**RESEARCH PAPER**

# Formulation and Evaluation of Crosslinked Mucoadhesive Curcumin Gel in Oral Ulcer Therapy

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**Abstract**
Oral ulcers are a very common and painful disease for which there are very less completely effective medical treatments available with delayed healing. The potential for the therapeutic application of bioadhesive systems containing curcumin, which is also known as wound healing and anti-inflammatory properties, appears to be extremely promising approach for the localized drug delivery. In the present study of the cross-linked mucoadhesive curcumin gel systems was prepared by a polymer gelation method at various Hydroxypropyl Methylcellulose (HPMC) concentrations (2%, 4%, and 6%) with gelatin and citric acid as cross-linking agent. The prepared Formulation F3, comprising 6% HPMC, displayed the best gelation temperature (34.5 °C) for the oral cavity. It showed the highest mucoadhesive strength (14326.23 dynes/cm), fastest spreadability (3.07 seconds), and lowest resistance to extrusion (400.36 N.mm). The in-vitro release of the drug showed a controlled release and sustained release, that F3 achieved the fastest drug release of 99.82% over 360 minutes. The Fourier Transform Infrared spectroscopy (FTIR) and Scanning Electron Microscopy (SEM) results ensures efficient chemical crosslinking, drug-polymer compatibility, and a homogenous, flexible polymeric network with uniformly entrapped curcumin particles. Overall, the optimized (F3) formulation represents a desirable functional and physicochemical properties, forming a flexible matrix for sustained drug delivery. The developed curcumin loaded mucoadhesive gel is a promising and patient-compliant delivery approach for the targeted treatment of oral ulcers.

**Keywords:** Mucoadhesive gel, Hydroxypropyl methylcellulose (HPMC), Curcumin; Oral ulcer, Scanning Electron Microscopy
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## Introduction

Oral ulcers are painful round or oval lesions that usually develop on the inside of the lips or in inner cheeks [1]. Lack of iron and vitamins, particularly B12 and C, poor oral hygiene, infections caused by bacteria, fear, bloating, physical cuts, dietary allergies, faulty hormones, dermatitis, and other medical conditions are the common causes of oral ulcers. Aphthous ulcers, a synonym for mouth ulcers, can cause pain when consuming food, drinking, or while cleaning of the teeth [2].

The rhizome of Curcuma longa, a member of the Zingiberaceae family, yields the orange-yellow crystalline powder known as curcumin. The curcumin exhibits antioxidant, anti-inflammatory and even anticancer properties. Some findings reported that various conditions like Alzheimer's disease, gastric ulcers, colitis, and many skin conditions helps in the prevention. Additionally, curcumin enhances the wound healing by stimulating the synthesis of DNA, it also helps in the promoting protein production, and increases the type III collagen deposition at the site of the injury, thereby facilitates the treatment of the oral ulcers leading to enhanced wound contraction, epithelialization, and enhancement in the tensile strength. [3-5].

The mucoadhesive drug delivery method delivers the drug at the action site while maintaining intimate contact with the mucous membrane and absorption tissue, improving bioavailability and both local and systemic effects. Mucoadhesive systems improve the duration of residency at the absorption site, increasing contact with the epithelial barrier, which makes them possibly beneficial as drug carriers. Using stimuli-sensitive drug transport systems, such as in situ thermoreversible polymers linked with a mucoadhesive system, improves the drug dosage form's potency and adherence among patients [6].

Mucoadhesive dosage forms, like pills, gels, and films has gained attention for treating the oral cavity disorders [7]. Mucoadhesive films or gels are an alternative to liquid formulations owing to their viscosity, which enables them to provide a wider and more comfortable surface coverage of releasing in the oral region for an extended amount of time [8, 9] and conformance in terms of flexibility and ease [10]. The gels and laminated patches, used primarily as buccal delivery systems, demonstrate certain limitations linked with the solvent casting method, however, such as environmental concerns, long manufacturing times, and expensive prices and look more practical compared to administer

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medications directly to a mucosal barrier [11].

Gel formulations have a number of benefits over other drug formulation types, such as relatively quick release of the incorporated drug as well as ease of setup; easier delivery and greater absorption and mucoadhesive permit adherence to mucosal membrane in the mouth cavity and quick excreation via various mechanisms involving catabolism; and minimize the chance of discomfort or allergic host responses at the site of the application. However, they are unable to transport a measured dosage of medicine to the area of application which is a limiting factor. Semisolid mucoadhesive forms of medication, including gels, or ointments, have been effective form of drug delivery for multiple routes of application, including oral, dermal, genital, and rectal administration and as a result there has been increase in the drug residence time of the oral cavity due to the adherence in the mucosal surface, although dosages of drugs obtained from these medications are less precise compared from pills, patches, or films. The oral mucosa readily absorbs mucoadhesive gels. With good efficacy and patient acceptability, a variety of adhesive gels are used to release antimicrobial agents or deliver drugs locally for the treatment of periodontitis or other autoimmune and infectious ailments of the mucosa and teeth [12, 13].

In order to treat oral ulcers, this study intends to create and assess a novel crosslinked mucoadhesive gel formulation for the localized delivery of curcumin. In order to maximize the sol-gel transition, mechanical strength, and mucoadhesive qualities in the physiological environment of the oral cavity, different concentrations of Hydroxypropyl Methylcellulose (HPMC) were crosslinked with citric acid using polymeric gelation technique. The patient-compliant targeted delivery system ensures the maximum sustained release of curcumin along with wound healing activity at the site of the lesion, thus providing a better therapeutic option for oral mucosal lesions, avoiding the early clearance phenomenon of conventional oral formulations.

## MATERIALS AND METHODS

### Materials:

Curcumin (Haleness wellspring Pt Ltd), Citric acid (Himedia), Hydroxypropyl methylcellulose (HPMC), Propylene glycol (Niram Chemicals), Gelation was purchased from Loba Chemie Pvt. Ltd., Methyl paraben was purchased from HiMedia Laboratories Pvt. Ltd. and distilled water was used as the solvent system. All other chemicals and reagent were used in the study were of analytical grade.

### Methodology:

The mucoadhesive gel formulation containing curcumin was prepared by the polymeric gelation technique. Three different gel formulations, i.e., F1, F2, and F3, were prepared by varying the concentration of HPMC, whereas the concentration of gelatin and other excipients remained constant [14]. In this study, curcumin was selected as a drug candidate owing to its anti-inflammatory and wound healing activities. In formulation F1, the gel formulation contains curcumin 0.5%, HPMC 2%, gelatin 1%, citric acid 0.3% as a cross-linking agent, propylene glycol 2% as a penetration enhancer and plasticizer, methyl paraben 0.1% as a preservative, and distilled water as a vehicle. In formulation F2, the composition of the gel formulation remains the same as in formulation F1, except for the concentration of HPMC. In formulation F2, the concentration of HPMC has been increased to 4%. In formulation F3, the concentration of HPMC was increased to 6%, whereas the concentration of other excipients remains constant. HPMC was slowly dispersed in the distilled water. This mixture was then allowed to hydrate sufficiently. In this study, gelatin was firstly dissolved in the distilled water to obtain the clear solution. After obtaining the clear solution it was slowly mixed in previously prepared HPMC solution. Then the drug curcumin separately was prepared using the propylene glycol solution until a clear yellow solution was formed. Citric acid was added to the gel formulation as a cross-linking agent to improve gel structure. Methyl paraben was added to the gel formulation as a preservative. Finally, distilled water was added to the gel formulation to obtain a uniform gel. The prepared gel was allowed to stand to facilitate hydration. This helps in removing air bubbles from the gel [15].

**Table 1:** Ingredient used and their proportion in the preparation of different Formulation.

| Ingredients | Function | F1 (%) | F2 (%) | F3 (%) |
|---|---|---|---|---|
| Curcumin | Active pharmaceutical ingredient | 0.5 | 0.5 | 0.5 |
| HPMC | Gelling agent | 2 | 4 | 6 |
| Gelatin | Film-forming agent | 1 | 1 | 1 |
| Citric Acid | Crosslinking agent | 0.3 | 0.3 | 0.3 |
| Propylene Glycol | Penetration enhancer & plasticizer | 2 | 2 | 2 |
| Methyl Paraben | Preservative | 0.1 g | 0.1 g | 0.1 g |
| Distilled Water | Vehicle (q.s. to 100 ml) | q.s. | q.s. | q.s. |

### Viscosity

The viscosity of the obtained gel was measured by using the Brookfield Viscometer with a T-shaped spindle (No. 63) was utilized, and the gel was carefully dispersed in the spindle ensuring that the gel is free from the air bubbles and spindle was attached to the viscometer and the Brookfield viscometer was switched on to stabilize and rotational speed was set about 100 rpm ensure the spindle is immersed properly not touching the container and the rotation was started after that the readings was

recorded then a calculation of the final viscosity in centipoise (cps) is performed with this formula: Viscosity = (300/N) x measured value, where N is revolutions per minute [16].

**Gelation Temperature**

In order to determine the precise point at which the liquid solution transforms to the semi-solid gel, the test tube was taken and filled with the solution and then placed it in the water bath. The temperature of the water bath was slowly increased about 1°C at every minute. At every temperature the test tube was tiled about 90° angle and after that at a precise point when the liquid stop flowing then that point was considered to be sol-gel transition. In order to be more accurate, we repeated this for three times [17].

**Checking the pH**

The surface pH of the formulated gel was observed for a 6-hour of period and it was remained consistently in the range of 6.7 to 7.0. As this range is close to the physiological pH and neutral pH for the human saliva, which tends to be in the range of 5.8 to 7.1, this ensure that the blend of polymers in the formulated gel is very compatible with the oral mucosa, thereby it reduces any chance of irritation for the patient [18].

**Spreadability testing**

The Spreadability of the formulated gel was obtained using a glass slide and also used a pulley system. The gel was placed between the glass slide to get a uniform distribution and approximately 2g of weight was subjected for about 2-3 minute to ensure a uniform thickness of the gel. After that a fixed weight was tied to a string and pulled over a pulley system, and then over this distance (L), a time (t) was measured to check how long it took for the top slide to be pulled over this distance and is calculated by using this formula: S = (M x L) / t, where M is a weight tied to a string [19].

**Extrudability**

The formulated gel was transferred into ordinary collapsible aluminium tubes with caps, and the ends were crimped shut. The tubes weight was noted. After being positioned between two glass slides, the tubes were clamped [20]. After applying 500 g to the slides, the cover was taken off. The quantity of the extruded gel was gathered and measured. It was determined with the percentage of the extruded gel. The results were analysed on the basis of following parameter: Above 90% extrudability shows excellent, above 80% extrudability is termed as good and above 70% extrudability is fair.

**Gelling Capacity**

The overall quality of the formulated gel was evaluated by visual inspection. The gelling capacity of the formulated gel was determined based on a few factors, such as how fast it gelled, how consistent it was, how well it maintained its integrity, and whether or not it was possible to reproduce good results with it time and time again [21].

**Measuring Gel Strength**

The gel strength of the formulated gel was measured by placing 1g of the prepared gel in the thermostatically controlled setup by maintaining about 37°C. A sudden weight was applied gradually at the surface of the gel, and the weight was required to achieve a penetration up to the depth for about 5cm which was recorded as the strength of the gel [22].

**Drug Release Estimation**

The in vitro drug release of the mucoadhesive gel of curcumin was studied by using Franz diffusion cell apparatus. A cellophane membrane was pre-soaked in a pH 6.8 buffer solution, and it was mounted between the donor and receptor compartments. Then due to the higher viscosity of the formulated gel, it was dispersed in a small quantity of the distilled water for the uniform distribution within the donor compartment and after that the receptor compartment was filled with 15 ml of prepared buffer and maintained temperature about 37 ± 1 °C and stirred constantly with a magnetic stirrer. At regular time intervals, 2 mL of this solution was removed and tested to determine the level of curcumin that had been released, and again it was withdrawn and replaced with fresh buffer immediately to maintain "sink" conditions. The exact amount of the drug release was determined by using the absorbance of Curcumin that was 420nm [23].

**Fourier Transform Infrared (FTIR) spectroscopy analysis**

FTIR spectroscopy was employed to authenticate the cross-linking in the muco-adhesive gel and detect functional groups. KBr pellet technique was employed to check the finely powdered form of the dry gel sample. IR spectra were recorded with a resolution of 4 $cm^{-1}$ in the wave number range of 4000-400 $cm^{-1}$. IR spectra of individual drug and gel formulations was compared to detect peak shifts, disappearance of peaks, and development of new peaks, which may reflect possible chemical interactions and cross-linking in the gel [24].

**Scanning Electron Microscopy analysis**

SEM was used to study the surface morphology of the cross-linked mucoadhesive gel. The freeze-dried gel samples were cut into small pieces and attached to aluminum stubs using a carbon tape. A thin layer of gold was sputter-coated on the gel samples to ensure conductivity. The samples were analyzed using high vacuum with an accelerating voltage of 5 to 20 kV. The results was obtained from the SEM and was used to evaluate the texture, porosity, and structural integrity of the gel [25].

## RESULTS AND DISCUSSION

**Viscosity**

Viscosity also plays an important role in mucoadhesive systems, as it affects the ease with which the system can be applied (extrudability) and the ability of the system to remain at the site of application. The viscosity of the gel

was measured at 100 rpm increased with an increase in the quantity of HPMC. The viscosity values increased from 1489.23 ± 3.61 cps for formulation F1 containing 2% HPMC to 1698.89 ± 5.23 cps for formulation F2 containing 4% HPMC. The viscosity values then increased to a maximum of 2289.22 ± 6.34 cps for formulation F3 containing 6% HPMC. This increase in viscosity for F3 indicates that a thicker and more entangled 3D polymer network have been formed due to the higher polymeric concentration in the formulation. This increase in thickness is expected for formulation F3, as it has a strong matrix that provides them with mucoadhesive strength and the release of curcumin in a controlled manner for an extended period of time.

**pH determination**

The pH of the prepared mucoadhesive gels was determined to check the compatibility for oral application. From the results, it was clear that the pH levels of all three gels were extremely stable and within an acceptable range. For F1, the pH was 6.8±0.04, for F2 it was 6.7±0.29, and for F3 it was 6.9±0.25, as seen in Table 2. The natural pH of saliva secreted in the mouth ranges from 5.8 to 7.1. This shows that when more HPMC polymer was added, the gels were not adversely affected. This proves that all gels were extremely biocompatible and suitable for use in the mouth. This implies that our gels will not cause any irritation, stinging, or discomfort when placed on a sensitive ulcer in the mouth.

**Gelation temperature**

The optimum temperature of the oral cavity is 33-37˚C. It was observed that the addition of the mucoadhesive polymer HPMC in increasing concentrations slightly increases the gelation temperature from 33±0.31 °C (F1 at 2% HPMC) to 34.5±0.25 °C (F3 at 6% HPMC) shown in **Table 2**. The highly hydrophilic nature of HPMC requires more thermal energy to disrupt the polymer-water bonds and initiate the cross-linking required for gelation.

Therefore, in the oral cavity, the formulated formulas guarantee the proper change of sol to gel. Compared to conventional ointments, the sol form will be simpler to apply, and the resulting gel will stick firmly to the mucosal lining.

**Gel strength**

The tensile strength of the gelled material is indicated by the gel strength. It shows how well the gelled mass can tolerate mechanical stress in vivo. According to **Table 2**, the gel strength of the formulation with different HPMC concentrations was found to progressively decline from 40.16±0.39 g (F1) to 32.99±0.31 g (F3). The slight reduction in rigidity can be attributed to the high water-retention capacity of HPMC. At a higher polymer concentration (6%), the extensive hydration creates a more flexible, swollen polymeric network rather than a rigidly brittle cross-linked mass, which is ideal for patient comfort without causing mucosal irritation.

**Gelling capacity**

The produced formulations demonstrated a high gelling capacity. As the concentration of HPMC increases, the gelling capacity was found to be better, progressing from F1 (+) to F3 (+++) shown in **Table 2**. Gelling in this highly concentrated system is due to the extensive cross-linking and physical entanglement of the HPMC polymeric chains. The fact that the HPMC swells rapidly can be thought to assist the gel matrix in gaining a better, more robust consistency almost immediately upon application.

**Table 2:** Viscosity and pH determination of mucoadhesive gel

| Formulation | Viscosity at 100 rpm (cPs) | pH | Gelation temperature (° C) | Gel strength (g)* | Gelling Capacity |
|---|---|---|---|---|---|
| **F1** | 1489.23±3.61 | 6.8±0.04 | 33±0.31 | 40.16±0.39 | + |
| **F2** | 1698.89.5±5.23 | 6.7±0.29 | 33.5±0.29 | 35.97±0.22 | ++ |
| **F3** | 2289.22±6.34 | 6.9±0.25 | 34.5±0.25 | 32.99±0.31 | +++ |

**Muco adhesive strength**

The observations indicated that the mucoadhesive strength of gels raised as the concentration of mucoadhesive polymers increased. Formulation F3 containing HPMC in the highest concentration (6%) shows higher mucoadhesive property (14326.23±2.99 dynes/cm) shown in **Table 3** as compared to the 2% and 4% formulations.

The larger molecular content of hydrophilic hydroxyl chains in the HPMC molecule structure, that confers more water-loving attributes resulting to greater swelling as well as better interaction with the hydrophilic glycoproteins found in mucin, serves as the cause of the increased mucoadhesive strength. According to the wetting theory of mucoadhesion, the stronger mucoadhesive force is caused by the profound physical entanglement and hydrogen bonding between mucin and the polymer.

**Spreadability**

The spreadability of the formulated gel containing varying levels of HPMC was found to be ranging from 3.07 to 3.51 seconds shown in **Table 3**. Interestingly, formulation F3 demonstrated the fastest spreadability time (3.07±0.15 Sec). This indicates that despite having the highest polymer content, the highly hydrated and shear-thinning nature of the un-gelled HPMC sol allows for smooth, uniform, and effortless application over the

target mucosal surface before the full sol-gel transition occurs.

**Extrudability**

The extrudability was found to be significantly improve (requiring less force) as the HPMC concentration increased, dropping from 560.32±0.95 N.mm (F1) to 400.36±0.27 N.mm (F3) shown in **Table 3**. This perfectly correlates with the gel strength findings; the slightly softer, highly lubricated matrix formed by the 6% HPMC formulation requires far less mechanical work to extrude, ensuring excellent patient compliance and ease of handling.

**Table 3:** Various physiochemical estimation of mucoadhesive curcumin gel.

| Formulation | Mucoadhesive strength (dynes/cm) | Spreadability (Sec)* | Extrudability (N.mm) |
|---|---|---|---|
| F1 | 13206.3±2.36 | 3.51±0.27 | 560.32±0.95 |
| F2 | 13403.1±3.03 | 3.36±0.23 | 450.25±0.27 |
| F3 | 14326.23±2.99 | 3.07±0.15 | 400.36±0.27 |

**Drug Release study**

The in vitro drug release profile of formulations F1, F2, and F3 increased with increasing time up to 360 minutes as shown in **Figure 1**. At 30 minutes, the release of the drug was less of different formulations F1, F2, and F3, i.e., 2.21%, 4.23%, and 5.52%, respectively, indicating a lag phase. After that, a gradual release of the drug was observed, with F3 showing higher release compared to F2 and F1. At 180 minutes, the release of the drug from F3 was higher, i.e., 45.19%, followed by F2 (40.25%) and F1 (35.69%). At the end of 360 minutes, maximum release of the drug was observed from F3 (99.82%), followed by F2 (98.26%) and F1 (96.99%).

The increased release of the drug from F3 may be attributed to the optimized concentration of the polymer used in the formulation, which increased the release of the drug from the gel network. F1, on the other hand, showed a slower release of the drug, which may be attributed to the rigidity of the polymer network. All formulations showed controlled release of the drug, with F3 being the most efficient formulation in terms of drug release performance.

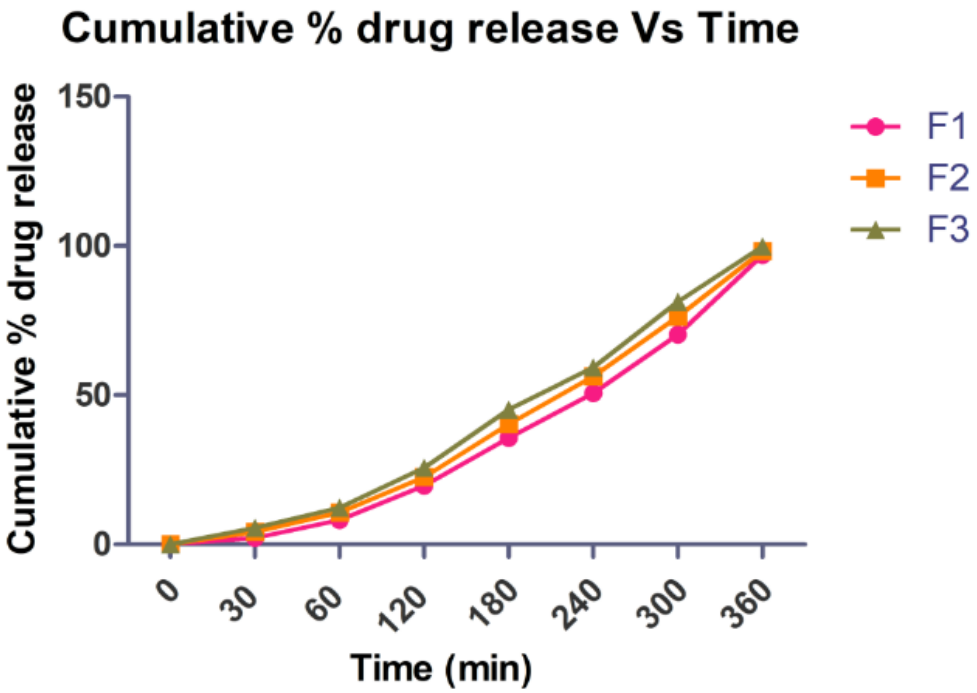


**Figure 1:** Drug release profile of three formulated crosslinked mucoadhesive curcumin gel.

**FTIR analysis of cross-linked mucoadhesive curcumin gel**

As the best performing gel was F3, it was further selected for FTIR analysis. For pure curcumin drug Figure (2A), the FTIR peaks at ~3500 $cm^{-1}$ for phenolic –OH stretches, ~1625 $cm^{-1}$ for conjugated C=O and C=C stretches, and ~1500-1450 $cm^{-1}$ for aromatic C=C stretches were indicative of a typical chemical structure. For the placebo gel Figure (2B), peaks at ~3200-3400 $cm^{-1}$ for –OH stretches and ~1000-1200 $cm^{-1}$ for C–O–C stretches were indicative of a polymer network for the mucoadhesive polymer. For the Curcumin-loaded gel Figure (2C), characteristic peaks for Curcumin was maintained with a slight shift and reduced intensity,

indicative of successful loading with possible hydrogen bonding between Curcumin and polymer.

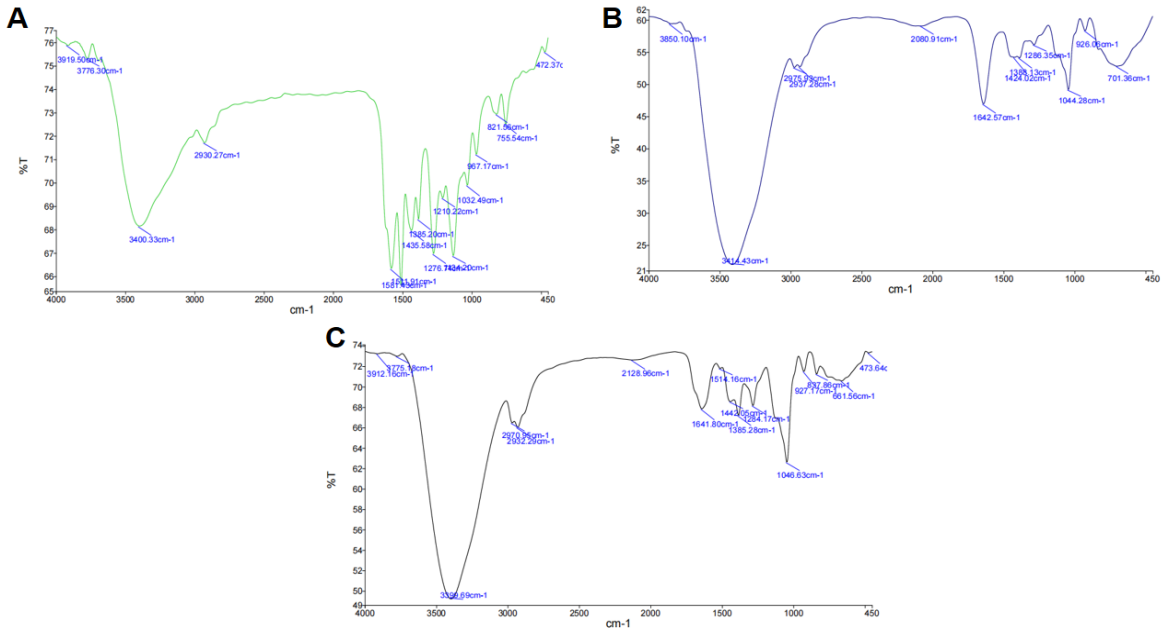


**Figure 2:** FTIR analysis of crosslinked mucoadhesive gel. (**A:** Pure curcumin; **B:** placebo gel and **C:** Crosslinked mucoadhesive curcumin gel of F3

**SEM analysis**

The surface morphology and microstructure of the optimized crosslinked mucoadhesive gel, namely, the HPMC gel formulation F3, was investigated using SEM. As shown in the micrographs, the surface morphology of the optimized HPMC gel formulation is relatively homogeneous and smooth. This is a direct result of the successful and extensive cross-linking of the HPMC chains, even at a high concentration. However, and perhaps more importantly, the micrographs indicate a lack of large, fractured, and agglomerated drug crystals on the surface of the HPMC gel. Rather, they indicate a thorough entrapment of the particulate matter, thus confirming a homogeneous dispersion of the curcumin within the gel. Such a homogeneous entrapment of the active compound is a highly desired feature of natural compound therapeutics, as it ensures a controlled and sustained release of the active compound over a period of time.

Perhaps even more significantly, the surface morphology of the HPMC gel, as shown in the micrographs, is indicative of a highly cohesive and flexible nature of the polymer matrix. Such a feature is a vital attribute of the mucoadhesive gel, as it is capable of easily conforming to the anatomical surface irregularities of the oral cavity. Such a micro-level conformational capability of the gel is a direct result of the excellent mucoadhesive strength of 14326.23 dynes/cm and the optimal spreadability of the HPMC gel, as shown during the physical evaluation of the optimized HPMC gel.

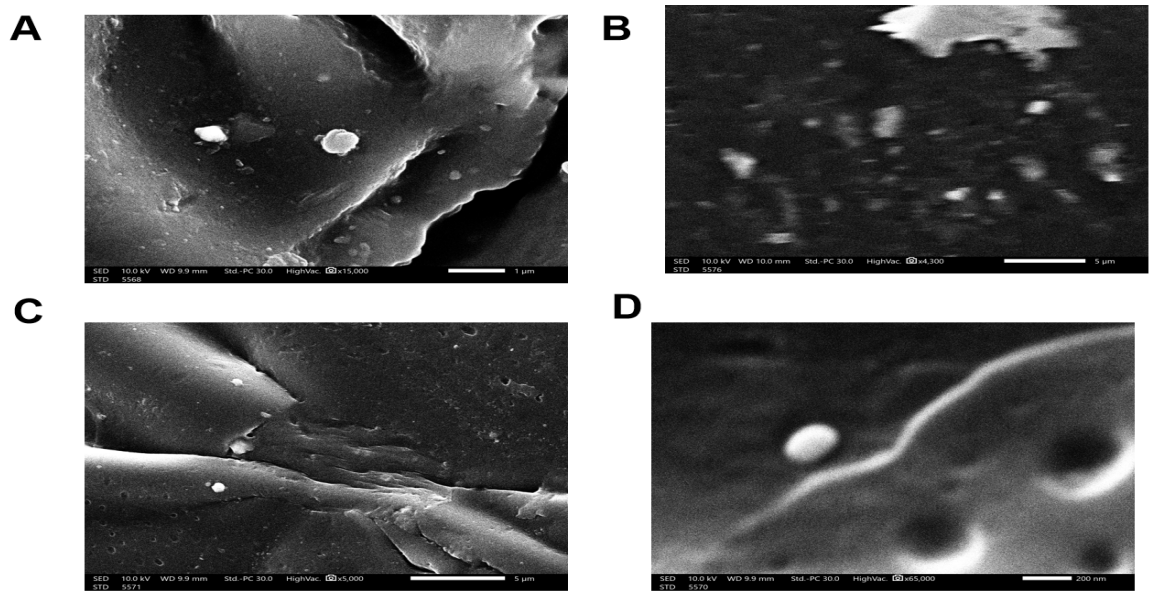


**Figure 3:** SEM analysis of F3 formulation.

## CONCLUSION

The present study successfully developed and evaluated an in situ–forming crosslinked mucoadhesive system for the controlled oral delivery of curcumin. The physicochemical characteristics and drug-release behaviour of the gel were effectively modulated by varying the concentration of the hydrophilic polymer HPMC. Among all formulations, F3 containing 6% HPMC emerged as the most optimized and efficient. It exhibited a gelation temperature of 34.5 °C, enabling a seamless transition from liquid to gel within the oral cavity. Furthermore, F3 demonstrated superior mucoadhesive strength (14,326.23 dynes/cm), ensuring prolonged contact time for enhanced wound healing, while maintaining excellent spreadability and extrudability to support patient compliance. In vitro studies revealed that F3 achieved the highest cumulative release of curcumin, reaching 99.82% within 360 minutes. Complementary instrumental analyses (FTIR and SEM) corroborated these findings, confirming polymer crosslinking, drug stability, and the formation of a flexible, uniform micro-matrix capable of efficiently encapsulating curcumin without agglutination. Overall, the optimized stimuli-responsive mucoadhesive gel effectively overcomes clearance limitations associated with conventional oral dosage forms, offering a practical and promising therapeutic approach for the treatment and management of oral ulcers.

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