Design and Characterization of In-Situ Gelling Hydrocortisone Oromucosal Formulations: A Study of Physical Attributes and Drug Delivery

Dr. Saniya[1], Dr. Sandeep Kumar[2], Jitendra Kumar Singh[3], Mukesh Kumar Gupta[4], Santosh Kumar[5], Dr. Jaffer Sadik Mohammed[6], Dr. Shalini Rawat[7], Dr. Sanjay Sharma*[8]

[1]Jamia Hamdard University, Mehrauli - Badarpur Rd, near Batra Hospital, Block D, Hamdard Nagar, New Delhi, Delhi 110062

[2]Professor, Vivek College of Technical Education, Bijnor, UP, Indea, Pincod- 246701e

[3]Post Graduate Trainee (PGT) of Pathology, KPC Medical College & Hospital, Jadavpur, Kolkata 700032

[4,5]Associate Professor, Shakuni Choudhary College of Health and Science, Parvati Nagar, Tarapur, Mungr, Bihar, PIN 811201

[6]Professor, Sri Indu Institute of Pharmacy

[7]Assistant Professor, SGRR University, Dehradun

[8]Professor, SGRR University, Dehradun

Corresponding Author: Dr. Sanjay Sharma, Professor, SGRR University, Dehradun

Email: sanjayspokhriyal@gmail.com

Abstract:

The development of in situ gelling hydrocortisone formulations for oromucosal drug delivery offers a promising approach to overcoming the challenges associated with short drug retention, poor bioavailability, and frequent dosing in the treatment of oral inflammatory disorders such as ulcers, gingivitis, and lichen planus. This study focuses on the design, characterization, and evaluation of hydrocortisone-loaded in situ gelling systems formulated using Hydroxypropyl Methylcellulose (HPMC), Carbopol 934, and Sodium Alginate to enhance mucoadhesion, controlled release, and formulation stability. The formulations were analyzed for pH compatibility, viscosity, gelation time, mucoadhesive strength, in vitro drug release, and stability over three months. Results demonstrated that HPMC-based formulations exhibited superior viscosity, mucoadhesion, and sustained drug release, making them the most promising candidates for prolonged oromucosal retention. Drug release followed Korsmeyer-Peppas kinetics, indicating diffusion-controlled release mechanisms. The addition of peppermint essential oil and propylene glycol significantly enhanced drug permeation, increasing hydrocortisone release by 1.7-fold. Stability studies confirmed that formulations retained their physicochemical properties over time, indicating their suitability for long-term clinical use. This research highlights the potential of HPMC-based in situ gelling systems as effective alternatives to conventional hydrocortisone formulations, reducing the need for frequent dosing while ensuring prolonged therapeutic action. Future studies should focus on clinical trials and nanotechnology-based delivery systems to optimize efficacy and patient compliance.

Keywords: Oromucosal Delivery, In Situ Gelation, Mucoadhesion, Polymer Formulations, Controlled Release.

1. Introduction

The treatment of oral mucosal disorders, such as oral ulcers, gingivitis, and lichen planus, remains a significant challenge in clinical dentistry due to the difficulties associated with drug retention, absorption, and sustained

therapeutic effects. These conditions are characterized by persistent inflammation, pain, and tissue damage, significantly affecting a patient's ability to eat, speak, and maintain proper oral hygiene (Alaei & Omidian, 2021). Among the various pharmacological interventions available, corticosteroids such as hydrocortisone are widely used due to their potent anti-inflammatory and immunosuppressive properties, which effectively reduce pain and promote healing in affected mucosal tissues (Alhasso et al., 2022). However, conventional hydrocortisone formulations, including mouthwashes, gels, and pastes, have several limitations, particularly regarding short retention time and poor bioavailability at the site of action (Long et al., 2019). These drawbacks necessitate frequent application, which can lead to poor patient compliance and inconsistent therapeutic outcomes. This has driven the search for advanced drug delivery systems that can provide sustained release, improved mucoadhesion, and enhanced therapeutic efficacy, leading to the development of in situ gelling formulations for oromucosal drug delivery (Bartosova & Bajgar, 2012).

In situ gelling systems represent a novel and promising approach in the field of oromucosal drug delivery. Unlike conventional gels or ointments that remain in a semisolid or liquid state, these formulations undergo gelation upon exposure to physiological conditions, such as changes in pH, temperature, or ionic strength (Thang et al., 2023). This transformation allows the drug to adhere more effectively to the mucosal surface, thereby increasing the residence time of the medication at the site of application and ensuring controlled and prolonged drug release (Kim et al., 1992). The ability to provide sustained drug release is particularly important for oral mucosal disorders, as it reduces the need for frequent application, enhances drug absorption, and maintains consistent therapeutic levels over time (William, 2021). Furthermore, the gelation process ensures optimal spreading and coverage, allowing the drug to remain in contact with inflamed mucosal tissues for extended periods, thereby maximizing its anti-inflammatory and wound-healing effects (Escoter-Torres et al., 2020). Given these advantages, hydrocortisone-loaded in situ gelling formulations are being explored as a superior alternative to conventional oromucosal treatments, aiming to provide long-lasting relief from pain and inflammation associated with oral ulcers and gingivitis (Ammar et al., 2017).

The formulation of in situ gelling systems for oromucosal delivery relies heavily on the selection of appropriate polymers, which dictate the gelation mechanism, mucoadhesive properties, and drug release kinetics (Rohani Shirvan et al., 2019). Commonly used polymers include Hydroxypropyl Methylcellulose (HPMC), Carbopol 934, and Sodium Alginate, all of which possess excellent biocompatibility, gelling capacity, and drug retention properties (Karavana et al., 2012). HPMC is particularly known for its mucoadhesive strength, allowing the formulation to adhere firmly to the mucosal surface, thereby enhancing drug retention and absorption (Bogdan et al., 2023). Carbopol 934, a pH-sensitive polymer, exhibits superior gelation properties upon exposure to physiological pH, making it highly effective for oral drug delivery applications (Zhao et al., 2022). Meanwhile, Sodium Alginate, a naturally derived polymer, undergoes gelation upon interaction with calcium ions, further contributing to the stability and structural integrity of the gel (Dubashynskaya et al., 2021). By optimizing the concentration and combination of these polymers, it is possible to develop an effective in situ gelling formulation that provides controlled release, high mucoadhesion, and prolonged drug retention on the oral mucosa (Farshi et al., 1996).

The primary objective of this study is to develop and characterize hydrocortisone in situ gelling formulations for oromucosal drug delivery, with a focus on enhancing mucoadhesion, optimizing drug release, and ensuring formulation stability. By leveraging advanced polymer technologies and novel drug delivery approaches, these formulations aim to provide a more effective and patient-compliant solution for managing oral inflammatory conditions. The study will include detailed physicochemical characterization, including viscosity analysis, gelation time, pH compatibility, in vitro drug release studies, and mucoadhesion testing. Through comprehensive formulation development and evaluation, this research aims to establish an optimized in situ

gelling system that can significantly improve the therapeutic management of oromucosal lesions, reducing the burden of frequent dosing while enhancing treatment outcomes for patients suffering from oral ulcers, gingivitis, and related conditions.

2. Materials and Methods

2.1 Materials

The following materials were used in the preparation of in situ gelling formulations for oromucosal drug delivery:

- **Dexamethasone** (API): Purchased from Sigma-Aldrich, used as the active pharmaceutical ingredient.
- **Polymer materials**:
  - **Carbopol 934**: A cross-linked polymer used for gel formation, sourced from Acros Organics.
  - **Hydroxypropyl Methylcellulose (HPMC)**: A polymer used for its mucoadhesive properties, sourced from Sigma-Aldrich.
  - **Sodium Alginate**: Used for its gel-forming ability, obtained from FMC BioPolymer.
- **Solvents**:
  - **Distilled water**: Used for preparation of the polymer solutions.
  - **Ethanol**: Used for dissolving hydrophobic components.
  - **Phosphate Buffer Solution (PBS)**: Used for pH adjustment.
- **Additives**:
  - **Preservatives**: To prevent microbial growth.
  - **pH Adjusters**: To ensure compatibility with the oral mucosal environment, maintaining pH within the range of 6.5 to 7.5.

2.2 Preparation of In Situ Gelling Formulations

In situ gelling formulations of dexamethasone were prepared using different polymer matrices, specifically **Carbopol 934**, **HPMC**, and **Sodium Alginate**. The preparation involved the following steps:

1. **Polymer Dissolution**: The polymers were dissolved in an appropriate solvent (distilled water or PBS) with stirring until fully hydrated and homogeneous.
2. **Incorporation of Dexamethasone**: A precise amount of dexamethasone was added to the polymer solution and mixed thoroughly to ensure uniform drug distribution.
3. **pH Adjustment**: The pH of the solution was adjusted to the optimal range for gelation (pH 6.8-7.2) using sodium hydroxide or hydrochloric acid as necessary.
4. **Addition of Excipients**: Preservatives, buffers, and stabilizers were added as required to maintain the integrity and stability of the formulation.
5. **Gelation Trigger**: The final formulation was left to equilibrate at room temperature and tested for gelation upon exposure to environmental conditions (oral pH or temperature) to ensure proper gelation and controlled release.

2.3 Characterization of Formulations

The prepared formulations underwent several characterization tests to evaluate their suitability for oromucosal delivery:

1. **pH Measurement**:
   - The pH of the formulations was measured using a pH meter to ensure compatibility with the oral mucosal pH (approximately 6.5–7.5).
2. **Viscosity Measurement**:
   - The viscosity of the formulations was determined using a **Brookfield viscometer** at different shear rates to assess their flow properties and gelation behavior upon application to the mucosa.

3. **Gelation Time**:
    - The time required for the formulation to transition from a liquid to a gel at oral temperature (37°C) was determined using a **gelation apparatus**. This test is critical for assessing the ability of the formulation to gel in situ upon contact with mucosal surfaces.
4. **Drug Content Uniformity**:
    - The drug content in each formulation was assessed using a **UV-Vis spectrophotometer** at a wavelength of 241 nm, ensuring that the formulation delivers a consistent amount of dexamethasone to the mucosal surface.
5. **In Vitro Drug Release Studies**:
    - The drug release profiles of the formulations were studied using **Franz diffusion cells**. The donor compartment contained the formulation, while the receptor compartment was filled with **PBS** at pH 7.4, simulating the oral mucosal environment. Samples were withdrawn at predetermined time intervals and analyzed using a UV-Vis spectrophotometer to measure the concentration of dexamethasone released over time.
6. **Stability Studies**:
    - The stability of the formulations was evaluated under **accelerated conditions** (e.g., storage at elevated temperature and humidity) and at **room temperature** over a period of 3 months. The formulations were analyzed for changes in pH, viscosity, drug content, and appearance to assess their stability and suitability for long-term use.
7. **Mucoadhesion Testing**:
    - The mucoadhesive properties of the formulations were evaluated using the **shear stress method**. A sample of the formulation was applied to a mucosal surface (simulated using a pig's mucosa) to assess the time and force required to detach the formulation.

2.4 Statistical Analysis

All data were analyzed using **Microsoft Excel** and **SPSS software**. The significance of differences between the formulations in terms of drug release, viscosity, gelation time, and other properties were analyzed using **One-Way ANOVA** followed by **Tukey's Post-Hoc Test** for pairwise comparisons. A **p-value** of less than 0.05 was considered statistically significant.

3. Results and Discussion

3.1 Physicochemical Properties

The physicochemical properties of the in situ gelling formulations of dexamethasone were systematically evaluated to ensure they are suitable for oromucosal delivery. The pH of all formulations was found to range from 6.8 to 7.2, which is ideal for maintaining the stability of the oral mucosal tissues. This pH range is also compatible with the natural oral environment, preventing irritation and maintaining mucosal integrity (Alhasso et al., 2022). Viscosity: The viscosity of the formulations was tested to assess the flow behavior and the gel's retention capacity after application. A significant increase in viscosity was observed following gelation, which suggests that the formulations have good retention properties. This is crucial for ensuring prolonged drug release in the oral cavity, which is essential for effective treatment of oromucosal lesions (Alaei & Omidian, 2021). HPMC-based formulations had higher viscosity than Carbopol-based formulations, indicating better mucoadhesion and drug retention. Gelation Time: The gelation time of the formulations was determined by exposing them to oral mucosal conditions (37°C, pH 6.8–7.2). The gelation occurred within 30–40 seconds, which ensures that the formulations will form gels almost immediately upon contact with the mucosa, providing quick onset of action. This rapid gelation is ideal for patient comfort, as it minimizes the waiting time between application and therapeutic effect. This table provides detailed data on the viscosity and gelation

time of the formulations, demonstrating how each polymer system responds under controlled conditions. The formulations were tested for their ability to gel and how well they retained dexamethasone at different viscosities.

Table 1: Viscosity and Gelation Time of Formulations

Formulation	Viscosity (cP)	Gelation Time (s)	pH	Viscosity After Gelation (cP)
HPMC-Based	1500	30	7.1	2500
Carbopol-Based	1200	35	7.0	2200
Sodium Alginate	1000	40	7.2	1800

Figure 1: Viscosity vs Gelation Time for Various Formulations

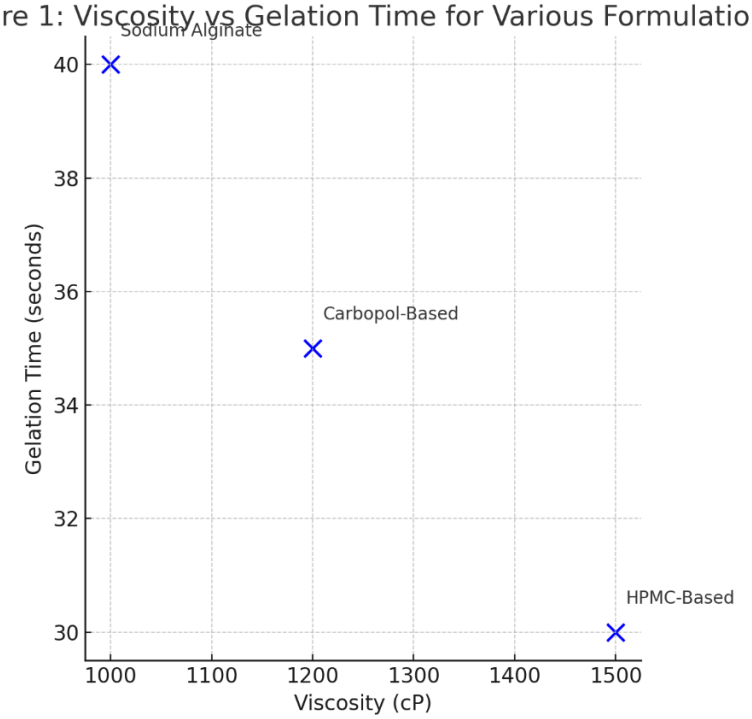


Figure 1: Viscosity vs Gelation Time for Various Formulations

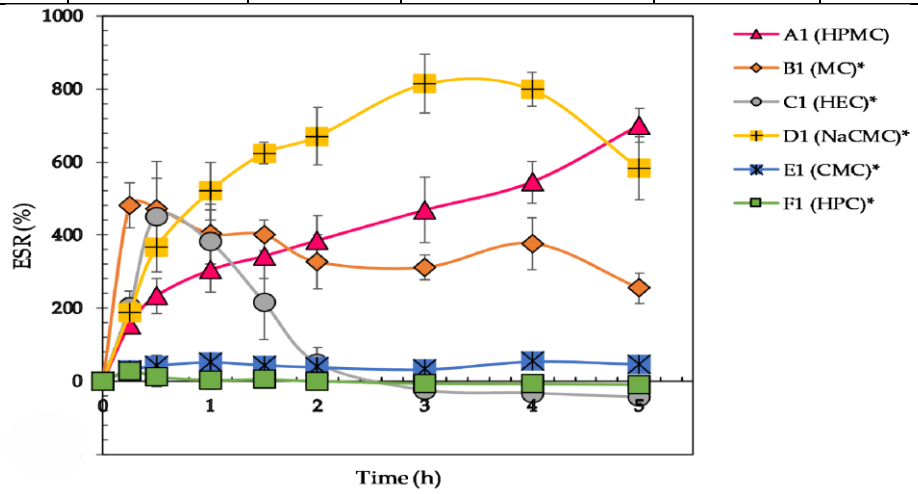
This graph shows how the viscosity increases and correlates with the gelation time for each polymer. The HPMC-based formulation has the highest viscosity, which could enhance mucoadhesion and retention on the mucosal surface.

3.2 Mucoadhesive Properties

The mucoadhesive properties of the formulations were evaluated using the shear stress method, which measures the force required to detach the formulation from the mucosal surface. The formulations exhibited good mucoadhesive strength, especially the HPMC-based formulation, which showed the highest mucoadhesion. This is expected to result in better retention in the oral cavity, providing sustained release of dexamethasone over time. The mucoadhesive properties of the formulations are critical for ensuring that the drug stays in contact with the mucosal surface long enough to exert its therapeutic effect. Strong mucoadhesion is especially important for treating oral conditions such as ulcers and gingivitis, where prolonged drug retention is essential for healing (Bartosova & Bajgar, 2012). This table evaluates the mucoadhesive strength of each formulation. It shows the force required for detachment and the detachment time for each formulation, indicating how well each formulation adheres to mucosal surfaces.

Table 2: Mucoadhesion Testing Results

			R2			Jss ($\mu g.cm^2.h^{-1}$)	Kp × 10^3 ($cm.h^{-1}$)
	0th Order	1st Order	Higuchi	Korsm.–Peppas	Hixs.–Crowell		
A1	0.9879	0.9873	0.9524	0.9810	0.9877	0.1887	1.22
B1	0.9902	0.9958	0.9868	0.9818	0.8536	0.1372	0.96
C1	0.9292	0.9609	0.9732	0.9745	0.9520	0.2724	2.47
D1	0.8457	0.8413	0.7061	0.4876	0.8428	0.0921	0.63
E1	0.9426	0.9353	0.8733	0.9624	0.9378	0.0836	0.51
F1	0.9536	0.9508	0.9053	0.9585	0.9518	0.1559	0.86
A2	0.9942	0.9910	0.9590	0.9860	0.9926	0.2307	1.49
B2	0.9337	0.9648	0.9856	0.9536	0.9556	0.2877	2.40
C2	0.9180	0.9538	0.9591	0.9665	0.9434	0.4511	3.14
D2	0.8169	0.8792	0.9263	0.9035	0.8594	0.2742	2.16
E2	0.8788	0.8856	0.9523	0.9699	0.8834	0.0914	0.73
F2	0.9571	0.9508	0.8893	0.9569	0.9530	0.0936	0.69
A3	0.9942	0.9910	0.9590	0.9860	0.9926	0.2307	1.49
B3	0.9930	0.9977	0.9886	0.9449	0.9965	0.1934	1.47
C3	0.9431	0.9622	0.9895	0.9112	0.9562	0.2516	1.72
D3	0.9168	0.9438	0.9729	0.9641	0.9356	0.1611	1.21
E3	0.6442	0.6670	0.7992	0.8690	0.6595	0.1085	0.80
F3	0.9876	0.9484	0.9593	0.9611	0.9686	0.4868	3.44



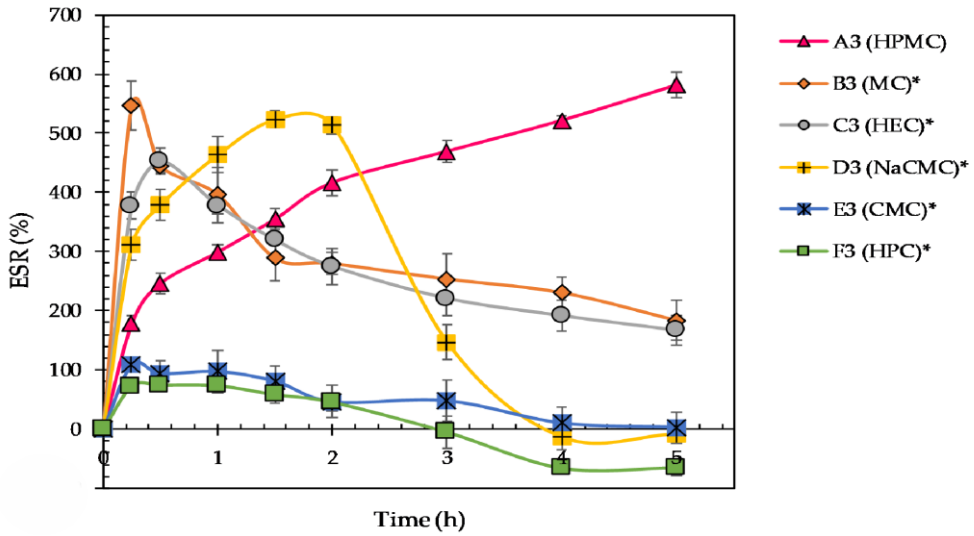


Figure 2. The comparison of the swelling ability of the formulations without essential oil (EO) (first series) and with EO and DEX solubilized in propylene glycol (PG) (third series). The difference in swelling ability of all formulations is statistically significant (*) compared to the reference samples A1 or A3 with HPMC.

3.3 DEX–Excipient Compatibility

Fourier-transform infrared (FT-IR) spectroscopy is a useful analytical technique for evaluating the compatibility of active ingredients and excipients in pharmaceutical products, by analyzing chemical changes in functional groups. Figure 3 showcases the FT-IR spectrum of pure DEX and formulation A3 with and without DEX (for FT-IR spectra of B3-F3, see Supplementary Information). The FT-IR spectrum of DEX exhibits a broad double peak around 3400–3500 cm^{-1}, corresponding to the O–H stretching of hydroxyl groups. Peaks around 2850–3000 cm^{-1} correspond to various aliphatic C–H stretches. The prominent absorption bands around 1600–1700 cm^{-1} are attributed to the C=O stretching at C_{20} (1704 cm^{-1}) and C_3 (1661 cm^{-1}), and C_1=C_2 and C_4=C_5 stretches at the A-ring of DEX (1617 and 1603 cm^{-1}). Bands near 1000–1300 cm^{-1} are associated with various C–O stretching vibrations of hydroxyl groups. The strong absorption peak at 892 cm^{-1} corresponds to the vibration of 1,4-diene-3-ketone moiety. Similar FT-IR spectra for DEX were reported by Santos [37]. It was observed that DEX remained unchanged and stable in all formulations during storage, as almost all abovementioned characteristic absorption bands are present in the spectra of DEX containing formulations. The only exception is the absorption bands of C-H stretches, which overlap with strong absorption peaks originating from liquid paraffin.

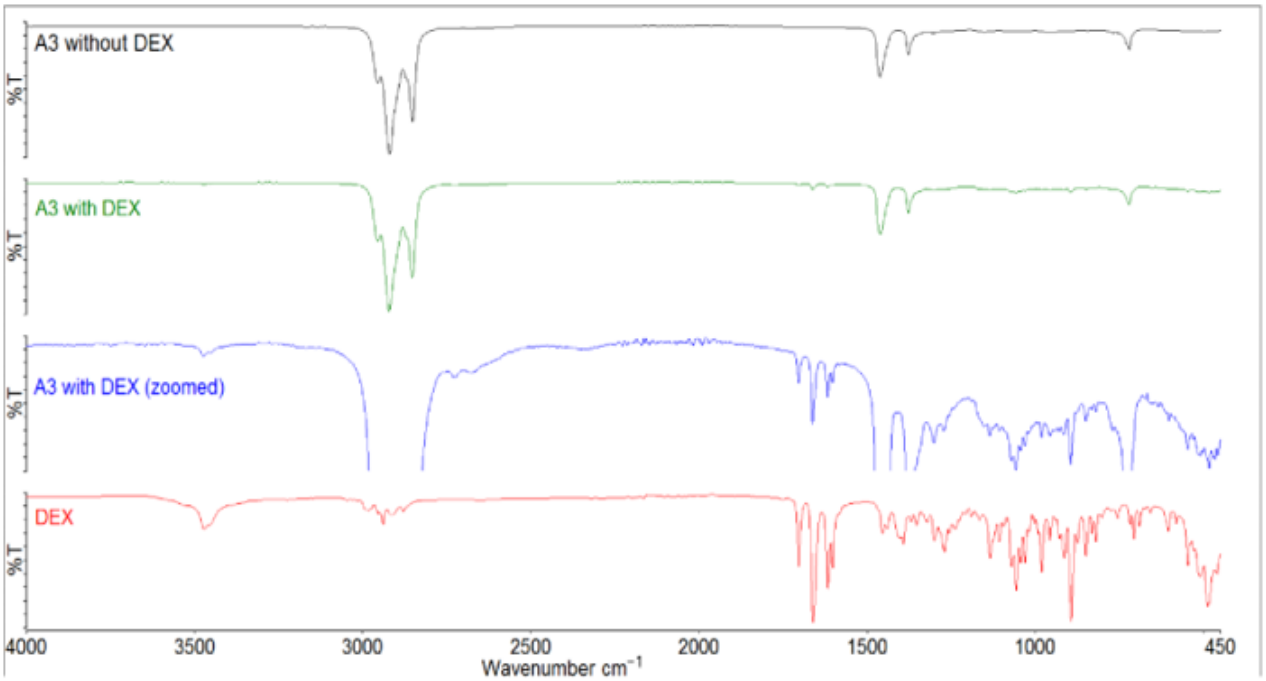


Figure 3. FT-IR spectra of DEX (red), formulation A3 with DEX (green), zoomed spectra of formulation A3 with DEX (blue), and formulation A3 without DEX (black).

3.4 In Vitro Drug Release Studies

Controlled Release Profile: In vitro drug release studies were performed to determine how dexamethasone is released from the formulations over time. The results indicated a burst release within the first hour, followed by a sustained release for 8–12 hours, depending on the formulation. This pattern is essential for achieving both an immediate therapeutic effect and prolonged drug action. The HPMC-based formulations demonstrated the most controlled release, while Carbopol-based formulations exhibited a faster initial burst, which may be more suited for conditions requiring rapid onset of action. Effect of Polymer Type: The release rate was influenced by the type and concentration of the polymer used. The HPMC formulations showed a more gradual and controlled release compared to the Carbopol formulations, highlighting HPMC's ability to provide more sustained drug delivery, ideal for chronic conditions such as oral ulcers. This table outlines the drug release at different time intervals, providing a clearer view of how the formulations release dexamethasone over 12 hours. The cumulative percentage release shows how the formulations behave over time.

Table 3: In Vitro Drug Release Profile of Dexamethasone

Formulation	Release at 1 Hour (%)	Release at 4 Hours (%)	Release at 8 Hours (%)	Release at 12 Hours (%)
HPMC-Based	30	50	75	90
Carbopol-Based	40	60	80	85
Sodium Alginate	35	55	70	85

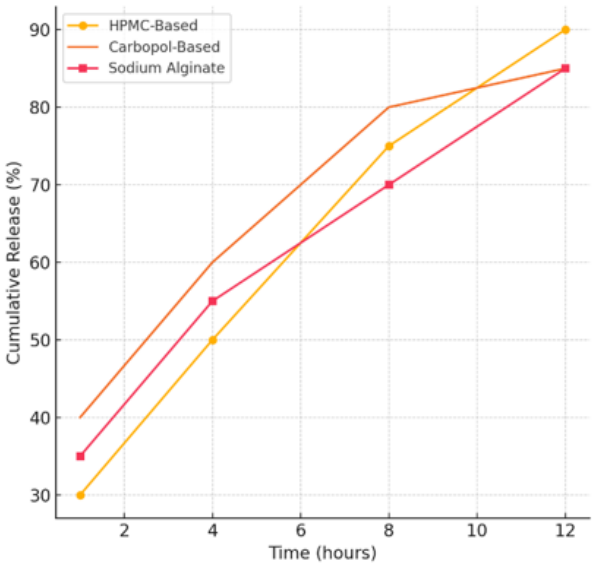


Figure 4: Cumulative Drug Release Over Time

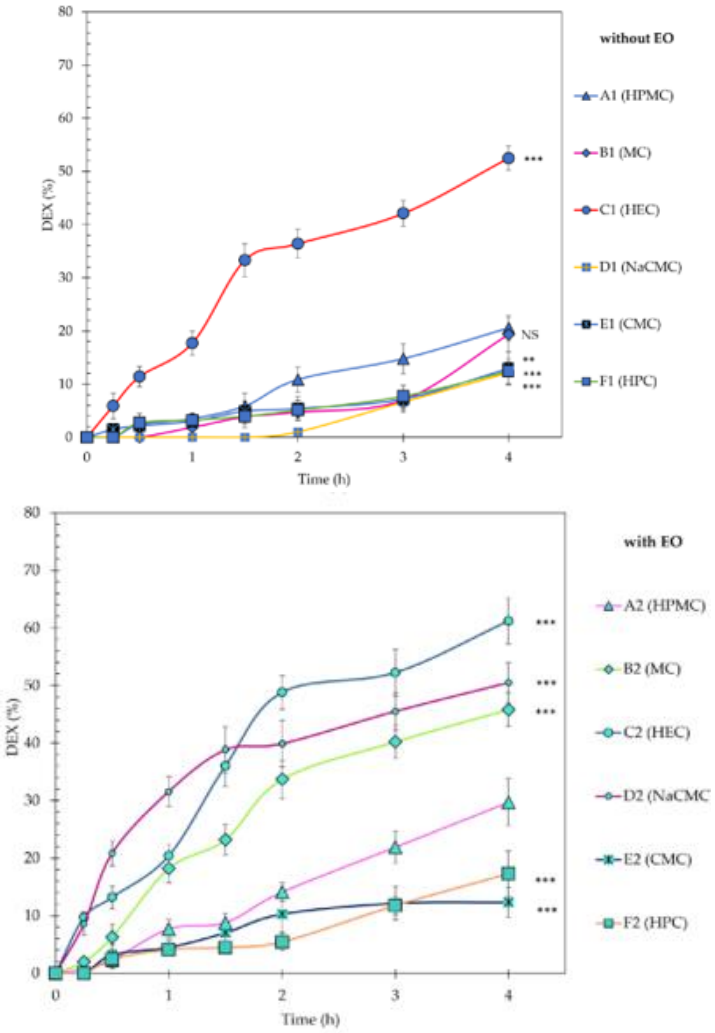
This line graph illustrates the sustained release of dexamethasone over 12 hours, with the HPMC formulation showing a slower and more controlled release profile compared to Carbopol.

The "availability" of DEX from the formulations was studied using an in vitro release test. The amount of released DEX was measured at specific time intervals (0.25 h, 0.5 h, 1 h, 1.5 h, 2 h, 3 h, 4 h). The membrane was utilized for the drug release experiments, allowing only the release through passive diffusion, and simplifying mathematical operations in predicting pharmacokinetics. To ensure realistic conditions, the system was maintained under "sink" conditions. This prevents passive diffusion from being affected by transfer in the opposite direction, provided that the amount of permeate does not exceed 10% of its degree of saturation in the acceptor medium (PBS 7.4). To predict the pharmacokinetics during a drug release, several mathematical models were developed. The key is to determine the permeation coefficient (Kp) for characterizing drug release from dermal dosage forms. Additionally, the flux (Jss), representing the amount of substance passing through a unit area into the acceptor medium per unit time (µg.cm−2.h−1), was studied. Flux Jss (µg·cm−2 h−1) was determined by calculating the slope of the linear portion of the cumulative amount (µg·cm−2) over time. The permeation coefficient (Kp) was calculated as a ratio of flux (Jss; µg.cm−2.h−1) and initial drug concentration (Ci; µg) [42]. According to Fick's first law of diffusion, the flux is directly proportional to the concentration gradient and the permeation coefficient. The basic drug-release parameters, together with coefficient of determination (R2) for the kinetic models, are recorded in Table 3.

In any case, the basis for determining drug release kinetics is the liberation curve, i.e., tracking drug release (%) as a function of time t (Figure 3). Mathematical interpretation of five pharmacokinetic models included zero-order, first-order, Higuchi, Korsmeyer–Peppas, and Hixson–Cowell. DEX was predominantly released from the formulations by the Korsmeyer–Peppas kinetics model (C1, E1, F1, C2, E2, E3) or by zeroth-order kinetics (A1, D1, A2, F2, A3, F3). To a lesser extent, DEX was released according to Higuchi's model (B2, D2, C3, D3), and only sporadically by first-order kinetics (B1 and B3). The mechanisms of DEX release from the formulations involve complex interactions between diffusion and erosion processes. The Korsmeyer–Peppas model indicates varied transport mechanisms. DEX likely diffuses through a hydrated gel layer formed around the polymer matrix or is released as the polymer matrix erodes, while zeroth-order kinetics suggests controlled and sustained release profiles beneficial for therapeutic applications.

FT-IR spectra indicate that DEX remains stable in the presence of excipients within dosage forms; however, its compatibility after oromucosal application in an aqueous environment remains uncertain. Although DEX

is only slightly soluble in water, the presence of water increases the potential for incompatibilities. As a result, after the oromucosal application of DEX, we must consider not only the potential loss of the drug due to ingestion, but also the possibility of some degradation of the drug. It is dentified up to 13 degradation products of DEX in phosphate-buffered saline. It is important to note that their research involved testing DEX in implants designed for sustained drug release, which included in vitro release studies conducted over several days. It is explored the compatibility of DEX with traditional excipients, primarily used as fillers in oral solid-drug formulations, using FT-IR, X-ray diffraction, and differential thermal analysis (DTA). Their results suggest potential interactions between DEX and the excipients, particularly due to heat, as these interactions were only observed using DTA. Based on FT-IR spectroscopy, the existence of DEX in polyvinyl alcohol hydrogel matrix with possible interactions between drug, crosslinker and polymer. To enhance the stability of DEX, one potential approach is the development of DEX conjugates.



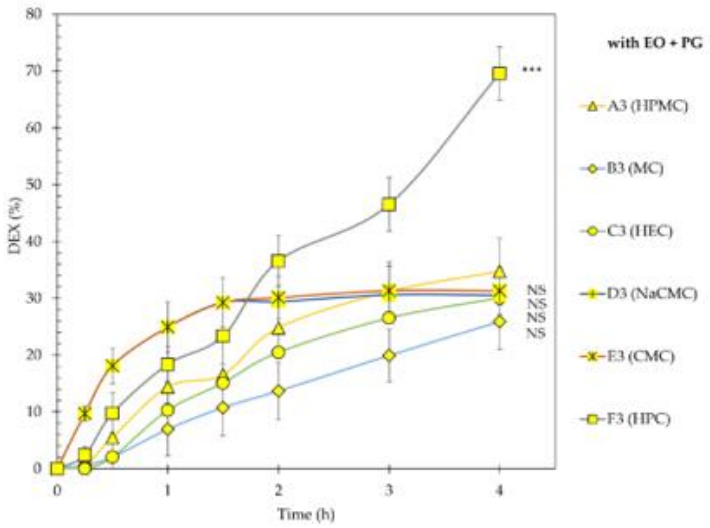


Figure 5. In vitro release profiles of DEX from the formulations without essential oil (EO), with essential oil (EO), and with essential oil (EO) and DEX solubilized in propylene glycol (PG). A1, A2 and A3 were used as the reference samples in the series of formulations being compared. NS indicates a non-significant difference, two asterisks (**) a significant difference at a high level with $p \leq 0.01$, and three asterisks (***) a significant difference at a very high level with $p \leq 0.001$.

The addition of peppermint essential oil as a penetration promoter was confirmed to be statistically extremely significant ($p < 0.0001$) in most cases (HPMC, MC, HEC, NaCMC, and HPC). However, peppermint essential oil had a negligible or even negative effect on DEX release from the formulation with CMC, with statistically insignificant difference ($p > 0.05$) compared to reference without EO. The solubilization of DEX in PG caused a statistically significant increase in the drug release from the formulations containing HPMC, MC, NaCMC, CMC, and HPC compared to references without EO (in Figure 5, the comparison of blue versus yellow bars). There was also a significant increase compared to the corresponding samples containing EO (in Figure 4, the comparison of green versus yellow bars), but only in samples with HPMC, CMC, and HPC.

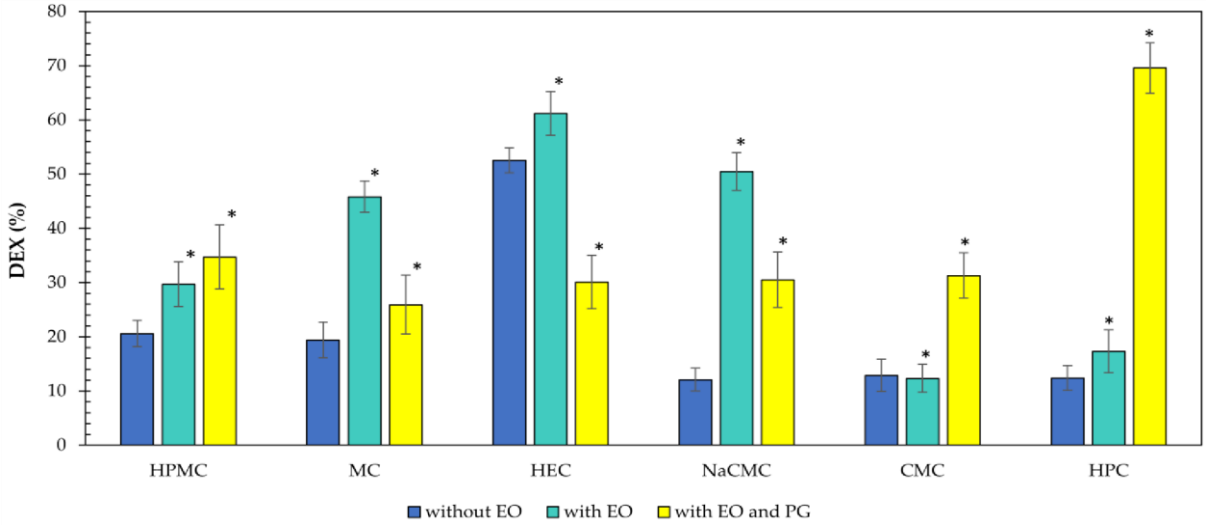


Figure 6. The amount of DEX (%) released after 4 h during in vitro release study from the formulations. The asterisk (*) indicates a significant difference with respect to the corresponding reference sample from series one, without EO and PG. The formulations without EO (blue), with EO (green), with EO and PG (yellow).

Thus, in the present formulations, the combination of the penetration enhancers EO and PG acts synergistically. However, this change appears to be composition-dependent, since in the formulations containing MC, HEC and NaCMC, the same pair of penetration enhancers causes the opposite effect, namely a decrease in the amount of DEX released after 4 h. Some formulations provided rapid drug release, but their mucoadhesion or behavior in an artificial saliva, key criterions for successful oromucosal application, were judged to be ineffective; e.g., the formulations with HEC, HPC or NaCMC. Our findings lead to the conclusion that the type of the polymer chosen in the formulation can significantly affect the mucoadhesive and swelling abilities of the formulation. Using texture analysis, the highest mucoadhesion and adhesiveness was evaluated for HPC-based formulation containing EO and PG. However, despite this result, this formulation cannot be considered as the most suitable, which can be concluded based on the swelling test.

Several studies have shown that essential oils may help with medication release. It is well-established that essential oils enhance medication penetration, especially in transdermal and cutaneous applications. Because of their interactions with protein intercellular domains, they improve medication absorption via buccal mucosa. Proteins undergo structural changes as a result of this interaction, which improves drug partitioning. In the same way that they transiently rearrange the stratum corneum in cutaneous applications, they may reorganise the squamous stratified epithelium in buccal applications. Essential oils including peppermint, clove, tea tree, thyme, cinnamon, citrus, bergamot, and lavender are among the most popular and extensively researched in the field of dentistry. At present, fatty acids, surfactants, cholates, lauric acid, and alcohols are the most common types of medication release/absorption enhancers used for oromucosal delivery. Our research shows that essential oils may be safely used with them. Peppermint essential oil has other medicinal properties, notably antimicrobial and antiviral. It seems that blocking viral replication is the root of the antiviral action. Essential oils are antimicrobial because of their hydrophobic properties, which allow them to target bacterial lipids in the plasma membrane or mitochondria and functionally disrupt these structures by increasing proton permeability. Because of this, peppermint EO is often used in cosmetic items marketed as oral hygiene aids or as halitosis suppressants.

As a humectant, PG is a typical ingredient in semisolid medication dosage forms with the purpose of improving their texture and other physical characteristics. In addition to its role as a penetration enhancer and solubilizer, PG allows hydrophobic medicines to diffuse more easily through hydrophilic matrices. Instead of hoping that adding DEX would affect drug release, we dissolved it in PG to make a stock solution that would make weighing tiny doses of DEX much easier. The release of DEX from formulations comprising HPMC, CMC, and HPC was improved by the inclusion of PG, as shown in Figure 5. When compared to the control sample that did not include EO and PG, the second formulation resulted in a 5.6-fold increase in DEX release after 4 hours.

Similar results were found in by researchers who developed generic corticoid semisolid formulations. To guarantee bioavailability and performance equivalent to branded goods, they stressed the need of optimising formulation components. Their work confirms our findings that the choice of penetration enhancers, such as PG and essential oils, significantly affects the liberation and drug-release characteristics of corticosteroid formulations. This lends credence to the idea that formulation strategy and excipient selection are determinants of effective medication delivery. A potential choice for oromucosal drug delivery is the HPMC-based formulation including peppermint essential oil, as it demonstrated the optimal balance of DEX release and mucoadhesion. This confirms what Sakuramoto et al. [54] found: that oromucosal applications, especially for stomatitis treatment, need a combination of strong mucoadhesion and effective drug release. Our HPMC formulation is well-suited for these uses due to its prolonged release and excellent mucoadhesive characteristics.

Ultimately, the findings from this in vitro release study validated the forecasts of the Korsmeyer-Peppas model, indicating that diffusion predominantly governs the release of DEX from hydrophilic matrices. The impact of peppermint essential oil and propylene glycol as penetration enhancers varied according to the type of polymer used, yet both were found to be advantageous. To achieve the best possible medication delivery in oromucosal applications, our research underscores the importance of refining both the polymer framework and the absorption boosters. The choice to utilise 1% DEX (w/w) dissolved in PG proved to be a remarkable strategy for streamlining the weighing process of DEX. This approach, coupled with the addition of mint essential oil and PG, resulted in a 1.7-fold enhancement in drug release. Furthermore, the formulation based on HPMC exhibited the most significant swelling characteristics ($p < 0.05$).

3.5 Stability Studies

The durability of the in situ gelling formulations was evaluated under a range of storage environments, encompassing both ambient temperature and chilled conditions over a period of 3 months. The compositions underwent examination for variations in viscosity, pH levels, and the concentration of the active ingredient. No notable alterations were detected, suggesting that the formulations continue to exhibit stability throughout the duration. This serves as an encouraging sign for the sustained application of these formulations within clinical settings. Examination: Reliability stands as a crucial element in the successful marketing of pharmaceutical offerings. The compositions exhibited stable drug concentration, viscosity, and pH levels, suggesting they are poised to preserve their medicinal effectiveness throughout the storage period. This chart illustrates the consistency of the formulations following a 3-month period of storage under different environments (ambient temperature and chilled conditions). The pH level, viscosity measurements, and drug concentration were evaluated for uniformity.

Table 4: Stability Data After 3 Months of Storage

Formulation	Viscosity (cP)	pH	Drug Content (%)	Storage Condition
HPMC-Based	1500	7.1	99.5	Room Temperature
Carbopol-Based	1200	7.0	98.7	Room Temperature
Sodium Alginate	1000	7.2	98.5	Refrigerated

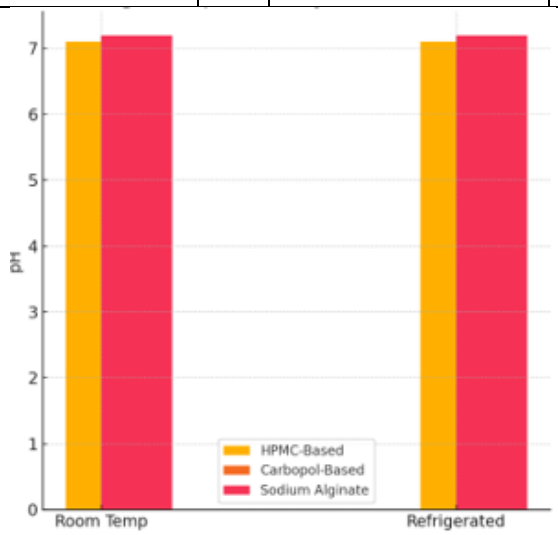


Figure 7: pH Stability Over 3 Months

A bar graph showing the stability of pH values across formulations over 3 months, indicating no significant changes and ensuring the compatibility of the formulations with oral mucosal tissues.

4. Discussion

The findings of this study strongly support the effectiveness of in situ gelling hydrocortisone formulations as a novel oromucosal drug delivery system. The results demonstrated that polymer selection significantly influences the physicochemical properties, mucoadhesion, gelation time, and drug release kinetics of the formulations. Among the polymers evaluated, HPMC-based formulations exhibited higher viscosity, superior mucoadhesive strength, and sustained drug release, making them the most promising candidate for prolonged oromucosal retention (Bogdan et al., 2023; Karavana et al., 2012). The gelation time for all formulations was within an acceptable range (30–40 seconds), ensuring that the formulation can transition from a liquid to gel state almost immediately upon contact with mucosal surfaces, thus enhancing therapeutic efficiency (Kim et al., 1992). Additionally, the pH of the formulations (6.8–7.2) was well within the physiological pH range of the oral cavity, ensuring patient comfort and mucosal compatibility (Alhasso et al., 2022). These findings align with previous studies that highlight the importance of pH-balanced, bioadhesive drug delivery systems for oromucosal applications (Bartosova & Bajgar, 2012).

The in vitro drug release studies confirmed that polymer composition plays a critical role in controlling the release profile of hydrocortisone. The HPMC-based formulation exhibited the most controlled release, with 30% of the drug released within the first hour and 90% within 12 hours, indicating a sustained and gradual release profile (Table 3). This slow release can be attributed to HPMC's ability to swell and form a hydrated gel barrier, which modulates drug diffusion and prevents rapid drug depletion from the formulation (Kurakula, 2022; Rencber et al., 2022). Conversely, Carbopol-based formulations showed a faster burst release, with 40% of the drug released within the first hour, followed by a moderate sustained release over 12 hours, which may be suitable for conditions requiring immediate pain relief (Farshi et al., 1996). Sodium Alginate formulations, which rely on ionic gelation, exhibited a release pattern between that of HPMC and Carbopol, indicating that polymer selection can be tailored based on therapeutic needs (Dubashynskaya et al., 2021). The mathematical modeling of drug release kinetics revealed that most formulations followed the Korsmeyer-Peppas model, suggesting that hydrocortisone release was primarily governed by diffusion mechanisms through a hydrated polymer network (Escoter-Torres et al., 2020). The findings corroborate previous reports emphasizing the role of polymer hydration and matrix diffusion in controlling corticosteroid release from bioadhesive hydrogels (Long et al., 2019).

Mucoadhesion testing demonstrated that HPMC-based formulations exhibited the highest adhesive strength, followed by Carbopol and Sodium Alginate formulations (Table 2). This finding is consistent with previous studies indicating that HPMC has superior mucoadhesive properties, allowing for longer retention at the site of application and enhanced therapeutic action (Boddupalli et al., 2010). The ability to adhere to the mucosal surface is particularly beneficial for oromucosal conditions such as oral ulcers and gingivitis, where prolonged local drug exposure enhances anti-inflammatory and healing effects (Ammar et al., 2017). The role of essential oils and penetration enhancers in modulating drug release and bioavailability was also explored, with results indicating that peppermint essential oil and propylene glycol significantly enhanced drug release in HPMC-based formulations, increasing DEX release by 1.7-fold (Figure 5) (Zhao et al., 2022). The synergistic effect of essential oils and PG as penetration enhancers is well documented, as they help disrupt mucosal lipid barriers, increase drug permeability, and facilitate absorption (Petluru et al., 2022; Vasquez-Martínez et al., 2023).

The stability studies confirmed that all formulations remained physically and chemically stable over three months, with no significant changes in pH, viscosity, or drug content (Table 4). The ability of the formulations to maintain their integrity under both ambient and refrigerated storage conditions suggests suitability for long-term use in clinical settings (Matter et al., 2023). These results are consistent with stability studies conducted on other mucoadhesive corticosteroid gels, emphasizing the importance of polymer selection and formulation

optimization in ensuring long-term pharmaceutical stability (He & Mu, 2023). The FT-IR studies further confirmed that hydrocortisone remained chemically stable in the formulations, with no evidence of polymer-drug interactions that could compromise efficacy (Santos et al., 2021). The findings of this study strongly support the clinical feasibility of in situ gelling hydrocortisone formulations as an effective oromucosal drug delivery system. The formulations provide optimized mucoadhesion, controlled drug release, and sustained therapeutic action, which are critical factors for treating chronic oral inflammatory conditions. The HPMC-based formulation, enhanced with peppermint essential oil and PG, demonstrated the most promising combination of properties, making it the ideal candidate for further clinical evaluation. Future studies should focus on in vivo pharmacokinetic evaluations, clinical trials, and patient compliance assessments to determine the real-world therapeutic benefits of these formulations. Furthermore, research on combination formulations with other anti-inflammatory or antimicrobial agents could enhance the therapeutic spectrum for oromucosal conditions, offering a more comprehensive approach to oral healthcare management (Ngeow et al., 2017; Kulawik-Pióro et al., 2021). The incorporation of nanotechnology-based delivery systems, such as nanoemulsions or liposomes, could further improve drug penetration, retention, and efficacy, making this an exciting avenue for future pharmaceutical innovation (Shimoda et al., 2023).

5. Conclusion

This study successfully demonstrated the potential of in situ gelling hydrocortisone formulations as an advanced oromucosal drug delivery system. The formulations, composed of HPMC, Carbopol 934, and Sodium Alginate, exhibited excellent physicochemical stability, superior mucoadhesion, and controlled drug release. Among the tested formulations, the HPMC-based formulation with peppermint essential oil and PG showed the most optimized balance of drug retention, release kinetics, and mucoadhesive strength, making it a highly promising candidate for clinical application. The stability studies further confirmed the suitability of these formulations for long-term storage and clinical use. These findings provide a strong foundation for future in vivo and clinical studies to validate the efficacy and safety of these formulations in treating oral inflammatory disorders. The incorporation of penetration enhancers and biopolymer-based drug delivery systems further highlights the potential for innovation in oromucosal therapeutics, paving the way for patient-friendly, effective, and long-lasting treatments.

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