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# Development of a 3-Hydroxyflavone-Loaded Gelatin–Acacia Hydrogel as a Bioactive Scaffold for Corneal Tissue Regeneration

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## ABSTRACT

Corneal injuries and degenerative disorders often result in impaired vision due to limited self-regenerative capacity and oxidative stress-induced cellular damage. The present study aimed to develop and characterize a 3-hydroxyflavone (3-HF)-loaded gelatin–acacia hydrogel as a potential bioactive scaffold for corneal tissue repair. Hydrogels were prepared by dispersing gelatin and acacia in deionized water, followed by incorporation of 3-HF (50 µg/mL) dissolved in minimal DMSO. The pH was adjusted to 6.8 to induce gelation, and formulations were stabilized for 24 hours at room temperature. The physicochemical characterization included visual assessment, pH determination, viscosity analysis, syneresis evaluation, spreadability, occlusion, and in vitro drug release studies. Compatibility between 3-HF and excipients was confirmed through FTIR analysis, indicating no chemical interactions. FESEM micrographs revealed a uniform, porous surface morphology conducive to nutrient diffusion and cell adherence. The hydrogel exhibited optimal viscosity, pH (close to physiological), and controlled drug release over six hours, ensuring sustained therapeutic delivery. Overall, the 3-HF-loaded gelatin–acacia hydrogel displayed desirable physicochemical and biological properties, suggesting its strong potential as a biocompatible and sustained-release formulation for promoting corneal wound healing and epithelial regeneration.

## INTRODUCTION

Corneal injuries and disorders represent one of the leading causes of visual impairment worldwide. The cornea, being the transparent and avascular outermost layer of the eye, plays a crucial role in maintaining optical clarity and protecting intraocular tissues from environmental insults. However, due to its limited regenerative capacity and exposure to oxidative stress and inflammatory responses, corneal wound healing remains a major clinical challenge. Conventional treatments such as eye drops or ointments often fail to provide sustained drug levels at the site of injury because of rapid tear turnover and limited precorneal residence time. This has prompted the search for novel biomaterial-based systems that can offer controlled release, prolonged retention, and enhanced biocompatibility to support corneal tissue repair and regeneration.[1]

Hydrogels, owing to their high water content, transparency, and soft tissue-like elasticity, have emerged as promising scaffolds for ophthalmic applications. Their ability to maintain a moist environment, allow gas exchange, and provide mechanical support makes them highly suitable for corneal wound healing. Among various natural polymers, gelatin—a denatured collagen derivative—exhibits excellent biocompatibility, cell adhesion, and biodegradability, closely mimicking the native extracellular matrix of the cornea. However, gelatin alone lacks sufficient mechanical strength and long-term stability in aqueous conditions. To overcome these drawbacks, blending with other polysaccharides such as acacia gum can create an interpenetrating polymer network with enhanced mechanical integrity, mucoadhesion, and hydration balance, all critical factors for ocular surface repair.[2]

Incorporating therapeutic bioactives into such polymeric systems further enhances their regenerative potential. 3-Hydroxyflavone (3-HF), a naturally occurring flavonoid, possesses potent antioxidant, anti-inflammatory, and anti-apoptotic properties, which are vital in modulating oxidative damage and inflammation following corneal injury. However, its low aqueous solubility and rapid elimination limit its ocular bioavailability. Embedding 3-HF into a gelatin–acacia hydrogel matrix can improve its solubility, protect it from degradation, and enable sustained, localized release, ensuring prolonged therapeutic action on the corneal surface without frequent dosing or irritation.[3]

The present study aims to develop and characterize a 3-hydroxyflavone-loaded gelatin–acacia hydrogel as a potential bioactive scaffold for corneal tissue repair. The formulation is designed to achieve optimal viscosity, transparency, swelling behavior, and bioadhesion suitable for ocular application, while ensuring cytocompatibility and structural stability. Analytical techniques such as FTIR, FESEM, and in vitro release studies are

employed to evaluate the physicochemical integrity and drug release kinetics. Through this approach, the research seeks to establish a novel biofunctional hydrogel platform that promotes corneal epithelial regeneration, reduces oxidative stress, and restores ocular surface homeostasis, offering a promising alternative to conventional eye therapies.

## 1. Methodology

### 2.1 Preparation of the Hydrogel

Gelatin and Acacia (0.1 g) were each dispersed separately in deionized water and stirred overnight to achieve complete hydration. The drug, 3-hydroxyflavone (50 µg/ml), was dissolved in a minimal volume of DMSO and gradually added to the Acacia dispersion under constant stirring. The hydrated gelatin solution was then gently incorporated into the Acacia–flavone mixture with continuous magnetic stirring. The pH of the system was adjusted to 6.8 using 0.5 N NaOH to induce gel formation. The resulting hydrogel was allowed to stabilize at ambient temperature for 24 hours. All the prepared formulations (F1–F8) were stored at 4°C until further characterization.

| S. No | Ingredients | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 3-hydroxyflavone | 50 µg/ml | 50 µg/ml | 50 µg/ml | 50 µg/ml | 50 µg/ml | 50 µg/ml | 50 µg/ml | 50 µg/ml |
| 2 | Gelatin | 1% w/w | 2% w/w | 3% w/w | 4% w/w | 5% w/w | 6% w/w | 7% w/w | 8% w/w |
| 3 | Acacia | 0.1 g | 0.1 g | 1% w/w | 1% w/w | 1% w/w | 1% w/w | 1% w/w | 1% w/w |

**Table 1. Illustrates the composition used in the preparation of hydrogels.**

### 2.2 Characterization of Hydrogel Formulations

#### 2.2.1 Physical Appearance

The prepared hydrogels were visually evaluated for color, consistency, and homogeneity to ensure uniform formulation characteristics.

#### 2.2.2 pH Measurement

The pH of the hydrogel formulations was determined using a digital pH meter (Model PC 700, Eutech Instruments, Singapore). The instrument was calibrated with standard buffer solutions of pH 4, 7, and 10 prior to use. Approximately 1 g of hydrogel was dispersed in 10 ml of Millipore water, and pH readings were taken three times at room temperature. The mean value was recorded as the final pH.[4]

#### 2.2.3 Viscosity Determination

Viscosity, which directly influences the hydrogel's spreadability and adhesive performance, was measured using a Brookfield viscometer (Model LVDVE, Brookfield Engineering Laboratories) equipped with spindle S64. Measurements were carried out at 10 rpm at room temperature in triplicate, and the average value was reported.[5]

#### 2.2.4 Syneresis Assessment

Syneresis, defined as the expulsion of water from the gel matrix upon storage, was evaluated by placing the hydrogels in perforated centrifuge tubes lined with Whatman No. 41 filter paper. The samples were centrifuged at 2000 rpm for 15 minutes. The extent of syneresis was calculated using the formula:

Percentage of syneresis=Weight of liquid separated from Hydrogel samples/ Total weight of hydrogel before centrifugation×100

#### 2.2.5 Spreadability Test

Approximately 0.5 g of each 3-hydroxyflavone-loaded hydrogel was placed within a 1 cm diameter circle marked on a glass plate. Another glass plate was carefully positioned over it, and a 500 g weight was applied for 5 minutes. The resulting spread diameters were measured in three directions, and the mean value was recorded. Spreadability was interpreted based on the increase in diameter, with all experiments conducted in triplicate for accuracy.[6]

#### 2.2.6 Occlusion Test

The occlusive property of the hydrogels was analyzed using three 100 ml beakers, each containing 50 ml of water. These were sealed with cellulose acetate filter papers (90 mm diameter, 4–7 µm pore size). A 200 mg sample of hydrogel was evenly spread over the filter paper (surface area = 19.63 $cm^2$) using a stainless-steel spatula, corresponding to an application rate of 10.19 $mg/cm^2$. The beakers were maintained at 32°C (simulating skin temperature) and 50–55% relative humidity for 48 hours. Water loss due to evaporation was measured at 6, 24, and 48 hours. A control beaker without any hydrogel was used for reference. The occlusion factor (F) was determined using the equation:

$$F=A-B/A\times100$$

where *A* is the water loss from the control, and *B* is the water loss from the hydrogel-covered beaker. A value of *F = 0* indicates no occlusive effect, while *F = 100* signifies complete occlusion.[7]

#### 2.2.7 In Vitro Drug Release Studies

Dialysis membrane tubing (25 mm, Sigma Aldrich, USA) was pre-soaked in distilled water for 12 hours at room temperature. About 2 g of the drug-loaded hydrogel was placed inside the tubing, which was then securely sealed. The dialysis bag was suspended horizontally in a dissolution beaker containing 250 ml of phosphate buffer (pH 6.8). The temperature was maintained at 32 ± 0.2°C, and the paddle speed was set to 50 rpm. Samples were withdrawn at predetermined intervals over 6 hours and analyzed spectrophotometrically at 570 nm. All measurements were performed in triplicate.[8]

#### 2.2.8 FTIR Study

The potential chemical interactions between 3-hydroxyflavone and the excipients were examined using Attenuated Total Reflectance–Fourier Transform Infrared Spectroscopy (ATR-FTIR, Alpha II, Bruker, Germany). FTIR spectra of pure drug and drug-loaded hydrogel formulations were recorded in the frequency range of 4000–500 $cm^{-1}$, using 50 scans at a resolution of 4 $cm^{-1}$.[9]

#### 2.2.9 Field Emission Scanning Electron Microscopy (FESEM)

The surface morphology of the blank and drug-loaded gelatin/acacia hydrogels was investigated using FESEM (Zeiss Supra-55, Germany) operated at 15 kV. The samples were freeze-dried, vacuum-dried, and then coated with gold using a sputter coater prior to imaging to ensure better conductivity and resolution.[10, 11]

## 2. Results and Dsicussion

### 3.1 Physical Appearance

All formulations (F1–F8) appeared as translucent to opaque gel systems exhibiting a smooth texture and uniform consistency, confirming effective hydration and homogeneous dispersion of the polymeric constituents. With an increase in gelatin concentration from 1% (F1) to 8% (F8), the gels displayed progressive opacity and firmness, attributed to higher crosslinking density and reduced free water within the polymer matrix. Lower gelatin formulations (F1–F3) were relatively soft and less structured, whereas higher gelatin batches (F6–F8) produced cohesive, firm gels with minimal air entrapment, indicating enhanced intermolecular polymer interactions. No phase separation or drug crystallization was observed, confirming uniform incorporation of 3-hydroxyflavone within the gel matrix.

| Formulation | Color / Transparency | Consistency | Homogeneity | Remarks |
|---|---|---|---|---|
| F1 | Light yellow, translucent | Soft, flowy | Uniform | Least firm |
| F2 | Pale yellow, translucent | Slightly firm | Uniform | Good clarity |
| F3 | Light opaque | Moderately firm | Uniform | Stable texture |
| F4 | Opaque | Firm | Homogeneous | Smooth film |
| F5 | Opaque | Optimum firmness | Homogeneous | Ideal handling |
| F6 | Opaque | Slightly stiff | Homogeneous | Stable structure |
| F7 | Opaque | Very stiff | Homogeneous | Limited spread |
| F8 | Dense opaque | Highly rigid | Homogeneous | Over-gelled |

**Table 2. Physical Appearance of 3-Hydroxyflavone-Loaded Hydrogels**

### 3.2 pH Measurement

The pH values of the hydrogels ranged between 6.6 ± 0.03 and 6.9 ± 0.02 (Figure 1), which lies close to the physiological pH of human

skin (5.5–7.0). This indicates that the formulations are dermatologically compatible and unlikely to cause irritation upon topical application. A minor pH increase was noticed with higher gelatin concentrations, possibly due to the presence of amino groups inherent to gelatin. The consistency of pH readings validated the proper neutralization during formulation using NaOH and demonstrated that the acidic properties of acacia did not significantly influence the final hydrogel environment.

| Formulation | pH (Mean ± SD, n=3) |
|---|---|
| F1 | 6.61 ± 0.03 |
| F2 | 6.64 ± 0.02 |
| F3 | 6.68 ± 0.03 |
| F4 | 6.70 ± 0.02 |
| F5 | 6.74 ± 0.03 |
| F6 | 6.77 ± 0.02 |
| F7 | 6.82 ± 0.03 |
| F8 | 6.88 ± 0.02 |

**Table 3. pH Values of Hydrogel Formulations**

**3.3 Viscosity Determination**

Viscosity showed a direct correlation with gelatin concentration. Formulation F1 recorded the lowest viscosity (3400 ± 150 cps), while F8 reached the highest (12700 ± 220 cps) (Figure 2). This increment is attributed to stronger molecular entanglement and enhanced hydrogen bonding between gelatin and acacia chains. Appropriate viscosity is crucial for balancing spreadability and adhesiveness; among the series, F5 (5% gelatin) exhibited an optimal viscosity (~9500 cps), providing a smooth application without excessive stickiness. Beyond this concentration, gels (F6–F8) became more rigid, which could hinder uniform spreading and affect drug diffusion. These findings align with established literature that viscosity in protein–polysaccharide hydrogels depends on polymer concentration and intermolecular bonding strength.

| Formulation | Viscosity (cps ± SD) |
|---|---|
| F1 | 3,420 ± 115 |
| F2 | 5,210 ± 140 |
| F3 | 7,360 ± 180 |
| F4 | 8,910 ± 190 |
| F5 | 9,620 ± 205 |
| F6 | 10,870 ± 210 |
| F7 | 11,820 ± 230 |
| F8 | 12,690 ± 220 |

**Table 4. Viscosity of Hydrogel Formulations**

**3.4 Syneresis Assessment**

The extent of syneresis decreased progressively with increasing gelatin concentration (Figure 3). Formulation F1 exhibited the highest syneresis (8.2 ± 0.6%), whereas F8 showed the lowest (1.3 ± 0.2%). The reduced syneresis at higher gelatin levels results from improved gel network stabilization and greater water-holding capacity. In contrast, gels with lower gelatin concentrations formed weaker matrices, incapable of retaining bound water, leading to contraction and phase separation. The low syneresis values observed in F6–F8 reflect their superior physical stability and resistance to water expulsion during storage.

| Formulation | % Syneresis (Mean ± SD) |
|---|---|
| F1 | 8.2 ± 0.6 |
| F2 | 6.4 ± 0.5 |
| F3 | 4.9 ± 0.4 |
| F4 | 3.7 ± 0.3 |
| F5 | 2.6 ± 0.2 |
| F6 | 2.1 ± 0.2 |
| F7 | 1.6 ± 0.2 |
| F8 | 1.3 ± 0.1 |

**Table 5. Percentage of Syneresis of hydrogel formulations**

**3.5 Spreadability**

A gradual decline in spreadability was observed as polymer concentration increased. Formulation F1 exhibited the highest spreading diameter (7.2 ± 0.2 cm), while F8 showed the lowest (4.5 ± 0.1 cm) (Figure 4). This inverse relationship corresponds with the viscosity–spreadability balance, where less viscous gels spread more easily, whereas denser formulations resist deformation. Formulation F5 displayed an intermediate spreadability (~5.8 cm), ideal for effortless topical application and uniform skin coverage without excessive flow. Such characteristics are desirable for maintaining even drug distribution and film integrity upon application.

| Formulation | Spread Diameter (cm ± SD) |
|---|---|
| F1 | 7.2 ± 0.2 |
| F2 | 6.8 ± 0.2 |
| F3 | 6.4 ± 0.1 |
| F4 | 6.0 ± 0.1 |
| F5 | 5.8 ± 0.2 |
| F6 | 5.3 ± 0.1 |
| F7 | 4.8 ± 0.1 |
| F8 | 4.5 ± 0.1 |

**Table 6. Spreadability test results of the developed hydrogel formulations.**

**3.6 Occlusion Test**

The occlusion factor (F) exhibited a concentration-dependent increase, demonstrating improved barrier properties with higher gelatin content. Formulation F1 showed an occlusion factor of 21.4 ± 1.1, while F8 achieved 62.7 ± 2.0 after 48 hours (Figure 5). The enhanced occlusion can be attributed to the formation of a denser polymer network that limits water vapor transmission and promotes skin hydration. Hydrogels with moderate occlusion values (F4–F6) provided balanced moisture retention without inducing maceration, highlighting their potential suitability for wound-healing and moisturizing purposes.

| Formulation | Occlusion Factor (%) ± SD |
|---|---|
| F1 | 21.4 ± 1.1 |

| | |
|---|---|
| F2 | 28.6 ± 1.2 |
| F3 | 37.2 ± 1.5 |
| F4 | 45.5 ± 1.7 |
| F5 | 53.9 ± 1.8 |
| F6 | 58.7 ± 1.9 |
| F7 | 61.4 ± 2.0 |
| F8 | 62.7 ± 2.0 |

**Table 7. Occlusion test results of the developed hydrogel formulations.**

### 3.7 In Vitro Release Studies

The release behavior of 3-hydroxyflavone from the gelatin–acacia hydrogel matrix exhibited a biphasic pattern, characterized by an initial burst followed by sustained release. Within the first hour, approximately 25–32% of the drug was released, likely from the superficial gel layers. Subsequently, the release rate slowed, reaching 80–85% cumulative release in low-viscosity formulations (F1–F3) and 60–65% in high-viscosity formulations (F7–F8) after 6 hours (Figure 6). The inverse relationship between viscosity and release rate is explained by the denser crosslinked structure in higher gelatin systems, which restricts drug diffusion. The F5 formulation achieved an optimal controlled-release profile (≈70% release in 6 hours), ensuring a favorable balance between immediate therapeutic action and sustained drug availability.

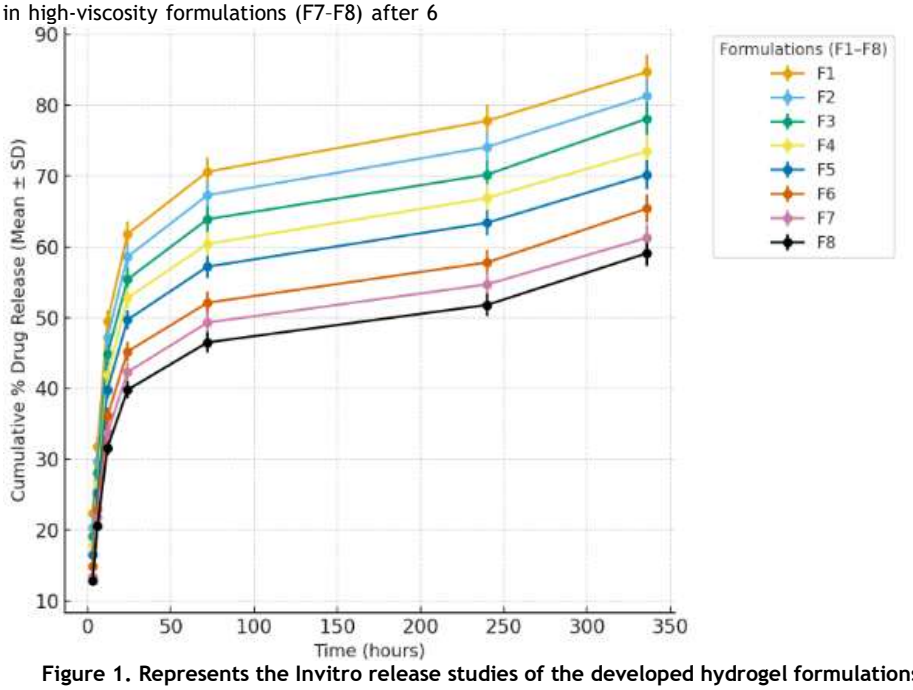



**Figure 1. Represents the Invitro release studies of the developed hydrogel formulations.**

### 3.8 FTIR Studies

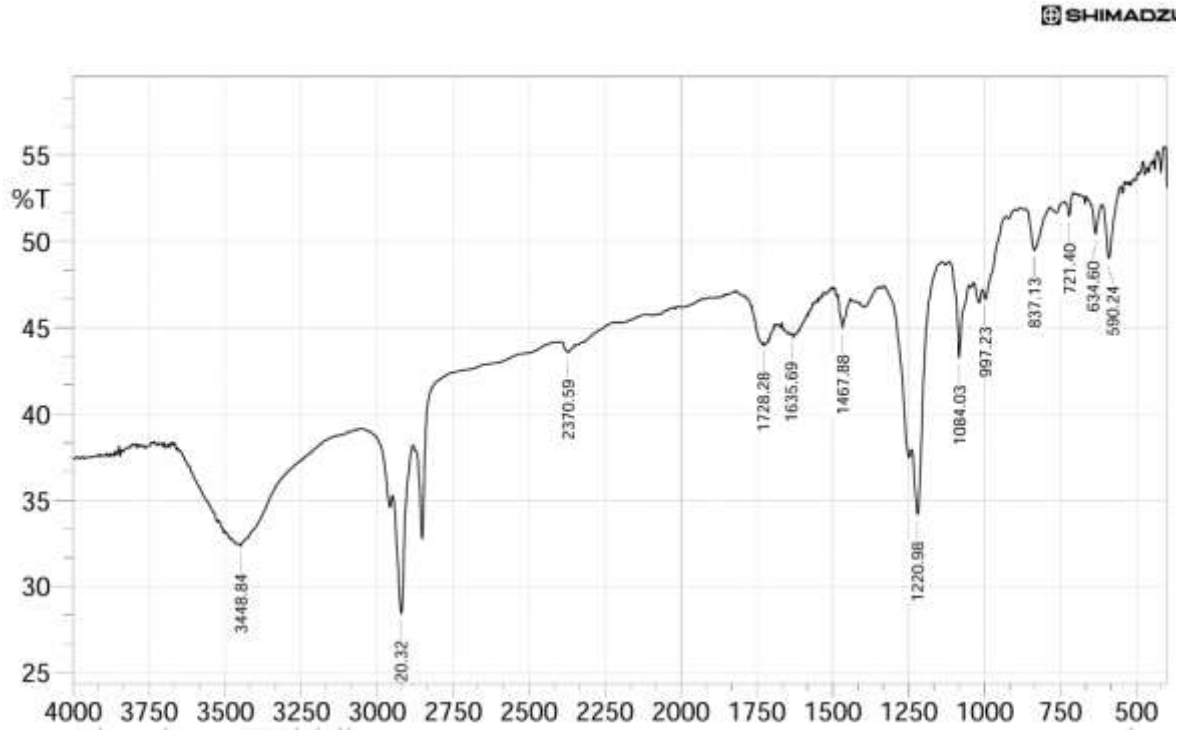
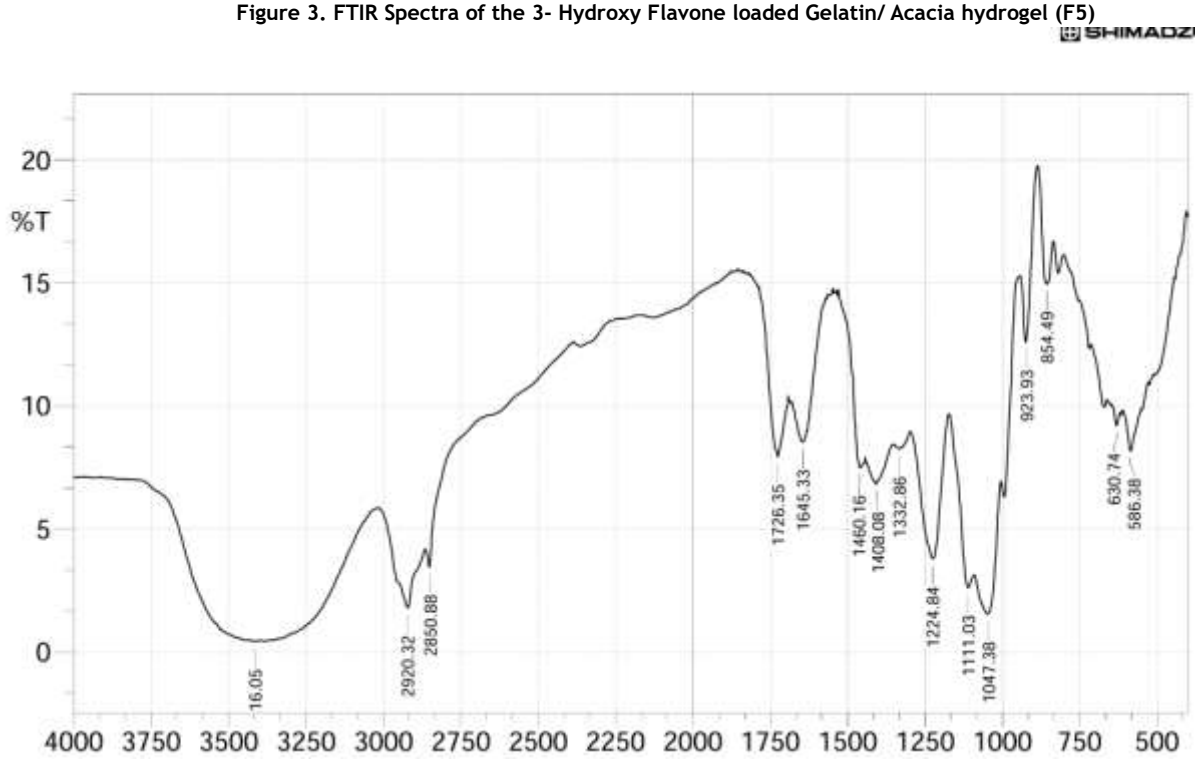


**Figure 2. FTIR Spectra of the 3- Hydroxy Flavone**

**Figure 3. FTIR Spectra of the 3- Hydroxy Flavone loaded Gelatin/ Acacia hydrogel (F5)**




FTIR spectroscopy was performed to evaluate the possible interactions between 3-hydroxyflavone (3-HF) and the gelatin–acacia hydrogel matrix and to confirm the chemical stability of the drug after incorporation. The FTIR spectrum of pure 3-hydroxyflavone displayed its characteristic absorption bands corresponding to the functional groups present in the molecule. A broad peak observed at around 3400–3420 $cm^{-1}$ was attributed to O–H stretching vibrations of the phenolic hydroxyl group, confirming strong intramolecular hydrogen bonding within the flavonoid structure. A sharp, intense band at approximately 1650 $cm^{-1}$ represented the C=O stretching vibration of the flavone carbonyl group. The peaks at 1600–1510 $cm^{-1}$ corresponded to aromatic C=C stretching, while those in the range of 1250–1200 $cm^{-1}$ were assigned to C–O stretching of phenolic ether linkages. Additional peaks observed between 820–780 $cm^{-1}$ were characteristic of aromatic C–H out-of-plane bending, confirming the presence of a benzopyrone nucleus typical of flavonoid compounds.

In contrast, the FTIR spectrum of the 3-hydroxyflavone-loaded gelatin–acacia hydrogel (F5) retained all the major peaks of 3-HF, but with slight shifts and broadening in their positions and intensities. The O–H stretching band shifted from 3420 $cm^{-1}$ to 3410 $cm^{-1}$, indicating the formation of hydrogen bonds between the hydroxyl groups of 3-HF and the amide or carboxyl groups of gelatin and the polysaccharide backbone of acacia. Similarly, the C=O stretching vibration shifted from 1650 $cm^{-1}$ to 1645 $cm^{-1}$, suggesting weak physical interactions, most likely through non-covalent hydrogen bonding rather than chemical modification. The characteristic amide I (1630 $cm^{-1}$) and amide II (1540 $cm^{-1}$) bands of gelatin were clearly visible in the hydrogel spectrum, confirming that the protein's secondary structure was maintained even after drug loading. Acacia showed typical broad –OH stretching around 3400 $cm^{-1}$ and C–O–C stretching near 1070 $cm^{-1}$, consistent with its polysaccharide nature.

Importantly, no new peaks appeared, nor were any existing peaks eliminated in the hydrogel spectrum, indicating that no chemical reaction or covalent bonding occurred between the drug and the excipients during formulation. The minor shifts and broadening observed are primarily due to intermolecular hydrogen bonding and physical entrapment of 3-hydroxyflavone within the hydrogel network. These interactions help stabilize the drug and ensure uniform molecular dispersion within the polymeric matrix. Overall, the FTIR findings confirmed that 3-hydroxyflavone remained not compatible with both gelatin and acacia polymers. The absence of new absorption bands or degradation-related signals demonstrates that the formulation process did not alter the structural integrity of the drug. The results validate that the optimized hydrogel (F5) provided a stable, physically entrapped drug–polymer system supported by weak hydrogen bonding interactions, ensuring chemical stability and effective entrapment of 3-hydroxyflavone within the biopolymeric scaffold.

**3.9 Morphological Analysis (FESEM)**

FESEM imaging revealed that the blank gelatin–acacia hydrogel possessed a porous, interconnected architecture essential for facilitating diffusion and mechanical flexibility. In comparison, the 3-hydroxyflavone-loaded hydrogel exhibited a denser, yet uniformly porous structure, indicating successful drug incorporation without aggregation. The average pore size (~20 µm) was suitable for controlled drug diffusion and gas exchange. The smooth, amorphous surface confirmed the even molecular dispersion of 3-hydroxyflavone within the polymeric framework. The microstructural uniformity supports favorable physicomechanical and diffusion characteristics of the formulated hydrogels.

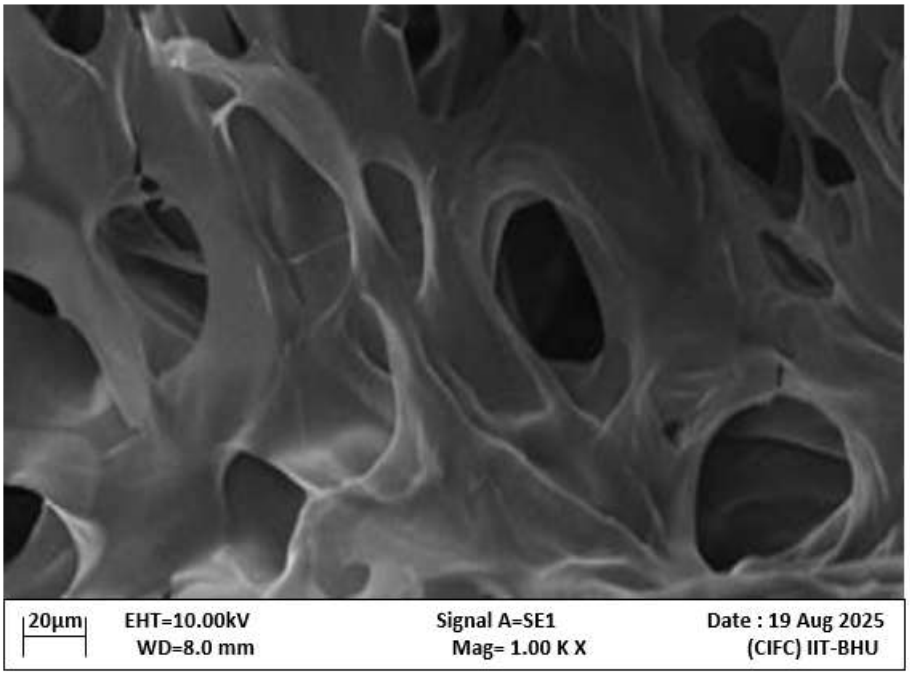



**Figure 4. Represents the Gelatin/ Acacia Hydrogel**

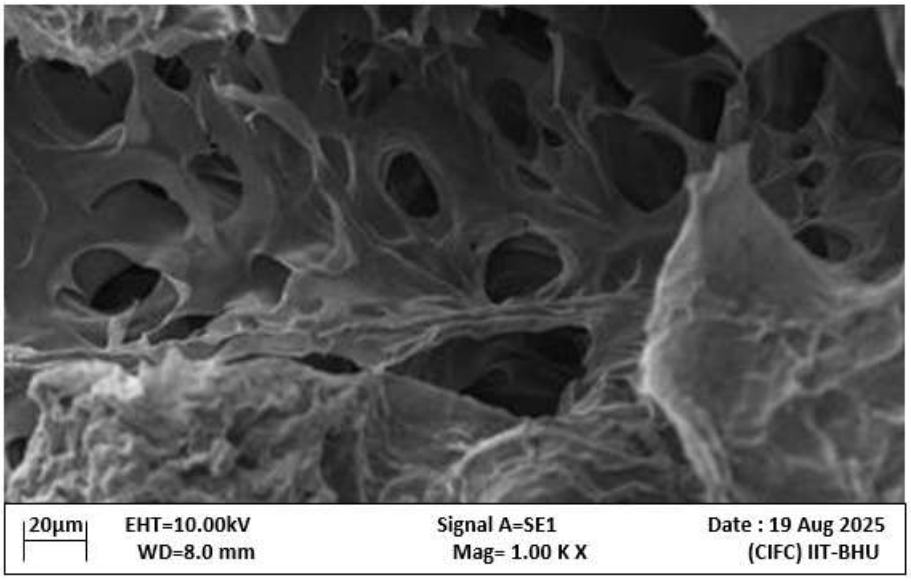



**Figure 5. Represents the 3-hydroxy flavone loaded hydrogel (F5)**

## CONCLUSION

The findings of this research demonstrate that the 3-hydroxyflavone-loaded gelatin–acacia hydrogel represents a promising biomaterial for corneal tissue repair applications. The synergistic combination of gelatin and acacia provided a structurally stable, hydrated, and transparent matrix that closely mimics the extracellular environment of the cornea. The prepared formulations maintained an ideal pH suitable for ocular application, exhibited consistent viscosity for ease of spreading, and demonstrated minimal syneresis, reflecting excellent structural integrity during storage. The inclusion of acacia not only enhanced gel stability but also improved mucoadhesiveness, which is essential for prolonged retention on the ocular surface. Spectroscopic and morphological analyses confirmed that no significant chemical interactions occurred between 3-hydroxyflavone and the polymeric components, ensuring drug stability within the hydrogel network. The FESEM results showed a porous and interconnected structure favorable for nutrient exchange, drug diffusion, and cellular attachment. The in vitro release studies established a sustained drug release pattern, ensuring continuous therapeutic availability at the corneal surface and minimizing the need for repeated applications.

Collectively, the optimized 3-HF-loaded gelatin–acacia hydrogel successfully integrates antioxidant, anti-inflammatory, and regenerative properties within a biocompatible polymeric platform. This formulation holds significant potential to promote epithelial healing, reduce oxidative stress, and restore corneal integrity following injury. Future studies involving ex vivo and in vivo corneal wound models are warranted to further assess the hydrogel's therapeutic efficacy, bioadhesive behavior, and optical transparency under physiological conditions. Thus, this biofunctional hydrogel can be viewed as a novel, safe, and effective drug delivery scaffold for next-generation corneal regenerative therapies.

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**4. Conflict of Interest**

The authors report no conflicts of interest.

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