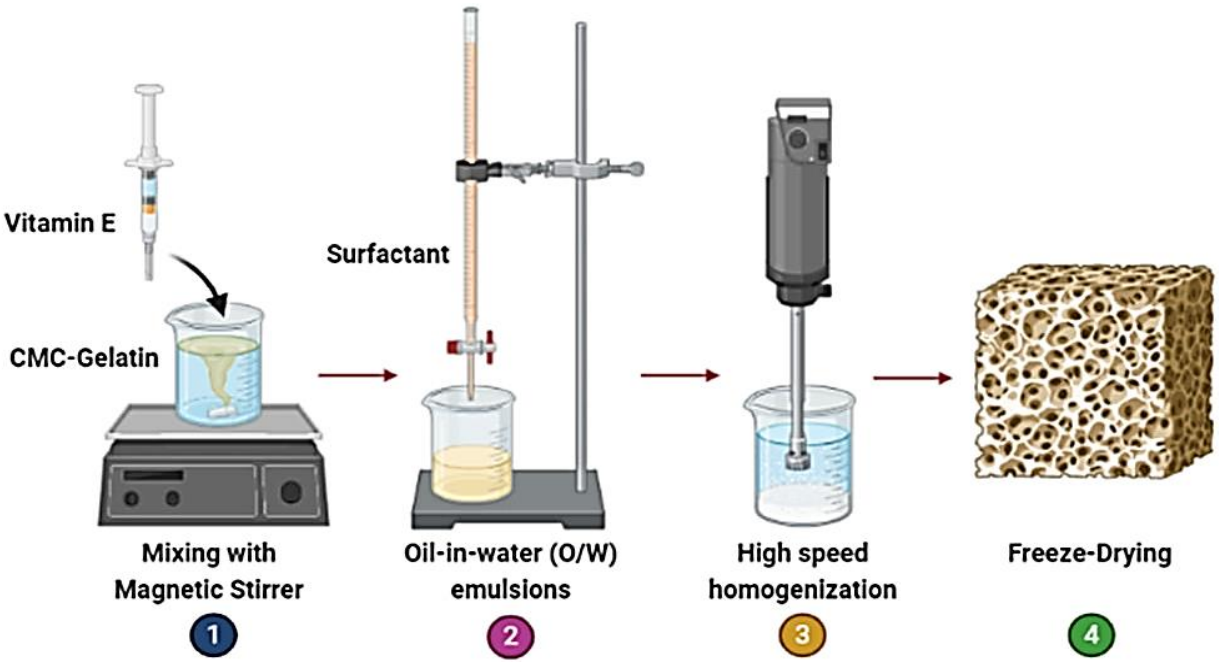

Figure 1. Steps to prepare CMC-Gel hydrogel containing vitamin E. Step 1) dissolving the Carboxymethyl cellulose and Gelatin in dd H_2O and stirrer with Vitamin E, step 2) Addition of Tween 80 to the CMC-Gel hydrogels, step 3) Homogenization of CMC-Gel-Vit E hydrogel, and step 4) Freezing and then freeze drying of hydrogel.

Fourier-Transform Infrared Spectroscopy (FTIR)

Fourier-transform infrared spectroscopy (FTIR) was employed to investigate the interactions among functional groups within various hydrogel structures, specifically CMC-Gel and CMC-Gel-VitE 200. The FTIR spectra were recorded over a wavelength range of 400 to 4000 cm^{-1} utilizing the FTIR spectroscopy technique (Spectrum GX, PerkinElmer, USA) (31).

Evaluation of hydrogels biochemical properties

The biochemical properties of hydrogels, including degradation, water uptake, blood compatibility, blood clotting index, pH values, and

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cytotoxic effects of hydrogels on NIH-3T3 fibroblasts, were evaluated by specific laboratory methods as previously described and published elsewhere (32).

Evaluation of Release of Vitamin E from Hydrogels

The determination of the quantity of Vitamin E released from the CMC-Gel hydrogel necessitates the construction of a standard curve for Vitamin E, utilizing a range of 20 values from 0.1 to 200 µL. Subsequently, CMC-gel hydrogels, each containing 1 mL, were immersed in 5 mL of simulated body fluid (SBF) within a shaker incubator maintained at 37 °C, operating at a rotational speed of 50 RPM. To assess the release of Vitamin E, the absorbance of the supernatants was measured at a wavelength of 295 nm using UV-visible spectroscopy at various time intervals, specifically at 2, 4, 6, 12, 24, 48, 72, and 96 h (33).Vitamin E concentration was quantified using a validated standard curve constructed from spectroscopic data of α-tocopherol standards. The concentration of Vitamin E was calculated by correlating their spectroscopic signals with the calibration curve.

In Vivo Studies

In Vivo Experiment Groups

18 adults' male Wistar rats weighing between 200–220 g was obtained from Shahroud University of Medical Sciences. The animals were housed under standard conditions, with food and water. All experimental procedures were performed based on the ethical guidelines committee of Ahvaz Jundishapur University of Medical Sciences, (ethics code: IR.AJUMS.REC.1402.513). Full-thickness skin wounds model (1.5 × 1.5 cm^2) was used to assess the effects of hydrogels on wound-healing (Figure 2).

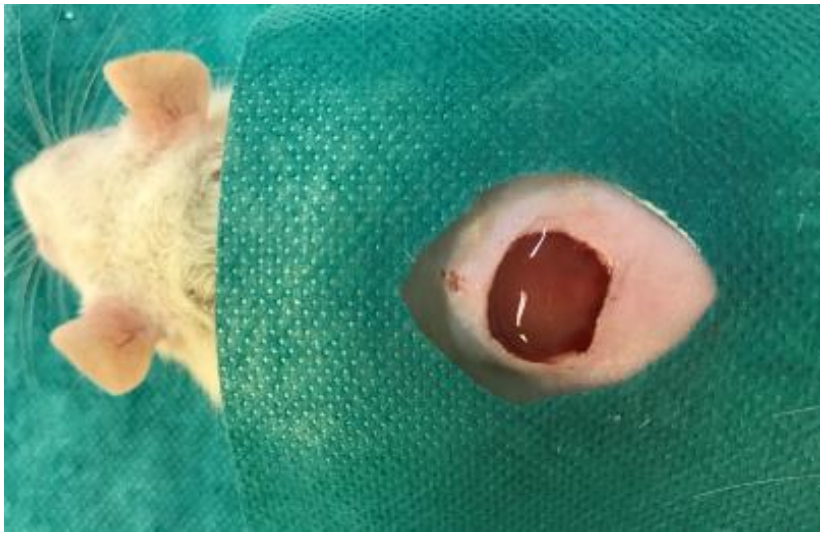

Figure 2. Full-thickness skin wounds (1.5 × 1.5 cm^2) was created by surgically on the backs of anesthetized Wistar rats. The model enables evaluation of wound healing dynamics, including re-epithelialization, granulation tissue formation, and contraction.

Briefly, anesthesia was induced in the rats using an intraperitoneal injection of 100 $mg.kg^{-1}$ ketamine and 10 $mg.kg^{-1}$ Xylazine. The dorsal rat skin was shaved, cleaned, and sterilized with 70% alcohol. The rats were then randomly divided to three groups, each consisting of six animals.

Group I: Negative control (treatment by sterile gauze applied), Group II: Treated with CMC-Gel hydrogel, Group III**:** Received CMC-Gel-VitE 100 hydrogel

After 14 days post-surgery, the animals were sacrificed, and defect tissue was taken for histological examination. Wound closure was assessed by measuring the percentage reduction in wound area (14).

Evaluation of Wound Closure

The wound healing processes were monitored through photographs taken on 14 days after surgery. Results were analyzed using Image J software. The percentages of wound closure were performed using the following Equation:

$$\text{Wound closure } (\%) = 1 - \frac{\text{wound area}}{\text{initial area}} \times 100$$

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Histological Analysis

The histological changes including re-epithelialization, collagen deposition, scar formation, angiogenesis, and granulation tissue development across the different groups were evaluated using Hematoxylin and Eosin (H&E) and Masson's trichrome (MT) staining. The harvested tissue specimens were fixed in 10% formalin for histopathological analysis. The samples underwent a dehydration process, were embedded in paraffin, and sliced into sections of 5 µm thickness (34). The histological slides were examined under a light microscope (Olympus BX51; Olympus, Tokyo, Japan).

Histomorphometry analysis

Histomorphometry analysis was performed to evaluate the process of epithelialization and vascularization. Semi-quantitative evaluation of re-epithelialization and angiogenesis on day 14 was performed according to a 5-point grading scale: 0.0 for absence of any new vascular or epithelial formation, 1.0 for minimal presence, 2.0 for moderate extent, 3.0 for significant occurrence, and 4.0 for complete (100%) formation. The findings were validated by a single independent observer who was blinded to the treatment groups during analysis (35).

Statistical Analysis

All statistical analyses were performed using Graph Pad Prism 10.2.2 software. The differences between groups were evaluated using ANOVA, followed by Tukey post-hoc test for multiple comparisons. A p-value < 0.05 was considered significant.

Results

Morphological Properties of hydrogels

The results of electron microscope analysis showed the details and surface structure of CMC-Gel and CMC-Gel-VitE 200 scaffolds (Figure 3). The electron microscope images clearly visualize the morphometric features. Based on this, the CMC-Gel lyophilized scaffold has a porous structure with a single pore and the scaffold containing vitamin E has a planar structure with fewer pores. Also, by measuring the average pores in the scaffolds, the diameters of 109.27±18.65 and 73.15±9.61 µm were obtained for CMC-Gel and CMC-Gel-VitE 200, respectively. Therefore, the addition of vitamin E to the structure of CMC-Gel hydrogel causes significant changes in morphology and porosity.

FTIR analysis

Fourier transform infrared spectroscopy (FTIR) analysis was used to identify functional groups and chemical composition of CMC-Gel and CMC-Gel-VitE 200 scaffolds. The fundamental characteristic peaks of CMC-Gel in the infrared spectrum are illustrated in Figure 4A.

The infrared spectrum of carboxymethylcellulose exhibits a prominent absorption band at 3346 cm^{-1}, which corresponds to the stretching frequency of the hydroxyl (OH) group and indicates the presence of both intramolecular and intermolecular hydrogen bonding (36-38).

Additionally, a peak observed at 2917 cm^{-1} is associated with the C-H stretching vibration. Furthermore, a newly identified band at 1588 cm^{-1} is attributed to the carboxylate (COO) group, while the bands at 1459 cm^{-1} and 1053 cm^{-1} are linked to CH_2 scissoring and CO-C stretching vibrations, respectively. Additionally, the peaks observed for Gelatin at 3308 cm^{-1} are linked to the presence of hydrogen-bonded water and amide-A, while the peak at 1599 cm^{-1} corresponds to amide-I. Furthermore, the band at 1244 cm^{-1} indicates amide-III, and the peaks ranging from 1460 cm^{-1} to 1380 cm^{-1} are attributed to the symmetric and asymmetric bending vibrations of the methyl group (39, 40).

The spectrum of CMC-Gel-VitE 200, illustrated in Figure 4B, reveals distinct peaks corresponding to various molecular vibrations. Specifically, the methyl asymmetric and symmetric bending vibrations are observed at 1455 cm^{-1} and 1366 cm^{-1}, respectively. Additionally, the C–O stretching associated with the phenolic group is detected at 1206 cm^{-1}, while the ether group manifests an absorption peak at 1107 cm^{-1}. Furthermore, the C–H stretching vibrations are represented by peaks at 2867 cm^{-1} and 2925 cm^{-1} (41-43). A comparative graph of CMC-Gel and CMC-Gel-VitE 200 lyophilized hydrogel is shown in Figure 3.

CMC-Gel-Vit E hydrogel increases NIH/3T3 fibroblast cell viability

The cytocompatibility of CMC-Gel and CMC-Gel-VitE hydrogel extracts was found to depend on both time and dosage. The biocompatibility of the extract

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obtained from the CMC-Gel and CMC-Gel-VitE (25, 50, 100, and 200 µL/mL) of hydrogels on the NIH/3T3 fibroblast cell line was assessed using an indirect MTT assay at 24 and 72 h , using cells seeded on a scaffold-free tissue culture plate as the control group. As depicted in Figure 5, the CMC-Gel-VitE 100 µL/mL composite scaffold exhibited an increase in cell viability (119.89±7.86% and 120.06±8.15% for 24 and 72h respectively), with absorbance values higher than those of the control group. In addition, after 72 h of the implantation period, the cells were effectively adapted to the environment, which confirmed the biocompatibility of the synthesized hydrogels. Therefore, in other in vitro and in vivo studies, CMC-Gel-VitE 100 µL/mL was used as the treatment group containing vitamin E.

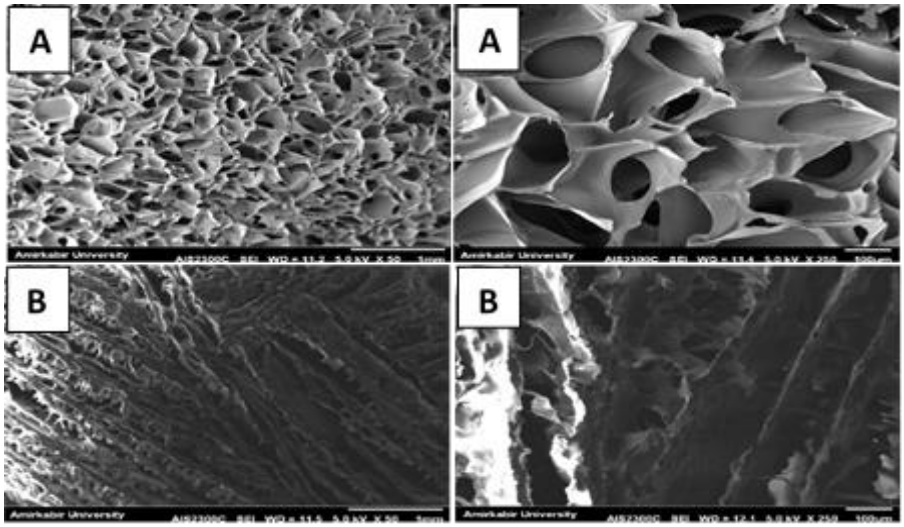

Figure 3. SEM images of CMC-Gel (A-A') and CMC-Gel-VitE 200 (B-B') with 50x and 250x magnification.

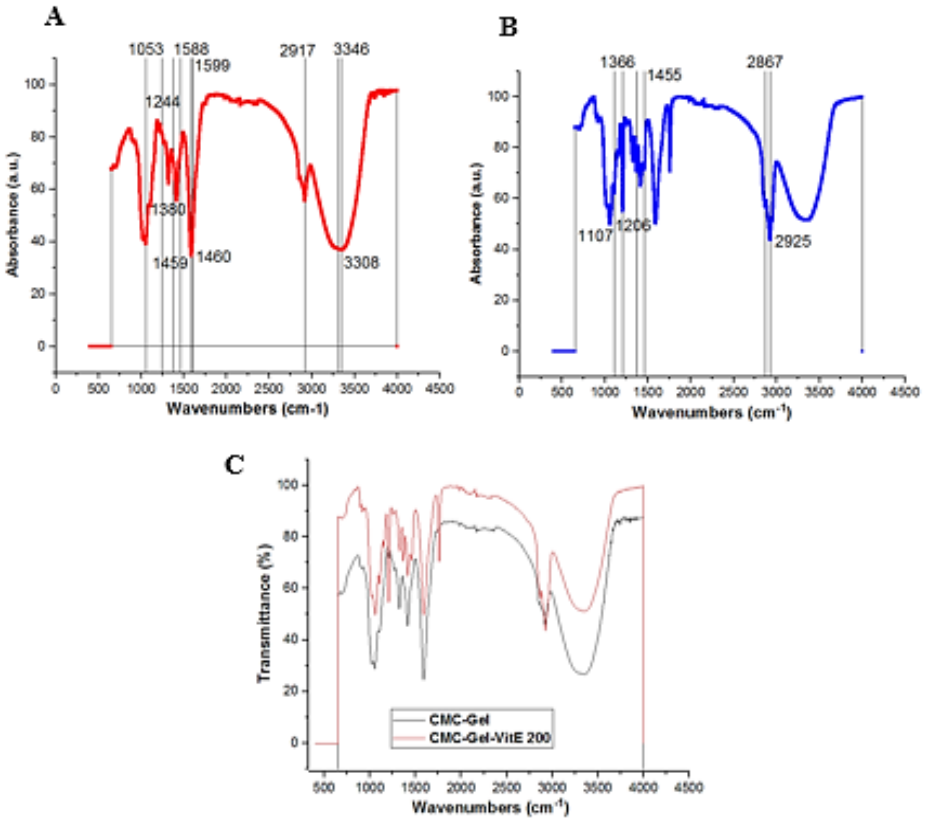

Figure 4. FTIR spectra of CMC-Gel (A), CMC-Gel-VitE 200 (B), and CMC-Gel/CMC-Gel-VitE 200 (C) hydrogels at 400 to 4400 cm^{-1}.

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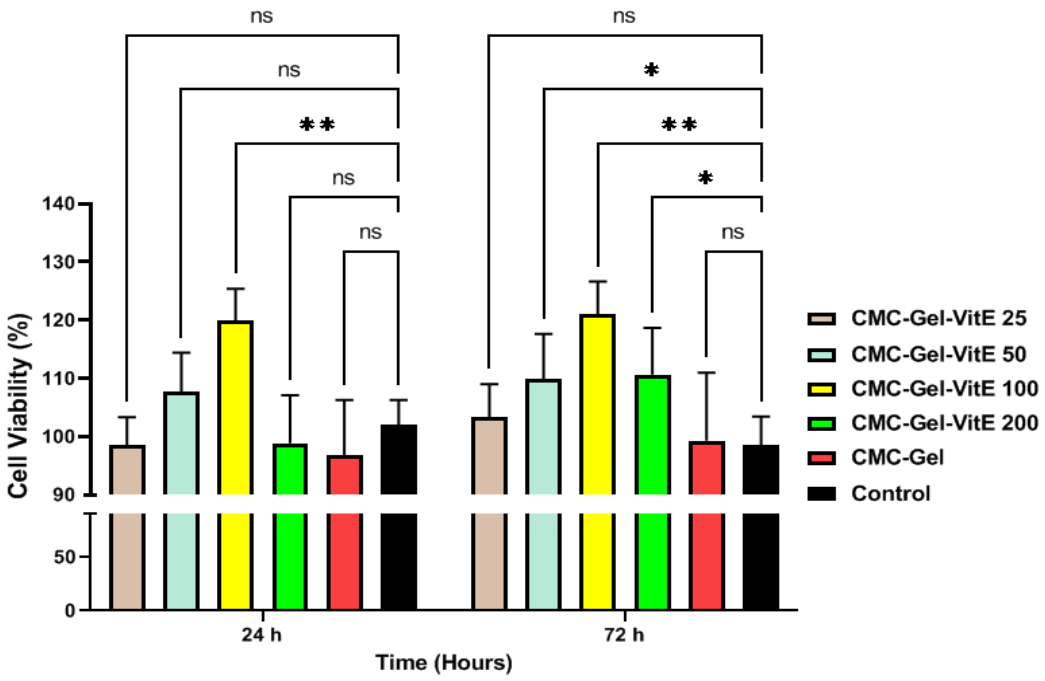

Figure 5. NIH/3T3 fibroblast cell viability % treated with the extract of hydrogels at two times. Values represent the mean ± SD, n = 3, *p < .05, **p < .01, and ns = non significant. SD: standard deviation.

Degradation rate of hydrogels

It is essential to align the degradation rate of a therapeutic scaffold with the regeneration rate of injured tissue (44). The degradation rates of the hydrogels were assessed at intervals of 2, 6, 12, 24, and 48 h, with the average values calculated and illustrated in Figure 6. The findings showed that the degradation rates of CMC-Gel and CMC-Gel-Vit E100 hydrogel well with the timeline of wound healing and showed that 93.85±4.12 and 83.12±7.92 percent of the hydrogels were degraded at the end of the 48 h, respectively. Based on the obtained results, CMC-Gel-VitE 100 hydrogel, despite the insoluble nature of vitamin E in water, has favorable biodegradability, which is not statistically different from CMC-Gel hydrogel group. The cause of this fact can be due to the appropriate concentration of vitamin E, which did not have a negative effect on the biodegradability of the scaffold.

Water Uptake behavior of hydrogels

To evaluate the potential of hydrogels as wound dressings, we investigated their swelling behavior in phosphate-buffered saline (PBS, pH 7.4) at 37 °C. An optimal wound dressing is expected to effectively absorb exudates from the wound while maintaining a moist environment conducive to healing (44). As illustrated in Figure 7, all seven hydrogel formulations exhibited a notable swelling capacity, attributed to their network structure with pores. The basic hydrogel (CMC-Gel) demonstrated water uptake rates that were comparable to and exceeded those of the CMC-Gel-VitE 100 variant. After 24 hours of treatment in PBS solution, no further increase in water absorption was observed and the maximum absorption of lyophilized hydrogel scaffolds of CMC-Gel and CMC-Gel-VitE 100 was 245.11±12.58% and 187.92±19.53%, respectively.

Consistent with the findings from the degradation analysis, the hydrophobic properties of vitamin E likely contribute to a reduction in swelling and fluid absorption. Nevertheless, the CMC-Gel-VitE 100 hydrogel continues to exhibit potential for liquid absorption, owing to the relatively low concentration of the active ingredient.

Blood compatibility behavior of hydrogels

In the early stages of inflammation, the relationship between hydrogels and erythrocytes is of paramount importance, particularly since wound dressings are frequently exposed to blood (45). Evaluating blood compatibility necessitates a thorough examination of the hemolysis rate of erythrocytes upon direct interaction with hydrogels and their active

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components. Consequently, we performed a hemolysis assay on the CMC-Gel and CMC-Gel-VitE 100 hydrogels prior to their application in wound care. The hemolysis ratio was determined by measuring the absorbance of the supernatant and comparing these values against established positive and negative controls. As illustrated in Figure 8, the hemolysis rates for CMC-Gel and CMC-Gel-VitE 100 hydrogels were found to be 4.07±0.81% and 1.91±1.05%, respectively (not statistically significant). These findings suggest that the hydrogels developed are compatible with blood, thereby affirming their potential applicability in the field of regenerative medicine.

Blood clotting index findings of hydrogels

The Blood Coagulation Index (BCI) serves as a crucial metric for assessing the coagulation efficacy of various dressings, where lower BCI values reflect enhanced coagulation performance (46). In this study, the blood clotting potential of CMC-Gel and CMC-Gel-VitE 100 hydrogels was analyzed through the BCI, which exhibited an inverse relationship with hemostatic capacity in vitro. Notably, the CMC-Gel demonstrated a lighter color in solution and a lower BCI compared to both the CMC-Gel-VitE 100 and control groups, suggesting its superior effectiveness in mitigating blood loss. The BCI values recorded was 27.84±2.51% for CMC-Gel, and 30.21±5.09% for CMC-Gel-VitE 100 (Figure 9).

The diminished hemostatic capability of the CMC-Gel-VitE 100 hydrogel can be attributed to the anticoagulant properties of vitamin E (47); however, this evaluation did not reveal any statistically significant differences among the groups.

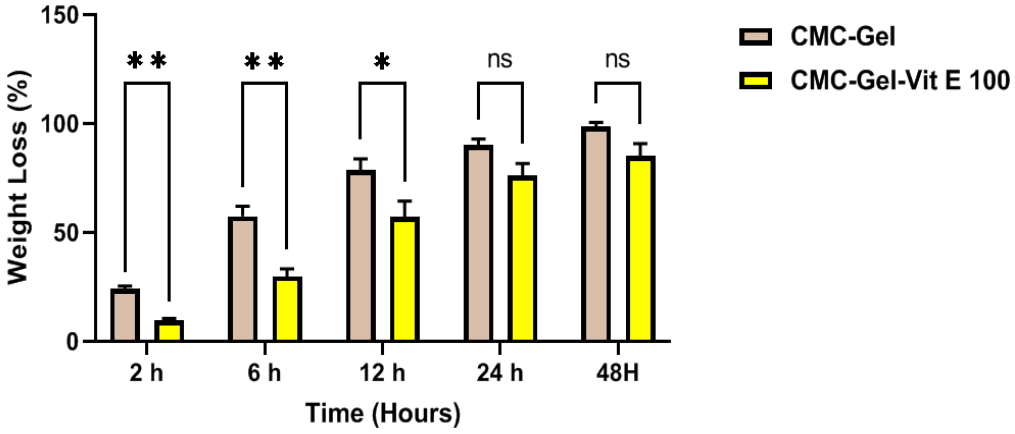

Figure 6. The percentage of weight loss in the hydrogels over 48 h. Values represent the mean ± SD, n = 3, *p < .05, **p < .01, and ns = non significant. SD: standard deviation.

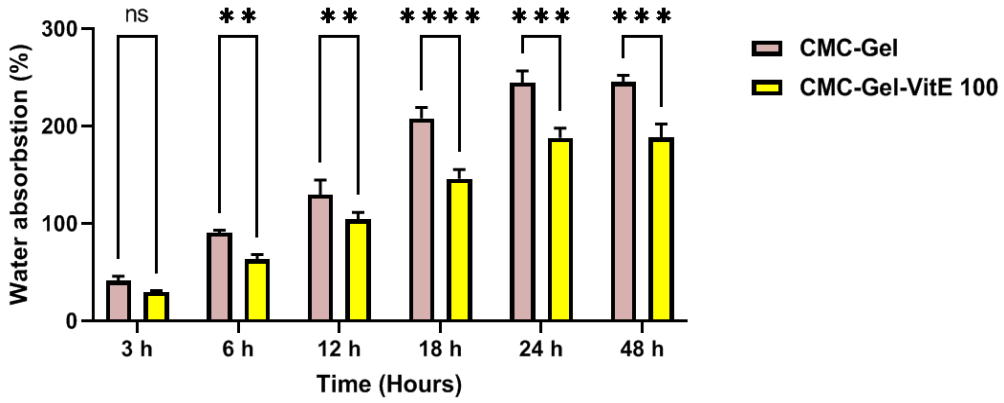

Figure 7. The percentage of water absorption by hydrogels over 48 h. Values represent the mean ± SD, n = 3, ns = non significant, *p < .05, **p < .01, and ***p < .001, and ****p < .0001. SD: standard deviation.

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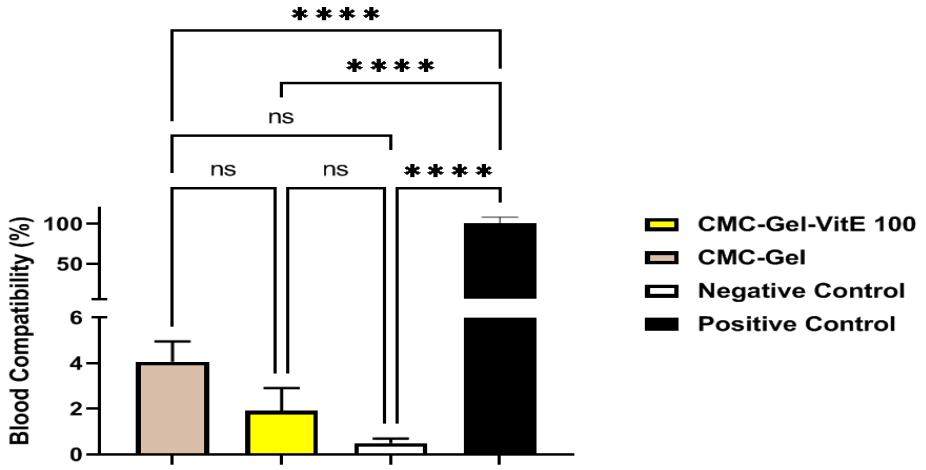

Figure 8. The percentage of hemolysis caused by hydrogels. Values represent the mean ± SD, n = 3, ns = non significant and ****p < .0001. SD: standard deviation.

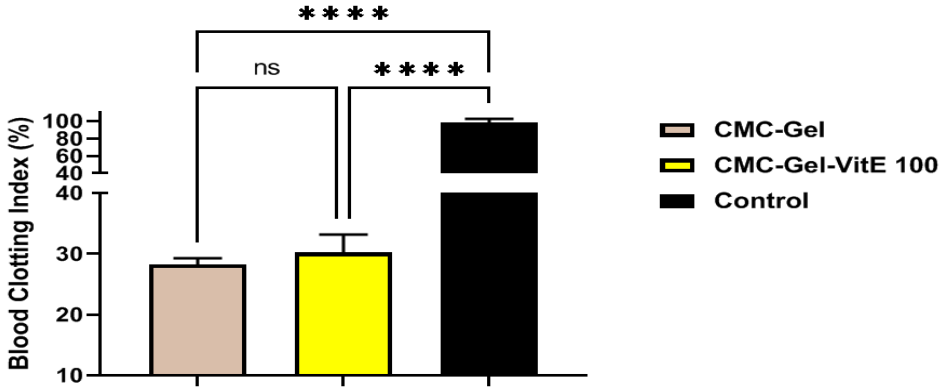

Figure 9. The percentage of coagulation caused by hydrogels. Values represent the mean ± SD, n = 3, ns = non significant and ****p < .0001. SD: standard deviation.

Release profile of Vitamin E from hydrogels

The release profile of Vitamin E is illustrated in Figure 10. The volume of Vitamin E released was determined by constructing a standard release curve. After the initial 2 and 6 h, the release amounts of Vitamin E from the CMC-Gel-100 hydrogel was 4.51±0.31 µg and 10.06±0.93 µg, respectively, followed with continued release, it reached its maximum value 29.57±4.23 µg at the fourth day. These findings indicate the gradual release of Vitamin E form CMC-Gel hydrogel, which enters the plateau phase after 48 h (28.66±3.94 µg), and no further release occurs after 72- and 96-hours period.

Hydrogels make a desirable pH for wound healing

Because of the optimal pH of the acute wound environment is acidic, as illustrated in Table 2, both CMC-Gel and CMC-Gel-VitE 100 hydrogels had an acidic pH, specifically between 6.71±0.23 and 6.79±0.39.

In vivo wound healing findings

The efficacy of the synthesized CMC-Gel and CMC-Gel-VitE 100 hydrogels in facilitating wound healing was assessed using a full-thickness excisional wound model, with macroscopic observations of wound closure documented in Figure 11A.

The negative control group, which had its wound covered with sterile gauze, displayed indications of infection and inflammation, resulting in incomplete healing after a two-week period. Additionally, the control group's wound site remained hemorrhagic at the two-week, in contrast to the treated groups, which demonstrated notable improvement during the same timeframe. Photographic assessments indicated that one-week post-surgery, the hydrogel groups showed a

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significant amount of exudate with minimal bleeding. Overall, the CMC-Gel-VitE 100 group exhibited the most favorable outcomes, showing no signs of infection or inflammation and achieving effective wound healing. To quantitatively assess the healing progress, the extent of wound closure was measured, as illustrated in Figure 11B. Wound closure for the negative control group, CMC-Gel and CMC-Gel-VitE 100 on days 7 and 14 of treatment were 19.66±11.27%, 39.92±14.48%, 51.05±9.73% and 68.31±13.59%, 82.56±12.70%, 91.36±8.23% respectively. The vitamin E hydrogel group had a significantly higher percentage of wound closure compared to the control and CMC-Gel groups, which indicates the high potential of CMC-Gel-VitE 100 hydrogel to reduce the healing time.

Histopathological findings

Histopathological and histochemical analyses of wound healing progression across experimental groups are presented in Figure 12 A–L. H&E staining revealed distinct tissue regeneration patterns following 14 days of treatment. Animals treated with CMC-Gel and CMC-Gel-Vit E exhibited formation of epidermal layer and complete re-epithelialization, with the CMC-Gel-Vit E group demonstrating superior epidermal thickness, structural reorganization, and maturation relative to the CMC-Gel. In contrast, the negative control (NC) group displayed a complete absence of stratified epidermal architecture (Figure 12-H, I, K, L; denoted by white stars). While neovascularization was most prominent in the NC group, the nascent vasculature lacked structural organization and maturity.

Conversely, both CMC-Gel and CMC-Gel-Vit E groups exhibited fewer blood vessels, but these displayed histologically mature morphology, including defined vascular walls (Figure 12-F, I, L; thin black arrows). Notably, dermal appendages—including hair follicles and sebaceous glands—were observed exclusively in the CMC-Gel and CMC-Gel-Vit E groups (Figure 12-H, K, L; thick yellow and blue arrows, respectively), signifying advanced stages of tissue regeneratin.

Collagen synthesis and maturation, assessed via H&E and Masson's trichrome staining, were markedly enhanced in the CMC-Gel-Vit E group, achieving levels comparable to the positive control (PC). This group exhibited dense, well-organized collagen fibers with mature deposition patterns (Figure 12-I, L; white arrowheads). Furthermore, dermal layer thickness in the CMC-Gel-Vit E was approximated that of uninjured tissue, indicating near-complete restoration of dermal architecture.

Masson's trichrome analysis corroborated these findings, highlighting significantly greater collagen density, alignment, and maturity in the CMC-Gel-Vit E group compared to both CMC-Gel and NC (Figure 13 a-h, Figure 13-i, white arrowhead). Epidermal thickness and re-epithelialization were also quantitatively superior in the CMC-Gel-Vit E group (Figure 13 a-h, Figure 13-h, i, k, l; white stars). Although the NC group displayed extensive neovascularization, these vessels lacked structural integrity, whereas CMC-Gel and CMC-Gel-Vit E treatments promoted the development of organized capillaries and mature vasculature (Figure 13 a-h, Figure 13-f, i; thin black arrows).

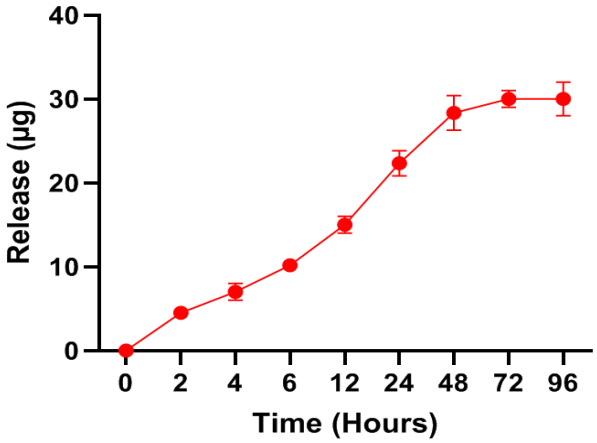

Figure 10. The release profile of Vitamin E from hydrogel. Values represent the mean ± SD, n = 3. SD: standard deviation.

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Table 2. The pH values of VitE solution and hydrogel solutions with and without VitE at different times

Samples/Time	2h	4h	6h	12h	24h	48h
VitaminE(Absoloute)	6.91±0.11	6.88±0.20	6.90±0.24	6.91±0.25	6.93±0.14	6.96±0.18
CMC-Gel	6.71±0.23	6.71±0.25	6.73±0.27	6.72±0.34	6.73±0.31	6.73±0.29
CMC-Gel-VitE 100	6.75±0.15	6.74±0.22	6.74±0.19	6.75±0.24	6.77±0.17	6.79±0.32

Values represent the mean ± SD, n = 3. SD: standard deviation

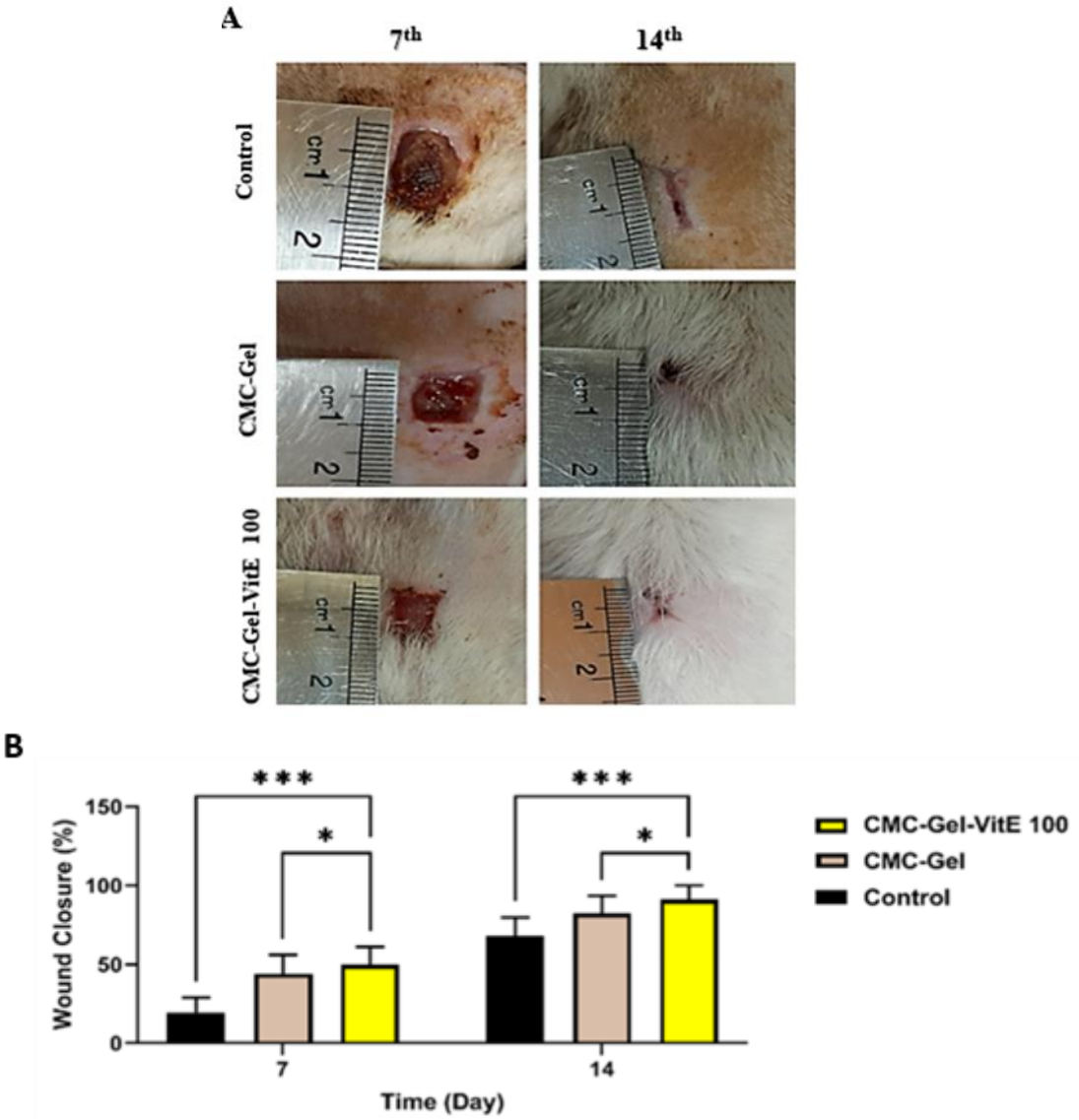

Figure 11. (A) Wound closure images in treated rats 7 and 14 days post-wounding (B) The percentage of wound closure in experimental groups 7 and 14 days post-wounding (b). Values represent the mean ± SD, *p<۰.05 and ***p < 0.001. SD, standard deviation.

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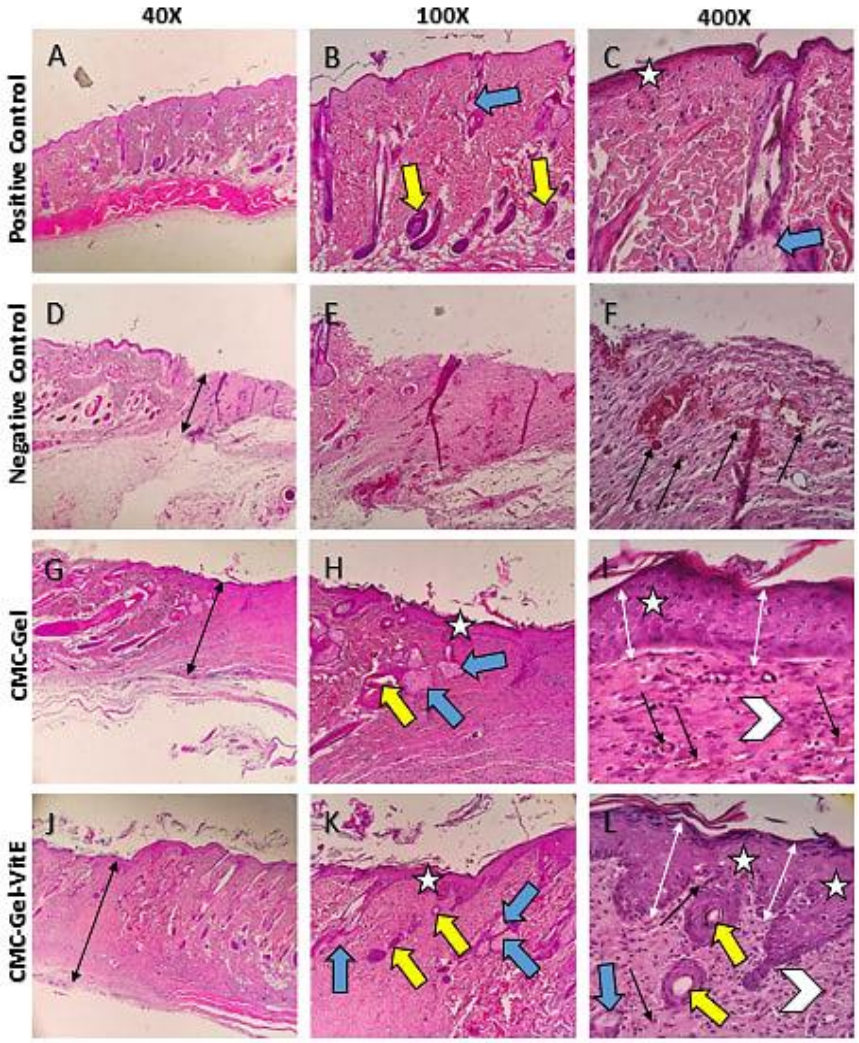

Figure 12. H&E-stained histological sections, 14 days post-wounding, are shown for positive control (A,B,C) negative control (D,E,F), CMC/Gel-treated, (G,H,I) and CMC-Gel-VitE 100 -treated groups (J,K,L)

Collectively, these data demonstrated that CMC-Gel-Vit E synergistically enhances wound regeneration by accelerating epidermal stratification, promoting organized collagen deposition, and facilitating the maturation of dermal and vascular structures, thereby surpassing the efficacy of CMC-Gel alone and untreated controls.

Histomorphometric findings

Histopathological examination revealed significant variation in re-epithelialization and angiogenesis among the groups under treatment after 14 days. The negative control group lacked the stratified epidermal reconstruction. Neovascularization was evident but immature and disorganized in this group. However, the CMC-Gel group showed compelet of re-epithelialization with well-organized vasculature formed by discrete luminal structures.

Interestingly, the CMC-Gel-Vit E group showed the highest re-epithelial coverage and most advanced vascular structure in all groups, where structurally intact, well-differentiated capillaries were present (Table3).

Table 3. Semi-Quantitative histopathological findings of the wound healing sites on Day 14 post-wounding.

Experimental Group	Re-epithelization (0-4)	Angiogenesis (0-4)
Negative Control (NC)	1	2
CMC-Gel	3	3
CMC-Gel-Vitamin E	4	4

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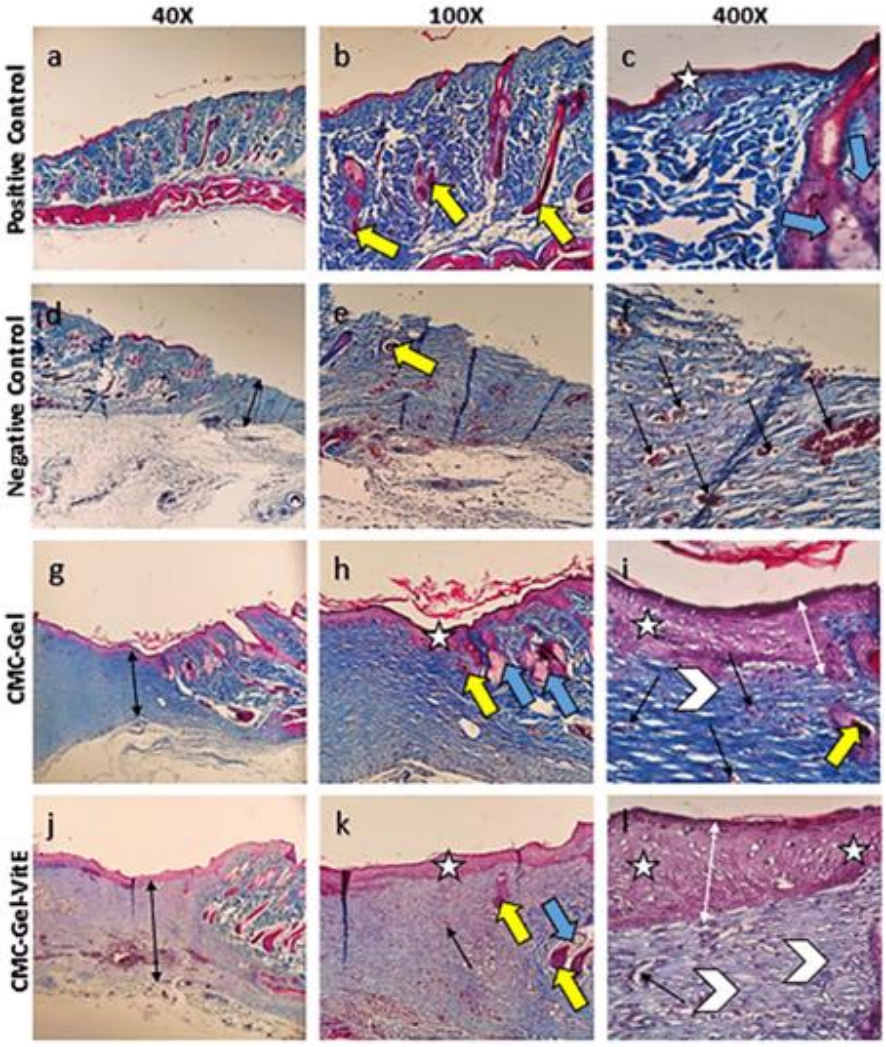

Figure 13. Masson's trichrome-stained histological sections, 14 days post-wounding, are shown for positive control (a, b, c), negative control (d, e, f), CMC/Gel-treated(g, h, i), and CMC-Gel-VitE 100-treated groups (j, k, l).

Discussion

Wound healing represents a multifaceted and dynamic biological process characterized by several distinct phases, namely hemostasis, inflammation, proliferation, and remodeling (48). The quest for effective wound management solutions has spurred the innovation of hydrogels, which are structured as three-dimensional networks of hydrophilic polymers capable of holding significant volumes of water.

These hydrogels create an optimal environment conducive to wound healing, owing to their capacity for moisture retention, controlled release of therapeutic agents, and support for cellular functions (49).Carboxymethyl Cellulose (CMC) is a cellulose derivative that is soluble in water and is extensively utilized in pharmaceutical and biomedical fields owing to its favorable characteristics, including biocompatibility, biodegradability, and non-toxicity (17, 50, 51). Gelatin, a natural polymer obtained from collagen, exhibits remarkable biocompatibility and fosters cellular growth and proliferation, rendering it particularly advantageous for tissue regeneration applications (19, 52, 53). When CMC and gelatin are combined within a hydrogel matrix, they create a synergistic effect that merges the moisture-retaining capabilities of CMC with the bioactive properties of gelatin, thereby facilitating cellular migration and proliferation at the site of wounds (54, 55). Zahra Soleimani et al. examined the impact of a hydrogel composed of carboxymethyl cellulose and gelatin infused with Cefdinir.

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The cytotoxicity assessment revealed that neither the drug-laden nor the drug-free wound dressings exhibited any toxic effects, as evidenced by a cell survival rate exceeding 75% after a 48 h period. Furthermore, the application of the wound dressing facilitated the formation of skin layers and expedited the healing process, resulting in a healing rate of 60% by the 9th day and surpassing 85% by the 15th day (56). Therefore, the CMC-Gel hydrogel can be enriched with various bioactive agents to further promote wound healing. In this investigation, Vitamin E, recognized for its potent antioxidant properties, was integrated into the hydrogel formulation.

Research has demonstrated that Vitamin E significantly contributes to wound healing by mitigating oxidative stress, regulating inflammation, and stimulating collagen synthesis. Additionally, it plays an essential role in stabilizing cell membranes, preventing lipid peroxidation, and enhancing the proliferation of epithelial cells (29, 57-61). Porosity within scaffolds plays a crucial role in enhancing cell migration and attachment, while the interconnected architecture supports gas exchange, nutrient diffusion and inhibiting the entry of microorganisms (62).

Research indicates that an optimal pore size ranging from 20 to 125 µm is beneficial for promoting wound healing (63). Scanning electron microscopy analysis has revealed that the average pore size of CMC-Gel and CMC-Gel-VitE hydrogels falls within this range (~100 µm).

The characteristics of this feature render the synthesized scaffolds appropriate for use in wound care applications, as they facilitate adequate space for cellular migration and proliferation, as well as the absorption of fluids from surrounding tissues. Additionally, the porous architecture allows for substantial swelling of the scaffold. But the morphology and uniformity of the pores are also important. The addition of vitamin E to the carboxymethyl cellulose and gelatin based water hydrogel led to the creation of a cluster structure and reduced pore regularity. The reason for this issue can be found in Vitamin E hydrophobicity.

Fluid absorption, biodegradability, and release profile of a designed wound dressing are very important for tissue engineering because it can lead to the improvement of the tissue regeneration process based on the timing of the wound healing stages (64-67). Fluid absorption is directly related to the secretions that come out of the wound (68). These secretions include lymph, blood, and fluids from damaged tissues. During the inflammation stage, which usually lasts 1 to 4 days, the pad or dressing must have a high absorption capacity to prevent infection. In the stage of regeneration and granulation tissue formation, the amount of secretions should also be reduced so as not to provide favorable conditions for the growth of bacteria (69). On the other hand, biodegradability means that the components of the scaffold are gradually decomposed based on the timing of tissue repair, and there is no need to change the dressing mechanically, which is mainly associated with pain and bleeding, especially in the early days (65, 70). During the first 4 days of healing, the dressing should break down while maintaining a small amount of moisture (to support the growth of fibroblasts) to release the effective components included in its structure (71).

It should be noted that slow biodegradability is directly related to continuous release of scaffold components. High biodegradability and immediate release lead to drug accumulation in the site, causing cytotoxicity and requiring quick dressing change. Low biodegradability and slow release also lead to the non-release of all the constituent and effective components of the dressing and therefore reduce the efficiency (72). Delivery of vitamin E in the network of CMC-Gel hydrogel can be in clustered form, so there can be controlled and sustained release. Structural organization prevents the local accumulation of vitamin E and provides steady uptake at the wound. The mechanism not only prevents oxidative stress but also enhances tissue regeneration through stimulation of collagen synthesis and extracellular matrix formation (73).

With the results obtained in the analysis of liquid absorption, biodegradability and release of Vitamin E from CMC-Gel hydrogel scaffold, it can be concluded that these parameters are in the same direction. Because in all 3 analyses after 48 hours, the maximum efficiency and effectiveness is achieved. It can be concluded that after changing the dressing for 48 hours, biodegradability was 93.85±4.12%, liquid absorption was 245.11±12.58% and maximum release occurred. If the 24-hour dressing change has a lower efficiency for the release of vitamin E due to lower biodegradability (79.34±5.03).

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Also, this decrease in efficiency leads to an increase in cost. Finally, the decrease in liquid absorption and biodegradability in the CMC-Gel-vitE group can be related to the hydrophobic nature of vitamin E, the smaller size of the pores of the scaffold and, of course, the lower penetration of liquids into the structure. The CMC-Gel hydrogel is capable of facilitating a regulated release of vitamin E, thereby ensuring that a stable therapeutic concentration is preserved at the wound site over an extended period. This continued release pattern is essential for sustaining therapeutic efficacy and enhancing the overall healing process, which in turn minimizes the frequency of dressing changes and promotes greater patient adherence to treatment protocols.

An appropriate microenvironmental pH can influence the internal conditions of a wound by promoting the proliferation of fibroblasts. Consequently, an ideal material should maintain a pH values ranging from 4.0 to 6.8, which aligns with the pH of natural, healthy skin (74). Our results indicated the pH of constructed hydrogels falls within this specified value, and ensuring that cannot induce significant alterations in the environmental pH when directly contacted with skin wounds.

In the early stages of inflammation, the relationship between hydrogels and erythrocytes is of paramount importance, particularly since wound dressings are frequently exposed to blood (45, 75). Evaluating the compatibility of these materials with blood necessitates a thorough examination of the hemolysis rate of erythrocytes upon direct contact with the hydrogel and any incorporated pharmaceuticals (76). Consequently, we performed a hemolysis assay on the synthesized hydrogels prior to their intended use in wound care.

The hemolysis ratio was determined by analyzing the absorbance of the supernatant and juxtaposing the results with established positive and negative controls. Prior research indicates that hemolysis rates under 5% are deemed acceptable for biopolymeric materials (77). The synthesized hydrogels in our study do not exceed the allowed hemolysis range and have a good potential for use in bleeding wounds.

The blood clotting index exhibits a negative correlation with the capacity for hemostasis in vitro (78). CMC-Gel and CMC-Gel-VitE hydrogel showed high hemostasis and coagulation ability (~30%). The internal structures of the hydrogels have the potential to absorb percolate and stimulate platelet activation, thereby improving hemostatic function (79). The group containing vitamin E prevents the formation of clots by preventing the binding of platelets (80). But according to previous studies (81), this capability is dose-dependent, so that it can increase the risk of bleeding by increasing the dosage. The amounts of 100 µL/mL vitamin E in CMC-Gel hydrogel led to a decrease in coagulation potential, but this difference is insignificant. Nevertheless, additional research is required to assess the effects of these hydrogels on skin lipids and their role in the restoration of the skin barrier. Therefore, the incorporation of vitamin E may potentially reduce the coagulation capacity of the hydrogel at certain concentrations, raising concerns for its application in wound therapy that requires rapid hemostatic action. Therefore, it is necessary to investigate the desirable concentration of vitamin E that effectively balances the coagulation and healing properties.

According to previous investigations, vitamin E significantly increased cell survival and proliferation. Vitamin E considerably boosted cell growth and cell activity at 24- and 72-hours following culture, according to the study's MTT results. These results represent that vitamin E added to the hydrogel structure due to its biocompatibility provides better conditions for cell growth and proliferation (82). To evaluate the effectiveness of vitamin E on NIH/3T3 fibroblast cells, we used MTT analysis, which can also represent the metabolic activity of cells in addition to survival. Based on the results, Vitamin E leads to the promotion of cell growth and proliferation in a dose-dependent manner. Carboxymethyl cellulose hydrogel prevents dryness and the formation of hard layers in the wound by maintaining moisture. In addition, it strengthens the growth of epidermal cells. Gelatin hydrogel acts as a source of amino acids and collagen building materials, which are very important in the regeneration and remodeling phase of wound healing.

Gelatin, by creating a structure similar to the extracellular matrix, also provides a suitable anchor for cell connections. The addition of Vitamin E also prevents oxidative stress with its antioxidant properties and minimizes tissue damage. Vitamin E helps to strengthen collagen synthesis without accumulation and thus leads to increased strength without creating scar tissue. Also, this effective substance facilitates the delivery of nutrients and oxygen to the repair site by

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improving blood circulation (83-85). The findings of this research hold considerable importance, indicating that the CMC-Gel hydrogel loaded with Vitamin E may function as a highly effective wound dressing, facilitating accelerated and more efficient healing processes. The integration of a natural polymeric framework with an antioxidant agent such as Vitamin E offers a promising approach for addressing full thickness skin injuries.

One significant limitation identified in the study pertains to the hydrophobic characteristics of Vitamin E, which adversely affected the structural integrity of the hydrogel. The addition of Vitamin E resulted in a decrease in the regularity of the pores and the emergence of cluster-like formations within the hydrogel matrix. Such an irregular pore architecture may impede effective fluid absorption and delay the release of therapeutic agents, including Vitamin E, from the hydrogel.

This situation could potentially compromise the hydrogel's efficacy in managing wound exudates and hinder the sustained release of active compounds, which is essential for maintaining therapeutic effectiveness over time. Therefore, further refinement of the formulation is necessary to achieve a more uniform and consistent pore size and structure, thereby enhancing the hydrogel's capacity for fluid absorption and facilitating controlled drug release.

In the study by P.S. Sharon Sofini et al., AgNPs dressing was applied to infected wounds due to its strong antibacterial properties. According to the findings of this study, silver can lead to cytotoxicity and bacterial resistance. While CMC-Gel/Vitamin E hydrogel, through antioxidant and anti-inflammatory mechanisms, can show fewer side effects and is more suitable for non-infected wounds (86). Past research involving growth factor-hydrogels has shown that although these factors are excellent at causing angiogenesis and tissue regeneration, it has been challenging to utilize them due to constraints such as their short half-life and being extremely expensive to synthesize. On the other hand, vitamin E is suggested as a less expensive option since it is more chemically stable and less expensive to make (49).

Subsequent investigations should aim to refine the hydrogel's formulation, which includes determining the optimal concentration of Vitamin E, assessing the release dynamics of the antioxidant, and evaluating the hydrogel's performance across different wound models, including acute, chronic, and diabetic wounds. Furthermore, it is essential to conduct clinical trials to confirm the hydrogel's efficacy and safety in human subjects. The feasibility of scaling up production and implementing the hydrogel in clinical environments represents a crucial advancement in the evolution of wound care therapies.

The Carboxymethyl Cellulose-Gelatin hydrogel with the inclusion of 100 µL/mL of Vitamin E is highly promising for application as a wound healing material, primarily on account of its higher properties of moisture retention, biodegradability, and fibroblast growth stimulation. However, some of the limitations require to be overcome before translation to the clinic, e.g., Vitamin E effect on the structural characteristics of the hydrogel, lack of in vivo confirmation, suboptimal release kinetics, and its potential effect on coagulation cascades.

To overcome these issues, future research must consider optimization of hydrogel formulation, optimal release profile and content of Vitamin E, as well as thorough in vivo characterization. Apart from that, the application of more advanced techniques—like quantitative reactive oxygen species assays, MAPK pathway activation analysis, cytokine profiling, and collagen maturation assessment—is strongly recommended.

Such techniques will enhance the scientific validity, accuracy, and reproducibility of the information, allowing further elucidation of antioxidant quality of the hydrogel, anti-inflammatory effect, cellular proliferation kinetics, and extracellular matrix remodeling. All these efforts altogether are important in making the CMC-Gel–Vitamin E hydrogel a viable and promising substitute for clinical wound care applications.

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