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Design and Fabrication of a Keratin/Tragacanth-Based Nanogel Containing Propolis Extract for Wound Healing

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Abstract
The main objective of this research is to improve topical drug delivery using nanohydrogels. Keratin is the main protein found in hair, nails, and bird feathers. Due to its inherent properties, such as biocompatibility, biodegradability, mechanical strength, and natural abundance, keratin-containing materials are considered a rich protein source. Tragacanth gum also exhibits wound healing and antibacterial properties, making it useful in medical applications. In this study, keratin was extracted from chicken feathers via reductive hydrolysis. Subsequently, nanohydrogel particles were synthesized using chemical crosslinking of natural keratin and tragacanth. Propolis extract, a herbal antimicrobial agent, was then added to the hydrogel to evaluate its release rate. SEM analysis of the optimized keratin/tragacanth nanoparticles revealed a near-spherical morphology with an average diameter of 191 ± 15 nm. After incorporation of propolis extract, the average size of particles increased to 297 ± 20 nm, resulting in a more uniform nanogel. Drug release test showed that incorporating 10% (w/w) propolis into the nanogel led to 50% release over 72 hours. Moreover, the antibacterial activity of propolis-loaded nanogels was reported to reach up to 98%, indicating their potential in wound healing applications.

Keywords: Keratin, Tragacanth gum, Nanogel, Propolis

1. Introduction

The skin functions as the body's first line of defence against injury. A wound refers to damage or degradation of the skin caused by stressful events. When the skin is damaged or wounded, it undergoes four complex healing phases: (1) hemostasis, (2) inflammation, (3) proliferation, and (4) remodelling [1]. Without proper treatment, complications may arise that can potentially lead to death. One of the methods to promote wound healing involves the development of biomedical dressings, gels, and topical creams based on natural or synthetic polymers combined with natural extracts or chemical drugs [1].

Surgical procedures are often unavoidable, and rapid healing of surgical wounds is critical for the patient's well-being, especially when the surgical site is visible. In such cases, both the healing speed and the absence of scarring (known as "scar") are essential for mental health. A significant portion of

the population has scars resulting from traumatic events or various surgeries, particularly cosmetic surgeries, which they remember vividly. This is especially true for facial scars [2]. One method for treating surgical wounds without leaving scars is the application of topical ointments to the sutured area. These ointments are typically based on honey or natural polymers. Hydrogels are three-dimensional networks of polymer chains that retain large amounts of water in their structure. Due to their unique physical and chemical properties, such as flexibility, softness, biodegradability, and biocompatibility, hydrogels have attracted considerable attention in biomedical applications. Both natural and synthetic polymers have been extensively studied for the development of hydrogels suited to specific uses. Hydrogels based on biopolymers offer advantages over synthetic ones in terms of enhanced cellular activity and lower immune responses [3].

Nanogels are nanoscale hydrogel particles formed through physical or chemical interactions. They possess high water absorption, biocompatibility, drug-loading capability, high stability, and responsiveness to external stimuli such as ionic strength, pH, and temperature. Stability of the drug-loaded carrier is crucial for targeted drug delivery. To address this issue, crosslinked nanocarriers, known as nanogels, are employed [4]. Drug delivery systems play a vital role in the pharmacological effects of drugs, as they can influence the release rate, distribution, and even side effects. An effective delivery system ensures that the active drug reaches the right site at the right time and remains there to exert its effect [5, 6].

Tragacanth gum is a natural polysaccharide that can be easily extracted from the stems and branches of various Astragalus species. This anionic polymer is recognized as biodegradable, non-allergenic, non-toxic, and non-carcinogenic. Its resistance to microbial degradation, heat, and acid makes tragacanth attractive for biomedical applications. The active components in tragacanth (tragacanthin and bassorin) aid in collagen formation and wound healing. In addition to its regenerative, wound-healing, and antimicrobial properties, tragacanth also provides controlled drug release in delivery systems [7, 8]. Foroughi et al. [9] developed a polymeric hydrogel network consisting of polyvinyl alcohol (PVA), chitosan, and gum tragacanth loaded with vitamin E using the freeze–thaw method. SEM images revealed that the freeze–thaw process reduced surface pore size, resulting in a smoother and more uniform surface. Additionally, the hydrophilic nature of gum tragacanth enhanced the water retention capacity of the gel network, ultimately leading to an increased gel fraction. Increasing the amounts of chitosan and tragacanth improved the swelling ratio and water vapour transmission rate (WVTR) of the samples compared to pure PVA. Furthermore, the incorporation of tragacanth enhanced tensile strength up to the breaking point. In another study [10], a tragacanth-based nanohydrogel was synthesized using microwave irradiation for the controlled release of ampicillin. Tragacanth gum was chemically grafted with itaconic acid through free radical copolymerization in the presence of N,N'-methylenebisacrylamide (MBA) as a crosslinker and potassium persulfate as an initiator. Drug release studies were conducted at different pH conditions in vitro. Antimicrobial testing against E. coli demonstrated that the nanohydrogel containing ampicillin was more effective than free ampicillin.

Keratin is a natural protein rich in cysteine, found in various sources such as hair, wool, feathers, horns, and human nails. It can be processed into various forms, including films, sponges, powders, and hydrogels [11]. Feathers are among the natural protein fibers that are annually discarded in large quantities as waste from poultry farms. Bird feathers, as a significant keratin source, contain disulfide bonds, hydrogen bonds, and hydrophobic interactions, making them suitable for biomedical applications. Advantages of keratin include its low cost compared to other polymers, availability, biocompatibility, and non-toxicity [12]. Zhai et al. [13] fabricated a keratin-chitosan nanocomposite hydrogel containing nano-ZnO. The resulting nanocomposite exhibited increased swelling and

enhanced antibacterial activity. Its biocompatibility was evaluated using normal human fibroblast cells. In vivo evaluations in rats indicated that the nanocomposite bandages improved wound healing, accelerated skin cell regeneration, and promoted collagen development. Shirazi et al. [11] also extracted keratin from chicken feathers using reductive hydrolysis and synthesized keratin/TG nanogels in various ratios using chemical crosslinking. They incorporated cinnamon as a herbal antibacterial extract into the nanogels and applied them to cotton fabric. The results showed that the nanogel with 10% cinnamon demonstrated strong antibacterial properties.

Propolis is a natural sticky and resinous substance collected by bees from buds and bark of various trees, then mixed with bee enzymes, pollen, and wax. It is also known as bee glue. Typically, propolis consists of approximately 50% resin (flavonoids and phenolic acids), 30% wax, 10% essential oils, 5% pollen, and 5% other compounds. El-Sakhawy et al. [14] reported that due to its unique properties, such as antibacterial, antifungal, antiviral, anti-inflammatory, anticancer, and antitumor activity, propolis has emerged as one of the most promising natural substances for creating advanced bioactive wound dressings. This valuable compound exhibits anti-inflammatory and antibiotic effects, promotes re-epithelialization, and stimulates skin regeneration. They concluded that propolis holds great potential for the development of novel therapeutic approaches in the treatment of skin wounds.

In this research, the primary objective was to design and fabricate a keratin/tragacanth-based nanogel system as a topical ointment for treating surgical wounds without leaving scars. Keratin was selected for its high biological activity and healing properties, and tragacanth for its anti-inflammatory and antibacterial features. Propolis, due to its antimicrobial, antifungal, antiviral, and anti-inflammatory effects, was incorporated into the nanogel as a natural extract and eventually embedded into a cold cream formulation. Characterization methods included DLS to determine particle size, FESEM for morphological analysis, and FTIR to assess molecular interactions. Additionally, drug release assays were conducted. Biological evaluations including cell culture, microbial testing, and cytotoxicity assessments, were also performed to assess the potential of the fabricated nanogels for wound healing applications.

2. Materials and Methods

2.1 Materials

White broiler chicken feathers were provided by a slaughterhouse in Iran. Tragacanth gum and propolis extract were supplied by the domestic market and Zardband Co. (Iran), respectively. Cold cream was purchased from Sepidaj Pharmaceutical Co. Other chemicals, such as PBS and hydrogen peroxide, were of analytical grade and obtained from Merck Co. (Germany).

2.2 Preparation of Keratin/Tragacanth Nanogel

Keratin was first extracted from poultry feather waste via chemical hydrolysis, based on the procedure described in previous research by Shirazi et al. [11]. To prepare the nanogel, keratin and tragacanth were mixed in two different weight ratios: 1:2 (GK12) and 2:1 (GK21). The samples were dissolved under a nitrogen atmosphere on a magnetic stirrer at room temperature for 1 hour. Subsequently, 2 mL of 30% w/w hydrogen peroxide was gradually added dropwise to each sample, followed by continuous stirring at 37°C for 24 hours. The mixtures were then transferred into dialysis bags and dialyzed for one day to remove impurities. Finally, the purified solutions were freeze-dried for 24 hours.

2.3 Loading of Propolis Extract into the Nanogel

After determining the optimal formulation, this sample was selected for loading with propolis. An amount equivalent to 10% propolis extract was added to the optimized keratin-tragacanth formulation. This concentration was selected based on a previous study [11], which demonstrated effective antibacterial performance and acceptable biocompatibility. The sample was dissolved under a nitrogen atmosphere and stirred at room temperature similar to the previous procedure.

2.4 Incorporation of Keratin/Tragacanth Nanogel with Propolis Extract into Cold Cream

At this stage, 1% w/w of the propolis-loaded nanogel was dissolved in 1 mL of distilled water and gradually added to 1 gram of cold cream. Cold cream is an emulsion composed of water and essential fatty acids for the skin. It is called “cold cream” because it leaves a cooling sensation on the skin upon application.

2.5 Characterization of Nanogels

To evaluate particle size distribution, the samples (1 mg/ml) were subjected to ultrasonication using an Ultrasonic Homogenizer (Misonix, S3000) at 20 kHz for 10 min. Dynamic Light Scattering (DLS) analysis was then performed using a ZEN3600 (Malvern, United Kingdom). To assess the morphology of the freeze-dried samples, a field emission scanning electron microscope (FESEM, Zeiss EM900, Germany) was used at an acceleration voltage of 25 Kv and magnifications ranging from 10,000× to 50,000×. The chemical structure of the samples was analyzed by Fourier-transform infrared spectroscopy (FTIR, Thermo Nicolet Nexus 870, United States) using KBr pellets.

For evaluating the release of the propolis extract, UV-Vis spectroscopy was carried out using a DR 5000™ UV-Vis Spectrophotometer (United States). PBS buffer solution was prepared, and at specific time intervals, samples were taken from the solution for UV testing. The absorption wavelength of the extract was first determined (320 nm for propolis), and then the absorbance of the samples was measured at this wavelength.

For the antibacterial assay, the agar well diffusion method was used with two bacterial strains: *Staphylococcus aureus* and *Escherichia coli*. Mueller-Hinton agar was used as the solid culture medium. A sterile swab was dipped into the bacterial suspension and evenly spread over the agar surface. Wells were then created using a sterile punch, and 100 µL of the extract was added to each well. After the extract was fully absorbed into the agar, the plates were incubated for 24 hours, after which the inhibition zones were measured.

The MTT assay, a widely recognized method for evaluating cell viability, was used to assess cytotoxicity. In each well of a 96-well culture plate, 1×10^4 cells in 100 µL of culture medium were seeded and incubated at 37°C for 24 hours to allow cell attachment. After confirming cell adhesion, the medium was carefully removed and replaced with 100 µL of prepared sample solutions at various concentrations. The cells were then incubated for 24 and 72 hours. Following incubation, the medium was removed and replaced with 100 µL of MTT solution (0.5 mg/mL) and incubated for 4 hours. After this period, the MTT solution was removed, and isopropanol was added to dissolve the purple formazan crystals. To enhance dissolution, the plate was placed on a shaker for 15 minutes. Absorbance was measured at 570 nm using an ELISA reader (BioTek ELx808, USA). Wells with more viable cells

showed higher optical density (OD) values. The number of viable cells was calculated using the following equations compared with the negative control (DMEM medium with 10 µL FBS).

$$\text{Toxicity } \% = (1 - \frac{\text{mean OD of sample}}{\text{mean OD of control}}) \times 100$$

$$\text{Viability } \% = 100 - \text{Toxicity } \%$$

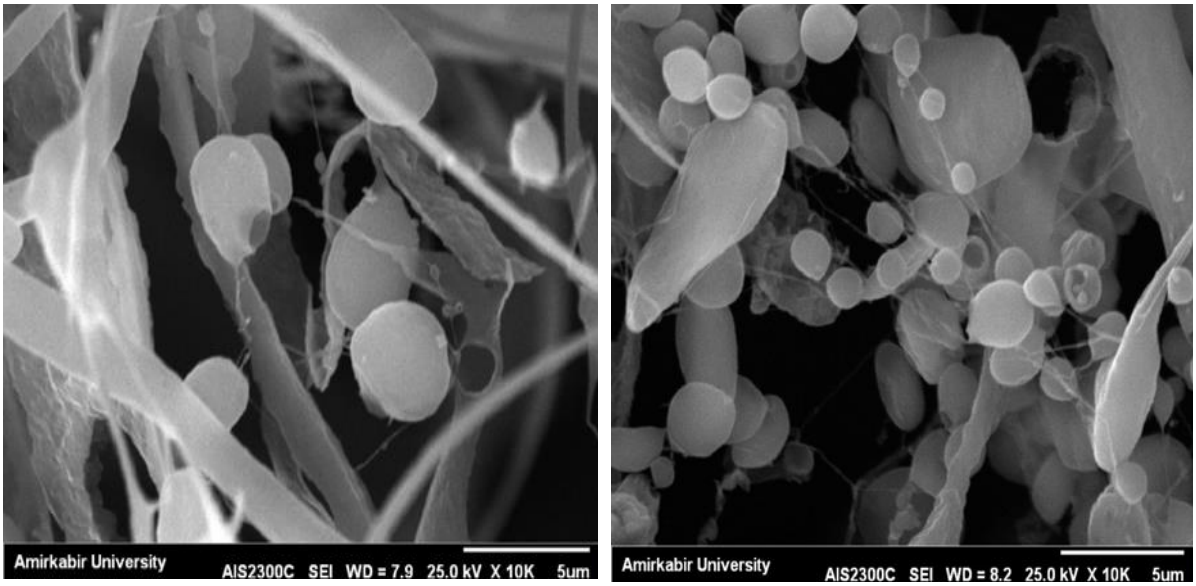
All experiments were performed in triplicate. The results are presented as mean ± standard deviation. One-way ANOVA was used to assess statistical significance between groups, and p-values less than 0.05 were considered significant.

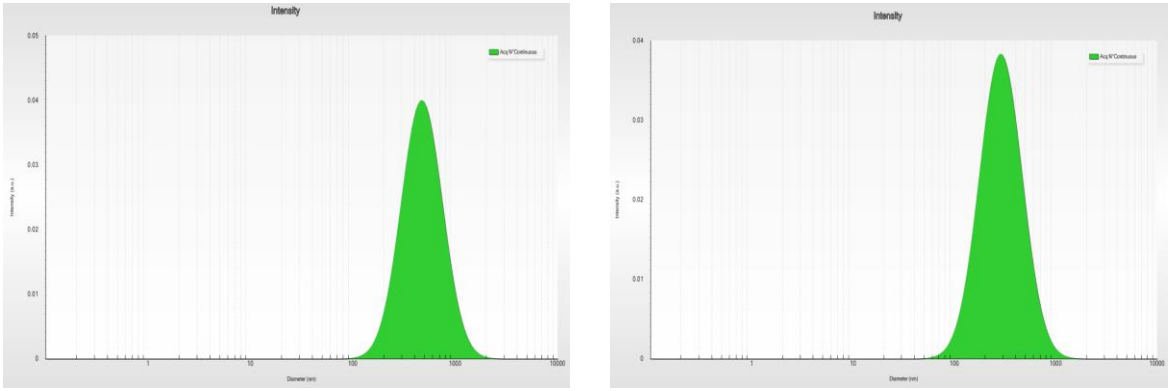
3. Results and Discussion

3.1 Characterization of Keratin/Tragacanth Nanogel

3.1.1 Morphology and Particle Size of the Nanogel

To evaluate the morphology of the nanogel, FESEM was used. Based on the images obtained in Figure 1 and the analysis performed using IMAGE J software, the average particle size of GK21 nanogel was reported to be 392±30 nm, while that of GK12 nanogel was 191±15 nm. Additionally, DLS results showed an average particle size of 202 nm for GK12 nanogel and 341 nm for GK21 nanogel, consistent with the SEM findings. Increasing the amount of tragacanth resulted in an increase in particle size, indicating that the optimal sample with the smallest size was achieved by reducing tragacanth content and increasing keratin content. According to the SEM images, increasing the keratin content and decreasing tragacanth led to more spherical and uniform nanoparticles.





(A) (B)

Figure 1. SEM images and DLS distribution plots of (A) GK21 and (B) GK12 nanogels.

3.1.2 FTIR Structural Analysis

Fourier-transform infrared (FTIR) spectroscopy was used to investigate the chemical structure of the samples. Figure 2 shows the FTIR spectra of various samples. The peaks at 3745 cm^{-1} and 3856 cm^{-1} correspond to hydroxyl (O–H) groups present in the tragacanth structure. These may also relate to N–H groups in the keratin protein structure. The peak at 2933 cm^{-1} is associated with C–H stretching vibrations, found in both keratin and tragacanth. In keratin, this peak can be attributed to methyl and methylene groups on the amino acid side chains.

The peak at 1650 $cm^{-1}$is typically linked to C=O stretching in amide groups of keratin. The 1539 cm^{-1} peak corresponds to amide II bands in keratin, indicating N–H and C–N bonds typical of protein structures like keratin and generally absent in polysaccharides such as tragacanth. The peak at 1238 cm^{-1} may represent C–O bonds in tragacanth or C–N bonds in keratin. The 1078 cm^{-1} peak is related to the polysaccharide structure of tragacanth and indicates O–C–C linkages in its glycosidic bonds [15, 16].

In pure tragacanth, a peak appears at 1748 cm^{-1}, which shifts to 1742 cm^{-1} in GK21 nanogel. This shift is due to intermolecular hydrogen bonding interactions between keratin and tragacanth. In pure keratin, a peak at 1657 cm^{-1} shifts to 1650 cm^{-1} in GK12 nanogel, again suggesting hydrogen bonding. These shifts confirm the presence of physical interactions between the two polymers. Overall, the FTIR spectra of GK21 and GK12 nanogels confirm the coexistence of both keratin and tragacanth, and the formation of intermolecular hydrogen bonds between them.

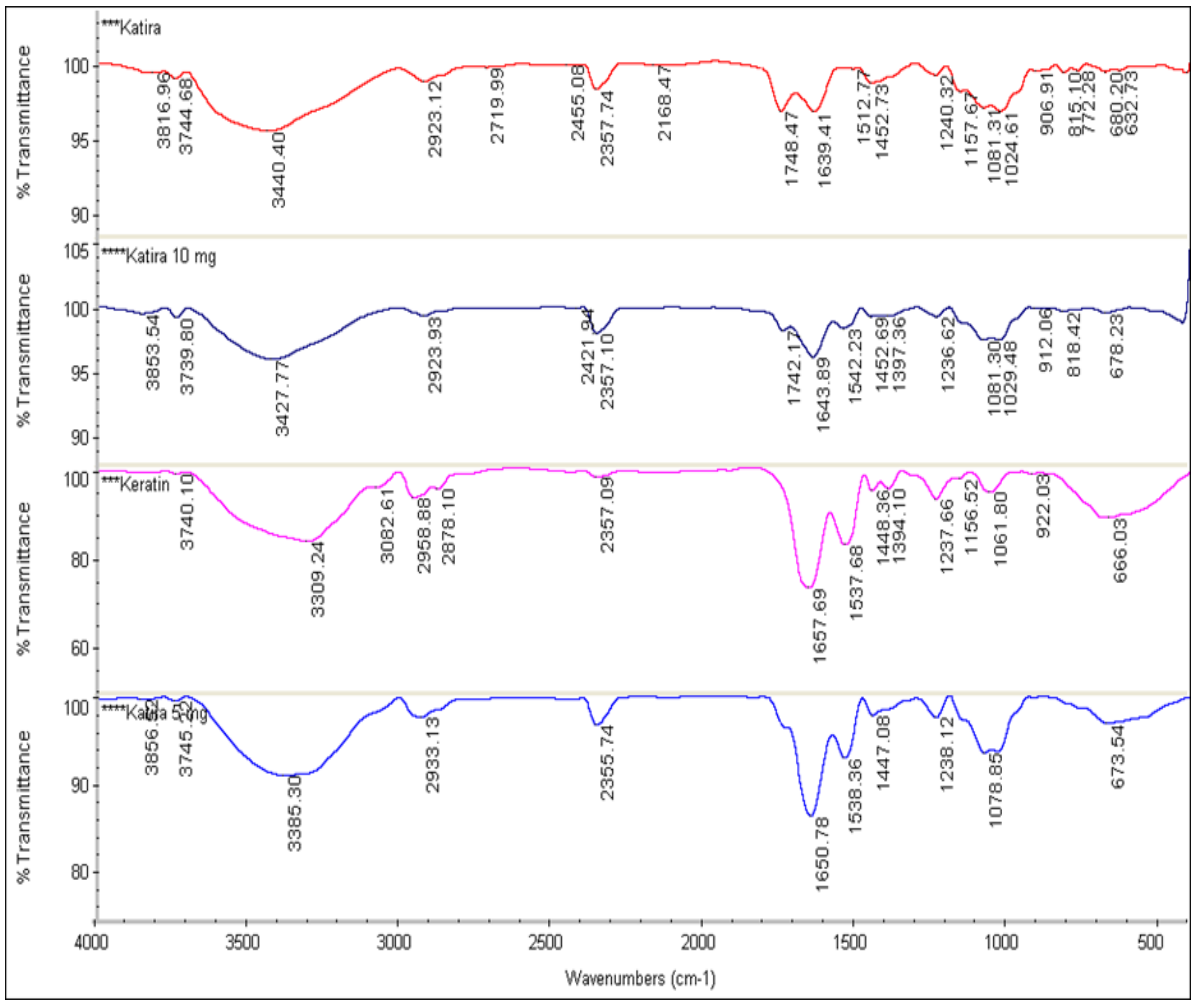
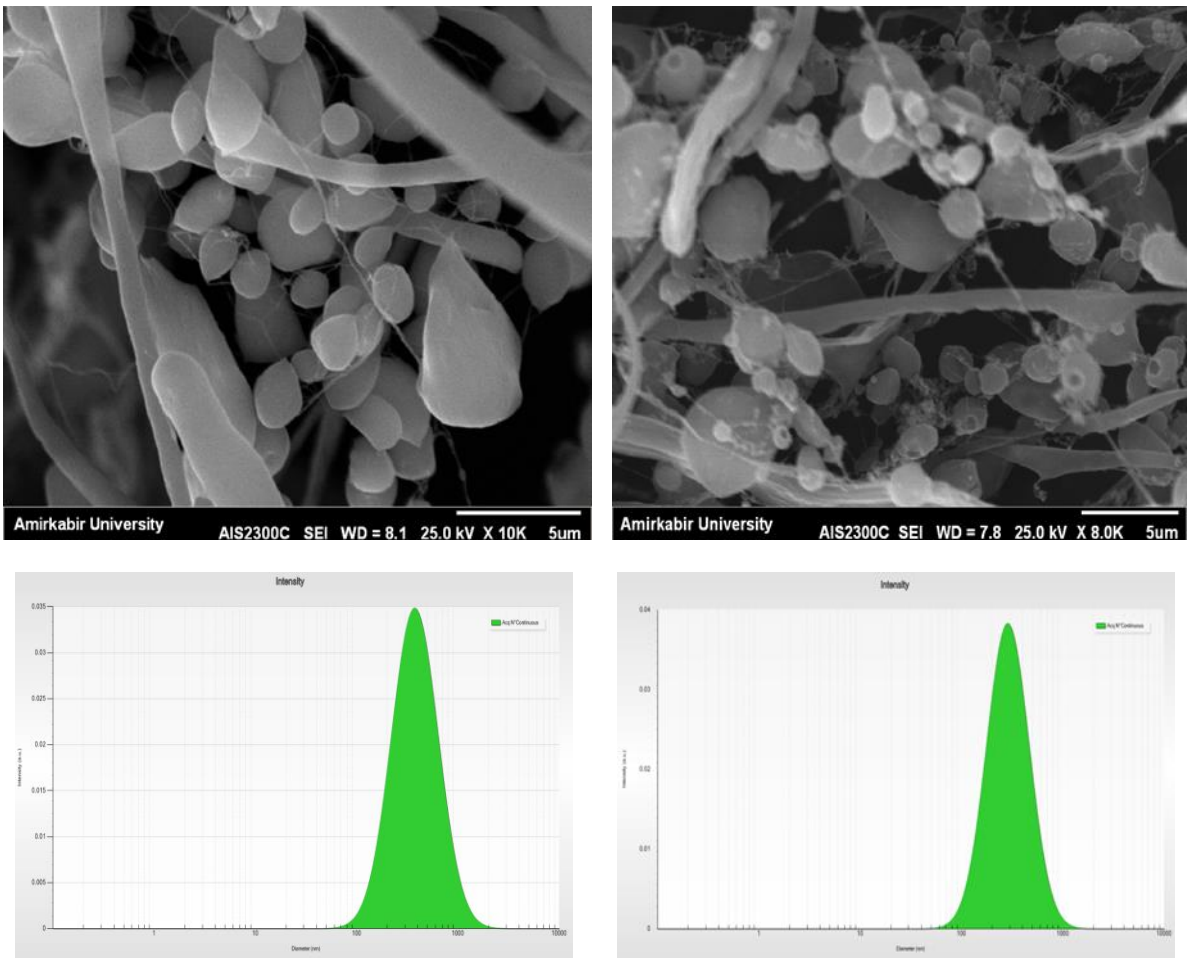


Figure 2. FTIR spectra of pure tragacanth, GK21, pure keratin, and GK12 (from top to bottom)

3.2 Characterization of Nanogel Loaded with Propolis

3.2.1 Morphology and Particle Size of the Nanogel

According to DLS results in Figure 3, the mean particle size increased from 202 nm to 245 nm after incorporating propolis, indicating that the particle size grew with the addition of the extract. SEM images also confirmed the increase in nanoparticle size upon propolis loading. Based on IMAGE J analysis, the average size of the optimized GK12 nanogel containing propolis was measured as 297 ± 20 nm (Figure A), while the same sample without propolis had a size of 191± 15 nm (Figure B). These findings are consistent with the DLS data.



(A) (B)

Figure 3. SEM images and DLS distribution plots of GK12: A) with propolis extract, B) without extract

3.2.2 FTIR Analysis

Figure 4 shows the FTIR spectrum of GK12 nanogel with and without propolis. Propolis is a complex mixture of resins, waxes, flavonoids, and other organic compounds. The broad band observed between 3200–3600 cm^{-1} corresponds to hydroxyl (O–H) groups, typically associated with phenolic and flavonoid compounds [17]. The peaks between 3652–3750 cm^{-1} correspond to free hydroxyl (O–H) groups, attributed to both tragacanth and propolis. The broad band at 3401 cm^{-1} corresponds to O–H and N–H groups, due to keratin's amine groups. Peaks at 2868 cm^{-1} and 2923 cm^{-1} are related to C–H stretching vibrations, indicating the presence of methyl and methylene groups. The peak at 1650 cm^{-1} corresponds to C=O groups, potentially from keratin proteins or compounds in the propolis extract. Peaks at 1079 and 1238 cm^{-1} are linked to C–O and aromatic vibrations, potentially arising from the more complex compounds in propolis and tragacanth [15, 16, 17]. Overall, these results confirm the presence of various functional groups compatible with keratin, tragacanth, and propolis extract.

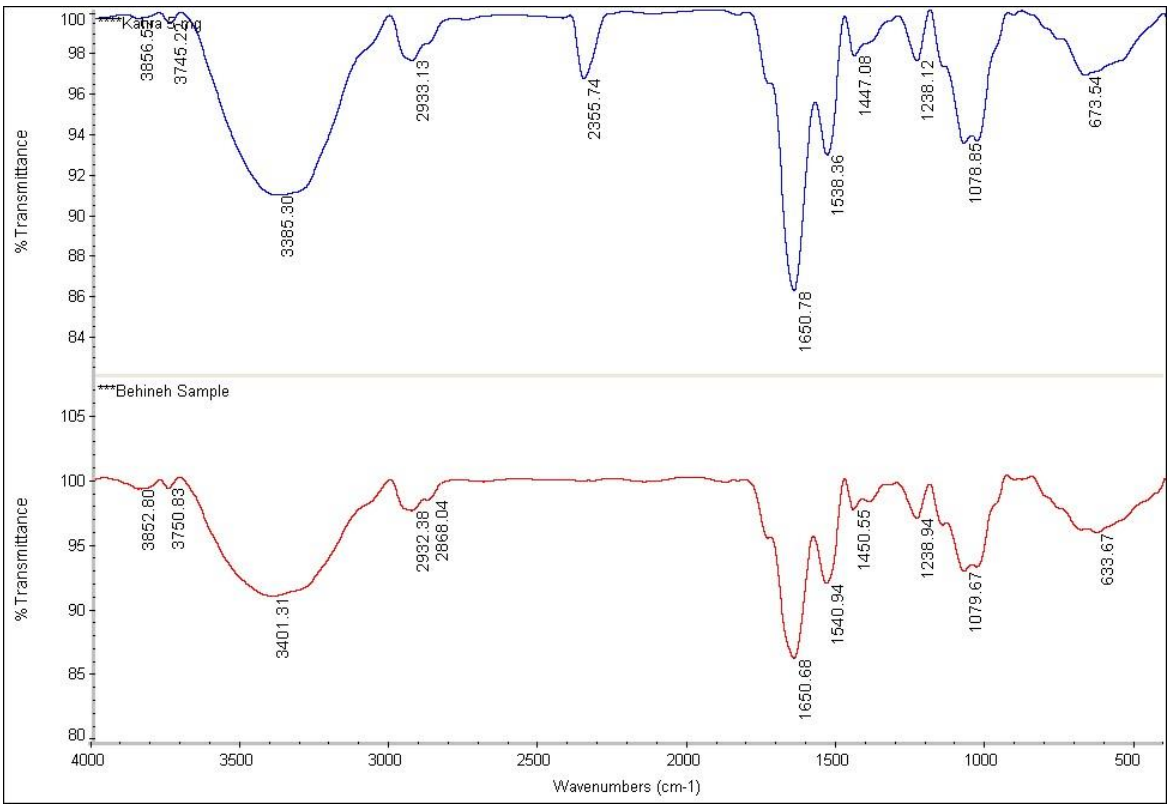


Figure 4. FTIR spectra of GK12 with (bottom) and without propolis (top)

3.2.3 Drug Release

Figure 5 illustrates the cumulative release percentage of propolis extract from the GK12 nanogel (in cream form). During the initial hours (0.5 to 6 hours), the release rate increased rapidly. This is generally attributed to the initial diffusion process, where molecules located on or near the surface are more easily released. After approximately 6 hours, the release rate decreased. In the first 12 hours, a faster release occurred, reaching about 39%. The highest release rate occurred during the first 24 hours, indicating that most of the releasable propolis was discharged during the early phase. From around 36 to 72 hours, the graph approaches a plateau, suggesting that only a small amount of propolis remains and the release process is nearing equilibrium. These release patterns are consistent with the findings reported by Shirazi et al. [11].

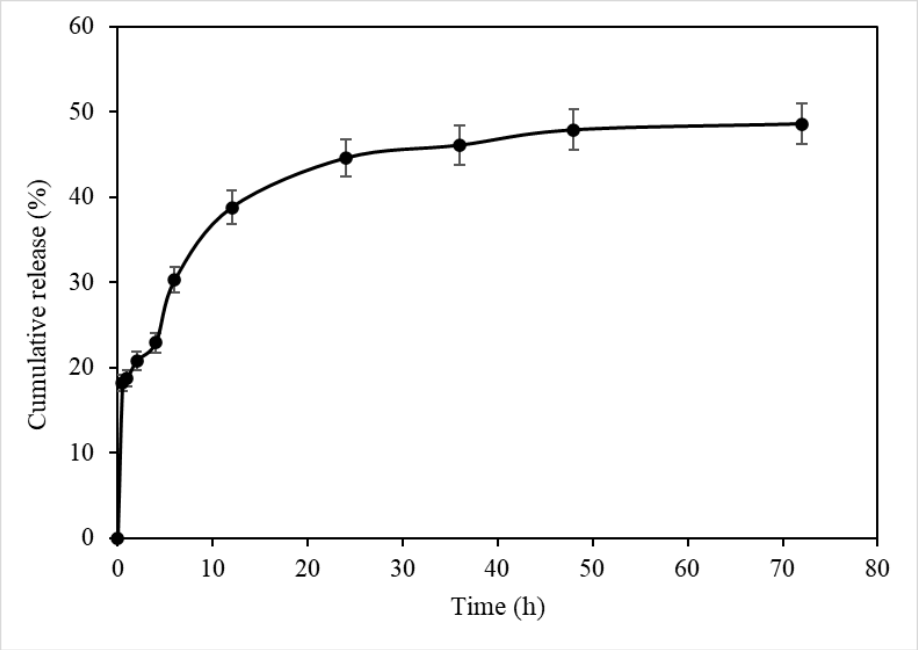
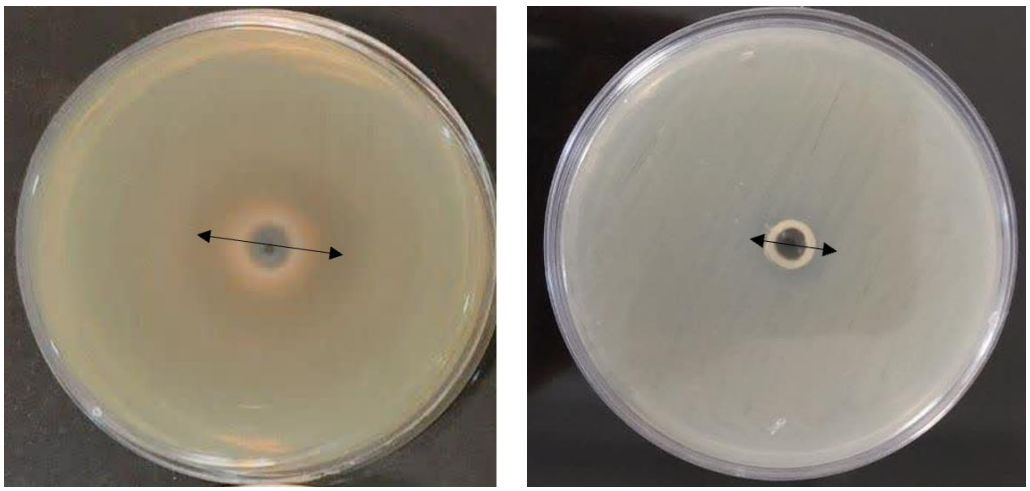


Figure 5. Cumulative release percentage of propolis extract

3.2.4 Antibacterial Activity

To evaluate the antibacterial activity of the propolis extract, the agar well diffusion method was used against two bacterial strains: *Staphylococcus aureus* and *Escherichia coli* (Figure 6). The diameter of the inhibition zone was measured to be 14 mm for *S. aureus* and 11 mm for *E. coli*, indicating the antibacterial properties of the extract. This antibacterial effect is attributed to the bioactive chemical compounds in propolis, particularly phenolic compounds and flavonoids, which can damage the bacterial cell membrane, disrupt essential bacterial enzyme function, and inhibit RNA, DNA, or protein synthesis. Propolis compromises the structural integrity of the bacterial cell wall and membrane [17].



(A) (B)

Figure 6. Inhibition zones of propolis extract against: A) *S. aureus*, B) *E. coli*

3.2.5 MTT Cytotoxicity Test

The MTT assay is one of the most recognized methods for evaluating cell viability. The main purpose of this test is to assess the cytotoxicity of compounds, drugs, or supplements on cells. Figure 7 shows the viability of fibroblast cells exposed to the GK12 nanogel loaded with propolis extract after 24 and 72 hours.

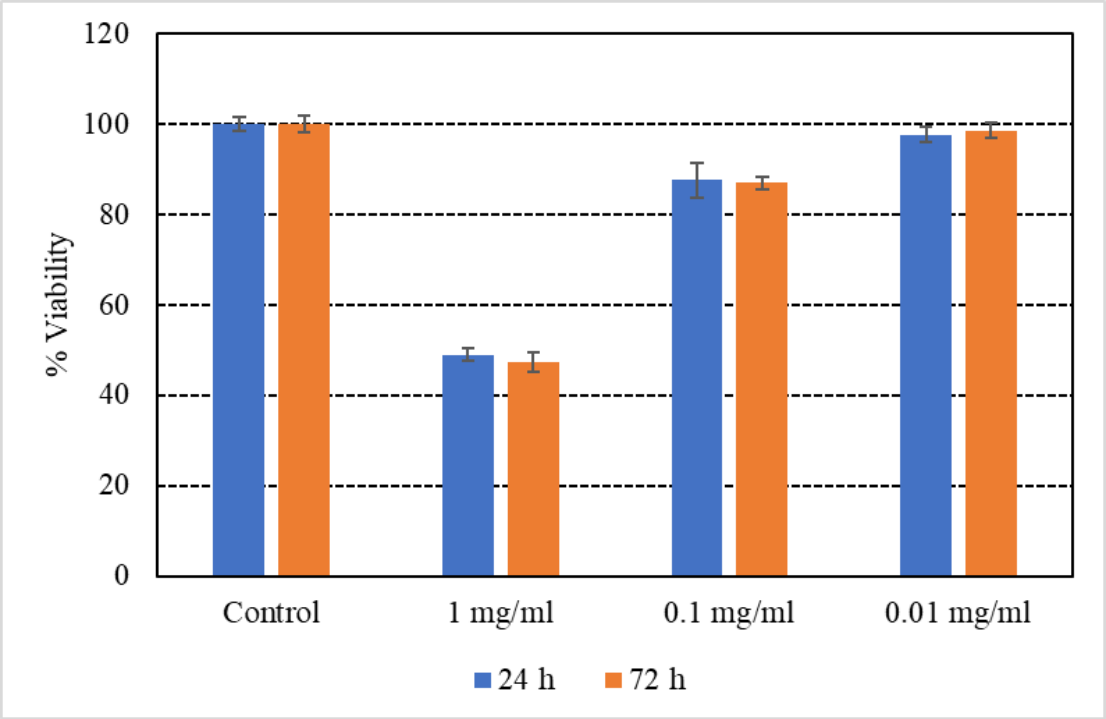


Figure 7. MTT test results for GK12 nanogel loaded with propolis extract after 24 and 72 hours

Results are presented as mean ± standard deviation (n = 3).

24-Hour Test

- Control: Cell viability was 100%, as the control serves as the reference baseline.
- 1 mg/mL: Cell viability was approximately 48.93%, indicating high cytotoxicity—thus, not suitable for biological applications.
- 0.1 mg/mL: Cell viability was 87.50%, above the 85% safety threshold, suggesting non-toxicity and acceptable safety.

  0.01 mg/mL: Cell viability was 97.56%, clearly indicating safety at this concentration.

72-Hour Test

- Control: 100% viability.
- 1 mg/mL: Viability dropped to 47.30%, indicating high toxicity.

- 0.1 mg/mL: Viability was 86.88%, confirming its safety.
- 0.01 mg/mL: Viability reached 98.55%, again confirming complete biocompatibility.

A significant difference in cell viability was not observed between 24-hour and 72-hour exposure times, indicating a time-independent response to the nanogel formulation.

These results confirm that both 0.1 mg/mL and 0.01 mg/mL concentrations are safe even after 72 hours of exposure. Overall, the MTT test results indicate that the GK12 nanogel containing propolis extract is non-toxic to skin fibroblast cells, making it a viable candidate for use as a topical cream.

3.3 Discussion

The observed increase in particle size after incorporation of propolis extract can be attributed to the adsorption of phenolic and resinous compounds from propolis onto the surface of keratin/tragacanth nanoparticles, leading to the formation of a larger hydrodynamic diameter, as also suggested by previous studies [14]. The shift in FTIR peaks further confirms the formation of intermolecular hydrogen bonds between the active compounds of propolis and the functional groups of keratin and tragacanth. The initial burst release of propolis during the first 6 hours is likely due to the diffusion of surface-adsorbed molecules, while the subsequent slower release phase corresponds to the gradual diffusion from the core of the nanogel matrix, in agreement with the release profiles reported by Shirazi et al. [11]. Similar to our previous study [11], as the release rate of the extract is concentration-dependent, it can be concluded that the observed release kinetics follows a first-order kinetics model.

Moreover, the antibacterial activity of the propolis-loaded nanogel was notable, with inhibition zones of 14 mm against S. aureus and 11 mm against E. coli, which are comparable or even higher than those reported by Shirazi et al. [11] for cinnamon-loaded nanogels and by El-Sakhawy et al. [14] for other propolis-based wound dressings. These findings confirm the potent antimicrobial potential of propolis in topical formulations. Compared to previously reported tragacanth-based systems [9], the keratin/tragacanth/propolis formulation developed in this study offers additional bioactivity while maintaining good biocompatibility, as demonstrated by the MTT assay results.

The 50% release of propolis within 72 hours observed in this study suggests a sustained delivery profile, which is desirable in wound healing applications. Compared to some commercial dressings that release active agents within 24–48 hours, this extended release may reduce the need for frequent dressing changes and provide prolonged antimicrobial action. Given the biocompatibility of the keratin/tragacanth matrix and the natural origin of the ingredients, the developed nanogel holds promise for further in vivo studies and clinical translation as a bio-based wound dressing.

From a clinical perspective, the sustained release of 50% propolis over 72 hours may offer significant therapeutic benefits, particularly in maintaining prolonged antimicrobial activity at the wound site. This release profile is comparable to or exceeds that of some commercial hydrogel dressings, which often require more frequent replacement. As stated by Oryan et al. [18], releasing propolis has a considerable effect not only on antibacterial activity, but also on tissue repair due to stimulating the synthesis of glycosaminoglycan and granulation tissue. Furthermore, the natural composition and biocompatibility of the keratin/tragacanth nanogel make it a promising candidate for future in vivo wound healing applications.

Overall, the combination of keratin, tragacanth, and propolis in a nanogel matrix provides a promising approach for wound healing applications, supporting both antimicrobial activity and controlled release of bioactives.

4. Conclusion

In this study, a hydrogel was prepared using tragacanth and keratin extracted from chicken feathers, and then propolis extract was incorporated into the system. SEM analysis showed that the nanoparticles were approximately spherical, with the optimized sample having an average particle size of about 191 ± 15 nm. According to FTIR results, the functional groups of keratin, tragacanth, and propolis extract were all present in the final hydrogel, and hydrogen bonding interactions were formed between the components. The drug release results demonstrated that the amount of extract released increased over time, with the highest release occurring within the first 24 hours, amounting to about 39%. The antibacterial test on the optimized sample containing propolis showed strong antibacterial activity, being more pronounced against the gram-positive bacterium *S. aureus* than the gram-negative *E. coli*. The cytotoxicity test revealed that the fabricated nanogel is non-toxic to skin fibroblast cells. Therefore, this nanogel can be safely used as a topical cream for wound treatment and healing.

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