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RESEARCH ARTICLE

Production and Characterization of Polyvinyl Alcohol (PVA)/Chitosan (CH) Wound Dressings Enriched with Hypericum perforatum extract

Evren Arıöz[*] Suzan Biran Ay Duygu Erkmen

Eskisehir Technical University, Faculty of Engineering, Department of Chemical Engineering, Eskisehir

ABSTRACT

Flexible, durable, and biocompatible wound dressing films with antibacterial and antioxidant properties were developed using polyvinyl alcohol (PVA) and chitosan (CH) blends enriched with Hypericum perforatum extracts. The films were fabricated using the solvent casting method with varying ratios of PVA (2% and 5%) and CH (1%), incorporating *Hypericum perforatum* extracts obtained at sol-id/liquid ratios of 1/10 and 1/20. The moisture content and uptake, water vapor transmission rate (WVTR), total phenolic content, anti-oxidant capacity, and antibacterial activity of the films were measured. Results demonstrated that the addition of plant extracts decreased the films' moisture content while higher PVA ratios increased moisture uptake. WVTR values ranged between 440 and 510 g/m^2/day, indicating appropriate moisture regulation for wound healing. Films containing plant extracts exhibited enhanced total phenolic content and antioxidant activity, with radical scavenging capacities up to 50%, highlighting their potential to reduce inflammation and accelerate wound recovery. Antibacterial tests against E. coli and S. aureus showed notable inhibition zones, confirming the films' effectiveness in preventing bacterial growth. The developed PVA/CH composite films demonstrate promising features such as advanced wound dressings with improved healing capabilities, combining moisture regulation, antioxidant, and antibacterial properties.

Keywords: Wound dressing, PVA, chitosan, Hypericum perforatum

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1. INTRODUCTION

Healthy skin helps protect the interior organs and regulate the physiological balance of the body. The skin also plays an important role in protection against germs, infections, thermal irregularities, mechanical, and chemical damages (1,2). Acute and chronic wounds can cause tissue damage. Traditional, low-cost wound dressings, such as cotton or gauze, are designed to protect wounds from contamination and external trauma. Dressings should provide an ideal environment in the wound region to promote healing in addition to covering and protecting the damaged area. Unfortunately, wound dressings do not significantly facilitate the healing process. Various wound dressings can be used to enhance wound healing process (3).

Wound dressings that are biocompatible and capable of retaining moisture at the wound site while also absorbing exudate and allowing for water vapor transmission are essential. Advanced wound dressings such as hydrogels, sponges, and film sheets have been developed to overcome the disadvantages of traditional wound dressings (4). Over the past 30 years, biomaterials have contributed to the development of new dressings. Incorporating natural substances including gelatin, pectin,

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[*] Corresponding author: evrenbayram@eskisehir.edu.tr,

starch, cellulose, alginate, chitin, collagen, and hyaluronates into artificial wound dressings has been demonstrated to enhance healing processes (5). Natural materials provide substantial advantages due to their low cost, abundance, biocompatibility, biodegradability, antimicrobial and antioxidant capacity, and nontoxicity, they are often incorporated in blends containing synthetic/semi-synthetic polymers to attain the desired properties in wound dressings (6).

Polyvinyl alcohol (PVA) is a vinyl polymer comprising carbon-carbon linkages. It is also highly biocompatible and capable of self-crosslinking because of the hydroxyl groups on the side chains (7). Due to its nontoxicity, biodegradability, water-solubility, film/gel forming and adhesive properties (8), PVA is one of the oldest and most frequently used synthetic polymers for wound dressing fabrication (9). However, films produced by PVA only, exhibited certain limitations such as poor mechanical properties, which restrict its use as a standalone material for wound dressing applications (10).

Chitosan (CH), on the other hand, is a natural polymer derived from the second largest carbohydrate, i.e. chitin. Many researchers have studied chitosan because it is biodegradable and can be used in many different applications, such as film production, coatings, and composites. In an acidic medium, chitosan acquires positive charges due to the protonation of its amino groups, allowing it to bind effectively with the negative residues in mucin, thereby enhancing its mucoadhesive properties. Additionally, chitosan is a biocompatible, antigenic, haemostatic, and non-toxic polymer that is widely used in various biomedical applications (11). These applications include serving as an antimicrobial and wound-healing biomaterial, drug delivery carrier, and scaffolding material (6,12), making it an ideal material for wound dressing applications (13).

Herbal medications are becoming increasingly recognized as complementary therapies for wound healing, burn and cut therapy, and long-term infection management (14). *Hypericum perforatum*, known as St. John's wort, is commonly applied topically to accelerate the healing of burns and other types of wounds. Various studies have recommended the use of *Hypericum perforatum* extract in wound therapy, skin illnesses, and infectious diseases due to its antimicrobial and anti-inflammatory properties (15,16).

Enhancing the selectivity of chitosan films by adjusting their chain flexibility is a promising strategy for producing composite materials with desired properties (17). One effective method for creating new polymeric materials for various applications is polymer blending. In this study, PVA/CH blends of different ratios were enriched with *Hypericum perforatum* extracts and used in the fabrication of wound dressings. The physico-chemical and antibacterial properties of the composite films were also investigated.

2. MATERIALS AND METHODS

2.1. Materials

Chitosan (low molecular weight, 75–85% deacetylated) was purchased from Oksilab, Turkey. Dried *Hypericum perforatum* L. leaves were purchased from the local market. All other chemicals were of analytical grade.

2.2. Production of PVA/CH films

Dried *Hypericum perforatum* leaves were ground before extraction. Extraction was carried out by the maceration method with distilled water at room temperature with solid/liquid ratios of 1:10 and 1:20. The extracts were filtered through Whatman No.1 filter paper and stored at 4°C until film casting.

Wound dressings were prepared by the solvent casting method using PVA, chitosan, and gelatin in different ratios. Films were first prepared using distilled water, 2% PVA, and 1% chitosan. 1% Gelatin was dissolved in distilled water at room temperature, and added to the films; however, due to the unsuitable textures of the gelatin-based films, the formulations were modified to eliminate the gelatin. PVA was dissolved directly in the film solutions. 1 g of low-molecular weight chitosan was stirred continuously overnight to completely dissolve in 100 mL of 1% acetic acid solution. Glycerol (3.33% (v/v)) was added to the film solutions as a plasticizer.

The films were then prepared again using pure *Hypericum perforatum* extracts obtained at solid/liquid ratios of 1/10 and 1/20 (w/v). PVA was added to the extracts at ratios of 2% and 5% (w/v), whereas chitosan was kept constant at 1% in all films. The prepared film solutions were poured into petri dishes and dried at 45°C for 24 hours.

2.3. Characterization of films

2.3.1. Moisture content

The moisture content of the films was determined via gravimetric analysis by measuring the mass of the films on an analytical balance before and after drying them in the laboratory oven at 105°C for 24 h. Percent moisture of composites were calculated using Equation 1 below.

$$\%\ \mathrm{Moisture\ Content} = \frac{\mathrm{W_i} - \mathrm{W_f}}{\mathrm{W_i}} \mathrm{x} 100 \qquad [1]$$

Where W_i and W_f are the initial and final mass of the films, respectively (18).

2.3.2. Moisture uptake

The films were weighed and placed in a closed chamber at 37°C and 100% RH. The humidity was maintained by placing a container filled with distilled water inside the chamber. The increase in films' mass was followed until constant weight was attained. The percent moisture uptake of the films was calculated from the formula below using the weight difference between the final weight (W_f) and the initial weight (W_i) (19).

$$\%\ \text{Moisture uptake} = \frac{W_f - W_i}{W_i} x100 \qquad [2]$$

2.3.3. Water vapor transmission rate (WVTR)

Water vapor transmission rates were determined using ASTM E96/E96M-15. Each film was fixed to the opening of a test tube filled with distilled water. The initial weight of film-covered test tubes was measured. Then, the tubes were placed in a closed container at 37 °C. After 24 hours, the weight of the samples was measured again. The WVTR of the films was calculated using Equation 3.

$$\begin{array}{c}\text{Water Vapor Transmission} \\ \text{Rate } (\text{g}/m^2.\text{day})\end{array} = \frac{W_i - W_f}{\text{Ax}10^6} \qquad [3]$$

Where, W_i is initial weight of the test tube with water and film, W_f is final weight of the test tube after 24 h. A is the glass tube opening's area (20).

2.3.4. Total phenolic content

Total phenolic content was determined by using Folin-Ciocalteu method with gallic acid as standard. 50 mg of film was dissolved in 5 mL water and the samples were placed on vortex to mix very well. 0.1 mL of the film solution was taken into a test tube and 0.5 mL of 10% (v/v) aqueous Folin-Ciocalteu reagent and 1.5 mL of 20% (w/v) aqueous Na_2CO_3 solution were added. Then, samples were kept in the dark at room temperature for 2 hours. The absorbance of samples was measured at 750 nm. The total phenolic content was calculated and expressed as mg gallic acid equivalents (GAE) per g film (21).

2.3.5. Antioxidant capacity

The antioxidant activity of the films was determined by the radical scavenging capacity of DPPH (1,1-diphenyl-2-picrylhydrazyl) according to the method described by Ertürk & Biran Ay (2022). Briefly, 50 mg of composite film were dissolved in 5 mL of water and vortexed. Then, 0.1 mL of aqueous film solutions was taken and mixed with 3.9 mL 0.56 mM DPPH in methanol and kept at ambient temperature in dark for 30 min. The absorbance of solutions was measured at 517 nm against methanol. Finally, the antioxidant activity was expressed as the percentage of DPPH free radical scavenging capacity and calculated by equation 4.

$$\begin{array}{c}\%\ \text{Radical} \\ \text{scavenging capacity}\end{array} = \frac{(A_{DPPH} - A_{film})}{A_{DPPH}} \times 100 \qquad [4]$$

where A_{DPPH} and A_{film} were the absorbances of DPPH in methanol and film solutions measured at 517 nm, respectively.

2.3.6. Antibacterial activity

The disc diffusion method was used to determine the antibacterial activity of composite films against Gram-negative *Escherichia coli* and Gram-positive *Staphylococcus aureus*. Plate count agar was used to isolate the freshly developed bacterial inoculum. The film samples were placed on the nutrient agar in the petri dishes and incubated for 24 hours at 30 °C. The formed halo zones around the films were an indication of antibacterial activity.

2.3.7. Fourier Transform Infrared - Attenuated Total Reflectance-Infrared (FTIR-ATR) Spectroscopy

Thermo-Nicolet IS10 FTIR-ATR spectrophotometer was used to determine the functional groups of composite films in the range of 650–4000 cm^{-1}.

3. RESULTS AND DISCUSSION

Thin and transparent films were produced from the blends of PVA-CH with different ratios and *Hypericum perforatum* extract amounts (Figure 1).

3.1. Moisture content

Maintaining optimal moisture content is a critical factor that significantly impacts the wound healing process, since it promotes cell migration, proliferation, and the formation of new tissue. Although the moisture content criteria of wound dressings depend on the type of wound, such as chronical, surgical, or acute, there is a general need for a balanced moist environment to facilitate effective healing. The moisture contents of the synthesized films are given in Figure 2. Addition of plant extract to film formulations resulted in a decrease in moisture content. Moreover, the films prepared with extracts having a high solid/liquid ratio (1/20) exhibited higher water contents. Lastly, an inverse relationship between moisture content and PVA amount was observed as it increased from 2 to 5% PVA, contrary to results reported by Srinivasa et al. (2003), who report an increase in moisture content as PVA/ CH ratio was increased (17).

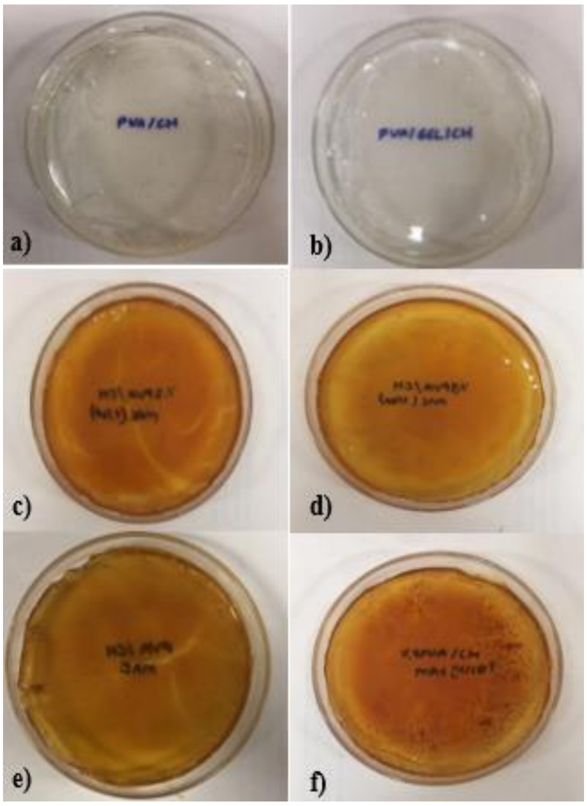

Figure 1. Synthesized films' compositions a)2%PVA/CH, b)2%PVA/CH/GEL, c)2%PVA/CH(1/20), d) 5%PVA/CH(1/20), e)2%PVA/CH(1/10), f) 5%PVA/CH(1/10)

Mehmood et al. (2023), in their study of hydrogels formed by cross-linking folic acid with chitosan, found the moisture content of the films to be between 13% and 17%. According to the data obtained, it has been proven that the moisture content of films containing chitosan has increased significantly compared to some values in the literature. It can be assumed that the structure of the cross-linking polymers also affects the moisture content (22).

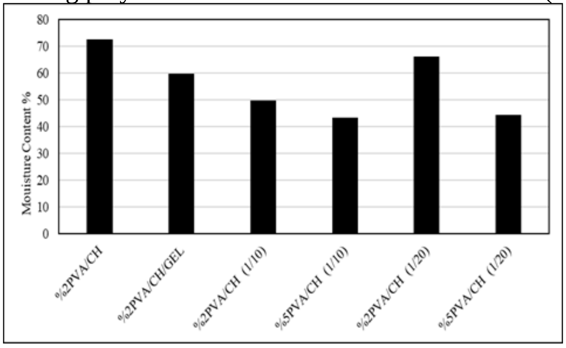

Figure 2. Moisture contents of the films

3.2. Moisture uptake

Moisture uptake is another important property desired for films used in wound healing, as wound exudate absorption is directly related to the ability of films' water holding capacity. The moisture uptake percentages of the films are given in Figure 3. While the composites of polymer blends exhibited 60-70% moisture absorption, the moisture uptake percentages of films containing *Hypericum perforatum* extract decreased to 45%, suggesting the presence of compounds depleting the water adsorption capacity of films. This was further illustrated by the moisture uptake percentages of films prepared with 1/20 extracts are higher than those prepared with 1/10 solid to liquid ratio. The former ratio (1/20) resulted in a dilute extract which probably contained lower amounts of humidity repelling components compared to the more concentrated extract obtained in the later solid/liquid ratio (1/10). Furthermore, when the films produced using the plant extract of the same concentration were compared, it was seen that moisture uptake increased with the increase in PVA ratio. In the study conducted by Yıldırım et al. (2020), chitosan and gelatin-based films containing St. John's wort were synthesized and it was stated that the moisture absorption capacity of the prepared films varied between 107-412%, and a decrease in the moisture absorption capacity was observed with the addition of St. John's wort extract. It can be assumed that the type of polymer in the film also affects moisture absorption (23).

The ability of PVA/CH films to absorb water from humid environments as well as wound exudate is a key factor in their adhesive properties (24). The moisture uptake values of fabricated films indicate their potential for stable adhesion to tissues.

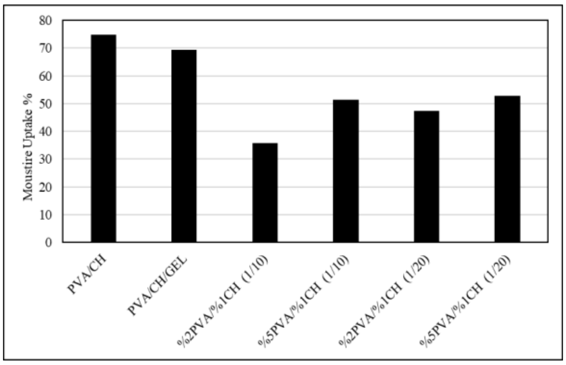

Figure 3. Moisture uptake percentages of the films

3.3. Water vapor transmission rate (WVTR)

Among the most crucial characteristics of wound dressings is WVTR. Ideal wound dressings bear water barrier characteristics which avoid the microbial infections (11). The capacity of the wound dressing to regulate the retention and absorption of wound exudate from the wound bed is investigated and the results are given in Figure 4. The values were found between 440 g/m^2.day and 510 g/m^2.day. The obtained values are compatible with similar WTRV values (530-718 g/m^2.day) in biocomposite films containing PVA and chitosan stated by Chen et al. (2020) (25).

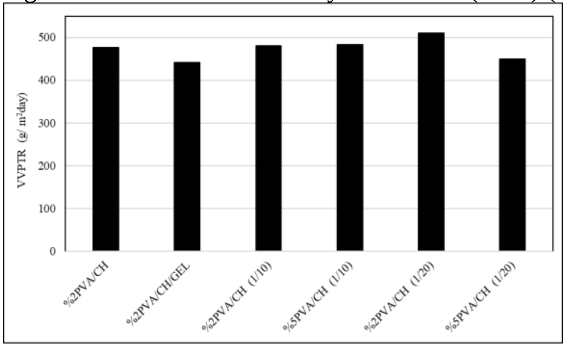

Figure 4. Water vapor transmission rates of the films

The wound dressing should prevent excessive dehydration and exudate formation on the wound. It has been reported in the literature that WVTR values are in the range of 76-9360 g/m^2.day (26). It was observed that the results obtained from the study were within the range reported in the literature.

3.4. Total phenolic content

The measured phenolic content is strongly dependent to the preparation process of the film, the origin of the phenolic compounds, the allowed release time, and the employed analytical method (27). Total phenolic content was measured by Folin–Ciocalteu reagent. Figure 5 demonstrates that the total phenolic compounds ranged from approximately 0.7 to 9 mg of gallic acid equivalents (GAE)/g of film. As expected, incorporating plant extract into film formulations resulted in a notable increase in the phenolics.

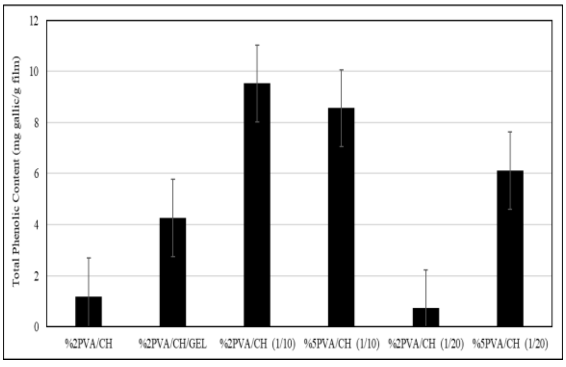

Figure 5. Total phenolic content of films

3.5. Antioxidant capacity

The overproduction of oxygen species is linked to wound inflammation and the development of chronic wounds. Consequently, scavenging excessive oxygen species can help reduce inflammation, enhance the clearance of dead cells by macrophages, and accelerate the wound recovery process (28). As seen in Figure 6, PVA/CH and PVA/CH/GEL composites showed no antioxidant activity. Addition of plant extract to film formulations exhibited a radical scavenging capacity reaching 50%. As mentioned before, the films produced by employing 1/20 solid/liquid ratio resulted in a dilute extract compared to the one prepared with 1/10 ratio. This effect was clearly observed in the antioxidant capacity of films prepared with plant extracts, the dilute ones having values between 20-30%, and concentrated extracts exhibiting 40-50% inhibition. The flavonoids and fatty acids in the plant extract could remove the free radicals in wound sites (28). The results in Figure 6 demonstrate that *Hypericum perforatum* extract is effective in neutralizing oxidative stress species. Therefore, the PVA/CH films containing plant extract can prevent and reduce inflammation by scavenging free radicals in the wound recovery process.

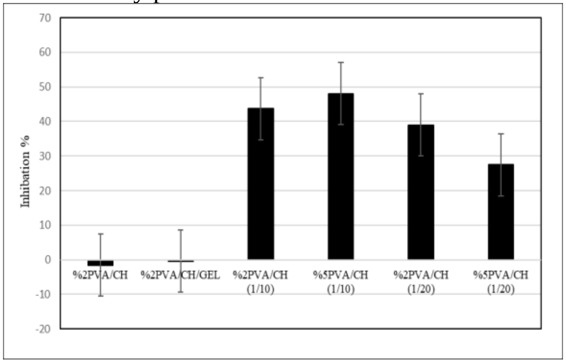

Figure 6. Antioxidant activities of PVA/CH based films.

3.6. Antibacterial activities

Microbial tests were conducted on *E. coli* and *S. aureus*, which represent gram-negative and gram-positive bacteria, respectively. The agar diffusion method (inhibition zone test) was used to evaluate the antibacterial properties of PVA/CH based biopolymer films. When an antibacterial agent is released from the film into the agar medium containing target microorganisms, an inhibition zone forms around the film. The presence of this zone indicates the release of antibacterial material from the film, preventing the growth of microorganisms in that area. The larger the inhibition zone, the more antibacterial material is released from the film. Figure 7 shows the antibacterial effect of PVA/CH composites containing *Hypericum perforatum* extract against both bacteria.

3.7. FTIR-ATR Spectroscopy

Figure 8 shows the FTIR-ATR spectra of the films. The peaks observed at 3300 cm^{-1} are associated with O-H stretching, while 1647 cm^{-1} are the H-O-H bending vibrations of absorbed water molecules (9). The characteristic absorption peaks of PVA, which are -CH$_2$- asymmetric and symmetric stretching and -OH and C-H bonding, were seen at 2905 cm^{-1} and 1340 cm^{-1}, respectively. The C=H stretch representing the amine peak linked to the C group of chitosan was observed at 2870 cm^{-1} (29).

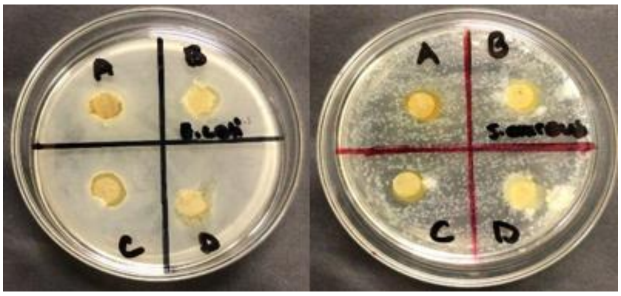

Figure 7. Antimicrobial properties of films containing Hypericum perforatum L. extract against *E. coli* and *S. aureus*. Film compositions: A- 2%PVA/CH (1/10), B- 5%PVA/CH (1/10), C- 2%PVA/CH (1/20), D- 5%PVA/CH (1/20).

The peaks observed between 2800 and 2900 cm^{-1} are related to the C-H stretching band. The carbonyl group (C=O) in the ester bonds specific to *Hypericum perforatum* was observed at 1750 cm^{-1} (7). C-O stretchings were seen around at 1100 cm^{-1} (29). The peaks seen between 900 cm^{-1} and 1000 cm^{-1} are assigned to attributed to the amide III group of C-H and the presence of the C-O-C bridge in the β-glycosidic bonds. The peaks observed between 911 and 744 cm^{-1} show the angular deformation of aromatic rings outside the C-H group plane (30).

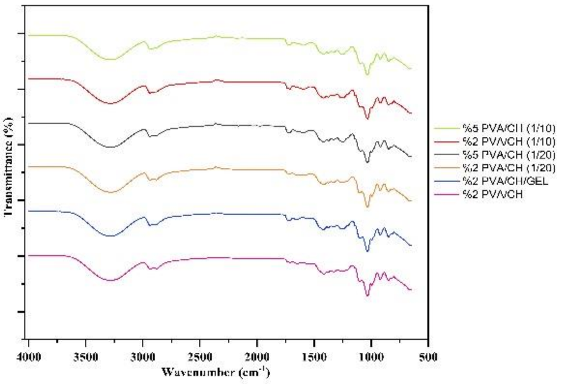

Figure 8. FTIR-ATR spectra of the films.

4. CONCLUSION

The development of PVA/CH wound dressings enriched with *Hypericum perforatum* extract has demonstrated promising features for advanced wound care. The study successfully fabricated films offering a combination of moisture regulation, antioxidant, and antibacterial properties. The incorporation of *Hypericum perforatum* extract notably increased the total phenolic content and the corresponding antioxidant capacity, reaching up to 50% inhibition, which is beneficial for reducing inflammation and accelerating wound healing. The antibacterial activity against *E. coli* and *S. aureus* further confirmed the films' ability to prevent bacterial infections, a crucial requirement for effective wound management. Consequently, the fabricated PVA/CH composite films containing *Hypericum perforatum* extract exhibited substantial medical application potential properties allowing to maintain a moist environment conducive to wound healing, effectively absorb wound exudate, expedite wound recovery, and inhibit bacterial growth.

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