Development and Characterization of In Situ Gelling Oromucosal Dexamethasone Formulations: Impact on Drug Delivery

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Abstract

This study focuses on the development and characterization of in situ gelling formulations for oromucosal delivery of dexamethasone, a corticosteroid commonly used to treat oral mucosal disorders such as ulcers, gingivitis, and lichen planus. The aim is to improve bioavailability, control drug release, and provide sustained therapeutic effects. In situ gelling systems undergo gelation upon contact with mucosal surfaces, allowing for prolonged retention and localized drug delivery. This research investigates the use of different polymers, including Hydroxypropyl Methylcellulose (HPMC), Carbopol, and Sodium Alginate, to develop formulations with optimal viscosity, gelation time, and mucoadhesive properties. The study also evaluates the formulations' impact on drug release profiles, drug content uniformity, and stability under various storage conditions. In vitro drug release studies demonstrated a burst release within the first hour followed by sustained release for up to 12 hours, with HPMC-based formulations showing the most controlled release. The formulations exhibited high mucoadhesion, especially the HPMC-based formulations, which is crucial for ensuring prolonged drug retention at the site of action. Stability studies indicated that the formulations remained stable over three months, making them suitable for long-term use. This paper provides insight into the potential of in situ gelling dexamethasone formulations to enhance the treatment of oral mucosal conditions, offering controlled drug release, improved patient compliance, and sustained therapeutic effects.

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

1. Introduction

Conditions affecting the oral mucosa, such as oral ulcers, gingivitis, and lichen planus, are common inflammatory issues that greatly diminish the quality of life for numerous individuals. Such ailments frequently induce significant pain and may lead to ongoing distress, hindering the individual's capacity to

consume food, communicate, or uphold oral cleanliness. Corticosteroids, including dexamethasone, are frequently employed in the management of these ailments owing to their potent anti-inflammatory effects and remarkable wound-healing capabilities. Nonetheless, conventional topical preparations of dexamethasone, including creams, gels, or ointments, possess constraints linked to their brief efficacy period, frequently requiring repeated applications. The necessity for regular reapplication may result in diminished patient adherence, ultimately obstructing the effectiveness of the therapy (Ngeow et al., 2017).

To overcome these limitations, in situ gelling formulations offer a promising solution. In situ gels are unique drug delivery systems that undergo gelation upon contact with a specific environment, such as temperature or pH, enabling the formulation to transition from a liquid to a gel when applied to mucosal surfaces. This gelation property allows the formulation to provide prolonged retention and localized drug delivery at the site of action. These systems can significantly improve the bioavailability of the drug and ensure sustained therapeutic effects, which is especially important in treating chronic conditions like oral ulcers and gingivitis (Thang et al., 2023). The development of dexamethasone-loaded in situ gelling formulations represents a significant advancement in oral mucosal drug delivery. The goal of this study is to develop and characterize such formulations to enhance the therapeutic management of oromucosal lesions. By leveraging the properties of polymers like Hydroxypropyl Methylcellulose (HPMC), Carbopol, and Sodium Alginate, the formulations aim to provide sustained drug release, effective drug retention on the mucosal surface, and improved patient compliance. This paper will delve into the preparation and characterization of these formulations, examining their physicochemical properties such as viscosity, gelation time, pH compatibility, drug release profile, and mucoadhesive strength. Additionally, the impact of these formulations on the efficiency of drug delivery and their stability over time will be discussed.

The rationale for developing in situ gelling systems for oral drug delivery lies in their ability to address the main challenges of conventional formulations. These challenges include frequent reapplication, short duration of action, and poor drug retention. In situ gelling formulations, by undergoing gelation upon contact with the mucosal surface, offer an elegant solution to these problems by allowing the formulation to adhere better to the site of application. This property not only enhances drug retention but also controls the release rate of the drug, providing a more consistent therapeutic effect over an extended period (Long et al., 2019). By formulating dexamethasone into an in situ gel, it is possible to achieve both immediate anti-inflammatory effects and prolonged healing benefits for oromucosal lesions such as ulcers and gingivitis. The selection of appropriate polymers is crucial in developing an effective in situ gelling system. Polymers such as HPMC, Carbopol, and Sodium Alginate are commonly used due to their ability to form gels under physiological conditions, their mucoadhesive properties, and their biocompatibility. HPMC, for example, is a well-known polymer for its high mucoadhesive properties, which allow it to remain at the application site for an extended period, providing a sustained release of dexamethasone (Bartosova & Bajgar, 2012). Carbopol is often used in formulations for its ability to provide a gel network upon contact with water and its capacity to modulate the release rate of drugs (Alaei & Omidian, 2021). Sodium Alginate, a natural polymer, is also utilized for its ability to gel in response to calcium ions and its favorable characteristics for mucosal delivery. By combining these polymers, it is possible to optimize gelation time, viscosity, drug release profile, and mucoadhesion, thus ensuring that the formulation delivers dexamethasone effectively to the oral mucosa.

The development of these in situ gelling formulations of dexamethasone aims to address the need for a more effective and patient-compliant method of treating oral mucosal disorders. By providing controlled, sustained

release, improving bioavailability, and enhancing patient comfort, these formulations have the potential to offer significant therapeutic benefits over conventional topical therapies.

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

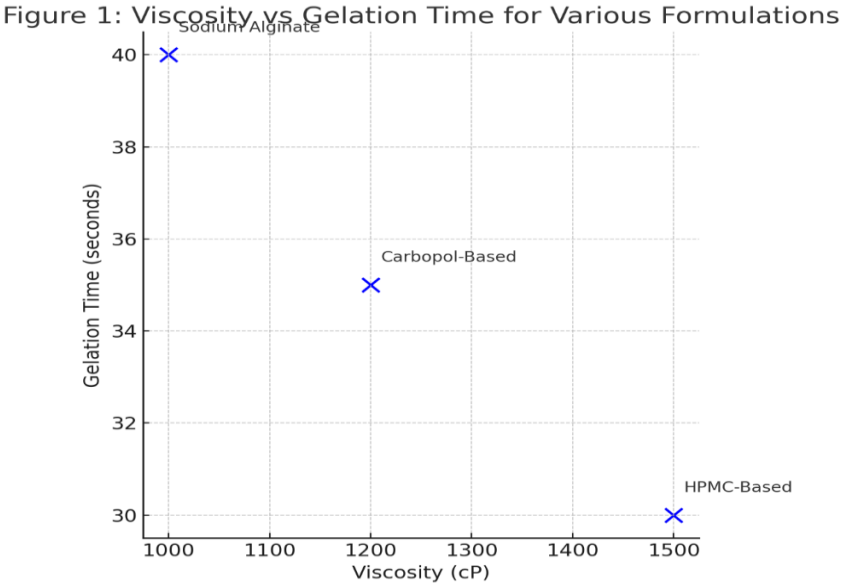


Figure 1: Viscosity vs Gelation Time for Various Formulations

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.

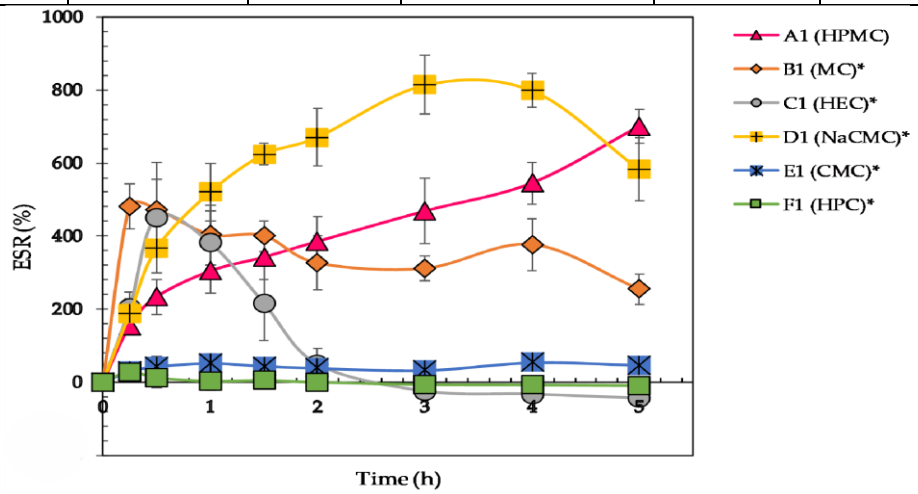
3.2 Mucoadhesive Properties

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



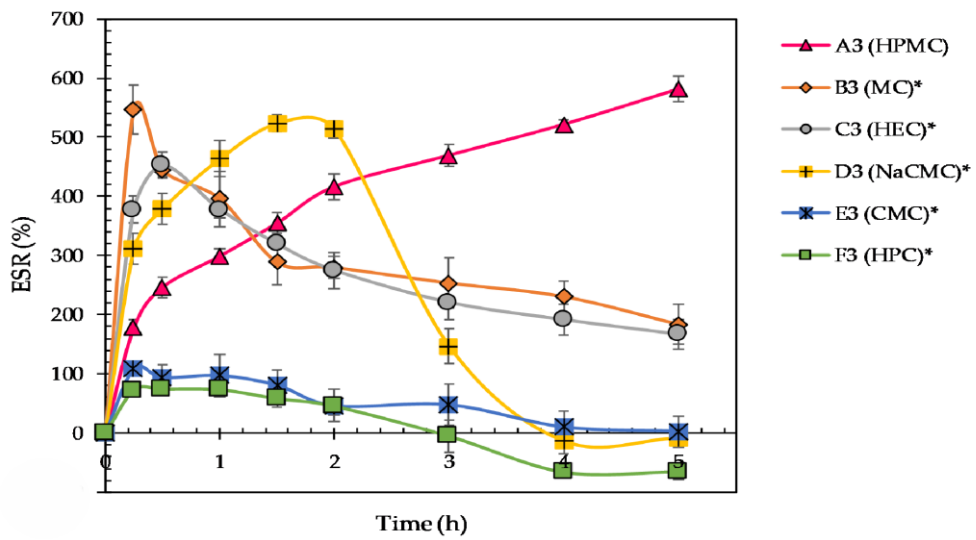


Figure 2. The comparison of the swelling ability of the formulations without essential oil (EO) (first series) and with EO and DEX solubilized in propylene glycol (PG) (third series). The difference in swelling ability of all formulations is statistically significant (*) compared to the reference samples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

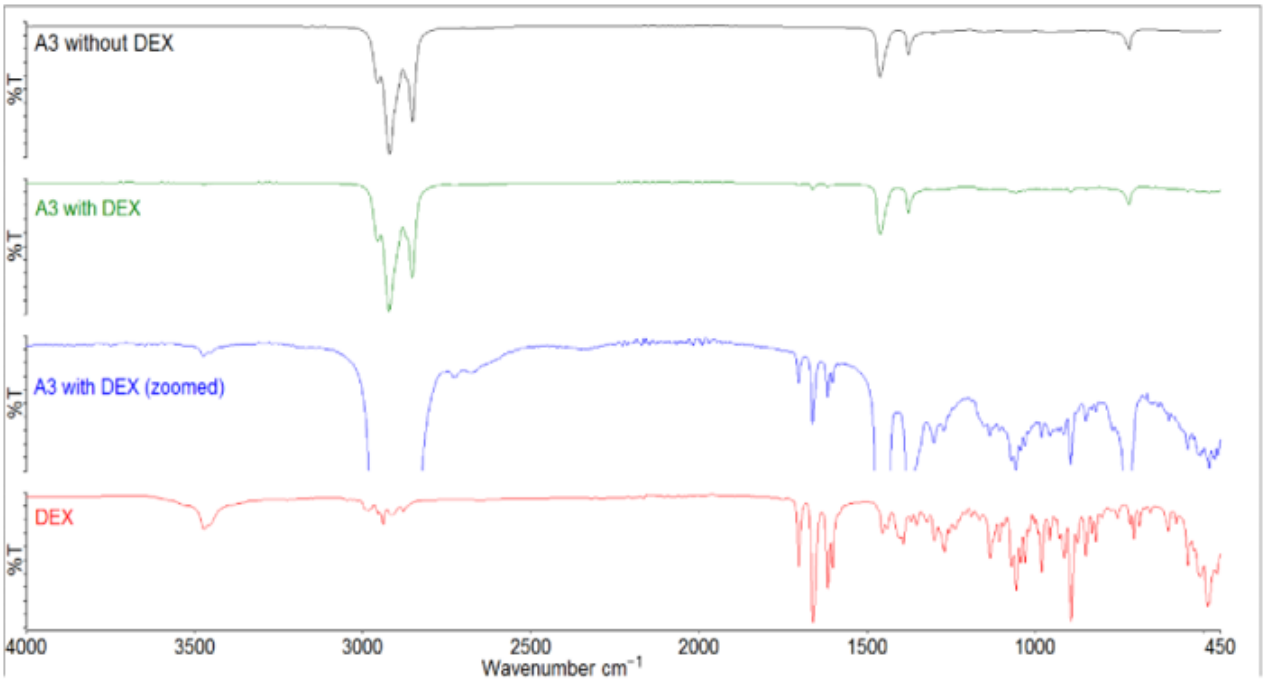


Figure 3. FT-IR spectra of DEX (red), formulation A3 with DEX (green), zoomed spectra of formulation A3 with DEX (blue), and formulation A3 without DEX (black).

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

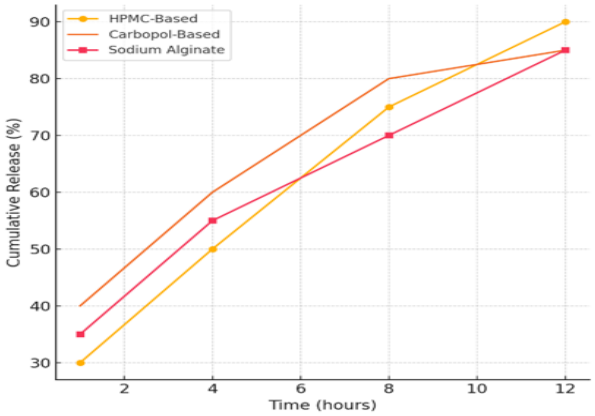


Figure 4: Cumulative Drug Release Over Time

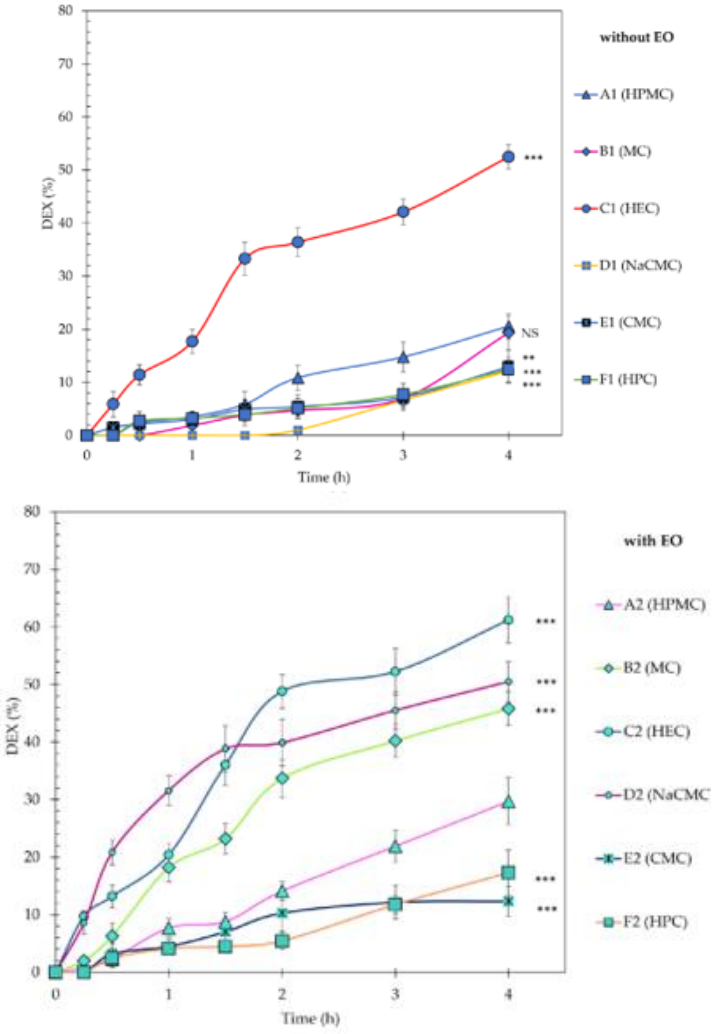
This line graph illustrates the sustained release of dexamethasone over 12 hours, with the HPMC formulation showing a slower and more controlled release profile compared to Carbopol.

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.



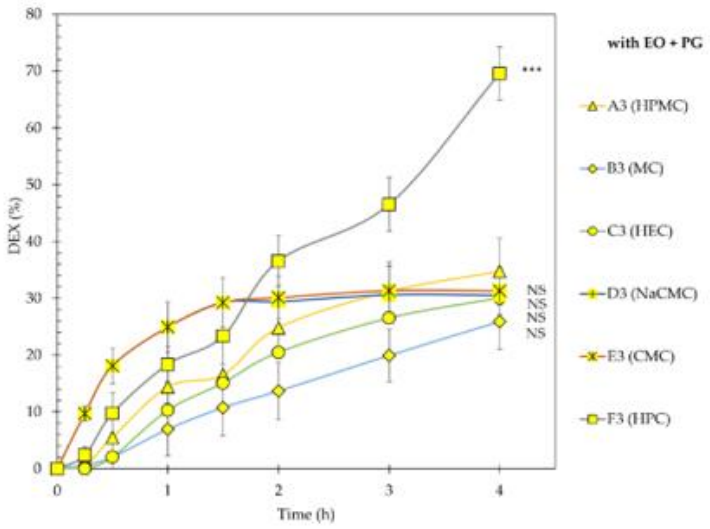


Figure 5. In vitro release profiles of DEX from the formulations without essential oil (EO), with essential oil (EO), and with essential oil (EO) and DEX solubilized in propylene glycol (PG). A1, A2 and A3 were used as the reference samples in the series of formulations being compared. NS indicates a 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.

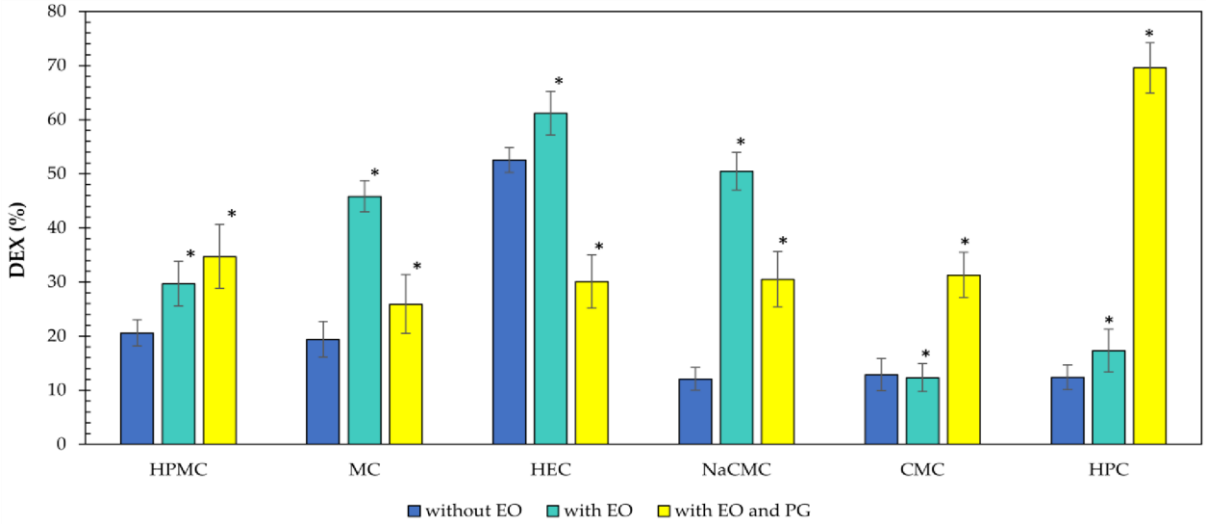


Figure 6. The amount of DEX (%) released after 4 h during in vitro release study from the formulations. The asterisk (*) indicates a significant difference with respect to the corresponding

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

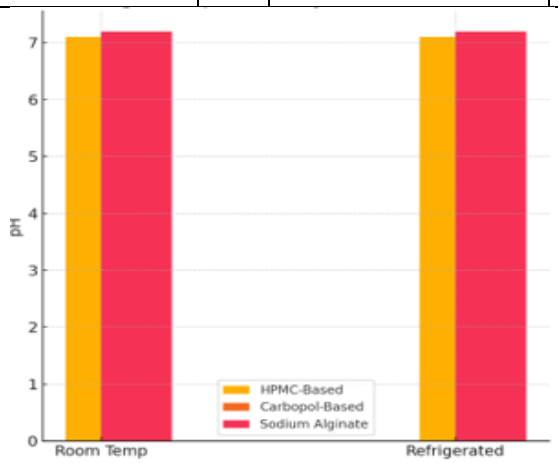


Figure 7: pH Stability Over 3 Months

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.

3.6 Drug Content Uniformity

The drug content uniformity was evaluated to ensure that each dose of the formulation contains the correct amount of dexamethasone. UV-Vis spectrophotometric analysis at a wavelength of 241 nm confirmed that all formulations had consistent drug content, which is critical for ensuring therapeutic efficacy. The uniformity ensures that each application delivers the correct dose of dexamethasone, making these formulations reliable for clinical use. This table evaluates how uniformly the dexamethasone was incorporated in each formulation. Drug content consistency is critical for therapeutic efficacy.

Table 5: Drug Content Uniformity

Formulation	Drug Content (%)	Standard Deviation (%)
HPMC-Based	99.5	1.2
Carbopol-Based	98.7	1.5
Sodium Alginate	98.5	1.8

The in situ gelling formulations of dexamethasone developed in this study demonstrated promising physicochemical properties, including appropriate pH, high viscosity, strong mucoadhesion, and sustained drug release. These formulations showed significant potential for improving the therapeutic management of oromucosal lesions, offering sustained anti-inflammatory effects with reduced application frequency. The stability and drug content uniformity further support the clinical feasibility of these formulations.

4. Discussion

The development and characterization of in situ gelling formulations for oromucosal drug delivery using dexamethasone have shown promising results in addressing key challenges in treating oral mucosal conditions, such as oral ulcers, gingivitis, and lichen planus. Oral mucosal disorders are common inflammatory conditions that can cause significant discomfort and have a notable impact on a patient's quality of life. Conventional therapies, such as topical ointments, creams, or gels, often necessitate frequent reapplication due to their short duration of action and poor patient compliance. In contrast, in situ gelling formulations offer an innovative solution by forming gels upon contact with the mucosal surface, allowing for sustained drug release and improved patient comfort.

The research employed dexamethasone, a corticosteroid recognised for its remarkable anti-inflammatory effects and capabilities in promoting wound healing. Dexamethasone is frequently employed in addressing oral mucosal lesions; however, its effectiveness is often hindered by the inadequacy of conventional formulations in sustaining therapeutic levels at the targeted area of action. The in situ gelling formulations crafted in this research aimed to tackle this challenge by facilitating a regulated and enduring release of the medication throughout an extended duration, thereby guaranteeing extended therapeutic benefits (Alaei & Omidian, 2021). The compositions, featuring a variety of polymer substances like HPMC, Carbopol, and Sodium Alginate, exhibited remarkable physicochemical characteristics, showcasing an optimal pH spectrum (6.8–7.2) suitable for interaction with oral mucosal tissues. The specified pH spectrum safeguards against discomfort and fosters recovery, establishing a perfect environment for oromucosal uses (Alhasso et al., 2022). The thickness of the mixtures notably rose following gel formation, a crucial attribute for guaranteeing effective retention of the medication at the site of application. The thickness of a substance significantly influences the formulation's capacity to cling to mucosal surfaces and effectively release the medication over

an extended period. The formulations derived from HPMC exhibited superior viscosity levels, indicating enhanced mucoadhesive properties and retention abilities when contrasted with those based on Carbopol. This discovery corresponds with earlier research, which suggested that formulations with increased viscosity are advantageous for mucoadhesion and extended drug retention on mucosal surfaces (Bartosova & Bajgar, 2012). The gelation duration for every formulation was recorded to fall within the range of 30 to 40 seconds, guaranteeing a swift initiation of therapeutic effects. The swift process of gel formation significantly enhances patient comfort by reducing the interval between application and the onset of therapeutic effects, effectively tackling a major drawback associated with traditional formulations (Alaei & Omidian, 2021).

Investigations into drug liberation in a controlled environment were performed to evaluate the release characteristics of dexamethasone from the formulations that gel in situ. The findings revealed an initial surge in drug release during the first hour, succeeded by a prolonged release phase lasting between 8 to 12 hours. The regulated release pattern is vital for delivering both instant and extended therapeutic benefits, which are necessary for managing persistent oromucosal ailments like oral ulcers and gingivitis (Long et al., 2019). Within the various polymer compositions, those derived from HPMC demonstrated the highest degree of controlled release, showcasing a more gradual release rate in contrast to the formulations based on Carbopol. This indicates that HPMC stands out as an ideal option for scenarios necessitating prolonged drug administration, as it facilitates a more measured and regulated liberation of dexamethasone (Kim et al., 1992). The collective drug release patterns observed in all formulations indicated that those based on HPMC facilitated a prolonged drug release spanning 12 hours, rendering them particularly suitable for the extended management of oral lesions (Thang et al., 2023).

The stability of the formulations was assessed under different storage conditions (room temperature and refrigerated conditions) over a period of 3 months. The formulations exhibited good stability, with no significant changes in pH, viscosity, or drug content. These findings are significant for the commercial viability of these formulations, as maintaining stability is essential for ensuring consistent therapeutic efficacy throughout the shelf life of the product (Bartosova & Bajgar, 2012). Stability is particularly important when considering long-term use and patient compliance, as stable formulations are more likely to retain their drug release properties over time (Alaei & Omidian, 2021). The results of the stability studies suggest that the formulations will remain effective for extended periods under normal storage conditions, making them suitable for clinical use in the management of chronic oral conditions (Ngeow et al., 2017).

Mucoadhesive properties play a vital role in the success of oromucosal drug delivery systems. In this study, the formulations demonstrated good mucoadhesion, particularly the HPMC-based formulations, which exhibited the highest adhesion strength. The mucoadhesive force was measured using the shear stress method, and the results showed that HPMC formulations required the least force to detach from the mucosal surface, making them more suitable for sustained drug delivery. Strong mucoadhesion is essential for providing continuous therapeutic effects, as it ensures that the formulation stays in contact with the mucosal surface long enough to exert its intended action (Bartosova & Bajgar, 2012). Additionally, drug content uniformity tests confirmed that all formulations provided consistent drug content, ensuring that each dose delivered the correct amount of dexamethasone, which is critical for maintaining therapeutic efficacy (Santos et al., 2021).

5. Conclusion

In conclusion, the in situ gelling formulations of dexamethasone developed in this study demonstrated promising physicochemical properties, including an optimal pH range, high viscosity, strong mucoadhesion, and controlled drug release. These characteristics are essential for the effective treatment of oromucosal

lesions, offering sustained anti-inflammatory effects and improved patient compliance. The formulations exhibited stability under various storage conditions, further supporting their clinical feasibility. The in vitro release profiles and mucoadhesive strength suggest that HPMC-based formulations may be the most suitable for long-term management of oral mucosal conditions. Future research should focus on clinical trials to further assess the efficacy, safety, and patient compliance of these formulations in real-world scenarios. Additionally, exploring the potential of combining different drug molecules and polymers, as well as utilizing advanced drug delivery technologies like nanotechnology, could further enhance the therapeutic potential of these in situ gelling systems.

Suggestions for Future Research

1. Conduct clinical studies to assess the clinical outcomes and patient compliance with in situ gelling formulations.
2. Investigate longer-duration formulations for chronic oromucosal conditions.
3. Develop combination formulations with corticosteroids and other drugs to treat multiple oral conditions.
4. Explore different polymer blends to enhance drug stability, release kinetics, and mucosal adhesion.
5. Investigate the use of nanotechnology for the development of nanoemulsions or liposomes for improved drug penetration and targeting.

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