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RESEARCH ARTICLE

Hydrocortisone-Loaded Polyvinyl Alcohol-Based Films for Buccal Delivery in the Treatment of Oral Aphthous Ulcers

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Hydrocortisone-Loaded Polyvinyl Alcohol-Based Films for Buccal Delivery in the Treatment of Oral Aphthous Ulcers

SUMMARY

Oral aphthous ulcers are recurrent, painful lesions of the oral mucosa that adversely affect patients' quality of life. Buccal films are crucial to enhance drug retention, achieve sustained therapeutic effect, and ultimately improve clinical outcomes in patients suffering from oral aphthous ulcers. The aim of this study was to develop and evaluate polyvinyl alcohol (PVA)-based buccal film formulations loaded with hydrocortisone (HC) for the local treatment of oral aphthous ulcers. Buccal films were prepared using the solvent casting method. The film formulations were characterized in terms of film thickness, moisture content, and contact angle. Mechanical properties were evaluated by determining tensile strength and elongation at break using a texture analyzer. Thermal behavior was assessed via differential scanning calorimetry (DSC), while chemical interactions were examined using Fourier-transform infrared spectroscopy (FTIR). Mucoadhesive performance was tested ex vivo using cow buccal mucosa, and in vitro drug release studies were conducted using Franz diffusion cells with phosphate buffer (pH 6.8) as the receptor medium. The PVA-based formulation exhibited suitable mechanical strength and high elongation at break. Ex vivo mucoadhesion studies showed that the films demonstrated adequate mucoadhesive properties in cow buccal tissue. In vitro release studies demonstrated a sustained release profile of HC over 8 hours. The findings indicate that PVA-based buccal films are promising candidates for effective localized therapy of oral aphthous ulcers and enhanced patient compliance.

Keywords: *Buccal film, Hydrocortisone, Oral aphthous ulcers, Solvent casting.*

Oral Aftöz Ülserlerinin Tedavisinde Bukkal Uygulama İçin Hidrokortizon Yüklü Polivinil Alkol Bazlı Filmler

ÖZ

Oral aftöz ülserler, ağız mukozasında tekrarlayan ve ağrılı lezyonlar olup hastaların yaşam kalitesini olumsuz etkiler. Bukkal filmler, ilacın bölgede kalış süresini artırmak, sürekli bir terapötik etki sağlamak ve nihayetinde oral aftöz ülser hastalarında klinik sonuçları iyileştirmek açısından önemlidir. Bu çalışmanın amacı, oral aftöz ülserlerin lokal tedavisi için hidrokortizon (HC) yüklü polivinil alkol (PVA) temelli bukkal film formülasyonlarının geliştirilmesi ve değerlendirilmesidir. Bukkal filmler, çözücü döküm yöntemi kullanılarak hazırlanmıştır. Film formülasyonları; film kalınlığı, nem içeriği ve temas açısı açısından karakterize edilmiştir. Mekanik özellikler, bir doku analiz cihazı kullanılarak çekme dayanımı ve kopma uzaması belirlenerek değerlendirilmiştir. Termal özellikleri diferansiyel taramalı kalorimetri (DSC) ile, kimyasal etkileşimler ise Fourier dönüşümlü kızılötesi spektroskopi (FTIR) ile incelenmiştir. Mukoadezif performans, inek bukkal mukozası kullanılarak ex vivo olarak test edilmiş; in vitro ilaç salım çalışmaları ise fosfat tamponu (pH 6,8) içeren Franz difüzyon hücrelerinde yürütülmüştür. PVA temelli formülasyon, uygun mekanik dayanım ve yüksek kopma uzaması göstermiştir. Ex vivo mukoadezyon çalışmaları, filmlerin inek bukkal dokusunda yeterli mukoadezif özellik sergilediğini ortaya koymuştur. In vitro salım çalışmaları, HC'nin 8 saat boyunca sürdürülebilir salım profilini göstermiştir. Elde edilen bulgular, PVA temelli bukkal filmlerin oral aftöz ülserlerin etkili lokal tedavisi ve hasta uyuncunun artırılması için umut verici adaylar olduğunu göstermektedir.

Anahtar Kelimeler: *Bukkal film, Hidrokortizon, Oral aftöz ülser, Çözücü döküm metot.*

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INTRODUCTION

Buccal drug delivery refers to the administration of medication to the buccal mucosa on the inner lining of the cheek (Shipp, Liu, Kerai-Varsani, & Okwuosa, 2022). The oral cavity is a preferred site for drug delivery because of its simplicity, safety, high patient compliance, improved bioavailability, and avoidance of first-pass metabolism (Dalei & Das, 2022). Oral aphthous ulcers are painful lesions associated with numerous disorders that develop in the oral cavity and are known to cause severe pain and difficulty in chewing and speaking, which has a significant impact on the quality of life of patients (Noor, Menzel, & Gasmi, 2021).

The primary goals in the treatment of oral aphthous ulcers are to alleviate symptoms, minimize the number and size of ulcers, and prolong the intervals between recurrences (Tarakji, Gazal, Al-Maweri, Azzeghaiby, & Alaizari, 2015). Topical treatment is the first-line approach and includes agents with antiseptic, anti-inflammatory, antibiotic, and steroid properties. Systemic treatment is initiated when these measures are insufficient due to the severity of the lesions or unidentified underlying causes (Belenguer-Guallar, Jiménez-Soriano, & Claramunt-Lozano, 2014). The use of topical corticosteroids in the treatment of oral aphthous aims to limit the inflammatory process. Corticosteroids may act on T lymphocytes or alter the effector cell response to the causes of immunopathogenesis (Barrons, 2001). Hydrocortisone is used to treat aphthous ulcers and to reduce the inflammatory cycle associated with the development of aphthae (Sanjana, Ahmed, & Bh, 2021).

In buccal drug delivery, mucoadhesive tablets, films/patches, gels/lozenges, and nano/micro carrier systems (such as liposomes, solid lipid nanoparticles, and niosomes) are utilized to enhance drug retention on the mucosal surface, enable controlled release, and improve bioavailability (Shirvan, Bashari, & Hemmatinejad, 2019). Buccal films have the advantages of being flexible, easily transportable, having a rapid onset of action, not requiring chewing and swallowing, bypassing first-pass metabolism, and providing protection against degradation by the drug, enzymes in the gastrointestinal tract, and acidic environment. They are also suitable for pediatric and geriatric patients, as well as for individuals with intellectual disabilities, physical impairments, or difficulty swallowing (Haneef, Sultana & Shahidulla, 2024). The film casting method is one of the most widely used methods for buccal film production, with the advantages of being easy to prepare, inexpensive, and easily adopted on a laboratory scale (Hanif, Zaman, & Chaurasiya, 2015). Polyvinyl alcohol (PVA) is a water-soluble, biocompatible, and biodegradable polymer with high film formation and plasticity (Aygün, 2025; Saar & Demiröz, 2023). Polyvinylpyrrolidone (PVP) is a water-soluble and biodegradable polymer. This study aims to develop hydrocortisone (HC)-loaded film formulations for the local treatment of oral ulcers. These films were designed for buccal application and characterized to ensure enhanced drug retention, controlled release, and improved patient compliance through the use of PVA and PVP polymers with different plasticizers.

MATERIALS AND METHODS

Materials

Hydrocortisone was kindly gifted by Gen İlaç, Türkiye. Polyviol 26/140 (80,000 Da, Wacker Chemie), PVP (M.W. 40,000, BASF, Germany), glycerine, Polyethylene glycol (PEG), and propylene glycol (PG) were used for the preparation of different formulations. NaCl, KH_2PO_4, $NaHPO_4$, HCl, distilled water and ethanol were used for simulated saliva fluid (pH 6.8). All chemicals were of analytical grade.

Preparation of buccal films

The buccal films were prepared using the solvent casting method. PVA and PVP were employed as film-forming polymers, while glycerine, PEG, and PG were used as plasticizers. PVA was dissolved in hot water at 90 °C under stirring at 500 rpm. Once the PVA was

completely dissolved, ethanol and PVP were added, and the mixture was stirred until a homogeneous solution was obtained. Subsequently, the plasticizer was incorporated into the solution and stirred to ensure uniform distribution. Entrapped air bubbles were removed by sonication. The formulations were then poured into Petri dishes and dried in an oven at 40 °C. The compositions and codes of the formulations are presented in Table 1.

Table 1. Content and codes of buccal film formulations

Formulation Code	HC (%w/v)	PVA (%w/v)	PVP (%w/v)	PEG (%w/v)	Glycerine (%w/v)	PG (%w/v)
F1	-	10	-	3		
F2	-	10	-		3	
F3	-	10	-			3
F4	-	7.5	2.5			3
F5	-	5	5			3
F6	0.2	10	-			3

Characterization studies of buccal films

Thermal analysis of buccal films

The thermal properties of HC, PVA, PVP, and the film formulations were evaluated using differential scanning calorimetry (DSC) (Shimadzu, DSC-60, Japan). Approximately 2 mg of each sample was weighed and pressed into aluminum pans. DSC analyses were conducted with heating rate of 10 °C/min under a nitrogen atmosphere up to 300 °C.

Fourier transform infrared (FT-IR) spectroscopy studies

The chemical interactions among HC, PVA, PVP, and plasticizers, as well as potential structural changes were investigated using Fourier Transform Infrared Spectroscopy (FTIR) (Perkin Elmer, Spectrum 400, USA). Spectra were recorded over the range of 600 - 4400 cm^{-1} at room temperature with an ATR probe.

Weight and thickness of buccal films

The thickness of the films was measured at different points using a digital micrometer (Mitutoyo Digital Micrometer, Japan), and the mean values were calculated. For weight determination, film specimens of 1 × 1 cm^2 were cut and weighed on a digital scale. The average values were reported. All experiments were performed in triplicate on films, and results are reported as mean ± standard deviation (SD).

Contact angle measurements

The wettability of the films was evaluated by measuring the contact angle with distilled water. An optical tensiometer (Attension, Theta Lite, Finland) equipped with a convex sample holder was used for the measurements. The shape of the droplet and the contact angle were determined using the Young–Laplace method via the instrument software (Gajewski, 2017). The experiment was conducted in three replicates (n = 3).

Mechanical properties of buccal films

The mechanical characterization of the buccal films was determined using a texture analyzer (TA. XTPlus Texture Analyzer, Stable Micro Systems, UK). Tensile strength and elongation at break were measured with a tensile grip apparatus. Film samples (3 × 1 cm) were mounted between the miniature tensile grips, and stress–strain curves were recorded. Rectangular strips were used for tensile testing to match the apparatus. Each experiment was performed in triplicate for all film formulations.

***Ex vivo* mucoadhesion studies of buccal films**

The mucoadhesive properties of the buccal films were evaluated using cow buccal mucosa and TA-

XT Plus Texture Analyzer (Stable Micro Systems, UK). The films were attached to the upper probe with double-sided adhesive tape, while the buccal mucosa was fixed on the lower platform. The Study was carried out at a speed of 1 mm/s, 60 seconds contact time of the probe, and probe force of 0.2 N (Tuğcu-Demiröz, Acartürk, & Erdoğan, 2013; Tuğcu-Demiröz, Acartürk, & Özkul, 2015). The work of mucoadhesion (W, mJ/cm^2) was calculated from the area under the force–distance curve (AUC) generated during the detachment of the mucoadhesion test. In this curve, the x-axis represents the probe displacement (distance, mm) and the y-axis represents the detachment force (mN). The AUC corresponds to the total energy required to separate the film from the mucosal surface. The work of mucoadhesion values were calculated with the formula (mJ/cm^2) =AUC/(πr^2) (Cevher, Sensoy, Taha, & Araman, 2008). *Ex vivo* mucoadhesion studies were conducted in triplicate (n = 3), and the results are expressed as mean ± SD.

In vitro drug release of buccal films

In vitro release of hydrocortisone (HC) from the buccal films was evaluated using Franz diffusion cells equipped with a dialysis membrane (12 kDa, Sigma®, USA). The films were placed in the donor compartment, while the receptor phase was filled with pH 6.8 phosphate buffer. Samples were taken from the receptor phase at certain time intervals (0.25, 0.5, 1, 1.5, 2, 3, and 4 h) and an equal volume of fresh buffer was immediately added to maintain sink conditions. Ultraviolet (UV) spectrometer (Cary 60 UVvis, Agilent Technologies, US) was used to determine the amount of HC at 248 nm. The analytical method was validated according to ICH guidelines in terms of linearity, accuracy, precision, limit of detection (LOD), and limit of quantification (LOQ). Release studies were conducted on three films (n = 3).

Statistical analysis

GraphPad Prism version 7.0 (GraphPad Software Inc., San Diego, CA, USA) was used for all statistical analyses. Comparisons across ≥3 formulations, one-way ANOVA with Tukey's post hoc test were used when parametric assumptions were met. Two-group comparisons employed Student's t-test or Mann–Whitney U where appropriate. The significance threshold was $\alpha = 0.05$.

RESULTS AND DISCUSSION

Thermal properties of buccal film formulation

Thermal analysis provides valuable information about the physical state of the drug within the formulations, polymer compatibility, and potential interactions in the film matrix. The DSC thermograms of HC, the polymers, and the film formulations are presented in Figure 1. The DSC analysis revealed an endothermic peak at 227.2 °C corresponding to the melting point of HC. Ahmed and Adinarayana reported a sharp endothermic peak for pure HC at 220.26 °C, which is consistent with our findings (Ahmed & Adinarayana, 2019). Compared with pure hydrocortisone, the melting point in the film formulation thermograms appeared to be reduced, and the presence of a broader endothermic peak indicated the amorphous nature of hydrocortisone. The DSC curve of PVA showed a peak around 195 °C, corresponding to its melting point. Literature values report a melting peak of approximately 202.7 °C for pure PVA; thus, the observed melting peak at 195 °C in this study is slightly lower but still consistent with reported literature values. Propylene glycol exhibited thermal events at lower temperatures due to its low molecular weight, hygroscopic nature, and partial volatility under heating. In the thermograms of the F3 and F6 films, the sharp melting endotherm of hydrocortisone was either shifted or significantly reduced in intensity. The absence of a distinct HC peak in F6 also supports the formation of an amorphous state. No thermal degradation or chemical incompatibility observed in the film formulation. These findings demonstrate that the selected polymer–plasticizer combination successfully incorporated hydrocortisone in a stable, amorphous form, which is favorable for uniform drug release from the buccal film.

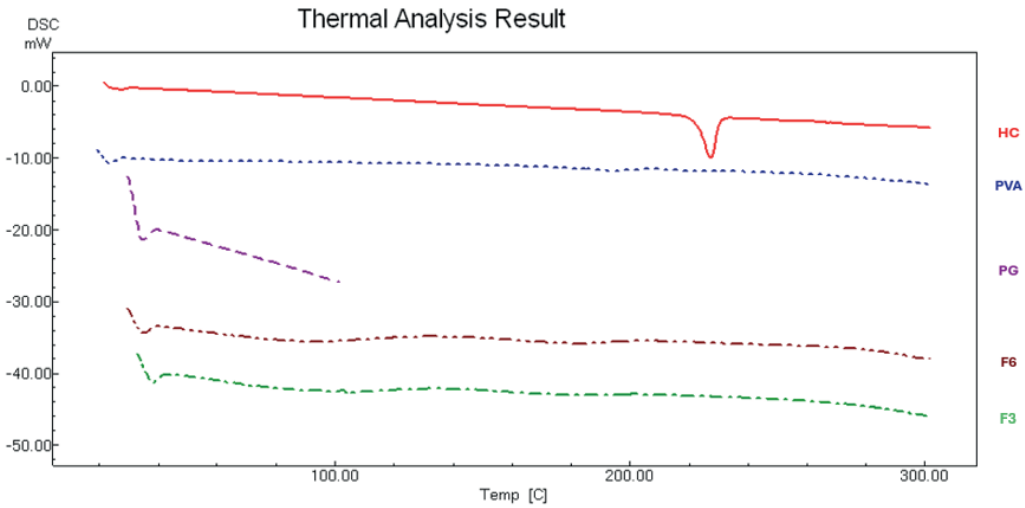

Figure 1. DSC thermograms of HC, PVA, PG, F3, and F6 formulation.

FTIR analyses

The FTIR spectrum of hydrocortisone exhibited characteristic absorptions at approximately 3410 cm^{-1} (O–H stretching), 2936 cm^{-1} (aliphatic C–H stretching), 1706 cm^{-1} (C=O carbonyl stretching), 1630–1641 cm^{-1} (C=C conjugated bond stretching), 1453 cm^{-1} (–CH_2 bending), and 1046 cm^{-1} (C–O stretching), which are consistent with previously reported values in the literature (Ahmed & Adinarayana, 2019; Altamimi et al., 2019). Characteristic peaks of PVA, F1 anf F6 formulations were identified in the FT-IR spectra at approximately 3316 cm^{-1} (O–H stretching due to intra- and intermolecular hydrogen bonding), 2901 cm^{-1} (asymmetric CH_2 stretching), 1432–1420 cm^{-1} (CH_2 symmetric bending), and 1377 cm^{-1} (CH–OH bending vibration) which are consistent with the literature (Reguieg, Ricci, Bouyacoub, Belbachir & Bertoldo, 2020; Saar & Demiröz, 2023). These results confirm that the film fabrication process did not alter the chemical integrity of PVA. The FTIR spectrum of PG showed a broad O–H stretching band around 3315 cm^{-1}, C–H stretching bands at 2970 cm^{-1}, and a C–O stretching peak at 1076 cm^{-1} (Ledniowska et al., 2022). The FTIR analyses confirmed the chemical compatibility and integrity of all components within the buccal film formulations (Figure 2). The characteristic peaks of hydrocortisone, PVA, and propylene glycol were clearly identified without the appearance of new peaks or significant peak shifts, indicating the absence of chemical interactions or degradation during the solvent casting process.

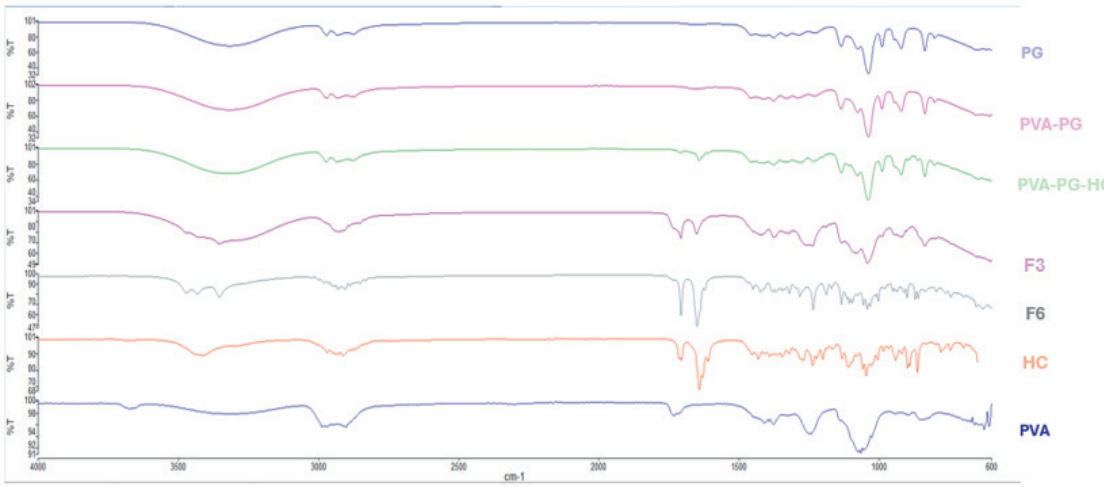

Figure 2. FTIR spectrum of HC, PVA, PG, PVA: PG, HC: PVA: PG, F3, and F6 formulation.

Weight and thickness of buccal film formulation

The uniformity in weight and thickness across different film samples indicates homogeneity of the production process, which is essential for dose accuracy and consistent drug release in buccal film formulations. In terms of weight, the lowest value was recorded as F2, and the highest as F6. In terms of thickness, the thinnest film was determined as F5, and the thickest as F6. As seen in Table 2, although there are certain differences between the weight and thickness values of all formulations, the low standard deviations indicate that the production process is homogeneous and repeatable. The low variability within each formulation batch confirms the homogeneity of the solvent casting method, supporting its suitability for producing reproducible buccal film dosage forms. The F6 film contains both the hydrocortisone and propylene glycol, which together increase total solids and solution viscosity relative to placebo films. PG is less volatile and more hygroscopic than PEG, and also reduces drying shrinkage. These factors plausibly lead to the slightly higher weight-per-area and thickness recorded for F6.

Table 2. Weight variation and thickness measurements of buccal film formulations (mean ± SD, n=3).

Formulation Code	Variation in mass (g)	Thickness (µm)
F1	0.0422 ± 0.0070	424.9640 ± 4.0825
F2	0.0322 ± 0.0013	282.3333 ± 5.4365
F3	0.0508 ± 0.0023	433.6667 ± 6.3421
F4	0.0466 ± 0.0031	376.3333 ± 2.8674
F5	0.0500 ± 0.0033	244.6667 ± 2.4944
F6	0.0626 ± 0.0052	463.3333 ± 5.3125

Mechanical properties of buccal film formulation

Buccal films should have sufficient tensile strength and high elongation at break to ensure mechanical stability and ease of application (Preis, Knop, & Breitkreutz, 2014). The tensile strength and elongation at break values are given in Figure 3. Both the type and concentration of the polymer affect these mechanical properties. Among all the formulations, F4 showed the highest tensile strength and elongation at break. These results suggest that the film can be applied

without damaging the mucosa during administration and are likely to support good patient compliance. The choice of plasticizer also affected the mechanical properties of the formulations. The F2 formulation, which uses glycerin as a plasticizer, showed the highest tensile strength. Statistical analysis revealed that the tensile strength of F2 was significantly higher than all other formulations ($p < 0.05$). Glycerin, when combined with PVA, provides both mechanical strength and flexibility. By contrast, the use of PEG reduced the elongation at break, while PG-containing formulations exhibited higher tensile strength and elongation compared with PEG-based films. The use of PEG in film formulations reduced elongation at break value. Formulations with PG showed higher tensile strength and elongation at break compared to PEG and PG-containing formulations. Mechanical characterization shows that all film formulations have sufficient tensile strength and flexibility for buccal application. Mechanical properties are crucial for ease of application, patient comfort, and retention. Preis and colleagues reported elongation values ranging from 4-26% for buccal film samples they prepared and 1-6% for commercially available products (Preis et al., 2014). The mechanical parameters of films are crucial factors not only in production or development but also in proper patient use. Buccal films require sufficient mechanical integrity to prevent breakage during application while maintaining flexibility to accommodate the dynamic movements of the oral cavity.

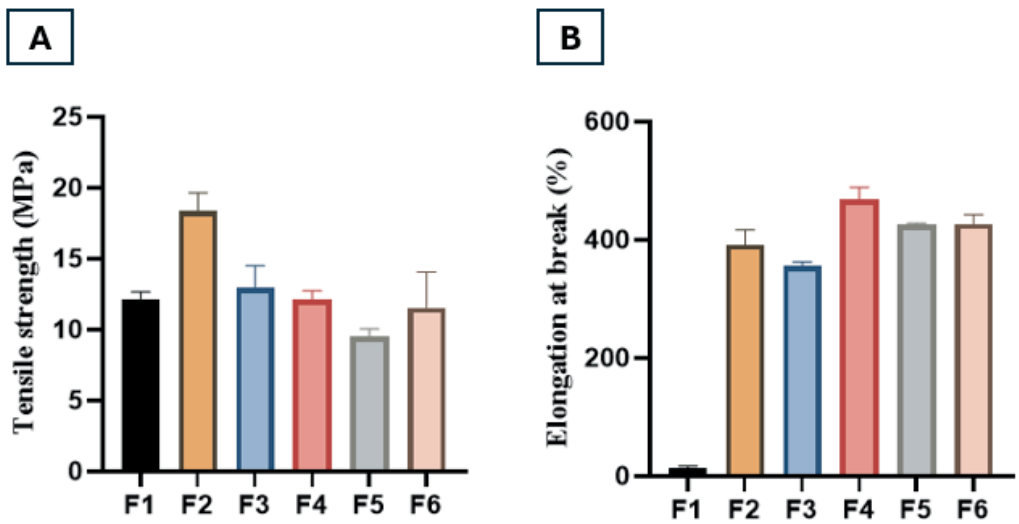

Figure 3. Mechanical properties of buccal film formulations: (a) tensile strength (MPa), and (b) elongation at break (%), measured using a texture analyzer with tensile grip setup (n = 3, mean ± SD).

Contact angle measurements of films

As shown in Figure 4, all film formulations exhibited contact angle values below 90°, indicating their hydrophilic character. Contact angle values were consistent with the properties of PVA-based materials, which are characterized by strong water affinity due to the abundance of hydroxyl groups in the polymer structure. This parameter plays a crucial role in enhancing the wettability and potential mucoadhesive performance of the films upon buccal application. Contact angle results align with literature reports on PVA-based films: for instance, Wu et al. (2020) found that pure PVA films have been shown to exhibit contact angles of approximately 45.5° ± 1.1° (Wu et

al., 2020). Similarly, in our study, contact angle values ranged from 55° to 67°, demonstrating hydrophilic characteristics and supporting the suitability of the films for buccal delivery. Statistical analysis revealed no significant differences among the contact angle values of the different formulations ($p > 0.05$).

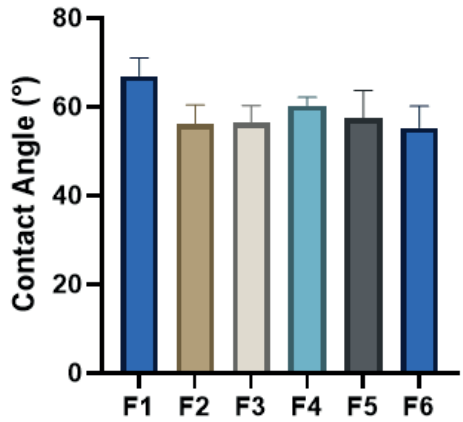

Figure 4. Contact angle values of buccal film formulations measured using distilled water (n = 3, mean ± SD)

***Ex vivo* mucoadhesion studies of buccal film formulation**

Mucoadhesive polymer systems that exhibit similar structures and functional groupings to the mucus layer can result in a greater degree of diffusibility of the polymer across the mucosal surface (Andrews, Laverty, & Jones, 2009). Plasticizers can alter the flexibility, tensile strength, and adhesion properties of film formulations (Saringat, Alfadol, & Khan, 2005). The presence of plasticizers may improve chain mobility and promote interpenetration with mucosal surfaces, but excessive plasticizers can also reduce cohesive strength and lead to lower mucoadhesion. In formulations containing PG, mucoadhesion was acceptable but slightly lower compared to those containing glycerin or PEG (Figure 5). Glycerin is known to increase hydrophilicity and plasticity, but it can cause excessive swelling of the hygroscopic structure, potentially compromising its structural integrity. PEG contributes to flexibility but can reduce adhesive interactions within the film matrix and potentially limit mucosal retention when used at high concentrations. Shojaei and Li examined the effects of hydration on mucoadhesion observed in PEG copolymers and reported that films with higher hydration had lower mucoadhesive strengths. This is because the mucoadhesive properties of the polymer film are reduced due to excessive elongation of the mucoadhesive bonds at higher hydration (Shojaei & Li, 1997). F5 exhibited the highest mucoadhesion performance, demonstrating the importance of optimal polymer-plasticizer ratios. F4 exhibited the lowest mucoadhesion performance despite its high mechanical properties. Although all formulations exhibited mucoadhesive properties, statistical analysis showed a significant difference between F4 and F5 ($p < 0.05$), suggesting that the polymer–plasticizer combination in F5 enhanced mucoadhesion. All film formulations exhibited adequate mucoadhesive strength for buccal application. These findings demonstrate the potential of PVA-based films to achieve effective and prolonged residence time in the buccal mucosa, which is essential for local drug delivery in oral ulcer treatment.

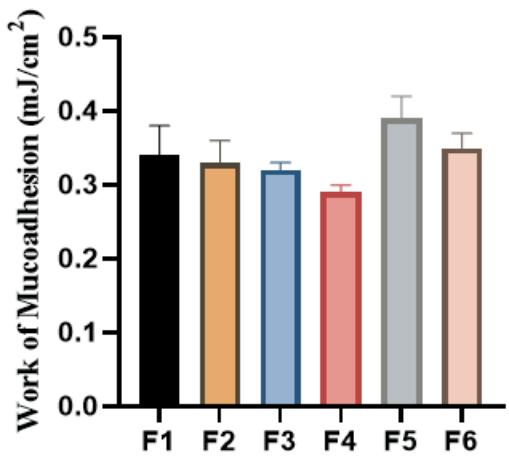

Figure 5. *Ex vivo* mucoadhesion performance of buccal film formulations evaluated on cow buccal mucosa using a texture analyzer (n = 3, mean ± SD).

***In vitro* drug release of buccal film formulation**

The *in vitro* release profile of the film formulations showed a controlled release without a burst effect within the first few hours. Among the prepared formulations, only F6 contained hydrocortisone (0.2% w/v) and therefore was selected for *in vitro* drug release studies (Figure 6). The other formulations (F1–F5) were primarily used to optimize polymer–plasticizer ratios, mechanical properties, and mucoadhesion performance before drug loading. Based on these evaluations, F6 exhibited the most favorable combination of mechanical strength, flexibility, and mucoadhesive performance, making it the optimal candidate for drug loading and subsequent release studies. The F6 formulation released HC at a rate of 93.2 ± 3.1 % over 8 hours. This suggests that the film matrix has a high drug retention capacity and a structure that supports controlled release. This controlled release was achieved by a combination of factors such as the PVA polymer and the type of plasticizer. HC release from PVA films occurs via a diffusion-based mechanism controlled by polymer swelling and dissolution. The 8-hour release duration suggests that once-daily dosing can achieve therapeutic efficacy and increase patient compliance. The release profile is suitable for maintaining local anti-inflammatory effects by providing sufficient residence time in the buccal mucosal area. In a study by Khan et al. (2024) the development of diclofenac sodium mucoadhesive films achieved a cumulative release of 80 ± 5 % over 8 hours, meeting the therapeutic criteria for anti-inflammatory efficacy (Khan et al., 2024). Extended release up to 8 hours supports reduced dosing frequency, thereby enhancing patient compliance.

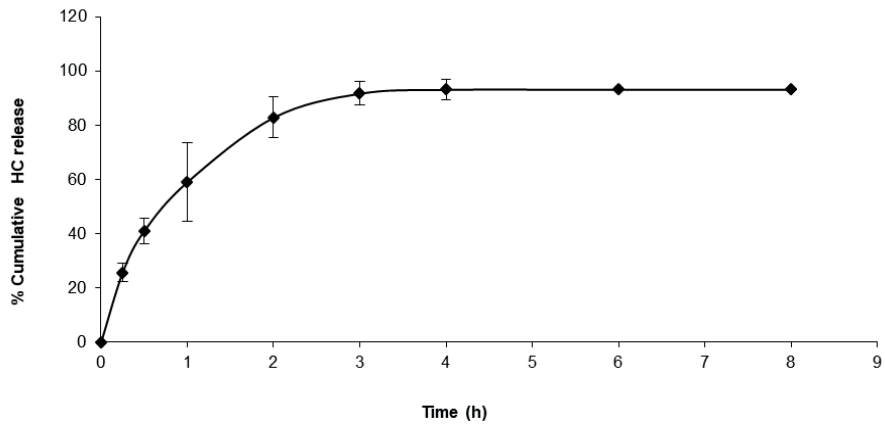

Figure 6. *In vitro* release profile of HC from F6 buccal film formulation using Franz diffusion cells over 8 hours (n=3, Mean±SD)

CONCLUSION

The films were successfully fabricated via the solvent casting method. In conclusion, PVA-based hydrocortisone-loaded buccal films exhibited promising physicochemical and mechanical properties suitable for buccal application. Blank films were characterized against mechanical integrity, surface wettability suitable for buccal use, and mucoadhesive performance. The formulation containing PVA and propylene glycol exhibited optimal tensile strength and high elongation at break for buccal application. The PG-plasticized blank formulation (F3) provided the best overall balance for robust processing and buccal retention and was therefore selected as the lead placebo. F6 was then generated by incorporating hydrocortisone into the F3 matrix, and *in vitro* release studies were conducted. The films demonstrated adequate mucoadhesion and controlled drug release, both of which

are critical for effective local treatment of oral ulcers. These findings suggest that film formulations could contribute to improved therapeutic outcomes in the management of oral aphthous lesions. Future studies should focus on *in vivo* performance, stability profiling, and patient-centric evaluations to further advance clinical applicability.

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AUTHOR CONTRIBUTION STATEMENT

BA: Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing. SS: Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing. FNT: Concept, Design, Data Collection or Processing, Literature Search, Writing.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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