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Original Article

Novel hydrogel with carrageenan, fucoidan, and titanium oxide nanoparticles for periodontal drug delivery

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Abstract

Background: Nonsurgical periodontal therapy combined with antimicrobial agents is crucial for effective periodontal care. As local drug delivery systems, hydrogels offer significant advantages for managing periodontal disease. Carrageenan, extracted from red seaweeds, offers anti-inflammatory benefits, while fucoidan provides antioxidant, anticancer, and antiviral effects. Titanium oxide nanoparticles enhance antimicrobial activity, synergizing with these agents.

Methods: This study was an experimental in-vitro investigation. Carrageenan powder (0.8 g) and fucoidan powder (0.8 g) were dissolved in 100 mL deionized water and boiled at 65 °C for four hours. The resulting supernatant was discarded, and the pellet was double-filtered. This process was repeated twice to obtain the carrageenan and fucoidan extract. Titanium oxide nanoparticles (0.1 g) and Carbopol (50 g) were added to the obtained extract. The prepared product was stored in graded tubes at a cool temperature. The samples underwent degradation analysis, swelling test, contact angle analysis, and anti-inflammatory analysis.

Results: The degradation test, conducted on three samples on days 4, 7, and 14, respectively, resulted in complete degradation by day 6. The swelling index demonstrated a significant weight decrease from the first hour to the 24th hour, measuring 0.385 g and 0.330 g, respectively. The contact angles on the left and right sides were 54.07° and 55.2°, respectively, indicating their hydrophilic nature. Anti-inflammatory analysis at 50 µL revealed a standard value of 84 and a hydrogel value of 80.

Conclusion: The formulated hydrogel demonstrated complete degradation by day six, supporting its use in controlled drug delivery. The swelling index confirmed its moisture-retention capacity, while the hydrophilic contact angles highlighted its adhesion with periodontal tissues. The anti-inflammatory efficacy comparable to the standard demonstrated its potential as an effective therapeutic agent, making it a promising addition to nonsurgical periodontal treatment.

Keywords: Anti-inflammatory agents, Carrageenan, Hydrogels, Nanoparticles

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Introduction

Periodontitis is an inflammatory condition that affects the supporting tissues of teeth and is caused by various factors, including microorganisms. It leads to gradual alveolar bone loss and the formation of periodontal pockets. Perioceutics, which involves administering therapeutic drugs via systemic and local routes alongside mechanical therapy, has revolutionized periodontal treatment. Non-surgical periodontal treatment, particularly scaling and root planing, supplemented by antimicrobial medications, is crucial for a successful treatment. Local drug delivery agents, such as hydrogels, offer a promising avenue for sustained drug release, inhibiting microbial growth.[1]

Carrageenan, a sulfated polysaccharide found naturally in red seaweed, is extracted through washing, drying, and alkaline agitation, resulting in a powder form.[2] There are three main types of carrageenan: ι-carrageenan, κ-carrageenan, and λ-carrageenan, each with distinct properties.[3] κ-carrageenan, the most abundant type, forms strong gels in the presence of potassium salts, while λ-carrageenan acts solely as a thickening agent.[4,5] Carrageenan has diverse applications and has shown promise in inhibiting virus growth.[6] Research on its role in local drug delivery is burgeoning due to its adhesive nature and positive surface charge.[7]

Similarly, derived from seaweed, fucoidan exhibits various biological activities, including antitumor, anti-HIV, and anti-inflammatory properties.[8] Studies have highlighted its efficacy in treating herpes labialis and recurrent aphthous ulcers.[9] Fucoidan's ability to reduce inflammation and limit biofilm formation underscores its potential in periodontal treatment.[10]

Titanium nanoparticles possess potent antibacterial properties, primarily attributed to their photocatalytic activity.[11] These nanoparticles effectively disrupt bacterial cell walls and inhibit microbial growth.[12] Incorporating titanium nanoparticles into dental materials offers preventive benefits against caries and tooth sensitivity.[13]

Due to the various advantageous properties of carrageenan, fucoidan, and titanium oxide nanoparticles, the present study aimed to evaluate the effectiveness of the carrageenan-, fucoidan-, and titanium oxide nanoparticle-based hydrogel as a local drug delivery agent. Assessing various properties of this formulation can enhance its suitability for clinical use in periodontal treatment.

Methods

Sample size calculation

The sample calculation was performed using G-Power software with a statistical power of 80% and an alpha error of 0.05. The adequate sample size for this in-vitro study was determined to be 31. This ensures that the study can adequately detect significant differences and provide reliable results.

Hydrogel formulation

The hydrogel, consisting of carrageenan, fucoidan, and titanium oxide nanoparticles, was fabricated as follows: 0.8 g of carrageenan powder and 0.8 g of fucoidan powder were dissolved in 100 mL of deionized water and heated to 65 °C for four hours. After boiling, the supernatant was removed, and the remaining pellet underwent double filtration. This process was repeated twice to obtain the carrageenan and fucoidan extract. Subsequently, 0.1 g of titanium oxide nanoparticles was added to the extract. Carbopol (50 g) was then used to enhance viscosity and thickening properties, facilitating hydrogel formation (Figure 1). The resulting product was transferred to graded centrifuge tubes and stored in a cool environment.[14]

The physical appearance of the formulated carrageenan-, fucoidan-, and titanium oxide nanoparticle-based hydrogel:

Clarity: opaque

Color: white

Homogeneity: homogenous

Consistency: semi-solid

Degradation test

The prepared sample was divided into three equal portions, each weighing 5 g, and placed into separate graded centrifuge tubes (Figure 2). To each sample, 30 mL of phosphate-buffered saline (PBS) was added to simulate physiological conditions. The hydrogel dispersion was then incubated at 37 °C with mechanical agitation to mimic physiological settings. At regular intervals, 1 mL of the released solution was collected from the centrifuge tubes and replaced with an equal volume of fresh phosphate buffer solution. The degradation test results were assessed on days 4, 7, and 14.[15]

Swelling test

The swelling test was conducted to quantify the water content of the formulated hydrogel. Three additional samples were obtained from the original prepared sample for the swelling test (Figure 3). These samples were placed onto a petri dish and dried in a hot air oven (Figure 4). Once completely dry, they were weighed again and transferred to clean centrifuge tubes containing 30 mL of freshly prepared phosphate-buffered saline at 37 °C. After 24 hours, the hydrogels were removed from the PBS solution, gently dried with Kimwipe wipers to remove excess water, and then re-weighed to measure swelling and fluid absorption. This process was repeated for a total duration of 48 hours, and the swelling test results were analyzed afterward. The swelling ratio (SR) was calculated using the following formula:

$SR = ((W2 - W1) / W1) \times 100\%$, where $W2$ and $W1$ represent the weight after and before swelling, respectively.[16]

Contact angle test

A goniometric approach was employed for the contact

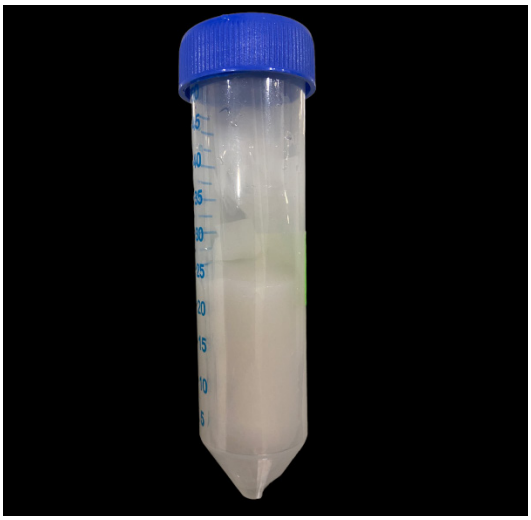

Figure 1. The fabricated hydrogel composed of carrageenan, fucoidan, and titanium oxide nanoparticles

Figure 2. The formulated hydrogel samples were taken for analysis of the degradation test

Figure 3. The formulated hydrogel samples are divided into three parts for the subsequent swelling test

Figure 4. The formulated hydrogel samples after being dried in the hot air oven

angle test, utilizing a K100 force tensiometer. One end of the original sample was cut and placed onto a clean glass slide for analysis (Figure 5). Advancing (right and forward) contact angle measurements were made by gradually adding water to a 0.46 gm drop at the end of a needle until the drop edge advanced, as observed by an operator using a digital imaging system. Receding angle measurements (left and backward) were taken by withdrawing water through the needle until the drop edge receded.[17]

Figure 5. The formulated hydrogel sample was cut and placed onto a clean glass slide for contact angle analysis

Anti-inflammatory efficacy test

This assay aimed to assess the anti-inflammatory efficacy of the formulated hydrogel, utilizing bovine serum albumin (BSA) as a model protein. The denaturation of BSA was quantified by measuring its absorbance at 660 nm post-treatment, with various concentrations of the formulated hydrogel.[18]

In each assay, 0.05 mL of the formulated hydrogel was combined with 0.45 mL of a 1% aqueous BSA solution (Figure 6). The pH of this mixture was maintained at a slightly acidic level of 6.3 by adding 1N of hydrochloric acid (HCl). Following preparation, the samples were incubated at room temperature for 20 minutes. Before incubation, the samples were preheated at 55 °C for 30 minutes and then cooled to room temperature. Diclofenac sodium was used as a standard control due to its recognized anti-inflammatory properties.[19]

Statistical analysis

The collected data was tabulated using a Microsoft Excel spreadsheet. Data were analyzed using IBM SPSS software (Version 23), a statistical tool with predefined variables. A significance level of $P < 0.05$ was set for all tests. Repeated measures ANOVA was used for the degradation test. The swelling test and contact angle analysis were evaluated using the paired *t*-test. The anti-inflammatory assay was analyzed using the independent *t*-test.

Results

Degradation test

The degradation assessment involved three samples derived from the original hydrogel compound, measured on days 4, 7, and 14. Initial measurements on day one showed sample weights of 0.761 g, 0.718 g, and 0.455 g, respectively. By day four, samples one and three were already degraded, with sample two weighing 0.518 g. Complete degradation was observed by day six, indicating a release of the hydrogel extract over four to six days, with approximately 80% to 90% released within the first three days as shown in Table 1.

Swelling test

The hydrogel's swelling index was monitored for 48 hours. After drying, the recorded weights for samples 1, 2, and 3 were 0.004 g, 0.004 g, and 0.008 g, respectively (Figure 7). Following the addition of phosphate buffer saline and analysis after one day, the sample weights were determined as 0.385 g for sample 1 and 0.330 g for sample 2, and the weight of sample 3 could not be determined. The modest increase in swelling ratio suggests minimal hydrogel degradation, indicating the potential for tissue nourishment and inflammation reduction, which is likely

Figure 6. The formulated hydrogel sample taken for assessing anti-inflammatory test activity

attributed to the high viscosity behavior of carrageenan.

Contact angle test

Contact angles on the left and right sides were measured at 54.07° and 55.2°, respectively, resulting in an average angle of 54.63° (Figure 8). The droplet width was recorded as 423 pixels, with the right contact point at 1003 pixels and the left at 580 pixels. Given that the average contact angle is less than 90°, the hydrogel was hydrophilic, suggesting effective tissue adhesion and rapid moisture absorption.

Anti-inflammatory test analysis

In the BSA assay, percentage inhibition was assessed at different concentrations. At 10 µL, the standard exhibited 47% inhibition compared to 42% for the hydrogel. At 20 µL, the standard showed 60% inhibition while the hydrogel showed 57% (Figure 9). This trend continued, with significant differences between the formulated hydrogel and the control, indicating its potential anti-inflammatory activity.

Discussion

Periodontitis induces the formation of localized periodontal pockets through progressive destruction of the periodontal ligament and alveolar bone, creating pathologically deepened sulci around affected teeth.[20,21] In instances of localized periodontal pockets, delivering the therapeutic agent administered locally is preferred over systemic administration. This ensures a high concentration of the therapeutic agent at the infection site and helps to prevent systemic resistance. Local delivery devices achieve therapeutic benefits by directly introducing the drug into the pocket, leading to sustained or controlled release of the biologically active compound.[22]

Numerous studies have highlighted the individual advantages of carrageenan, fucoidan, and titanium oxide nanoparticles. This study combined these three materials to formulate a hydrogel, capitalizing on their synergistic effects. Carrageenan was chosen for its antioxidant properties, fucoidan for its anti-inflammatory properties,

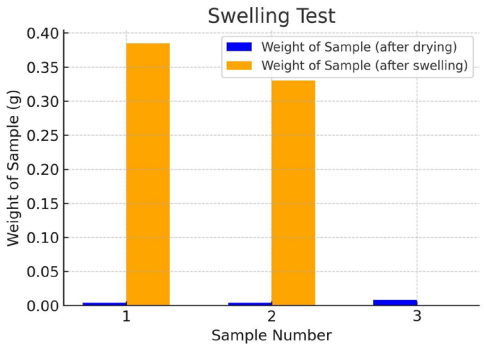

Figure 7. The swelling index displays initial sample weights and sample weights after 24 hours

Table 1. Representation of degradation test results on days one, four, and six

	Day 1	Day 4	Day 6
Sample 1 weight (g)	0.761	0	0
Sample 2 weight (g)	0.718	0.518	0
Sample 3 weight (g)	0.455	0	0

The sample weights are measured in grams (g)

and titanium

nanoparticles for their antimicrobial properties, as demonstrated in previous research.[23]

This study innovatively combines these materials to create a hydrogel that promises enhanced therapeutic efficacy and offers a multifaceted approach to treating periodontal diseases. This approach ensures targeted delivery of the therapeutic agents, maximizing their effectiveness while minimizing potential side effects.

The formulated gel containing carrageenan, fucoidan, and titanium oxide nanoparticles underwent in-vitro characterization. The resulting gel exhibited a white color, homogeneous consistency, opacity, and semi-solid texture. It demonstrated good flexibility and a smooth and uniform surface.

Hydrogels are preferred for their ability to sustain the delivery of various local therapeutic agents. Incorporating carrageenan enhances the antibacterial properties of the hydrogel[24]. Fucoidan, known for its diverse therapeutic effects, demonstrated antimicrobial properties against *Streptococcus mutans* and *Porphyromonas gingivalis*. It also inhibited bacterial adhesion to tooth structures.[25,26]

The degradation index of the hydrogel revealed significant and sustained drug release over a four to six-day period, with around 80% to 90% of the drug released within the first three days. These findings are consistent with previous studies, such as Egle and colleagues' research, which utilized fucoidan/chitosan hydrogels for sustained delivery of bioactive molecules contained in platelet-rich fibrin.[27]

The swelling behavior of the hydrogel is a crucial characteristic for its applications in both food and pharmaceutical industries. The swelling index was monitored for the formulated hydrogel from the 1st hour

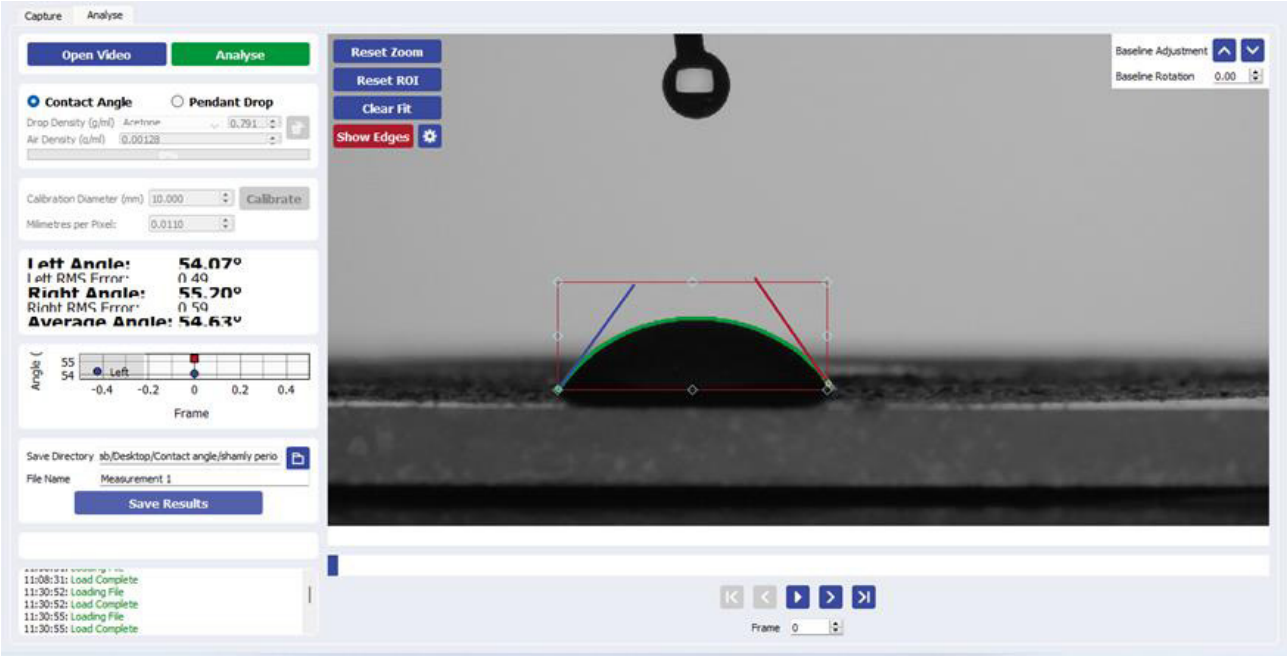

Figure 8. Contact angle analysis conducted with a goniometer indicates a left contact angle of 54.07° and a right contact angle of 55.2°, indicating the hydrogel's hydrophilic nature

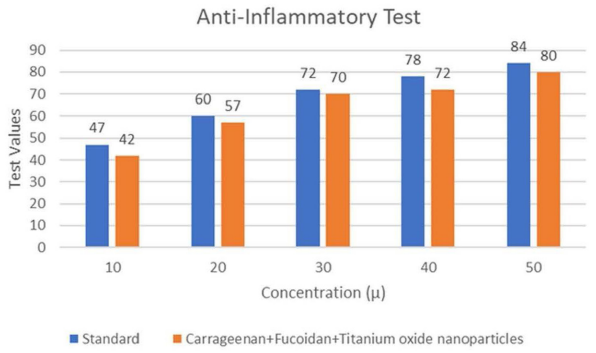

Figure 9. Percentage inhibition test of the carrageenan, fucoidan, titanium oxide nanoparticle-based hydrogel, and diclofenac sodium in BSA (bovine serum albumin assay) at various concentrations in microliters (10 µL, 20 µL, 30 µL, 40 µL, 50 µL)

up to 48 hours after gel formulation. Our observations revealed rapid swelling, facilitated by the porous nature of the hydrogels, allowing for significant surface area and quick solvent absorption. However, it was noted that the swelling did not increase substantially, indicating the hydrogel's resistance to rapid degradation. This property suggests that the hydrogel can provide sustained nutrition to tissues and promote cell migration, thus aiding inflammation reduction. The presence of carrageenan, a hydrophilic polymer, in the hydrogel likely contributes to this behavior.[28]

The contact angle measurement reflects the hydrogel's wettability or ability to spread on a surface upon contact with a liquid. The formulated hydrogel's average contact angle was 54.63 degrees, indicating its hydrophilic nature. This characteristic enhances the hydrogel's adhesion to tissues, making it particularly suitable for injectable applications, such as drug delivery into periodontal pockets. The formulated hydrogel could be conveniently injected using a 26-gauge needle.

In one study, the anti-inflammatory activity of fucoidan extracts was evaluated in vitro, and the findings demonstrated that all fucoidan extracts reduced cytokine production in LPS-stimulated human peripheral blood mononuclear cells and a human macrophage line (THP-1) in a dose-dependent manner. In addition, it was noted that fucoidan extracts from all species exhibited significant anti-inflammatory effects, with the lowest molecular weight subfractions showing maximal effects at low concentrations.[29] These findings contribute to the reliability of our study, as the anti-inflammatory test of the formulated hydrogel yielded a result of 80 at 50 µL, confirming its efficacy as an anti-inflammatory agent.

Titanium oxide nanoparticles have good biocompatibility and excellent antimicrobial properties. Their slow drug exchange capability and high drug-carrying capacity make them an attractive option for local drug delivery systems in oral disease treatment.[30] A study on the green synthesis of titanium oxide nanoparticles with rosemary and ginger assessed their bactericidal action against *Staphylococcus aureus*. The study concluded that there was a reduction in the overall bacterial count when the nanoparticles were introduced into the wells of a microplate containing cultured *S. aureus*.[31]

Another study assessed the antibacterial activities of titanium oxide nanoparticles and found compelling evidence of their superior effectiveness against pathogenic *E. coli* bacteria. This underscores the potential applications

of titanium oxide nanoparticles in biomedical and medical fields.

Various agents, including zinc, curcumin-based topical nanogels, and chlorhexidine mouthwash as a control, have been investigated for the treatment of gingivitis and periodontitis patients and showed successful results.[32,33]

Technology advancements have significantly enhanced oral care standards, emphasizing the importance of understanding nanotechnology and its relevance in oral hygiene product development. Considering the myriad benefits of titanium oxide nanoparticles, carrageenan, and fucoidan, our study distinguishes itself as the first to evaluate the combined in-vitro effects of titanium oxide nanoparticles, carrageenan, and fucoidan hydrogel.

Based on our findings, we can infer that the addition of carrageenan and fucoidan to titanium oxide nanoparticles elicits a synergistic effect, making the resulting hydrogel a promising candidate for periodontal therapy. Further exploration of these nanoparticles in future research could lead to the development of innovative therapeutics capable of addressing a broad spectrum of periodontal diseases. Moreover, the integration of titanium oxide nanoparticles with carrageenan and fucoidan offers potential advantages regarding reduced cytotoxicity and cost-effectiveness, indicating promising use in the future.

Strengths and limitations

The study's strength lies in developing a unique hydrogel formulation, which has been tested to confirm its anti-inflammatory properties and demonstrate its efficacy. One limitation of this study was the lack of evaluation of the antimicrobial efficacy of the formulated hydrogel against periodontal pathogens. Future research should include antimicrobial studies to determine the effectiveness of the hydrogel against a broader range of microorganisms. Additionally, further in-vivo clinical studies are warranted to assess the clinical efficacy of the formulated hydrogel as a local drug delivery agent in periodontal therapy.

Conclusion

The findings of this study demonstrate that the formulated hydrogel, containing carrageenan, fucoidan, and titanium oxide nanoparticles, exhibits sufficient properties as an anti-inflammatory agent and is hydrophilic, making it suitable for use as a local drug delivery agent in periodontal therapy. Carrageenan and fucoidan are widely available in most countries, and titanium oxide particles offer versatility, indicating various potential applications for the treatment of different periodontal diseases. However, further research is necessary to accurately analyze and understand the effects of the formulated hydrogel on clinical periodontal parameters.

Areas of future research

Building upon the findings of this study, future research can explore pioneering solutions, with a particular focus on guided tissue regeneration within periodontal defects. Hydrogels have the potential to act as scaffolds for this purpose. Investigations may center on integrating titanium oxide nanoparticles through carrageenan and fucoidan mediation.

Such endeavors could lead to innovative and precisely targeted therapeutic strategies for

addressing diverse periodontal diseases.

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Competing Interest

None.

Data Availability Statement

Data will be available upon request from the corresponding author.

Ethical Approval

Not applicable as this is an in-vitro study.

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