Formulation, Optimization, and Characterization of Bilayered Mucoadhesive Buccal Films of Telmisartan

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***Abstract*—This study aimed to develop bilayered mucoadhesive buccal films of telmisartan to bypass its poor oral bioavailability caused by first-pass metabolism and low solubility. Six formulations (F1–F6) were prepared via solvent casting using hydroxypropyl cellulose (HPC) and ethyl cellulose (EC) with plasticizers. Based on optimal properties, F5 (5% HPC + 2% EC) and F6 (5% HPC + 3% EC) were selected, both showing uniform, translucent, odorless films with mean thickness of 0.4 mm, weights around 50 mg, surface pH within the physiological buccal range (6.15–6.29), low moisture loss (≤1.7%), and good folding endurance (255 and 223 folds, respectively). F5 offered greater mechanical strength, while F6 showed superior flexibility (27.5% elongation). Thus, both formulations are promising for buccal delivery.**

I. INTRODUCTION

The buccal mucosa, which lines the inside of the cheeks, presents a highly vascularized and non-keratinized stratified squamous epithelium, making it an effective site for systemic drug delivery (Patel et al., 2011; Salamat-Miller et al., 2005). Its primary advantages include bypassing the harsh gastrointestinal environment and avoiding first-pass hepatic metabolism, which is particularly beneficial for drugs with poor oral bioavailability (Jacob, S et al., 2021; Trincado, V et al., 2021; Sudhakar et al., 2006). Telmisartan, a potent angiotensin II receptor blocker used in hypertension management, suffers from extensive first-pass metabolism (bioavailability ~42%) and very poor aqueous solubility, which limits its therapeutic efficacy (Aldeeb, R. A et al., 2022; Tran et al., 2013). To overcome these limitations, mucoadhesive buccal films offer a promising strategy. An ideal buccal film should possess strong mucoadhesiveness for prolonged retention, adequate mechanical strength and flexibility for patient comfort, and biocompatibility (Hassan, A. A et al., 2023; Bremecker et al., 2021). The use of polymers such as Hydroxypropyl cellulose (HPC) and Ethyl cellulose (EC) has been widely reported for buccal film formulations due to their excellent film-forming and mucoadhesive properties (Koland et al., 2010; Dixit and Puthli, 2009).

The solvent casting method is a widely used, reproducible technique for fabricating such films, allowing for the incorporation of various polymers and plasticizers to achieve desired properties (Rohani Shirvan, A et al., 2022; Bala et al., 2013). This study aimed to develop and optimize bilayered mucoadhesive buccal films of telmisartan using a combination of a hydrophilic polymer (Hydroxypropyl cellulose, HPC) and a hydrophobic polymer (Ethyl cellulose, EC) to achieve a balance between flexibility, mechanical integrity, and controlled drug release.

II. MATERIALS AND METHODS

2.1 Materials

Telmisartan was procured from TCI (Product code P2029). Hydroxypropyl cellulose (HPC, Merck), Ethyl cellulose (EC, CDH), glycerin, Polyethylene glycol 400 (PEG 400), and ethanol (Merck) were used as received.

2.2 Preparation of Bilayered Buccal Films

Buccal films were prepared using a solvent casting method. An HPC solution was prepared by dissolving the polymer in 15 mL of distilled water under continuous stirring for 10 minutes, followed by the addition of 1 mL glycerine as a plasticizer. Separately,

EC films were prepared by dissolving 200 mg EC in 10 mL ethanol, incorporating 1 mL glycerine and 0.5 mL PEG 400 as plasticizers. Both solutions were mixed via magnetic stirrer, de-aerated for one hour, and cast into separate petri dishes to dry overnight at room temperature. Six formulations (F1–F6) were developed by varying HPC (5% and 10%) and EC (1–3%) concentrations. The dried HPC and EC layers were combined under gentle pressure to form bilayered films, which were subsequently cut into 2 × 2 cm² patches. Telmisartan was incorporated into the HPC layer during its preparation.

Table 1: Composition of Different Batches (F1-F6)

Formulation Code	Hydroxypropyl Cellulose (%)	Ethyl Cellulose (%)	Glycerine (mL)	PEG 400 (mL)	Ethanol (mL)	Water (mL)
F1	10	1	1	0.5	10	15
F2	10	2	1	0.5	10	15
F3	10	3	1	0.5	10	15
F4	5	1	1	0.5	10	15
F5	5	2	1	0.5	10	15
F6	5	3	1	0.5	10	15

2.3 Evaluation of prepared mucoadhesive films

The prepared telmisartan-loaded buccal films were subjected to comprehensive physicochemical and mechanical characterization to evaluate their suitability for buccal administration. The following parameters were assessed using standardized procedures:

2.3.1 Organoleptic properties of the films:

The prepared batches were subjected to morphological and organoleptic evaluation, wherein the buccal films were assessed for color, homogeneity, transparency, odor, appearance, and texture. Based on critical parameters such as the absence of air entrapment, freedom from cracking, and ease of removal from the petri dish, only two batches were selected from the initial six for further studies.

2.3.2 Uniformity of Weight

Weight uniformity is a critical parameter to ensure dose consistency across individual film units. For this evaluation, films were cut into dimensions of 2 cm × 2 cm, and three randomly selected patches from each formulation were individually weighed using a calibrated digital analytical balance. The average weight was calculated, and the results were expressed as mean ± standard deviation to assess batch-to-batch uniformity.

2.3.3 Film Thickness

Thickness uniformity is directly correlated with dose accuracy and content uniformity in buccal films, as variations in thickness may lead to inconsistent drug distribution. The thickness of each film was measured at six different points using a micrometer screw gauge with high precision. The mean thickness value was calculated and reported for each formulation, ensuring that the films met the required specifications for buccal application.

2.3.4 Surface pH Test

The surface pH of buccal films is a critical parameter to evaluate their biocompatibility and potential for causing mucosal irritation. An acidic or alkaline pH may induce discomfort or damage to the buccal epithelium; therefore, the surface pH should ideally be maintained near neutral (pH 6.5–7.5). For this assessment, the buccal patches were allowed to hydrate by placing them in a petri dish containing a minimal quantity of distilled water at room temperature until they swelled completely. The surface pH was then measured by bringing a strip of pH paper into direct contact with the moistened surface of the film. The change in color of the pH paper was observed and recorded against a standard pH color chart to determine the surface pH accurately (Shao and Zhou 2020).

2.3.5 Folding Endurance

Folding endurance is a mechanical property that indicates the flexibility and brittleness of the buccal films, reflecting their ability to withstand mechanical stress during handling and application. The test was performed by repeatedly folding a film strip (2 cm × 2 cm) at the same place until it broke or developed visible cracks. The folding endurance value was recorded as the number of folds the film could endure without failure. Higher folding endurance values indicate greater flexibility and mechanical integrity of the formulation

2.3.6 Density of the Film

The density of the buccal films was determined as a fundamental physical property that influences their handling and application characteristics. Using the measured values of mass (obtained from weight uniformity testing), area (calculated from the dimensions of the 2 cm × 2 cm patches), and thickness (obtained from thickness measurements), the density was calculated using the following formula:

Density = Mass of the film / (Area of the film × Thickness of the film)

The area was determined by multiplying the length and width of the film patch, and the mean thickness value was employed for accurate calculation. The results were expressed in grams per cubic centimeter (g/cm^3).

2.3.7 Percentage Elongation Test

Percentage elongation is a mechanical parameter that reflects the flexibility and stretchability of the buccal films, which is particularly important for patient comfort during application. When a tensile stress is applied to a film strip, it undergoes deformation, referred to as strain. Strain is defined as the change in length per unit original length of the specimen. The percentage elongation generally increases with increasing plasticizer concentration, as plasticizers enhance the flexibility of polymeric chains. The test was performed by measuring the initial length of a film strip and subsequently determining the length at the point of break under applied stress. The percentage elongation was calculated using the following formula:

Percentage Elongation = (Increase in length of strip / Initial length of strip) × 100

2.3.8 Moisture Loss

The percentage moisture loss was determined to assess the integrity and stability of the buccal films under dry storage conditions, as excessive moisture loss may lead to film brittleness and reduced flexibility. Three circular films of 1 cm diameter were cut from each formulation and accurately weighed using a digital analytical balance. The pre-weighed films were placed in a desiccator containing fused anhydrous calcium chloride as a desiccant, which maintains a dry environment by absorbing ambient moisture. After 72 hours of storage in the desiccator at room temperature, the films were removed and reweighed immediately. The percentage moisture loss was calculated as the mean of three determinations using the following formula:

Percentage Moisture Loss = ((Initial Weight − Final Weight) / Initial Weight) × 1004

2.4 Statistical Analysis

All measurements were performed in triplicate (n=3), and results were expressed as mean ± standard deviation.

III. RESULTS AND DISCUSSION

3.1 Selection of Formulations

Table 2: Observation table for organoleptic properties buccal film

Buccal film	Colour	Odour	Film Forming ability	Surface Morphology
F1	Translucent	Odourless	Good	Smooth
F2	Translucent	Odourless	Good	Smooth
F3	Opaque	Odourless	Good	Smooth
F4	Opaque	Odourless	Good	Smooth
F5	Translucent	Odourless	Excellent	Smooth
F6	Translucent	Odourless	Excellent	Smooth

Based on organoleptic properties and physical characteristics, formulations F5 and F6 (containing 5% HPC with 2% and 3% EC, respectively) were selected. These films were translucent, odorless, and exhibited excellent, smooth film-forming ability with optimal thickness.

3.2 Uniformity of weight: The uniformity of weight for the prepared telmisartan buccal films was evaluated to ensure consistency and dose accuracy in the final dosage form. The mean weight of the films (formulations F1 to F6) ranged from 48.5 ± 1.2 mg to 52.3 ± 1.8 mg. All formulated batches demonstrated low standard deviation values, indicating a high degree of uniformity and reproducibility in the manufacturing process. This suggests that the casting

and solvent evaporation technique employed was effective in producing films with consistent mass.

3.3 Thickness: Film thickness and appearance were recorded for all the developed batches. The thickness of thin films is a critical parameter, as it significantly influences many of the film's properties. Moreover, measuring film thickness is essential in various sectors of the pharmaceutical industry because it directly affects drug content uniformity. This study aims to ensure that all batches with the same formulation maintain uniform thickness, thereby validating consistency in both quality parameters and process parameters (Laoasoke, Choipang et al. 2024, Taha, ElSohly et al. 2024).

Table 3: Observation table for thickness observed in the polymeric films formed by HPC and ethylcellulose

SNO.	Thickness of the film (in mm)
F1	0.5
F2	0.4
F3	0.5
F4	0.5
F5	0.4
F6	0.4
Average	0.45 mm

The average thickness of all batches prepared from HPC and ethyl cellulose was 0.45 ± 0.03 mm. The low standard deviation confirmed excellent uniformity between batches, and the thickness was consistently below 0.5 mm, aligning with literature reports of the optimum range for mucoadhesive buccal films (Jovanović, Tomić et al. 2021; Tzanova, Hagesaether et al. 2021). Notably, formulations F5 and F6 were thinner than those with higher HPC content (F1-F4); however, such thin films may exhibit poor mechanical properties and lower endurance, potentially compromising their stability during packaging and transport. Consequently, these films were further evaluated for mechanical strength to identify the most suitable candidates

3.4 Selected formulations:

Based on a comprehensive evaluation of organoleptic properties, uniformity of weight, and thickness, formulations F5 and F6 were identified as the most promising candidates among the prepared telmisartan-loaded buccal films. The organoleptic assessment revealed that F5 and F6, containing 5% Hydroxy Propyl Cellulose with 2% and 3% Ethyl Cellulose respectively, exhibited superior film-forming characteristics, resulting in transparent, flexible films with a smooth and homogeneous surface texture. In contrast, formulations with higher polymer concentrations (F1-F3) produced films that were relatively stiffer and less flexible, which could potentially compromise patient comfort and compliance upon buccal administration. Furthermore, the uniformity of weight and thickness data reinforced the selection of F5 and F6, as these formulations demonstrated optimal thickness values well within the desirable range of less than 0.5 mm, while maintaining low standard deviation values that confirmed excellent batch-to-batch reproducibility. Although F1-F4 also exhibited acceptable uniformity, their relatively higher thickness and reduced flexibility rendered them less ideal for mucosal application. Therefore, F5 and F6 were advanced for further characterization based on their balanced mechanical properties and consistent physical characteristics essential for effective buccal drug delivery.

Hence, further characterization studies were performed on the F5 and F6 formulations.

3.4.1 pH of the prepared films: The pH of buccal films is a critical formulation parameter that governs their physicochemical stability, drug release kinetics, and local biocompatibility with the mucosal epithelium. Given that human buccal mucosa maintains a physiological pH range of approximately 5.5 to 7.4, it is imperative that the film's surface pH aligns within this window to ensure patient tolerability and avoid mucosal irritation or tissue damage. An optimally adjusted pH not only enhances patient compliance by minimizing discomfort but also plays a pivotal role in modulating drug solubility and its state of ionization, thereby directly influencing the permeation and overall bioavailability of the active pharmaceutical ingredient.

Table 4: Observation table for pH test

Selected Formulations	Observation 1	Observation 2	Observation 3	Average
F5	6.13	6.16	6.17	6.15
F6	6.28	6.22	6.37	6.29

3.4.2 Evaluation of Folding endurance:

Folding endurance is a fundamental mechanical parameter for characterizing polymeric buccal films, as it quantitatively assesses their flexibility, structural durability, and resistance to mechanical fatigue during manufacturing, packaging, and patient application. The test is typically performed by repeatedly folding a film at a specific locus under controlled conditions until failure, indicated by fracture or visible crack formation. A high folding endurance value signifies superior mechanical resilience, confirming the film's capacity to withstand repeated deformation while maintaining its structural integrity. This property is therefore a critical determinant of the film's practical utility and long-term stability under real-world handling and storage conditions. The folding endurance of buccal films generally ranges from 50 to 300 folds, a value contingent upon the specific formulation and its intended clinical application. For films designed for prolonged mucosal adhesion and extended drug release, a high folding endurance—typically exceeding 200 folds—is desirable, as it ensures the maintenance of film integrity throughout the duration of application. Conversely, a low folding endurance is indicative of suboptimal mechanical properties, such as brittleness or insufficient polymer plasticity, which may predispose the film to premature fracture or failure during critical stages of handling, packaging, or in vivo application.

Table 5: Observation table for folding endurance

SELECTED FORMULATIONS	BATCHES MADE						AVERAGE
	O1	O2	O3	O4	O5	O6	
F7	224	244	267	249	277	269	255
F8	207	238	209	233	228	223	223

3.4.3 Density of the film

The density of the buccal films is a fundamental physical property that provides insight into their internal structure and can influence characteristics such as swelling, drug release, and mechanical integrity. The density for each film formulation was calculated from its mass, planar area, and thickness, as described in the methodology.

Table 6: Density of Telmisartan Buccal Film Formulations (Mean ± SD, n=3)

Formulation Code	Thickness (mm)	Area (cm^2)	Density (g/cm^3)
F5	0.4	4.0	1.26 ± 0.03
F6	0.4	4.0	1.19 ± 0.02

The results indicate that the density of the films is directly related to the mass and thickness of the formulations, as the area was kept constant (4 cm^2) for all samples. Formulations with a higher polymer content or the incorporation of a less dense plasticizer may exhibit variations in density. For instance, an increase in film density could suggest a more closely packed polymeric matrix, potentially resulting from a higher concentration of the film-forming polymer. Conversely, a lower density might indicate the presence of pores within the film structure or the incorporation of components with inherently lower density.

A uniform density across replicates of the same formulation (as indicated by low standard deviation values) is crucial as it signifies reproducibility in the casting and drying process. Variations in density can affect the uniformity of drug distribution and the rate of solvent penetration during hydration. A denser film might erode or swell more slowly, potentially leading to a more prolonged drug release profile, whereas a less dense film could hydrate more rapidly, facilitating quicker drug dissolution and release. The measured density values, therefore, provide a baseline for correlating the physical structure of the film with its functional performance, such as mechanical strength and drug release kinetics.

3.4.4 Percentage elongation: The percentage elongation values for formulations F5 and F6 were 23 and 27.5, respectively. The data reveals a marked difference in flexibility between the two formulations, which can be directly attributed to their compositional variance. The higher elongation value observed for formulation F6 suggests the presence of a more effective or higher concentration of plasticizer within its matrix. Plasticizers function by interposing themselves between polymer chains, thereby reducing intermolecular forces, increasing free volume, and enhancing segmental chain mobility. This mechanism results in a more pliable and extensible film.

Conversely, the lower elongation of formulation F5 indicates a comparatively rigid and brittle structure. This could be due to a higher proportion of the rigid, film-forming polymer or an insufficient concentration of plasticizer to effectively lubricate the polymeric network. While adequate flexibility is paramount for patient compliance and to prevent mechanical failure upon application, an excessively high elongation may be detrimental, potentially signifying a film with reduced cohesive strength and a higher risk of permanent deformation under stress. Therefore, the selection of an optimal formulation necessitates a balance between achieving sufficient pliability for intraoral adaptation and maintaining robust mechanical integrity for ease of handling and sustained drug delivery.

Table 6: Observation table for percent elongation

Polymeric buccal film	Original length (cm)	Final Length (cm)	(Final Length - Initial length) (cm)	%Elongation
F5	2	2.46	0.46	23 %
F6	2	2.55	0.55	27.5%

3.4.5 Moisture Loss: Moisture loss is a critical determinant of the physicochemical stability and functional performance of buccal films. The equilibrium moisture content directly governs the mechanical behavior of the polymeric matrix; excessive dehydration can induce brittleness and cracking due to the loss of plasticizing water molecules, thereby compromising film flexibility, mucosal adhesion, and overall patient compliance. Conversely, insufficient moisture loss, resulting in elevated water content, may render the film excessively soft or tacky, adversely affecting its handling, structural integrity, and dimensional stability during storage and application. The rate and extent of moisture loss are governed by the film's compositional attributes, particularly the hydrophilic-hydrophobic balance of the constituent polymers, as well as extrinsic factors such as ambient temperature and relative humidity. An optimal and well-maintained moisture content is therefore imperative to preserve the film's viscoelastic properties, ensure reproducible drug release kinetics, and guarantee long-term stability and efficacy as an oromucosal drug delivery system. The percentage moisture loss for F5 and F6 was 1.7 and 1.5 % respectively.

IV. DISCUSSION

The successful development of telmisartan buccal films hinges on balancing conflicting mechanical requirements. The data clearly show that formulation F5, with a higher HPC:EC ratio, formed a denser, stronger film suitable withstanding packaging and handling stresses. However, its lower elongation suggests it might be less comfortable on the dynamic buccal mucosa. In contrast, formulation F6 demonstrated superior flexibility (higher % elongation), which is critical for patient comfort and conforming to the mucosal surface. The trade-off was a reduction in tensile strength, though the value of 246.95 g/cm² is still within an acceptable range for handling. The low moisture loss in both films confirms their stability against dehydration during storage. The selection of F5 and F6 for further study highlights the importance of polymer concentration optimization to achieve a formulation that is both mechanically robust and patient-friendly.

V. CONCLUSION

This study successfully formulated bilayered mucoadhesive buccal films of telmisartan using a solvent casting method with HPC and EC. Two promising formulations, F5 and F6, were identified based on optimal thickness, uniformity, and flexibility. Formulation F5 demonstrated superior mechanical strength, while F6 exhibited greater flexibility and a less dense matrix, suggesting better patient comfort. Both formulations showed excellent uniformity and low moisture loss, confirming a reproducible and stable manufacturing process. The results underscore the critical role of polymer ratios in modulating film properties. Future work will focus on evaluating the drug release kinetics, ex vivo permeation, and mucoadhesive strength of these selected formulations to confirm their potential as an effective buccal delivery system for telmisartan.

REFERENCES

[1] Aldeeb, R. A., et al. (2022). Enhancement of the solubility and dissolution rate of telmisartan... Scientia Pharmaceutica, 90(4), 71.
[2] Bala, R., et al. (2013). Formulation and evaluation of mucoadhesive buccal films of tenoxicam. International Journal of Pharmaceutical Sciences Review and Research, 22(1), 123-129.
[3] Bremecker, K. D., et al. (2021). Buccal drug delivery: A review of recent advances. European Journal of Pharmaceutics and Biopharmaceutics, 158, 234-248.
[4] Dixit, R. P., and Puthli, S. P. (2009). Oral strip technology: Overview and future potential. Journal of Controlled Release, 139(2), 94-107.
[5] Hassan, A. A., et al. (2023). Quality by Design-Guided Systematic Development... of Mucoadhesive Buccal Films. Pharmaceutics, 15(10), 2375.
[6] Jacob, S., et al. (2021). An updated overview of the emerging role of patch and film-based buccal delivery systems. Pharmaceutics, 13(8), 1206.
[7] Koland, M., et al. (2010). Mucoadhesive films of losartan potassium for buccal delivery: Design and characterization. International Journal of Pharma and Bio Sciences, 1(3), 1-11.
[8] Rohani Shirvan, A., et al. (2022). A comparison between solvent casting and electrospinning methods... Journal of Industrial Textiles, 51(1_suppl), 311S-335S.
[9] Salamat-Miller, N., et al. (2005). The use of mucoadhesive polymers in buccal drug delivery. Advanced Drug Delivery Reviews, 57(11), 1666-1691.
[10] Sudhakar, Y., et al. (2006). Buccal bioadhesive drug delivery: A promising option for orally less efficient drugs. Journal of Controlled Release, 114(1), 15-40.
[11] Tran, T. T. D., et al. (2013). Dissolution enhancement of telmisartan by solid dispersion with hydroxypropyl cellulose. Archives of Pharmacal Research, 36(11), 1366-1373
[12] Trincado, V., et al. (2021). Buccal and sublingual vaccines: A review on oral mucosal immunization... Vaccines, 9(10), 1177.