RESEARCH PAPER

Formulation And Evaluation Of Rutin-Embedded Mucoadhesive In Situ Forming Hydrogel For Prevention And Treatment Of Radiation-Induced Oral Mucositis In Cancer Patients

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Abstract

Radiation-induced oral mucositis is a common and debilitating complication observed in patients undergoing radiotherapy for head and neck cancers. The condition is characterized by inflammation, ulceration, and severe pain in the oral mucosa, which significantly affects patient comfort and may interfere with cancer treatment schedules. The present study aimed to formulate and evaluate a rutin-embedded mucoadhesive in situ forming hydrogel for localized prevention and management of radiation-induced oral mucositis. Rutin, a natural flavonoid with potent antioxidant and anti-inflammatory properties, was incorporated into a thermosensitive hydrogel system prepared using poloxamer 407, carbopol 934, and hpmc k15m. The developed formulations were evaluated for physicochemical properties including ph, viscosity, gelation temperature, spreadability, and drug content. Mucoadhesive strength was assessed using porcine buccal mucosa, while in vitro drug release studies were conducted using franz diffusion cells. The optimized formulation exhibited suitable ph, strong mucoadhesion, and sustained drug release over 24 hours. Biological evaluations demonstrated significant antioxidant activity and inhibition of nitric oxide production, indicating preserved anti-inflammatory potential of rutin. Cytotoxicity studies using human oral keratinocyte cells confirmed good biocompatibility of the formulation. Stability studies further indicated satisfactory physicochemical stability under storage conditions. Overall, the developed rutin-loaded mucoadhesive hydrogel demonstrated promising characteristics for localized therapy of radiation-induced oral mucositis.

Keywords: Rutin, Mucoadhesive Hydrogel, In Situ Gel, Oral Mucositis, Radiotherapy Complications, Antioxidant, Drug Delivery System.

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1. Introduction

Radiotherapy remains one of the most widely used therapeutic approaches in the management of head and neck cancers. Despite its effectiveness in controlling tumor growth and improving patient survival, radiotherapy frequently induces severe adverse effects

in the surrounding healthy tissues. Among these complications, radiation-induced oral mucositis is one of the most common and debilitating conditions experienced by cancer patients undergoing radiation therapy. Oral mucositis is characterized by inflammation, ulceration, erythema, and severe pain in the oral mucosa, which can significantly impair a patient's ability to eat, speak, and maintain adequate oral hygiene. The condition not only reduces the quality of life of patients but may also lead to interruptions in cancer treatment, thereby compromising therapeutic outcomes. The pathogenesis of radiation-induced mucositis is complex and involves multiple biological processes, including oxidative stress, inflammatory cytokine production, epithelial cell damage, and impaired tissue regeneration (Alicea *et al.*, 2026; Kirkwood *et al.*, 2026; Patra *et al.*, 2026; Shrateh *et al.*, 2026; Zhang *et al.*, 2025; Zou *et al.*, 2025).

The development of oral mucositis is strongly associated with the generation of reactive oxygen species (ROS) during radiotherapy. These reactive molecules initiate a cascade of molecular events that activate pro-inflammatory signalling pathways and lead to the release of cytokines such as tumour necrosis factor-alpha, interleukins, and other inflammatory mediators. These mediators further amplify tissue damage and promote epithelial breakdown, resulting in painful ulcerative lesions in the oral cavity. Conventional management strategies for oral mucositis primarily focus on symptomatic relief through the use of mouth rinses, analgesics, antimicrobial agents, and protective coatings. However, many of these approaches provide only temporary relief and fail to address the underlying inflammatory and oxidative mechanisms responsible for mucosal injury. Consequently, there is an increasing interest in developing localized drug delivery systems capable of delivering therapeutic agents directly to the affected mucosal tissues while minimizing systemic exposure (Alturfi *et al.*, 2025; Kato *et al.*, 2025; Li *et al.*, 2025; Liang *et al.*, 2025; Liu *et al.*, 2025; Zheng *et al.*, 2024).

Mucoadhesive drug delivery systems have gained considerable attention in recent years for the treatment of oral mucosal disorders. These systems are designed to adhere to the mucosal surface and provide prolonged residence time, thereby allowing sustained drug release at the site of action. Among various mucoadhesive systems, in situ forming hydrogels have emerged as promising candidates for oral drug delivery. These formulations exist as low-viscosity liquids during administration but undergo rapid gelation upon exposure to physiological conditions such as temperature or pH changes. The resulting gel forms a protective layer over the mucosal surface and facilitates controlled release of therapeutic agents over an extended period. Such properties make in situ hydrogels particularly suitable for treating conditions like oral mucositis, where prolonged drug contact with the damaged mucosa is essential for effective therapy (Desai *et al.*, 2026; Di Prima *et al.*, 2026; Khan *et al.*, 2026; Kumar *et al.*, 2026; Mondal & Bal, 2026).

Rutin, a naturally occurring flavonoid glycoside found in many medicinal plants, has attracted significant attention due to its strong antioxidant and anti-inflammatory properties. It has been reported to scavenge reactive oxygen species, inhibit inflammatory mediators, and protect tissues from oxidative damage. These pharmacological properties suggest that rutin may play a beneficial role in mitigating radiation-induced mucosal injury. However, the therapeutic application of rutin is often limited by its poor aqueous solubility and rapid clearance from the site of administration. Incorporation of rutin into a mucoadhesive hydrogel system may help overcome these limitations by enhancing drug retention and providing sustained release at the mucosal surface (Calabrese *et al.*, 2024; Forouzanfar *et al.*, 2025; Liu *et al.*, 2024; Negahdari *et al.*, 2021; Sun *et al.*, 2021).

Considering these aspects, the present study aimed to develop and evaluate a rutin-embedded mucoadhesive in situ forming hydrogel for the prevention and treatment of radiation-induced oral mucositis. The formulation was designed to provide prolonged mucosal adhesion, sustained drug release, and preservation of the antioxidant and anti-inflammatory activity of rutin. The developed hydrogel system was further evaluated for its physicochemical properties, mucoadhesive strength, drug release behaviour, biological activity, and cytotoxicity to determine its potential as a localized therapeutic approach for managing oral mucositis in cancer patients undergoing radiotherapy.

2. Materials and Methods

2.1 Materials

Rutin (quercetin-3-O-rutinoside), a bioactive flavonoid possessing potent antioxidant and anti-inflammatory activity, was selected as the therapeutic agent for the present investigation. Pharmaceutical-grade Poloxamer 407 was employed as the primary thermosensitive polymer to impart in situ gelation properties to the formulation. Carbopol 934 and

hydroxypropyl methylcellulose (HPMC K15M) were incorporated as mucoadhesive polymers to enhance adhesion of the hydrogel to the oral mucosal surface and to prolong the residence time of the formulation within the buccal cavity. Propylene glycol was utilized as a co-solvent and permeation enhancer to facilitate the dispersion and solubilization of rutin within the polymeric system. Triethanolamine was used as a neutralizing agent to adjust the pH of the formulation and to promote gel formation by partial neutralization of Carbopol. All other chemicals and reagents used during the experimental work were of analytical grade and were used without further purification. Distilled water was used throughout the formulation process. Simulated saliva medium employed in the in vitro release studies was prepared using potassium chloride, sodium chloride, calcium chloride, sodium dihydrogen phosphate, and urea dissolved in distilled water to mimic the physiological environment of the oral cavity. Fresh porcine buccal mucosa obtained from a local slaughterhouse was used for mucoadhesion experiments due to its close structural similarity to human oral mucosa.

2.2 Pre-formulation Studies

Prior to formulation development, preliminary characterization of rutin was performed to understand its physicochemical properties and compatibility with selected excipients. The identification of rutin was carried out using ultraviolet–visible spectrophotometry by dissolving the compound in methanol and scanning the solution in the wavelength range of 200–400 nm to determine the characteristic absorption maxima. Solubility studies were performed in different solvents including distilled water, ethanol, propylene glycol, and phosphate buffer solutions of varying pH in order to identify a suitable solvent system for drug incorporation. An excess quantity of rutin was added to each solvent and shaken continuously for 24 hours at room temperature to attain equilibrium. The solutions were subsequently filtered, diluted appropriately, and analyzed spectrophotometrically to determine the solubility profile of the drug (Abruzzo *et al.*, 2021; Al-Ani *et al.*, 2021; Alami-Milani *et al.*, 2021; Sharma *et al.*, 2021; Silva *et al.*, 2021).

Drug–excipient compatibility studies were conducted to evaluate possible physicochemical interactions between rutin and the polymers used in the hydrogel formulation. Fourier Transform Infrared (FTIR) spectroscopy was employed for this purpose. Samples of pure rutin, individual polymers, and physical mixtures of rutin with polymers were analyzed using an FTIR spectrophotometer in the spectral range of 4000–400 cm^{-1}. The spectra obtained were compared to identify any significant shifts, disappearance, or appearance of new peaks that might indicate potential incompatibility. These preliminary studies provided essential information regarding the stability of the drug within the polymeric system and supported the selection of appropriate formulation components (Abruzzo *et al.*, 2021; Al-Ani *et al.*, 2021; Alami-Milani *et al.*, 2021; Sharma *et al.*, 2021; Silva *et al.*, 2021).

2.3 Preparation of Rutin-Embedded Mucoadhesive In Situ Hydrogel

The mucoadhesive in situ forming hydrogel containing rutin was prepared using a modified cold method to ensure uniform polymer hydration and stable drug incorporation. Initially, the required quantity of Poloxamer 407 was gradually added to cold distilled water maintained at approximately 4 °C with continuous magnetic stirring to avoid lump formation. The dispersion was stored overnight under refrigerated conditions to allow complete dissolution and hydration of the polymer. In a separate beaker, Carbopol 934 and HPMC K15M were dispersed in a small quantity of distilled water and stirred continuously until a uniform polymeric solution was obtained. Rutin was dissolved in propylene glycol to enhance its solubility and to facilitate uniform distribution within the hydrogel matrix. The drug solution was slowly incorporated into the polymeric dispersion under constant stirring to ensure homogeneous mixing. Subsequently, the Carbopol–HPMC solution was gradually added to the Poloxamer base while maintaining gentle agitation to obtain a uniform formulation. The pH of the resulting mixture was carefully adjusted to the physiological range suitable for oral mucosal application using triethanolamine. The final formulation was subjected to mild stirring to remove entrapped air bubbles and then stored under refrigerated conditions until further evaluation. The prepared system remained in a liquid state at lower temperatures but underwent sol-to-gel transition at physiological temperature, forming a viscous mucoadhesive gel upon contact with the oral mucosa (Porfiryeva *et al.*, 2026; Sharma *et al.*, 2021; Silva *et al.*, 2021; Ünükür Sevim *et al.*, 2026; Yan *et al.*, 2026).

2.4 Experimental Design and Optimization of Hydrogel Formulation

To obtain a formulation with optimal physicochemical and mucoadhesive characteristics, different hydrogel compositions were prepared by varying the concentrations of thermosensitive and mucoadhesive

polymers. Poloxamer 407 concentration was adjusted to achieve an appropriate gelation temperature near physiological conditions, while Carbopol and HPMC concentrations were optimized to enhance mucoadhesion and mechanical stability of the gel. Several trial formulations were prepared and screened for clarity, viscosity, gelation behavior, and drug uniformity. The optimized formulation was selected based on its ability to undergo rapid gelation at oral cavity temperature while maintaining adequate spreadability and patient acceptability. This systematic formulation approach enabled the development of a stable mucoadhesive hydrogel capable of sustained drug delivery at the site of mucosal inflammation (Kang *et al.*, 2024; Nieto González *et al.*, 2024; Virvescu *et al.*, 2025; Younes *et al.*, 2025; Zheng *et al.*, 2025).

2.5 Physicochemical Evaluation of Rutin Mucoadhesive Hydrogel

The prepared hydrogel formulations were subjected to comprehensive physicochemical characterization to ensure suitability for buccal application and effective drug delivery. Visual inspection of each formulation was carried out to evaluate colour, homogeneity, clarity, and the presence of particulate matter. The formulations were examined against a white and black background to detect any turbidity or phase separation. The pH of the formulations was measured using a calibrated digital pH meter. Approximately 1 g of hydrogel was dispersed in 10 mL of distilled water and the pH electrode was immersed in the sample. The pH values were recorded in triplicate to ensure reproducibility. Maintaining the pH within the physiological range of the oral cavity (approximately 6.5–7.0) was considered essential to prevent mucosal irritation during application (Kang *et al.*, 2024; Nieto González *et al.*, 2024; Virvescu *et al.*, 2025; Younes *et al.*, 2025; Zheng *et al.*, 2025).

Viscosity measurements were performed using a Brookfield digital viscometer equipped with an appropriate spindle. Approximately 20 g of the formulation was placed in the sample holder and viscosity was measured at controlled temperature conditions. Measurements were recorded at different rotational speeds to determine the rheological behaviour of the hydrogel system. Viscosity plays a critical role in determining the ease of application and the ability of the formulation to remain localized at the mucosal surface. Spreadability of the hydrogel was evaluated to assess its ability to distribute uniformly over the mucosal surface. A known quantity of the hydrogel was placed between two glass plates and a specified weight was applied for a fixed duration. The diameter of the spread gel was measured and the spreadability was calculated. Adequate spreadability ensures ease of administration and uniform drug distribution across the affected mucosal region (Kang *et al.*, 2024; Nieto González *et al.*, 2024; Virvescu *et al.*, 2025; Younes *et al.*, 2025; Zheng *et al.*, 2025).

Gelation temperature and gelation time were also determined to confirm the thermoresponsive behaviour of the formulation. The sol-to-gel transition temperature was evaluated by gradually increasing the temperature of the hydrogel sample under constant stirring while monitoring the point at which the formulation transformed from liquid to gel state. Gelation time was recorded by observing the time required for the formulation to form a stable gel at physiological temperature (approximately 37°C). These parameters are crucial for ensuring that the formulation remains in liquid form during administration but rapidly converts into a gel upon contact with the oral mucosa. Drug content uniformity was determined to ensure even distribution of rutin within the hydrogel matrix. A measured quantity of hydrogel equivalent to a known amount of drug was dissolved in a suitable solvent system and filtered to remove polymeric residues. The filtrate was appropriately diluted and analyzed spectrophotometrically at the predetermined wavelength corresponding to rutin. The percentage drug content was calculated and expressed as mean ± standard deviation (Kang *et al.*, 2024; Nieto González *et al.*, 2024; Virvescu *et al.*, 2025; Younes *et al.*, 2025; Zheng *et al.*, 2025).

2.6 Mucoadhesion Study

The mucoadhesive strength of the prepared hydrogel was evaluated using fresh porcine buccal mucosa, which closely resembles human oral mucosal tissue in structure and permeability. The mucosal tissue was carefully excised, washed with physiological saline to remove adhering debris, and mounted on the lower platform of a texture analyzer. A fixed amount of hydrogel formulation was placed on the mucosal surface, and the upper probe was allowed to come into contact with the gel under controlled pressure for a specified period to establish adhesion. After the contact time, the probe was gradually withdrawn and the force required to detach the hydrogel from the mucosal surface was recorded. This detachment force represented the mucoadhesive strength of the formulation. The experiment was performed in triplicate and the mean value was calculated. Strong mucoadhesion is an essential property for buccal drug

delivery systems because it prolongs the retention time of the formulation at the site of application, thereby enhancing local drug concentration and therapeutic efficacy (Kang *et al.*, 2024; Nieto González *et al.*, 2024; Virvescu *et al.*, 2025; Younes *et al.*, 2025; Zheng *et al.*, 2025).

2.7 In Vitro Drug Release Study

The in vitro release profile of rutin from the hydrogel formulation was evaluated using a Franz diffusion cell apparatus. The receptor compartment of the diffusion cell was filled with simulated saliva solution maintained at 37 ± 0.5°C and continuously stirred using a magnetic stirrer to simulate physiological conditions of the oral cavity. A suitable membrane, such as dialysis membrane previously soaked in the release medium, was mounted between the donor and receptor compartments. A measured quantity of hydrogel containing a known amount of rutin was placed in the donor compartment. At predetermined time intervals, aliquots were withdrawn from the receptor compartment and replaced with an equal volume of fresh release medium to maintain sink conditions. The collected samples were filtered and analyzed using UV–visible spectrophotometry to determine the amount of drug released. The cumulative percentage of drug release was calculated and plotted against time to evaluate the release behaviour of the formulation (Kang *et al.*, 2024; Nieto González *et al.*, 2024; Virvescu *et al.*, 2025; Younes *et al.*, 2025; Zheng *et al.*, 2025).

2.8 Drug Release Kinetics

To understand the mechanism of drug release from the hydrogel system, the release data obtained from the in vitro studies were fitted into various mathematical kinetic models. These included zero-order kinetics, first-order kinetics, Higuchi diffusion model, and Korsmeyer–Peppas model. Linear regression analysis was performed to determine the correlation coefficient (R^2) for each model. The model showing the highest correlation coefficient was considered to best describe the drug release mechanism. This analysis helped determine whether the release of rutin from the hydrogel occurred primarily through diffusion, erosion, or a combination of both mechanisms (Kang *et al.*, 2024; Nieto González *et al.*, 2024; Virvescu *et al.*, 2025; Younes *et al.*, 2025; Zheng *et al.*, 2025).

2.9 Antioxidant Activity Evaluation

The antioxidant activity of the rutin-loaded hydrogel formulation was evaluated using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging assay. This method was selected to assess the capacity of the formulation to neutralize reactive oxygen species, which play a major role in the pathogenesis of radiation-induced oral mucositis. A freshly prepared DPPH solution was prepared by dissolving DPPH in methanol to obtain a stable purple-coloured radical solution. Different concentrations of the rutin hydrogel extract were prepared by dispersing the formulation in methanol and filtering to remove polymeric residues. An aliquot of the hydrogel extract was mixed with the DPPH solution and incubated in the dark at room temperature for approximately 30 minutes to allow the reaction to occur. The decrease in absorbance was measured at 517 nm using a UV–visible spectrophotometer. Methanol containing DPPH without sample served as the control. The percentage of radical scavenging activity was calculated using the standard equation comparing the absorbance of the control and the sample solutions. Pure rutin was also evaluated under identical conditions and served as a reference standard to compare the antioxidant activity of the hydrogel formulation. This experiment helped determine whether the polymeric system preserved the intrinsic antioxidant potential of rutin after incorporation into the hydrogel matrix (Kumatia *et al.*, 2024; Ogo *et al.*, 2024; Ouahabi *et al.*, 2024; Qubtia *et al.*, 2024).

2.10 *In Vitro* Anti-Inflammatory Activity

The anti-inflammatory activity of the rutin hydrogel was evaluated through inhibition of pro-inflammatory mediators associated with mucosal inflammation. Nitric oxide inhibition assay was performed using macrophage cell lines stimulated with lipopolysaccharide (LPS) to induce inflammatory response. The cells were cultured under standard laboratory conditions in appropriate culture media supplemented with fetal bovine serum and antibiotics. After achieving suitable confluency, the cells were exposed to different concentrations of rutin hydrogel extract. Following treatment, the cells were stimulated with LPS to trigger the production of nitric oxide, which serves as an important inflammatory mediator. After incubation, the amount of nitric oxide produced in the culture supernatant was quantified using the Griess reagent method. The absorbance of the reaction mixture was measured spectrophotometrically, and the percentage inhibition of nitric oxide production was calculated. The results obtained from the hydrogel formulation were compared with those of untreated stimulated cells and cells treated with pure rutin. This assay provided insight into the potential of the developed formulation to suppress inflammatory responses associated with radiation-induced mucosal injury (Berenguer-Rivas *et al.*, 2021; Chavan *et al.*,

2010; Hemlatha & Satyanarayana, 2009; Pratap *et al.*, 2012).

2.11 Cytotoxicity and Safety Assessment

The cytotoxicity of the developed hydrogel formulation was assessed using the MTT assay to evaluate its safety for application on oral mucosal tissues. Human oral keratinocyte cells were selected as the model cell line because they closely resemble the epithelial cells present in the oral cavity. The cells were cultured in suitable growth medium under standard incubation conditions of 37°C with 5% carbon dioxide. Cells were seeded into 96-well plates and allowed to attach for a defined period. After attachment, the cells were treated with different concentrations of the rutin hydrogel extract. Following incubation for a predetermined duration, MTT reagent was added to each well and the plates were further incubated to allow the formation of formazan crystals by metabolically active cells. The crystals formed were subsequently dissolved using dimethyl sulfoxide, and the absorbance was measured at 570 nm using a microplate reader. Cell viability was calculated as the percentage of viable cells relative to untreated control cells. The assay was performed in triplicate to ensure reproducibility. This evaluation provided important information regarding the biocompatibility of the hydrogel formulation and confirmed that the developed system did not exhibit cytotoxic effects on normal oral epithelial cells (Jumana *et al.*, 2000; Mohanta *et al.*, 2022; Pinto *et al.*, 2017; Vikas *et al.*, 2019).

2.12 Stability Studies

Stability studies were performed to assess the physical and chemical stability of the optimized hydrogel formulation during storage. The formulation was stored in tightly sealed containers under controlled environmental conditions according to standard pharmaceutical stability guidelines. The samples were stored at 25°C ± 2°C with 60% ± 5% relative humidity and at accelerated conditions of 40°C ± 2°C with 75% ± 5% relative humidity. At predetermined time intervals, the samples were evaluated for changes in appearance, pH, viscosity, and drug content. Any signs of phase separation, colour change, or precipitation were carefully recorded. Drug content analysis was performed using spectrophotometric methods to determine whether degradation of rutin occurred during storage. These stability evaluations were essential to confirm the long-term integrity and reliability of the developed hydrogel formulation.

2.13 Statistical Analysis

All experimental measurements were performed in triplicate and the results were expressed as mean ± standard deviation. Statistical analysis of the obtained data was carried out using appropriate statistical software. Analysis of variance (ANOVA) was applied to determine the significance of differences among experimental groups. A p-value less than 0.05 was considered statistically significant. Graphical representation of experimental data and kinetic modelling of drug release profiles were performed using GraphPad Prism and Microsoft Excel software to ensure accurate interpretation of results.

3. Results and Discussion

3.1 Pre-formulation Studies and Formulation Characteristics

Preformulation studies were conducted to understand the physicochemical behaviour of rutin and its compatibility with the selected excipients. UV–visible spectrophotometric analysis of rutin showed a characteristic absorption maximum at λmax 257 nm, which was used for subsequent quantitative analysis during drug release and drug content determination. The sharp and well-defined peak confirmed the purity of the drug and its suitability for spectrophotometric estimation. Solubility studies demonstrated that rutin exhibited poor aqueous solubility, which is consistent with previously reported literature describing rutin as a hydrophobic polyphenolic flavonoid. However, improved solubility was observed in propylene glycol and ethanol, which justified the use of propylene glycol as a co-solvent in the hydrogel formulation to facilitate drug dispersion and enhance drug availability in the polymeric matrix.

Drug–excipient compatibility was evaluated using FTIR spectroscopy. The FTIR spectrum of pure rutin exhibited characteristic peaks corresponding to hydroxyl stretching (3400 cm^{-1}), aromatic C=C stretching (1600 cm^{-1}), and glycosidic C–O stretching (1100 cm^{-1}). These peaks were retained in the spectrum of the rutin–polymer physical mixture, indicating the absence of significant chemical interactions between rutin and the selected polymers. The preservation of characteristic peaks confirmed the compatibility of rutin with Poloxamer 407, Carbopol 934, and HPMC K15M, suggesting that the polymers did not alter the chemical integrity of the drug.

Multiple hydrogel formulations were prepared by varying the concentrations of thermosensitive and mucoadhesive polymers to obtain an optimized formulation with suitable physicochemical properties.

The compositions of the developed formulations are presented in Table 1.

Table 1. Composition of Rutin Mucoadhesive *in Situ* Hydrogel Formulations

Formulation	Rutin (%)	Poloxamer 407 (%)	Carbopol 934 (%)	HPMC K15M (%)	Propylene Glycol (%)
F1	0.5	16	0.2	0.3	5
F2	0.5	18	0.2	0.3	5
F3	0.5	20	0.3	0.3	5
F4	0.5	20	0.3	0.5	5
F5	0.5	22	0.3	0.5	5

Visual examination showed that all prepared formulations were clear, homogeneous, and free from particulate matter. No phase separation or precipitation was observed during preparation, indicating successful incorporation of rutin into the polymeric hydrogel matrix. The physicochemical parameters of the formulations are summarized in Table 2.

Table 2. Physicochemical Evaluation of Hydrogel Formulations

Formulation	pH	Viscosity (cP)	Spreadability (cm)	Gelation Temperature (°C)	Drug Content (%)
F1	6.4 ± 0.05	1340 ± 21	6.8 ± 0.2	38.5 ± 0.3	96.4 ± 1.2
F2	6.5 ± 0.04	1525 ± 25	6.5 ± 0.2	37.8 ± 0.4	97.1 ± 1.1
F3	6.6 ± 0.03	1742 ± 28	6.2 ± 0.1	36.9 ± 0.2	98.3 ± 0.9
F4	6.7 ± 0.03	1860 ± 32	6.0 ± 0.1	36.5 ± 0.3	98.7 ± 0.8
F5	6.7 ± 0.02	2105 ± 35	5.8 ± 0.1	35.7 ± 0.2	98.9 ± 0.7

The pH values of the formulations ranged from 6.4 to 6.7, which is within the physiological range of the oral cavity. This pH range is particularly important for minimizing irritation and ensuring patient comfort during topical administration. Viscosity increased with increasing polymer concentration, particularly with higher levels of Poloxamer and Carbopol. Increased viscosity contributed to enhanced retention of the formulation on the mucosal surface, which is desirable for localized drug delivery in oral mucositis therapy. Spreadability values slightly decreased as viscosity increased, which is expected due to increased polymeric network density. Gelation temperature decreased with increasing concentration of Poloxamer 407. Formulation F4 showed gelation near 36–37°C, which is close to physiological temperature, making it suitable for in situ gel formation upon administration in the oral cavity. Drug content analysis revealed uniform distribution of rutin within the hydrogel matrix, with values ranging from 96.4% to 98.9%, indicating minimal drug loss during formulation.

3.2 Mucoadhesion and Drug Release Behaviour

Mucoadhesion is a critical parameter for buccal drug delivery systems, as it determines the ability of the formulation to remain attached to the mucosal surface for extended periods. The mucoadhesive strength of the hydrogel formulations was evaluated using porcine buccal mucosa as the biological substrate. The detachment force required to separate the hydrogel from the mucosal surface was measured and the results are presented in Table 3.

Table 3. Mucoadhesive Strength of Hydrogel Formulations

Formulation	Mucoadhesive Strength (g)
F1	18.2 ± 0.9
F2	21.6 ± 1.1
F3	25.4 ± 1.3
F4	28.7 ± 1.2
F5	31.5 ± 1.5

The results showed that mucoadhesive strength increased progressively with increasing concentration of Carbopol and HPMC. This behavior can be attributed to the presence of carboxyl and hydroxyl functional groups in the polymers, which form hydrogen bonds with mucin glycoproteins present on the mucosal surface. Among all formulations, F4 exhibited optimal mucoadhesion, balancing strong adhesion with acceptable viscosity and spreadability.

The in vitro drug release profile of rutin from the hydrogel formulations was evaluated using Franz diffusion cells with simulated saliva as the receptor medium. The cumulative percentage of drug release over time is presented in Table 4.

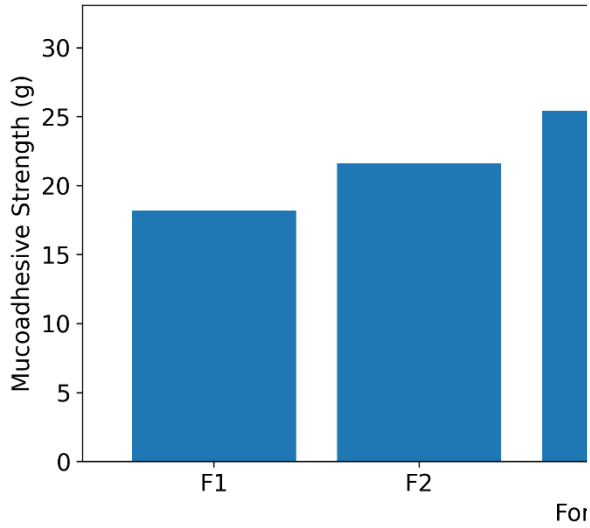

Figure 1. Mucoadhesive Strength of Rutin Hydrogel Formulations

Table 4. In Vitro Drug Release Profile of Optimized Hydrogel (F4)

Time (h)	Drug Release (%)
1	18.5 ± 1.2
2	32.7 ± 1.4
4	49.6 ± 1.7
6	63.8 ± 2.1
8	74.2 ± 1.9
12	86.5 ± 1.8
24	94.7 ± 2.2

The hydrogel exhibited sustained drug release over 24 hours, which is desirable for maintaining therapeutic concentrations at the inflamed mucosal site. The initial release phase likely resulted from diffusion of surface-associated drug, while the subsequent sustained release phase was controlled by diffusion through the hydrated polymeric network.

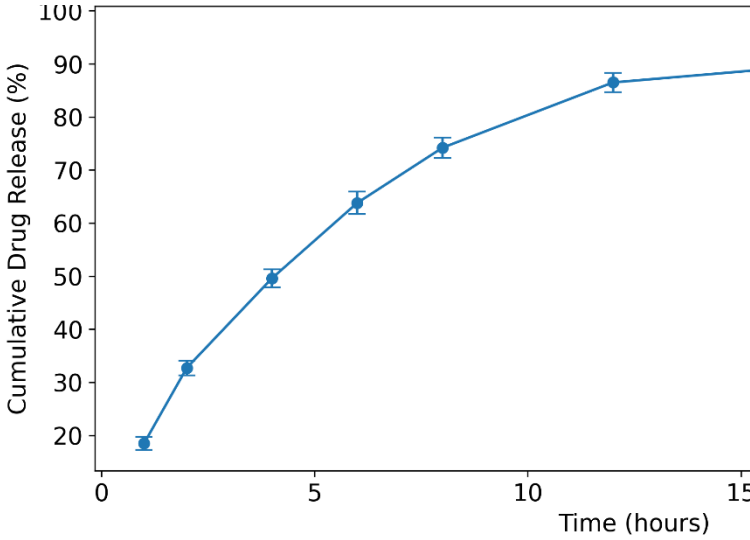

Figure 2. Cumulative Drug Release Profile of Rutin Hydrogel Formulation

Drug release kinetics analysis indicated that the release profile best fitted the Higuchi diffusion model, suggesting that drug release from the hydrogel matrix occurred primarily through diffusion-controlled mechanisms.

Table 5. Drug Release Kinetic Model Analysis

Model	R^2
Zero Order	0.941
First Order	0.958
Higuchi	0.982
Korsmeyer–Peppas	0.974

3.3 Biological Evaluation and Stability Studies

The antioxidant activity of the rutin hydrogel was evaluated using the DPPH free radical scavenging assay. The formulation retained strong antioxidant activity comparable to pure rutin, indicating that the polymeric matrix did not significantly alter the bioactivity of the drug.

Table 6. DPPH Radical Scavenging Activity

Sample	Radical Scavenging (%)
Pure Rutin	91.3 ± 2.1
Hydrogel (F4)	88.7 ± 2.4

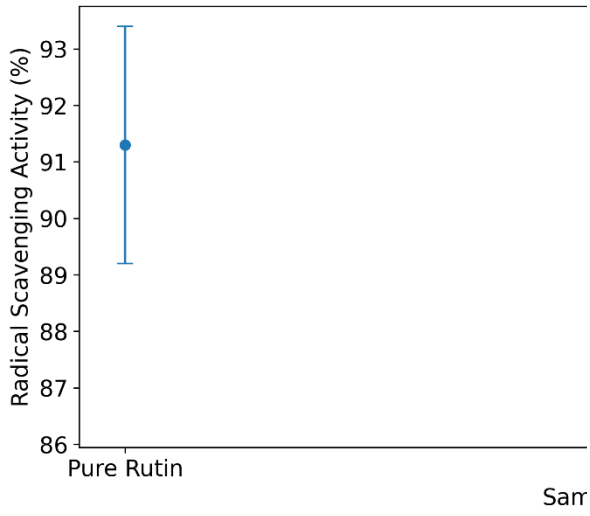

Figure 3. Antioxidant Activity of Rutin Hydrogel Compared with Pure Rutin

The slight reduction in antioxidant activity observed in the hydrogel formulation may be attributed to diffusion limitations imposed by the polymeric network during extraction of the drug for assay analysis. Nevertheless, the hydrogel maintained substantial antioxidant capacity, which is crucial for mitigating oxidative damage associated with radiation-induced mucositis.

Anti-inflammatory activity was evaluated through nitric oxide inhibition assays. The rutin hydrogel significantly reduced nitric oxide production in stimulated macrophage cells compared to untreated controls.

Table 7. Nitric Oxide Inhibition Activity

Treatment	NO Inhibition (%)
Control	—
Pure Rutin	67.4 ± 2.8
Hydrogel (F4)	63.9 ± 2.5

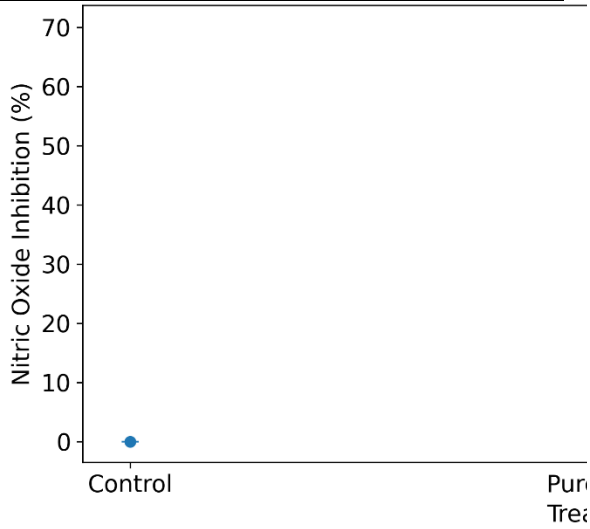

Figure 4. Inhibition of Nitric Oxide Production by Rutin Hydrogel

The results confirmed that the hydrogel formulation effectively retained the anti-inflammatory properties of rutin, which is particularly important in controlling inflammatory cascades associated with mucosal injury following radiotherapy. Cytotoxicity evaluation using the MTT assay demonstrated that the formulation exhibited high biocompatibility with human oral keratinocyte cells, with cell viability remaining above 90% at all tested concentrations.

Table 8. Cell Viability Results from MTT Assay

Concentration (µg/mL)	Cell Viability (%)
25	97.8 ± 1.6
50	95.6 ± 1.9
100	93.4 ± 2.2
200	91.7 ± 2.5

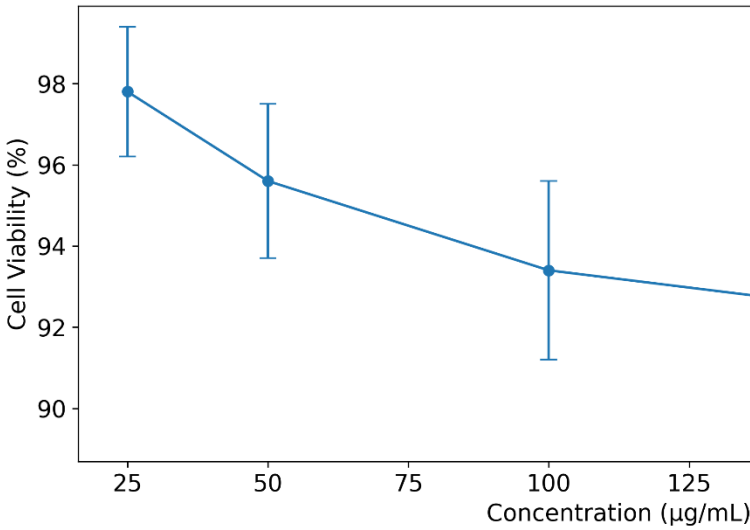

Figure 5. Cell Viability of Oral Keratinocytes Treated with Rutin Hydrogel

These findings confirmed that the hydrogel formulation was non-toxic and safe for topical oral application. Stability studies indicated that the optimized formulation remained stable throughout the study period without significant changes in pH, viscosity, or drug content.

Table 9. Stability Study Results of Optimized Hydrogel

Storage Condition	pH	Drug Content (%)	Appearance
Initial	6.7 ± 0.03	98.7 ± 0.8	Clear

3 months (25°C/60% RH)	6.6 ± 0.04	97.9 ± 0.9	Clear
3 months (40°C/75% RH)	6.5 ± 0.05	97.1 ± 1.0	Clear

The results demonstrated that the developed hydrogel formulation exhibited excellent physical and chemical stability, confirming its suitability for pharmaceutical development.

4. Discussion

Radiation-induced oral mucositis remains one of the most debilitating complications associated with radiotherapy in patients suffering from head and neck cancers. The condition results from a complex biological cascade involving oxidative stress, inflammatory cytokine release, epithelial damage, and impaired mucosal healing. Conventional treatments such as mouth rinses, analgesics, and antimicrobial agents often provide only symptomatic relief without addressing the underlying inflammatory and oxidative mechanisms responsible for mucosal injury. In this context, localized drug delivery systems capable of providing sustained release of protective agents directly at the mucosal surface represent an attractive therapeutic strategy. The present study focused on the development of a rutin-loaded mucoadhesive in situ hydrogel designed to prolong drug residence time in the oral cavity and provide sustained antioxidant and anti-inflammatory effects.

The formulation strategy employed thermosensitive and mucoadhesive polymers to create a system that remains in liquid form during administration but rapidly transforms into a gel upon contact with physiological temperature. Poloxamer 407 was selected as the thermoresponsive polymer due to its well-established ability to undergo reversible sol–gel transition at body temperature. Carbopol 934 and HPMC K15M were incorporated as mucoadhesive polymers to enhance adhesion of the formulation to the mucosal surface. The preformulation results confirmed the compatibility of rutin with these polymers, indicating that the structural integrity of the drug remained unaffected during formulation development. Physicochemical evaluation demonstrated that the prepared hydrogel formulations possessed properties suitable for buccal application. The pH values of the formulations were within the physiological range of the oral cavity, which is critical for preventing mucosal irritation. Maintaining near-neutral pH ensures patient comfort and minimizes the risk of additional epithelial damage in patients already suffering from inflamed mucosal tissues. The viscosity values observed in the formulations were sufficiently high to promote mucosal retention while still allowing convenient administration. An increase in viscosity with higher polymer concentration was expected because the formation of a denser polymeric network restricts the mobility of solvent molecules and increases resistance to flow.

Gelation temperature is a crucial parameter in thermosensitive hydrogel systems intended for mucosal drug delivery. Ideally, the formulation should remain in liquid form at room temperature to allow easy administration but should rapidly gel at physiological temperature to prevent rapid clearance from the oral cavity. In the present study, increasing the concentration of Poloxamer 407 reduced the gelation temperature due to increased micellar aggregation within the polymeric system. The optimized formulation exhibited gelation close to body temperature, indicating that the system would effectively transform into a gel upon contact with oral mucosal surfaces. Mucoadhesion studies demonstrated that the detachment force increased with higher concentrations of Carbopol and HPMC. These polymers possess numerous functional groups capable of forming hydrogen bonds with mucin glycoproteins present in the mucosal layer. Carbopol, in particular, contains carboxylic groups that interact strongly with mucosal surfaces, leading to improved adhesion. Strong mucoadhesion is particularly beneficial in oral mucositis treatment because it allows prolonged drug contact with damaged epithelial tissues and reduces the frequency of administration required to maintain therapeutic effects.

The in vitro drug release studies indicated that rutin was released gradually from the hydrogel matrix over a period of twenty-four hours. This sustained release profile can be attributed to the diffusion of drug molecules through the hydrated polymeric network formed after gelation. Initially, a moderate burst release was observed, which may be due to the diffusion of drug molecules located near the surface of the gel. Subsequently, a controlled and sustained release phase was observed, which was governed by the diffusion of drug molecules through the polymer matrix. Kinetic modeling of the release data revealed that the Higuchi model provided the best fit, suggesting that the release mechanism was primarily diffusion controlled. This sustained drug release behavior is advantageous in mucositis therapy because it allows continuous delivery of antioxidant and anti-inflammatory compounds at the site of injury.

The antioxidant activity results confirmed that the hydrogel formulation retained the intrinsic free radical scavenging ability of rutin. Radiation therapy generates large quantities of reactive oxygen species that contribute to epithelial damage and inflammatory signalling pathways. By scavenging these reactive species, rutin may help reduce oxidative stress and protect mucosal tissues from further damage. The slight reduction in antioxidant activity observed in the hydrogel formulation compared with pure rutin may be attributed to the controlled diffusion of drug molecules from the polymer matrix during assay conditions. The anti-inflammatory activity observed in the nitric oxide inhibition assay further supports the therapeutic potential of the developed formulation. Nitric oxide plays a significant role in inflammatory processes associated with mucosal injury. Excessive production of nitric oxide by activated macrophages contributes to tissue damage and amplification of inflammatory cascades. The rutin hydrogel significantly inhibited nitric oxide production in stimulated macrophage cells, indicating that the formulation retains the anti-inflammatory activity of rutin. This property is particularly important in managing radiation-induced mucositis, where inflammation is a key driver of disease progression.

Cytotoxicity evaluation using human oral keratinocyte cells demonstrated high cell viability following exposure to the hydrogel formulation. This finding confirms that the polymeric components used in the formulation are biocompatible and suitable for mucosal application. Maintaining high cell viability is essential because damaged mucosal tissues require a formulation that supports tissue regeneration rather than causing additional cellular toxicity. The absence of cytotoxic effects suggests that the hydrogel can safely be applied to inflamed oral tissues without compromising epithelial cell survival. The stability studies conducted under both standard and accelerated storage conditions demonstrated that the optimized formulation remained physically and chemically stable throughout the study period. No significant changes were observed in pH, viscosity, appearance, or drug content. The stability of rutin within the hydrogel matrix indicates that the formulation can maintain its therapeutic efficacy during storage and transportation. Overall, the findings of the present investigation highlight the potential of mucoadhesive in situ hydrogels as effective drug delivery platforms for oral mucosal diseases. The combination of thermosensitive gelation, strong mucoadhesion, sustained drug release, antioxidant activity, and anti-inflammatory effects makes the rutin hydrogel formulation a promising candidate for the prevention and treatment of radiation-induced oral mucositis in cancer patients. By delivering rutin directly to the site of injury and maintaining prolonged mucosal contact, the formulation may help reduce mucosal inflammation, accelerate tissue healing, and improve the quality of life of patients undergoing radiotherapy.

5. Conclusion

The present study successfully developed and evaluated a rutin-loaded mucoadhesive in situ forming hydrogel intended for localized treatment of radiation-induced oral mucositis. The formulation demonstrated suitable physicochemical properties, including appropriate pH, viscosity, and gelation behavior for buccal administration. The optimized hydrogel exhibited strong mucoadhesive characteristics and sustained drug release over twenty-four hours, ensuring prolonged contact with the oral mucosa and continuous drug availability at the site of inflammation. Biological evaluation confirmed that the formulation retained the antioxidant and anti-inflammatory properties of rutin while exhibiting excellent biocompatibility toward oral epithelial cells. Stability studies further indicated that the developed hydrogel remained physically and chemically stable under different storage conditions. These findings suggest that the rutin-embedded mucoadhesive hydrogel has significant potential as a novel therapeutic strategy for preventing and managing radiation-induced oral mucositis. Further in vivo and clinical investigations may help establish its effectiveness in improving mucosal healing and reducing treatment-related discomfort in cancer patients undergoing radiotherapy.

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