Formulation and Evaluation of Vancomycin Loaded Chitosan/Aloe Vera Hydrogel: A Novel Antibacterial Biopolymeric System

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Abstract: The combination of herbal and biopolymeric agents holds significant potential for enhancing wound healing. Aloe vera, known for its anti-inflammatory, antimicrobial, and regenerative properties, has long been used to treat wounds and burns. Chitosan, as a well-known biopolymer, promotes collagen synthesis, fibroblast recruitment and aiding granulation tissue formation. This study explored the formulation of a chitosan/Aloe vera hydrogel loaded with vancomycin, as a potential wound care product. The hydrogel was prepared using chitosan and aloe vera in 1:1 and 1:2 ratios. After homogenization, 1% vancomycin was incorporated. All physical characterizations, drug loading and drug release studies were performed on prepared formulations. Antimicrobial activity also was evaluated against *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Moreover, both physical and performance properties of gels were assessed over three months under room temperature and refrigerated conditions. The study found that the gels remained stable, with no changes in color, flowability, uniformity, or viscosity during stability assessments. Both formulations released their entire drug content within two hours when kept at room temperature and in the refrigerator. No signs of separation or degradation were observed over the three-month period, demonstrating the gel's stability. Formulations showed acceptable antimicrobial activity against both mentioned bacterial strains. In conclusion, the chitosan/Aloe vera gel containing vancomycin showed desirable properties, making it a promising candidate for wound healing. Its antimicrobial activity and ability to support tissue regeneration suggest it as a valuable treatment for accelerating the wound-healing process.

Keywords: Biopolymeric hydrogel, Chitosan, Aloe vera, Antibacterial, Wound healing.

1. INTRODUCTION

An ideal wound dressing is often described as one that mimics many of the properties of human skin. In addition to providing adhesion, elasticity, durability, and impermeability to bacteria, such dressings should also promote healing while preventing infections. Many wound dressings are loaded with antimicrobial agents or healing-promoting substances that can act against infectious organisms, helping to prevent severe conditions such as sepsis [1]. Therefore, the development of effective wound dressings that not only possess therapeutic efficacy but also align with the skin's structure and offer comfort to patients is a critical objective in wound care research.

Wound healing involves a complex process comprising four overlapping phases: 1) hemostasis, 2) inflammation, 3) proliferation, and 4) remodeling [2]. Wound dressings primarily serve to prevent microorganism entry, keep the wound hydrated, and absorb exudate [3]. Traditional dressings, such as sterile gauze, are widely used but are not always effective because they lack hydrating properties and often adhere to wounds and causing pain when removed. Furthermore, the frequent removal required due to the application of various antimicrobial ointments can lead to discomfort and inconvenience [4, 5].

Modern dressings are designed to adapt to different wound types and patient needs, preventing infections while promoting healing without scarring. These dressings are engineered to maintain appropriate hydration and interact with wounds through the release of bioactive molecules that accelerate the healing process [6, 7]. Consequently, novel wound dressings, such as patches, foams, gels, hydrocolloids, nanoparticles, nanofibers, films, and membranes, are now being developed with bio-based properties [8, 9].

Aloe vera (AV), belonging to the Liliaceae family, is a well-known plant species used in traditional medicine for thousands of years [10]. The leaves of Aloe vera consist of three layers: the inner transparent gel, which contains 99% water along with glucomannans, amino acids, lipids, sterols, and vitamins; the middle latex layer, which contains bitter anthraquinones and glycosides; and the outer thick layer, which serves a protective role. Aloe vera contains 75 potential active compounds, including vitamins, enzymes, minerals, sugars, lignins, saponins, salicylic acid, and amino acids and has multiple healing mechanisms include anti-inflammatory effects, collagen production, and antioxidant activities [11, 12].

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Chitosan, a natural biopolymer derived from chitin, is another promising material for wound healing due to its excellent biocompatibility, biodegradability, and antimicrobial properties [13]. It is widely sourced from the shells of crustaceans like crabs and shrimp, as well as insects and algae. Chitosan's biological properties, such as its ability to enhance wound healing, promote blood clotting, and prevent bacterial infections, make it an ideal candidate for biomedical applications. In wound care, chitosan-based gels have shown great potential by accelerating wound contraction and reducing inflammation, thereby improving healing outcomes [7].

This study aims to explore the formulation of a vancomycin loaded chitosan-aloe vera hydrogel, combining the antimicrobial properties of vancomycin with the healing potential of Aloe vera and chitosan. The resulting biopolymeric system could provide a novel wound dressing with enhanced antibacterial activity, biocompatibility, and accelerated wound healing properties.

2. MATERIALS AND METHODS

2.1. Materials

High molecular weight Chitosan (1500 kDa) was obtained from Iran chitosan company (Iran). Aloe vera powder was purchased from Titrachem Company (Iran). Vancomycin was obtained from Dana pharmaceutical company. All the other analytical grade reagents were obtained from Merck (Darmstadt, Germany).

2.2. Formulation of Chitosan/Aloe Vera Biopolymeric Hydrogel

To prepare of chitosan/aloe vera gel, chitosan (CS) powder was first weighed and dissolved in 1% acetic acid for preparation of chitosan 2% solution. Afterward, the weighed amounts of aloe vera (AV) powder with different ratio of chitosan/aloe vera (1:1 and 1:2 w/w) and vancomycin (VC) powder were simultaneously added to the solution for creation vancomycin 1%, and the mixture was stirred for 2 hours to ensure complete homogeneity of the gel.

To adjust the pH, sodium hydroxide solution (NaOH, 1N) was added dropwise to the gel while continuously monitoring the pH using a pH meter. Once the pH reached a value between 5 and 6, the adjustment process was stopped.

2.3. Characterization of Prepared Biopolymeric Hydrogels

2.3.1. Physical Characterization

The prepared gels were evaluated for various characteristics such as color, flowability, uniformity, viscosity and pH. The color of the formulations was assessed visually by placing a transparent container with the product in front of a white background under a light source.

For the uniformity test, a small amount of each gel was placed between the thumb and forefinger, compressed, and examined for the presence of particles or clumps. If the gels spread smoothly on the skin without breaking apart or containing any detectable particles is considered as uniform gel.

For flowability test, a flat, dry glass plate (20 × 20 cm) was used to assess the flowability. The glass plate was inclined at a 60-degree angle relative to the horizontal plane using a protractor, and a light source was positioned in front of it. Then, 1 gram of gel was placed at the upper edge of the inclined glass and its movement was observed for speed, uniformity, and the absence of clumps or fragment formation during its flow across the surface. Marketed Diclofenac topical gel was used as a standard for comparison.

The pH of the formulations was determined using pH indicator paper, and the measurement was repeated three times for accuracy. Furthermore, the viscosity of the prepared gels was measured at 25 ± 0.5 ºC using the cone and plate method with a Brookfield viscometer.

2.3.2. Drug Loading Evaluation

To establish a standard calibration curve for vancomycin, different concentrations (150, 100, 80, 50, 25, 20, and 15 µg/mL) of vancomycin were prepared in 1% acetic acid. Each diluted solution was then analyzed using a UV-Vis spectrophotometer at a wavelength of 280 nm to measure absorbance. The blank solution used in this study was 1% acetic acid. A standard calibration curve was plotted based on the measured absorbance against the corresponding concentrations of vancomycin.

To determine the amount of vancomycin loaded in the prepared gels, 100 mg of the drug-containing gel was accurately weighed and transferred into a 50 mL Erlenmeyer flask containing 50 mL of 1% acetic acid. A magnetic stirrer was added, and the mixture was stirred

for 2 hours to ensure thorough dissolution of the gel. After stirring, the solution was filtered through a 0.45 micron filter to remove any particulate matter. Subsequently, 2 mL of the filtered solution was transferred into a cuvette and analyzed using a UV-Vis spectrophotometer at a wavelength of 280 nm.

Using the previously established standard calibration curve and the corresponding equation derived from it, the amount of vancomycin loaded in 100 mg of the gel was calculated. The blank solution for this analysis was 1% acetic acid.

2.3.3. Drug Release Study

Two grams of the drug-containing gel were accurately weighed and placed in a mesh filter. The filter was then suspended in a beaker containing 250 mL of 1% acetic acid, with a magnetic stirrer placed inside. The mixture was stirred at a speed of 50-100 rpm. Over a period of 2 hours, 2 mL samples of the solution were withdrawn every 15 minutes using a sampler and transferred into microtubes. Following each withdrawal, an additional 2 mL of 1% acetic acid (as a blank) was added to the release medium. At the end of the 2-hour period, a total of 8 samples were collected, and their absorbance was measured at 280 nm using a UV spectrophotometer at ambient temperature.

2.4. Antimicrobial Activity Evaluation

The prepared formulations were evaluated for their antimicrobial activity against *Pseudomonas aeruginosa* and *Staphylococcus aureus* using the agar diffusion method. Initially, a suspension equivalent to a 0.5 McFarland standard was prepared from the bacterial strains of interest in a tube containing physiological saline. The suspension was then inoculated onto Mueller-Hinton agar plates (Merk, Germany). Subsequently, wells with a diameter of 8 mm were created on the surface of the plates using a sterile punch, and 100 µL of the prepared formulations including CS/AV/VC 1:1 and 1:2, CS/AV without vancomycin with different ratio 1:1 and 1:2, CS 2%, AV with two different amounts 150 mg and 300 mg (2% and 4% w/v) according to the final formulation CS/AV 1:1 and 1:2) and vancomycin 1% as positive control, were loaded into the wells. Finally, the plates were incubated at 37°C for 24 hours. After this period, the diameters of the zones of inhibition were measured and recorded.

2.5. Stability Study

The prepared formulations were placed at room temperature and in a refrigerator (4ºC). After three months, they were evaluated for pH, color, uniformity, flowability, viscosity, content assay, and drug release profile.

2.6. Statistical Analysis

All the experiments were implemented in triplicate samples. The result as mean ± standard error (SD) was reported. GraphPad Prism 8 software was used for analysis.

3. RESULTS

3.1. Physical Characterization of Prepared Biopolymeric Hydrogels

According to the obtained results in Table **1**, the formulations containing 2% chitosan exhibited a milky color and were fully uniform. The formulations spread easily on the skin without fragmenting or giving a particulate sensation, and they displayed a clear appearance. The pH was within the range of 5-6. In terms of flowability, gels with CS/AV ratios of 1:1 and 1:2 demonstrated good flow properties.

Furthermore, the prepared formulations were analyzed for viscosity using a rheometer, as shown in supplementary files. The obtained plastic viscosity for CS/AV/VC 1:1 and CS/AV/VC 1:2 was 370.1 cP (centipoise).

Table 1: Characterization of Biopolymeric Chitosan/Aloe Vera Hydrogels

Formulation	pH	Color	Flowability	Uniformity
CS/AV 1:1	5-6	Milky	Passed	Uniform
CS/AV 1:2	5-6	Milky	Passed	Uniform
CS/AV/VC 1:1	5-6	Milky	Passed	Uniform
CS/AV/VC 1:2	5-6	Milky	Passed	Uniform

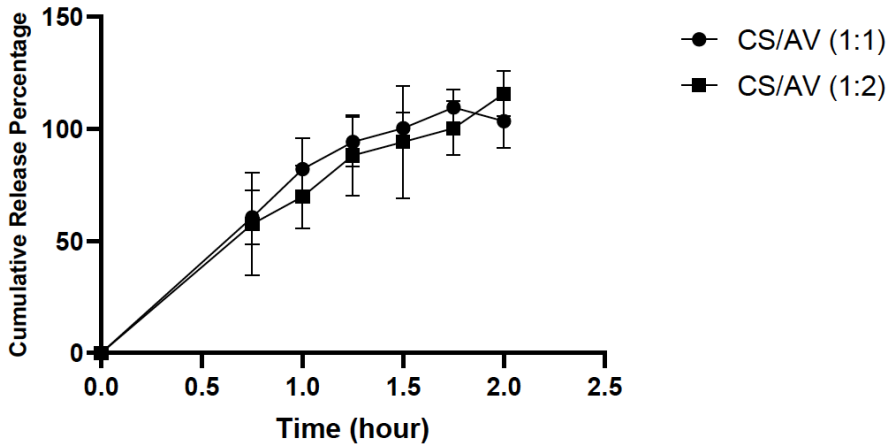

Figure 1: The drug release profile in different gel formulations.

3.2. Drug Loading Evaluation

Based on the results obtained in supplementary files, the linear equation derived from the graph is y=0.0043x+0.0215, with a correlation coefficient of r=0.998. The amount of drug loading in different gel formulations was calculated. Both 1:1 (CS/AV) and 1:2 (CS/AV) formulations could load 100% of the drug.

3.3. Drug Release Profile

The drug release profile was evaluated according to mentioned procedure. The results indicated that there was no significant difference in drug release profile between the 1:1 and 1:2 gels within the first 2 hours. Furthermore, after 2 hours, the entire drug loaded in the gel was released (Figure **1**).

3.4. Antimicrobial Study

According to the obtained results (Figures **2** and **3**), the formulations of 2% chitosan gel and 2% aloe vera (without vancomycin) showed no antimicrobial activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa*. However, the other formulations exhibited antimicrobial effects against both bacterial strains. Among these formulations, vancomycin 1%, CS/AV 1:1 and CS/AV 1:2 loaded by vancomycin demonstrated the highest antimicrobial activity against *Staphylococcus aureus*. The results indicated that vancomycin exhibited the greatest antimicrobial activity against *Pseudomonas aeruginosa*, while the chitosan-aloe vera formulations containing vancomycin showed less antimicrobial activity against this bacterium.

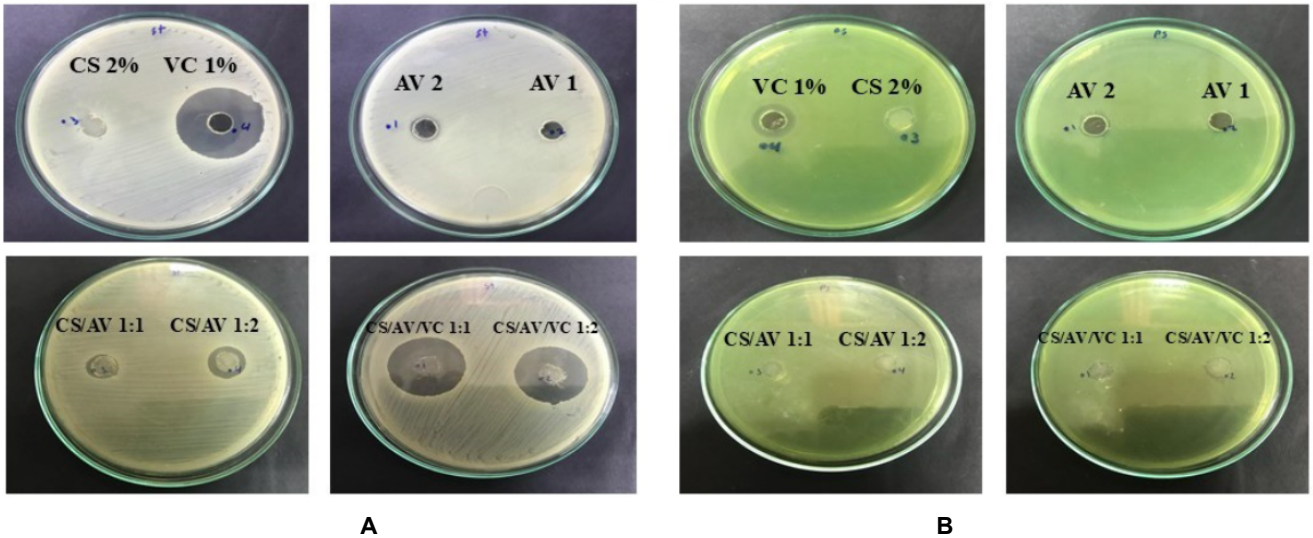

Figure 2: Inhibition zone of different formulation against **A**) *Staphylococcus aureus* and **B**) *Pseudomonas aeruginosa.* The formulations include: AV 1 and AV 2 (Aloe Vera 2% and 4%), CS/AV 1:1 (Chitosan 2%/Aloe Vera 2% ratio 1:1), CS/AV 1:2 (Chitosan 2%/Aloe Vera 4% ratio 1:2), CS/AV/VC 1:1 (Chitosan 2%/Aloe Vera 2%/Vancomycin 1% ratio 1:1), CS/AV/VC 1:2 (Chitosan 2%/Aloe Vera 4%/Vancomycin 1% ratio 1:2), CS 2% (chitosan 2%) and VC (Vancomycin 1%).

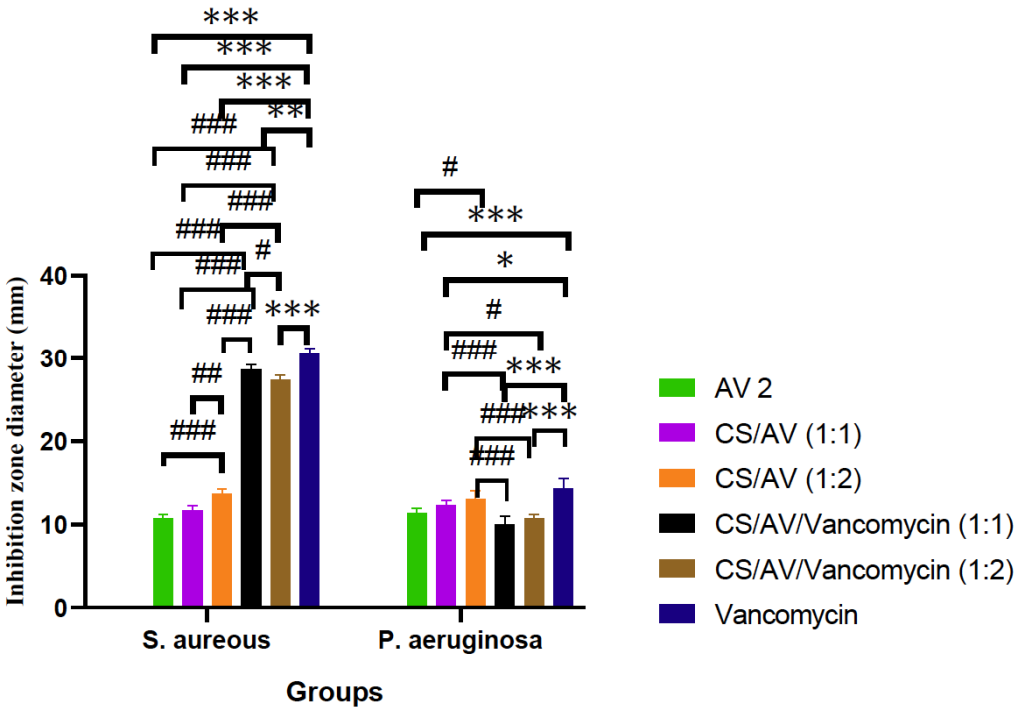

Figure 3: Results of the antibacterial activity assessment of various formulations. The formulations include: AV 2 (Aloe Vera 4%), CS/AV 1:1 (Chitosan 2%/Aloe Vera 2% ratio 1:1), CS/AV 1:2 (Chitosan 2%/Aloe Vera 4% ratio 1:2), CS/AV/Vancomycin 1:1 (Chitosan 2%/Aloe Vera 2%/Vancomycin 1% ratio 1:1), CS/AV/Vancomycin 1:2 (Chitosan 2%/Aloe Vera 4%/Vancomycin 1% ratio 1:2), and Vancomycin (Vancomycin 1%), n=3.

*Statistical comparison of Vancomycin with other groups:- P < 0.05, **- P = 0.002, ***- P < 0.0001.

#Statistical comparison of the prepared formulations with other groups: #- P < 0.05, ##- P = 0.002, ###- P < 0.0001.

3.5. Stability Study

The stability results after three months under different conditions are presented in Table **2**. The prepared gels were evaluated after three months for color, flowability, uniformity, and pH at room temperature and in the refrigerator. The results indicated that no changes in color were observed in the gels in either environment. All gels were completely uniform, and the pH remained unchanged within the range of 5-6. In terms of flowability, the formulations stored at both refrigerator and room temperature exhibited good flow properties.

Furthermore, measured viscosity of the prepared gels at ratios of 1:1 and 1:2 did not show significant changes at both refrigerator and room temperatures compared to month zero and after three months, the gels exhibited acceptable viscosity levels. Accordingly, the viscosity of CS/AV 1:1 and 1:2 loaded by Vancomycin in refrigerator were 371 and 299 cP respectively and in room temperature were 324 and 336 cP respectively (supplementary files).

Additionally, the drug release results after 3 months of stability indicated (Figures **4**) that all prepared hydrogels with ratios of 1:1 and 1:2 released their

Table 2: Stability Study after 3 Months in Different Conditions for CS/AV/VC Biopolymeric Gels with 1:1 and 1:2 Ratios

Storage condition	Color	pH	Flowability	Uniformity	Content assay (mg)
CS/AV/VC 1:1					
Refrigerator (4°C)	Milky	5-6	Passed	Uniform	1.14 ± 0.11
Room Temperature (25°C)	Milky	5-6	Passed	Uniform	1.06 ± 0.06
CS/AV/VC 1:2					
Refrigerator (4°C)	Milky	5-6	Passed	Uniform	1.10 ± 0.17
Room Temperature (25°C)	Milky	5-6	Passed	Uniform	1.10 ± 0.13

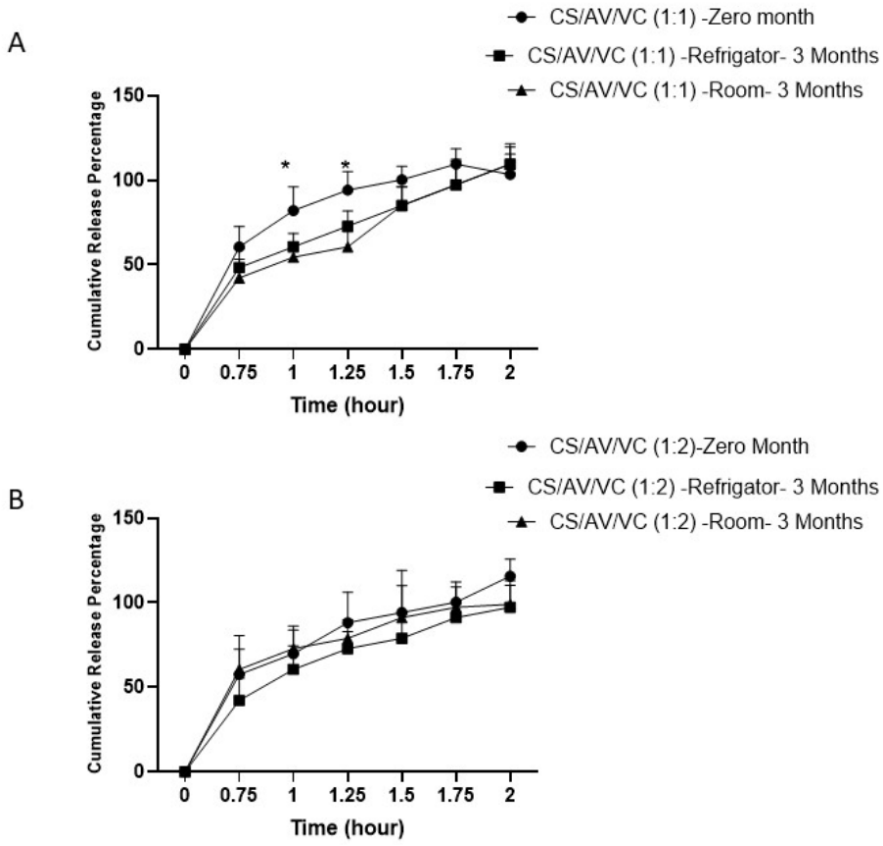

Figure 4: The release profile of CS/AV/VC biopolymeric gels with different ratio **A**) 1:1 and **B**) 1:2 after 3 months stability study in refrigerator and room temperature. *Statistical differences $P < 0.05$.

entire drug content after 2 hours, both at month zero and after three months of storage at different temperatures (refrigerator and room temperature). However, for the 1:1 gel, a slight significant difference in drug release was observed after 1 hour. In this formulation, the drug release rate decreased after three months of storage at room temperature and in the refrigerator, with 80% of the drug released after 1 hour at month zero, compared to only 50% released after 1 hour at three months. In contrast, for the 1:2 ratio, no differences in drug release rate were observed at either month zero or after three months.

4. DISCUSSION

The therapeutic effects of herbal medicines have been reported for many years. Compared to synthetic drugs, herbal medicines and products are not only less expensive but also have good efficacy and lower toxicity [14]. Complete wound healing and prevention of scar formation are primary concerns in skin care. In recent years, there has been special attention on using natural materials for the care and improvement of skin wounds. Aloe vera has long been recognized as a medicinal plant. Treatment of wounds and burns is one of the main applications of aloe vera. Previous researches have shown that aloe vera has anti-inflammatory, antimicrobial, angiogenic, and antioxidant properties that promote wound healing. The biological benefits of aloe vera gel are attributed to a wide range of active biological components such as amino acids, enzymes, vitamins, minerals, polysaccharides (pectin, cellulose, and glucomannan), and other low molecular weight substances. Bradykinin and thromboxane found in aloe vera relieve pain and accelerate wound healing by increasing the shedding of dead cells. The ability of aloe vera gel to provide the necessary conditions for skin wound healing (e.g., micronutrients, moisture, control of excessive inflammation, and fibroblast proliferation) has been proven [15].

On the other hand, the effects of chitosan on improving skin wounds and controlling inflammation have also been widely reported. Chitosan increases the synthesis of collagen type III and the absorption of fibroblast cells, which enhances and forms granulation tissue. It also inhibits pro-inflammatory cytokines [16]. Overall, these positive properties, such as promoting wound contraction and cellular differentiation, make

chitosan-based gels suitable candidates for wound treatment [17].

Results from this study displayed that both prepared formulations showed superior physical properties that means patient acceptance and compliance. Moreover, 100% loading of vancomycin in these formulations can be very promising for large scale and market acceptance in future. Logic release profiles of both 1:1 and 1:2 formulations is another beneficial property of each formulations that means in real condition, all loaded drug can provided to the wound after 2 hours. Based on stability study results, after three months of storage at room temperature and in the refrigerator, formulations exhibited no changes in color, flowability, uniformity or pH. No change in the color of the gels was observed in either environment, all gels were completely uniform, and pH remained in the range of 5-6 with no change. The stored formulations showed good flowability in both the refrigerator and room temperature. The viscosity of the prepared gels in 1:1 and 1:2 ratios at refrigerator and room temperatures did not show significant changes after three months. The viscosity of the gels prepared in this study ranged from 320 to 380, which based on studies, can be considered suitable viscosity for topical gels, providing adequate spreadability [18]. The obtained results regarding the antimicrobial effects of the prepared formulations showed that both chitosan/aloe vera 1:1 and chitosan/aloe vera 1:2 loaded by vancomycin exhibited antimicrobial effects against *Pseudomonas aeruginosa* and *Staphylococcus aureus*. However, their effects on the studied bacteria were less than that of pure vancomycin. One possible explanation is that when vancomycin is combined with aloe vera and chitosan, its antibacterial effect may be reduced, possibly due to competition between the gel components for inhibiting the growth of microorganisms along with vancomycin. This condition also already has been reported by some researches [19, 20].

Chitosan exhibits antibacterial effects against both Gram-positive and Gram-negative bacteria, attributed to the interaction of this polycation with bacterial cell membranes, leading to increased permeability and structural changes in the bacterial cell membrane, ultimately resulting in leakage of intracellular materials (such as enzymes, nucleotides, and proteins) and bacterial cell death [21].

As shown in the current study, both CS/AV 1:1 and 1:2 gels combined with vancomycin exhibited antimicrobial effects against both Gram-negative and Gram-positive bacteria. However, their effect was less than of pure vancomycin. In a study conducted by Ahmad Khan and colleagues in 2022, the addition of ofloxacin to a chitosan-aloe vera hydrogel was investigated to enhance its antibacterial properties. In that study, the antimicrobial activity of chitosan-aloe vera hydrogel containing ofloxacin (CA/AV/OX) and chitosan-aloe vera hydrogel without the drug (CA/AV) against Gram-positive and Gram-negative bacteria was evaluated using the agar disk diffusion method. Maximum activity against Gram-positive bacteria (*S. aureus*) and Gram-negative bacteria (*E. coli*) was observed in the drug-containing hydrogel, with a zone of inhibition of 25 mm against *S. aureus* and 24.5 mm against *E. coli*. In contrast, the zone of inhibition in the CA/AV hydrogel without the drug was 11 mm against *S. aureus* and 9.5 mm against *E. coli*. Studies have shown that while the chitosan-aloe vera hydrogel without the drug exhibited good antimicrobial properties, the addition of ofloxacin significantly enhanced the antibacterial properties of the hydrogel [22].

5. CONCLUSION

In conclusion, this study has shown that the chitosan/aloe vera biopolymeric hydrogel containing vancomycin is effectively stable over three months and meets acceptable criteria regarding viscosity, uniformity, flowability, pH, loading efficiency and release profile. Additionally, evidence suggests that the use of this three-component biopolymeric hydrogel not only provides satisfactory antibacterial effects but also can contribute significantly to wound healing through the regenerative properties of chitosan and aloe vera. This dual functionality positions the biopolymeric hydrogel as a potential candidate for wound dressing applications. Further future research could explore its clinical potential in treating chronic wounds or skin infections.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest regarding this study. Any potential conflicts between corresponding authors and co-authors have been clarified.

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SUPPLEMENTARY FIGURES

The supplementary figures can be downloaded from the journal website along with the article.

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