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RESEARCH ARTICLE

Formulation and Evaluation of a Polyherbal Mucoadhesive Buccal Film Containing *Syzygium aromaticum*, *Glycyrrhiza glabra*, and *Aloe vera* for Localized Oral Antimicrobial and Ulcer Management

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Abstract: Localized inflammatory lesions and microbial infections of the oral mucosa, such as recurrent aphthous stomatitis, often regarded as a therapeutic challenge due to rapid salivary clearance and mechanical displacement of conventional topical formulations. This study describes the design, preparation, and biophysical characterization of a polyherbal mucoadhesive buccal film engineered for the sustained delivery of bioactive extracts from *Syzygium aromaticum* (clove), *Glycyrrhiza glabra* (liquorice), and *Aloe vera* gel. The films were fabricated using a polymeric blend of hydroxypropyl methylcellulose and Carbopol 934 by solvent casting optimized with glycerol as a plasticizer. The resulting formulations were subjected to rigorous physicochemical and mechanical profiling, including thickness uniformity, weight variation, folding endurance, surface pH, swelling kinetics, and *in vitro* disintegration behavior. The optimized buccal films exhibited a highly uniform thickness of 0.42 ± 0.03 mm, a swelling index of 30.4 ± 1.8%, and a surface pH of 6.50 ± 0.08, matching the physiological range of human saliva to prevent mucosal irritation. Mechanical evaluation showed a folding endurance exceeding 100 folds, indicative of high structural flexibility. *In vitro* microbiological assays revealed a distinct zone of inhibition of 16.2 ± 0.8 mm against oral pathogens, validating the preserved antimicrobial efficacy of the encapsulated phytoconstituents. These results show that the integrated polymeric matrix successfully prolongs localized drug retention, offering a stable, flexible, and clinically viable mucosal patch for treating oral ulcerative and infectious conditions.

Keywords: Polyherbal mucosal patch; Mucoadhesive polymers; *Syzygium aromaticum*; *Glycyrrhiza glabra*; Oral drug localization.

1. Introduction

The oral mucosa represents a highly specialized barrier protecting underlying anatomical structures from mechanical trauma, chemical insults, and pathogenic microbial invasion. Disruption of this barrier leads to the development of oral ulcers, clinically defined as the erosion of the mucosal epithelial layer exposing the highly innervated lamina propria and underlying connective tissue [1]. This pathological denudation is typically surrounded by an erythematous halo resulting from localized vasodilation and inflammatory cell infiltration [2]. Among these mucosal pathologies, recurrent aphthous stomatitis is highly prevalent, periodically affecting up to 25% of the global population, with heightened susceptibility observed in young adults, females, and individuals under chronic physiological stress [2, 3]. Ulcerative lesions of the oral cavity are classified chronologically and etiologically to guide therapeutic intervention. Acute ulcers are transient lesions that typically resolve within a period of fourteen days [3]. These acute manifestations are commonly triggered by localized mechanical trauma, accidental biting, chemical burns, or acute viral infections. In contrast, chronic oral ulcers persist beyond the fourteen-day threshold and are frequently symptomatic of deeper systemic pathologies, including autoimmune disorders, severe nutritional deficiencies, gastrointestinal inflammatory diseases, or localized malignancies [3]. Regardless of the underlying etiology, the exposed connective tissue within the ulcerated bed experiences constant exposure to the complex, fluidic environment of the oral cavity. This exposure results in intense nociceptive signaling, severe localized pain, and functional impairment, hindering essential activities such as mastication, deglutition, and speech. The therapeutic management of oral ulcers aims to accelerate mucosal re-epithelialization, alleviate acute pain, reduce localized inflammatory cascades, and prevent secondary opportunistic bacterial or fungal infections. Historically, clinical interventions have relied on conventional topical dosage forms, including semi-solid gels, ointments, suspensions, and medicated mouthwashes [4]. Although these formulations are easy to apply, their therapeutic efficacy is severely limited by the physiological dynamics of the oral cavity.

The primary barrier to successful topical therapy is the constant secretion and flow of saliva. Saliva promotes rapid clearance of topically applied active agents, a phenomenon termed salivary washout [5]. Additionally, continuous mechanical movements of the

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tongue, cheeks, and lips during speech and mastication accelerate the physical displacement of semi-solid preparations from the target site. Conventional gels and rinses exhibit poor retention times, often remaining at the lesion site for only a few minutes. To compensate for this rapid clearance, clinical protocols require frequent dosing regimens. This high dosing frequency leads to substantial fluctuations in localized drug concentration, reduced patient compliance, and an increased risk of systemic drug absorption and associated side effects.

To address the challenges of localized oral therapy, incorporating natural bioactive agents with multi-target pharmacological profiles has emerged as a promising strategy. *Syzygium aromaticum*, commonly known as clove, contains a dense reservoir of bioactive volatile compounds, with the phenylpropanoid eugenol (4-allyl-2-methoxyphenol) serving as the primary active phytoconstituent [8]. Eugenol possesses highly potent broad-spectrum antimicrobial properties, destabilizing microbial cell membranes through lipid bilayer permeabilization and the disruption of intracellular enzymatic systems [8, 9].

In addition to its direct bactericidal and fungicidal activities, *Syzygium aromaticum* exhibits significant localized anesthetic and anti-inflammatory properties. Eugenol suppresses the activity of cyclooxygenase-2 (COX-2) and lipoxygenase enzymes, thereby inhibiting the synthesis of pro-inflammatory prostaglandins and leukotrienes at the ulcer site. This biochemical inhibition directly reduces localized edema, erythema, and inflammatory pain. The localized anesthetic effect of clove extract provides rapid, symptomatic relief to the exposed nerves of the ulcerated mucosa, matching the efficacy of synthetic local anesthetics without inducing localized tissue toxicity.

The dried roots and rhizomes of *Glycyrrhiza glabra*, or liquorice, provide complementary therapeutic actions essential for mucosal healing. The principal bioactive component of *Glycyrrhiza glabra* is glycyrrhizin (glycyrrhizic acid), a triterpenoid saponin known for its exceptional anti-inflammatory, cytoprotective, and soothing properties [10]. Upon topical application, glycyrrhizin downregulates the expression of pro-inflammatory cytokines, specifically tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6), which are primary drivers of mucosal tissue destruction in aphthous ulcers [11].

Glycyrrhiza glabra stimulates localized mucous secretion and enhances the structural integrity of the mucosal barrier. It accelerates the proliferation of epithelial cells and promotes angiogenesis, two critical phases in the wound-healing cascade. The active components of liquorice extract protect the exposed nerve endings from salivary enzymes and mechanical irritation by establishing a physical and chemical barrier over the denuded epithelial tissue facilitating rapid and structured tissue regeneration.

The inner parenchymal gel of *Aloe vera* leaves contains high concentrations of mucilaginous polysaccharides, most notably acemannan, a beta-(1,4)-acetylated polymannose [12]. Acemannan acts as a natural immunomodulator, stimulating localized macrophages and fibroblasts to secrete epidermal growth factor (EGF), fibroblast growth factor (FGF), and transforming growth factor-beta (TGF-β). These growth factors accelerate collagen synthesis, myofibroblast differentiation, and rapid wound contraction [12].

Additionally, the high water-retaining capacity of *Aloe vera* gel provides exceptional moisturizing and cooling properties, reducing the burning sensation associated with acute mucosal inflammation. The gel forms a natural, protective viscoelastic layer over the ulcerated tissue. This layer shields the lesion from dietary irritants, such as acidic or spicy foods, while continuously hydrating the damaged epithelial cells to support optimal physiological healing.

Mucoadhesive drug delivery systems have been developed to overcome the limitations of salivary clearance and secure prolonged localization of these herbal extracts. Mucoadhesion is defined as the state in which two materials, at least one of which is of a biological nature, are held together for extended periods by interfacial forces [4]. In buccal drug delivery, this process involves the interaction between a synthetic or natural hydrophilic polymer and the mucosal membrane. The mucosal surface is coated with a continuous mucus gel layer composed primarily of mucin, a highly glycosylated glycoprotein rich in sialic acid and sulfonic acid residues, which impart a net negative charge at physiological pH [13]. The phenomenon of mucoadhesion is categorized into the contact phase and the consolidation phase [13, 14]. The contact phase involves the initial wetting and swelling of the polymer when placed in contact with the moist mucosal surface, facilitating intimate physical contact. The consolidation phase involves the interpenetration of the hydrated polymeric chains into the glycoprotein networks of the mucus layer, driven by various physical and chemical forces. This interaction is explained by several thermodynamic theories:

$$\text{Total Adhesive Force } (F_a) = F_{\text{electrostatic}} + F_{\text{diffusion}} + F_{\text{adsorption}} + F_{\text{hydration}}$$

Wetting Theory: Focuses on the surface tension and contact angle of the liquid-solid interface, determining the ability of the polymeric formulation to spread and conform to the irregular mucosal topography.

Diffusion-Interpenetration Theory: Explains that the polymeric chains and mucin glycoproteins physically interpenetrate across the interface, forming a semi-permanent physical entanglement. The depth of this interpenetration is directly proportional to the molecular weight, chain flexibility, and hydration state of the polymer [14]

Adsorption Theory: Postulates that secondary chemical bonding drives adhesion. This includes hydrogen bonding, van der Waals forces, and hydrophobic interactions between the functional groups of the polymer (such as hydroxyl, carboxyl, and amide groups) and the oligosaccharide chains of the mucin molecules [15]

Electronic Theory: Suggests that attractive electrostatic forces arise from electron transfer across the interface due to differences in the electronic structures of the polymer and the mucosal substrate, forming a double layer of electrical charge [13]

Among various mucoadhesive configurations, including tablets, gels, patches, and sprays, mucoadhesive buccal films offer distinct clinical and pharmaceutical advantages [15, 16]. Buccal films are ultra-thin, flexible polymeric sheets designed to adhere securely to the mucosal surface. They provide a precise dose of active therapeutic agents directly to the localized lesion. Their thin profile and structural flexibility minimize foreign body sensations in the oral cavity, significantly improving patient compliance compared to bulky buccal tablets [16, 17]. A mucoadhesive film acts as a protective physical barrier by adhering directly over the ulcerated lesion, shielding the wound from mechanical trauma during speech and mastication. Similarly, the hydrophobic or hydrophilic polymeric matrix controls the diffusion of encapsulated phytoconstituents directly into the inflamed tissue. This localized delivery bypasses the harsh environment of the gastrointestinal tract and avoids first-pass hepatic metabolism, ensuring maximum localized bioavailability and rapid therapeutic action. This study aims to establish a stable, clinically effective topical system for managing oral ulcers through the synergistic combination of *Syzygium aromaticum*, *Glycyrrhiza glabra*, and *Aloe vera* into an optimized mucoadhesive polymeric drug delivery system.

2. Materials and Methods

2.1. Raw Materials and Reagents

Hydroxypropyl methylcellulose (HPMC E15, viscosity 15 cP for 2% w/v aqueous solution at 20∘C) and Carbopol 934 were procured as the primary film-forming and mucoadhesive polymers. Glycerol (purity ge 99.5%) was obtained for use as a plasticizing agent. Sorbitan monooleate (Tween 80) was acquired as a non-ionic surfactant and permeation enhancer. Sodium saccharin and anhydrous citric acid of analytical grade were selected as the sweetening agent and salivary stimulant, respectively. Peppermint oil was obtained as a pharmaceutical-grade flavoring agent. Deionized, double-distilled water was utilized as the primary aqueous solvent throughout the formulation processes. Dried flower buds of *Syzygium aromaticum* (clove) and rhizomes of *Glycyrrhiza glabra* (liquorice) were procured from local authenticated botanical sources. Fresh, mature leaves of *Aloe vera* (L.) Burm.f. were harvested from the institutional medicinal garden and authenticated prior to processing.

2.2. Extraction Procedures of Bioactive Phytoconstituents

2.2.1. Extraction of Syzygium aromaticum (Clove)

The extraction of bioactive volatile and non-volatile components from *Syzygium aromaticum* was executed utilizing a standardized cold percolation methodology. Dried clove buds were mechanically pulverized to obtain a coarse powder. An accurately weighed mass of 100 g of the coarse powder was transferred to a sealed glass container and moistened with 150 mL of 70% v/v aqueous ethanol. This mixture was allowed to stand for 24 hours to permit uniform swelling and cellular imbibition [18]. The moistened material was then packed uniformly into a cylindrical glass percolator equipped with a stopcock. Additional 70% v/v ethanol was introduced into the percolator until the liquid column stood approximately 2 cm above the packed drug bed. The system was closed and allowed to macerate for an additional 24 hours. Following maceration, the lower valve was opened, and percolation was conducted at a controlled rate of 1.5 mL/min. The crude percolate was continuously collected until exhaustion of the drug mass was confirmed. The collected liquid extract was subjected to concentration under reduced pressure at 40∘C utilizing a rotary vacuum evaporator. The resulting dark brown, viscous semi-solid clove extract was stored in light-resistant, airtight glass vials at 4∘C until formulation.

2.2.2. Extraction of Glycyrrhiza glabra (Liquorice)

The extraction of triterpenoid saponins, specifically glycyrrhizin, from *Glycyrrhiza glabra* was performed using a modified aqueous-etholic percolation process. The dried rhizomes of the plant were sliced, dried, and ground into a coarse powder. A quantity of 100 g of this powder was weighed and moistened with 150 mL of 70% v/v ethanol. The mixture was allowed to stand for a maceration period of 24 hours to facilitate cell wall softening. The swollen material was packed into a vertical glass percolator, ensuring the complete absence of air channels within the column [19]. Aqueous ethanol (70% v/v) was poured over the column until the bed

was fully submerged. After a static maceration period of 12 hours, percolation was initiated at a constant drip rate of 1.0 to 2.0 mL/min. The extraction process was maintained until a total volume of approximately 900 mL of percolate was recovered, indicating complete exhaustion of the active constituents. The liquid was concentrated at 45∘C under vacuum to yield a thick, dark reddish-brown liquorice extract, which was desiccated and stored in a moisture-free environment.

2.2.3. Processing of Aloe vera Parenchymal Gel

Freshly harvested *Aloe vera* leaves were subjected to rigorous washing with running tap water followed by a rinse with sterile distilled water to remove external dirt and exudates. The thick outer green epidermis was carefully separated using a sterile stainless steel scalpel to expose the inner mucilaginous, transparent parenchymal gel. This gel was immediately washed with cold, sterile distilled water to remove any traces of yellow aloin-containing latex. The purified gel matrix was mechanically homogenized in a sterile blender. The homogenized mass was filtered through a fine nylon mesh to separate structural fibrous components. The liquid filtrate was subsequently concentrated under controlled thermal conditions at 35∘C under vacuum to yield a concentrated *Aloe vera* gel extract. This processed gel was stabilized by the addition of a trace amount of ascorbic acid (0.1% w/v) as an antioxidant and stored at 4∘C.

2.3. Preparation of Polyherbal Mucoadhesive Buccal Films

The polyherbal mucoadhesive films were prepared utilizing an optimized solvent casting methodology. Hydroxypropyl methylcellulose (HPMC E15) and Carbopol 934 were utilized as the film-forming and mucoadhesive polymeric platforms, respectively. The compositions of the finalized casting solutions were engineered to ensure suitable viscoelastic properties for film casting and subsequent peelability. Table 1 outlines the exact composition of the formulation calculated for a single casting plate (glass petri dish with a diameter of 9 cm), which yields five functional buccal film units after drying and cutting.

Table 1. Composition of the Polyherbal Mucoadhesive Buccal Film per Casting Plate (5 Films)

Sr. No.	Component	Quantity	Specific Function in Formulation
1.	*Glycyrrhiza glabra* extract	50.0 mg	Active agent (Anti-inflammatory / Mucoprotective)
2.	*Syzygium aromaticum* extract	50.0 mg	Active agent (Antimicrobial / Local Anesthetic)
3.	*Aloe vera* parenchymal gel	50.0 mg	Active agent (Wound healing promoter / Humectant)
4.	Hydroxypropyl methylcellulose (HPMC)	500.0 mg	Hydrophilic film-forming polymer matrix
5.	Carbopol 934	100.0 mg	Mucoadhesive polymer / Viscosity builder
6.	Glycerol	0.3 mL	Plasticizer (Enhances elasticity and flexibility)
7.	Tween 80	1.0 mL	Surfactant / Solubilizer / Permeation enhancer
8.	Sodium saccharin	10.0 mg	Non-cariogenic sweetening agent
9.	Anhydrous citric acid	5.0 mg	Salivary stimulant / Local pH modifier
10.	Peppermint oil	2 to 3 drops	Flavoring and cooling agent
11.	Distilled water	15.0 mL	Primary casting solvent

Organic solvents such as 70% v/v ethanol utilized during the percolation and extraction of plant materials were completely removed during vacuum concentration and are not present in the final film matrix.

To prepare the polymeric casting solution, 100.0 mg of Carbopol 934 was dispersed in 7.5 mL of distilled water and allowed to hydrate for 2 hours to form a uniform, swellable gel structure. In a separate vessel, 500.0 mg of HPMC E15 was dissolved in 7.5 mL of distilled water under continuous stirring at 500 rpm using a magnetic stirrer, and was allowed to hydrate completely for 1 hour to form a clear polymeric solution. The hydrated Carbopol dispersion was slowly incorporated into the HPMC solution under steady agitation to generate a homogeneous, viscous binary polymeric blend.

Following the formation of the base polymeric blend, glycerol (0.3 mL), Tween 80 (1.0 mL), sodium saccharin (10.0 mg), and anhydrous citric acid (5.0 mg) were added sequentially while maintaining constant stirring. The active plant extracts, comprising 50.0 mg of *Glycyrrhiza glabra* extract, 50.0 mg of *Syzygium aromaticum* extract, and 50.0 mg of processed *Aloe vera* gel, were premixed with a minimal quantity of distilled water to form a uniform slurry and then introduced dropwise into the polymeric blend. Finally, peppermint oil was added to the mixture.

The resulting dark brown, viscous mixture was subjected to continuous magnetic stirring for 1 hour to ensure complete molecular dispersion of the phytoconstituents. The entrapped air bubbles, which can cause structural defects such as micro-pores in the dry films, were removed by allowing the solution to stand undisturbed for 1 hour under mild vacuum deaeration. The deaerated solution (15 mL) was carefully poured into a clean, leveled 9 cm glass petri dish. The casted solution was dried in a hot air oven maintained at a controlled temperature of 45 ± 2∘C for a duration of 12 to 16 hours. Once dry, the flexible polymeric film was carefully peeled from the glass substrate, visually inspected for physical integrity, and cut into square patches of 2 × 2 cm^2 dimensions using a sharp

surgical blade. The individual film units were wrapped in aluminum foil and stored in a laboratory desiccator containing anhydrous silica gel to prevent moisture absorption.

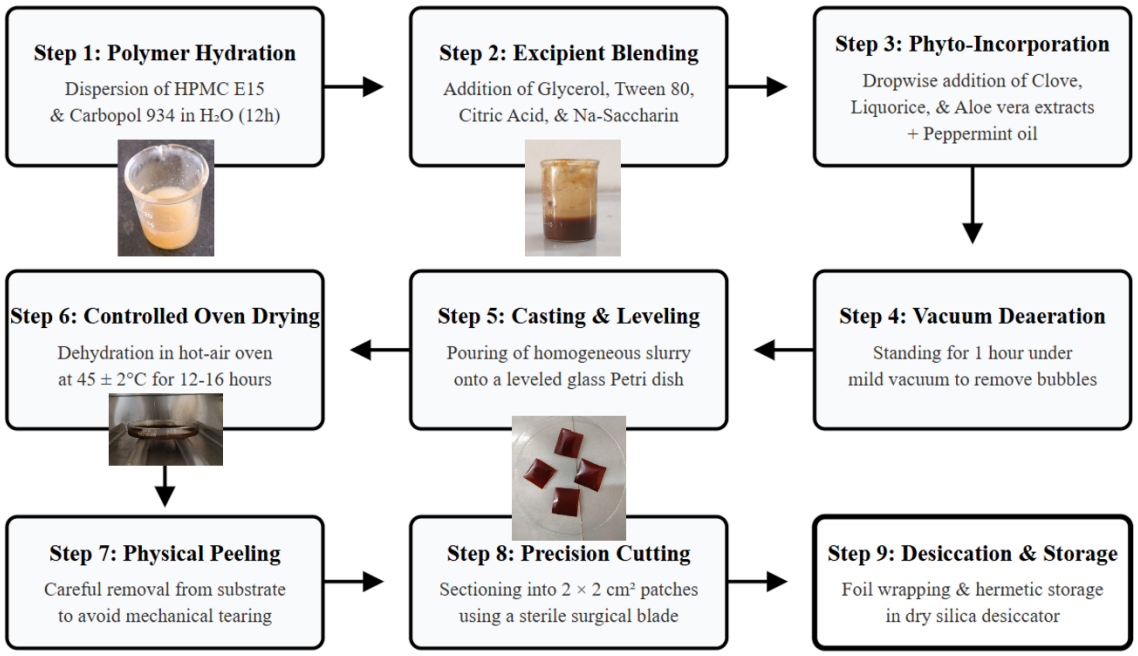

Figure 1. Preparation of Polyherbal Mucoadhesive Buccal Film

2.4. Physicochemical and Biophysical Characterization

2.4.1. Physical and Organoleptic Characteristics

The fabricated polyherbal buccal films were subjected to detailed qualitative and visual inspections. The parameters evaluated included color uniformity, surface texture, transparency, and subjective odor profile. Individual film units were examined under a polarized light source to check for the presence of phase separation, recrystallization of active phytoconstituents, and micro-cracks.

2.4.2. Mass Uniformity and Thickness

Mass uniformity was assessed by weighing ten randomly selected film units (2 ×2 cm^2 each) individually on an analytical electronic balance with a high sensitivity of 0.1 mg. The average mass of the films was calculated, and individual weight deviations were analyzed to ensure they remained within acceptable pharmacopoeial limits of ± 5%. The thickness of the buccal patches was quantified at five distinct geographical points (one at the center and four at each of the corners) using a calibrated digital micrometer. The mean thickness and corresponding standard deviation (n = 6) were calculated to ensure dimensional consistency across the casted area.

2.4.3. Folding Endurance and Tensile Strength

Folding endurance was evaluated to determine the mechanical flexibility of the films under structural stress, simulating physical forces experienced during application and salivary movement. A single film unit was repeatedly folded at the same hinge point through an angle of 180∘ until the film broke or cracked. The maximum number of consecutive folds sustained by the film without mechanical failure was recorded as the folding endurance value (n = 6).

2.4.4. Determination of Surface pH

The surface pH of the polyherbal mucoadhesive film was measured to assess potential *in vivo* mucosal irritation. Since acidic or alkaline formulations can cause localized tissue necrosis or pain, the surface pH must align with the physiological range of human saliva (6.5 to 7.2). A film unit was placed in a glass petri dish and hydrated with 1.0 mL of double-distilled water for 30 seconds. A

calibrated micro-electrode of a digital pH meter was brought into direct contact with the wet surface of the film, and the pH value was recorded after stabilization of the electronic reading (n = 3).

2.4.5. Hydration and Swelling

The swelling kinetics of the hydrophilic polymeric matrix were quantified to evaluate the water absorption capacity of the film, which directly influences mucoadhesion and drug release. Pre-weighed dry film patches (W_0) were placed on the surface of an agar plate (2% w/v agar in phosphate buffer pH 6.8) maintained at 37 ± 0.5∘C, simulating the moist oral mucosal interface. At regular intervals (5, 10, 15, 30, 45, and 60 minutes), the swollen films were removed, carefully blotted with a filter paper to remove excess surface water, and weighed (W_t). The Swelling Index (SI) was calculated as a percentage using the following equation:

$$SI = \left(\frac{W_t - W_0}{W_0}\right) \times 100$$

Where W_t represents the weight of the hydrated film at time t, and W_0 is the initial dry weight of the film (n = 3).

2.4.6. Moisture Content and Moisture Uptake

To assess physical stability under variable environmental conditions, the moisture content and moisture absorption profiles were quantified. The percentage moisture content was determined by weighing three fresh film units ($W_{initial}$) and placing them in a desiccator containing activated silica gel at room temperature for 72 hours. The films were re-weighed periodically until a constant dry weight (W_{dry}) was achieved. The percentage moisture content was calculated as:

$$\text{Moisture Content } (\%) = \left(\frac{W_{\text{initial}} - W_{\text{dry}}}{W_{\text{initial}}}\right) \times 100$$

Moisture uptake behavior was evaluated by placing pre-weighed dry films in a closed desiccator maintained at 75 ± 5% relative humidity using a saturated solution of sodium chloride at 25∘C. After 72 hours of exposure, the films were removed and weighed (W_{humid}). The percentage moisture uptake was calculated as:

$$\text{Moisture Uptake } (\%) = \left(\frac{W_{\text{humid}} - W_{\text{dry}}}{W_{\text{dry}}}\right) \times 100$$

2.4.7. In Vitro Disintegration and Dissolution Studies

The disintegration time of the polyherbal patches was measured using a USP disintegration test apparatus containing simulated saliva fluid (phosphate buffer pH 6.8, maintained at 37 ± 0.5∘C). A 2 ×2 cm^2 film unit was placed in the basket of the apparatus, and the time required for the film to completely soften, rupture, and break down into fine fragments was recorded as the disintegration time (n = 6).

2.4.8. In Vitro Mucoadhesive Strength

The *ex vivo* mucoadhesive strength of the films was quantified utilizing a modified double-beam physical balance system. Freshly excised porcine buccal mucosa was obtained from a local abattoir and transported to the laboratory in cold Krebs-Ringer bicarbonate buffer solution. The mucosal tissue was secured onto the surface of a glass block, which was then placed inside a vessel filled with phosphate buffer pH 6.8 maintained at 37 ± 0.5∘C such that the mucosal surface remained moist but not completely submerged.

The polyherbal film unit (2 ×2 cm^2) was adhered to the lower surface of a suspended Teflon cylinder connected to the left arm of the physical balance. The cylinder was lowered to bring the buccal film into contact with the porcine mucosa. A contact force of 50 g (0.49 N) was applied for a duration of 3 minutes to facilitate polymer-mucin chain interpenetration. Following this consolidation phase, water was added dropwise at a constant flow rate of 2.0 mL/min to a collection beaker suspended from the right arm of the balance. The addition of water was continued until the film detached from the mucosal surface. The weight of water required to cause detachment was recorded as the mucoadhesive force in grams. The corresponding detachment force (expressed in Newtons) was calculated using the gravitational acceleration equation:

$$\text{Mucoadhesive Force } (F) = \frac{m \times g}{1000}$$

Where m is the mass of water required for detachment (g), and g is the acceleration due to gravity (9.81 m/s^2). The mucoadhesion was further normalized per unit surface area of the patch (n = 3).

2.4.9. Determination of Drug Content Uniformity

To confirm the uniform distribution of the plant extracts within the polymeric matrix, the concentration of key bioactive markers was quantified. Due to the multi-component nature of the polyherbal film, eugenol from *Syzygium aromaticum* and glycyrrhizinic acid from *Glycyrrhiza glabra* were selected as index marker compounds. A 2 × 2 cm^2 film unit was dissolved in 50 mL of phosphate buffer pH 6.8 under continuous magnetic stirring for 4 hours. The solution was filtered through a 0.45 mum membrane filter to eliminate insoluble polymeric residues. The filtrate was analyzed spectrophotometrically utilizing a double-beam UV-Visible spectrophotometer. The concentration of glycyrrhizin was quantified at its characteristic absorption wavelength of λ_{max} = 254 nm, and eugenol was quantified at λ_{max} = 282 nm. The experiment was performed in replicate (n = 6), and the results were expressed as a percentage of the theoretical drug loading.

2.4.10. In Vitro Microbiological Assays

The localized antimicrobial efficacy of the optimized polyherbal buccal films was evaluated using the agar well diffusion method. The therapeutic potential of the films was assessed against key pathogenic microorganisms commonly associated with opportunistic oral infections and secondary ulcer contamination: *Streptococcus mutans* (MTCC 497, a primary cariogenic bacterium) and *Candida albicans* (MTCC 3017, a opportunistic fungal pathogen).

Müller-Hinton agar and Sabouraud dextrose agar plates were prepared and sterilized for the bacterial and fungal cultures, respectively. Pure cultures of the test organisms were grown in nutrient broth to a turbidity matching the 0.5 McFarland standard (approximately 1.5 times 10^8 CFU/mL). The microbial suspensions were inoculated uniformly across the agar plates using sterile cotton swabs to produce a confluent lawn of growth.

Wells of 8 mm diameter were punched into the agar using a sterile cork borer. Three test conditions were established:

- Test Group: A 2 ×2 cm^2 polyherbal film unit dissolved in 1.0 mL of sterile phosphate buffer pH 6.8.
- Positive Control Group: 100 μL of a clinically approved 0.2% w/v chlorhexidine gluconate solution.
- Negative Control Group: A blank polymer film unit (containing HPMC, Carbopol, and plasticizer without the active herbal extracts) dissolved in sterile phosphate buffer.

The respective test and control solutions were introduced into the designated agar wells. The plates were incubated at 37 ± 0.5∘C for 24 hours for the bacterial cultures, and at 28 ± 0.5∘C for 48 hours for the fungal cultures. Following incubation, the circular zones of inhibition surrounding the wells were measured in millimeters using a digital vernier caliper (n = 3).

3. Results and Discussion

3.1. Physical and Organoleptic Characteristics

The physical and organoleptic properties of the formulated polyherbal mucoadhesive buccal films are fundamental determinants of patient acceptability, ease of application, and manufacturing reproducibility. Visual and tactile evaluation of the casted patches revealed a highly homogeneous, flexible, and non-tacky structural matrix. The films exhibited a characteristic translucent, reddish-brown color, which is directly attributed to the natural pigmentations of the concentrated *Glycyrrhiza glabra* and *Syzygium aromaticum* extracts. The absence of dark particulate agglomerates or localized color variations confirmed the uniform molecular dispersion of the botanical extracts within the blended HPMC E15 and Carbopol 934 polymeric network.

The surface texture of the dry patches was smooth, dry, and free of physical defects such as pinholes, surface cracks, or entrapped micro-voids, validating the efficiency of the mild vacuum deaeration and controlled oven drying processes. Subjective gustatory and olfactory assessments indicated an agreeable profile. The integration of sodium saccharin successfully masked the inherent bitterness of the triterpenoid saponins from liquorice, yielding a pleasant, sweet initial taste. This was complemented by a distinct, cooling peppermint aroma and a mild localized cooling sensation from the volatile fractions of peppermint oil and clove extract, which is highly advantageous for clinical compliance in patients suffering from painful oral mucosal lesions.

3.2. Thickness and Weight Uniformity

Thickness and weight consistency across the casted polymeric area are critical quality attributes that ensure dosage uniformity of the incorporated herbal bioactives and guarantee reproducible mechanical and drug release kinetics. Quantitative evaluation of thickness using a digital micrometer at five distinct locations across randomly selected patches (2×2 cm^2) yielded a mean thickness of 0.42 $\pm$ 0.03 mm (n = 6). The low standard deviation shows that the solvent casting methodology on a leveled glass platform provides a highly uniform dry film thickness, well within the target pharmaceutical limits of 0.2 to 0.7 mm recommended for comfortable buccal mucosal application [20].

The mass uniformity analysis of the individual patches showed a mean dry weight of 45.2 $\pm$ 1.2 mg (n = 10). The individual percentage weight variation was calculated to be -3.44 $\pm$ 0.52%, which is well within the acceptable pharmacopoeial limit of $\pm$ 5%. This high level of consistency confirms that the viscous polymeric blend possessed appropriate rheological characteristics prior to casting, allowing uniform flow and self-leveling across the petri dish substrate without establishing thickness gradients or localized polymer pooling.

3.3. Folding Endurance and Mechanical Strength

Folding endurance serves as a direct indicator of the physical flexibility, mechanical integrity, and durability of the buccal film. This parameter measures the capacity of the patch to withstand physical manipulation, masticatory stress, and the dynamic movements of the oral cavity (such as speech and swallowing) without experiencing mechanical fracture. The fabricated polyherbal buccal patches exhibited an exceptional folding endurance value exceeding 100 folds (112 $\pm$ 8 folds, n = 6).

This mechanical resilience is explained by the optimal incorporation of glycerol as a plasticizing agent at a concentration of approximately 30% w/w relative to the total dry polymer weight. At a molecular level, glycerol molecules intercalate between the linear chains of HPMC E15 and the cross-linked networks of Carbopol 934. Glycerol increases the free volume of the matrix by establishing intermolecular hydrogen bonds with the hydroxyl groups of the polymers reduces the localized glass transition temperature, and decreases the rigidity of the polymer blend [21]. This results in highly flexible polymer chains that can slip past one another under physical strain, transforming a brittle, glassy matrix into a highly elastic and tough film capable of conforming to the contoured topology of the oral mucosa.

3.4. Surface pH and Mucosal Tolerance

Since mucosal application requires extended contact between the polymeric device and the vascularized oral epithelium, maintaining a biocompatible surface pH is crucial to prevent localized chemical irritation, pain, or tissue damage. The surface pH of the hydrated polyherbal buccal patch was determined to be 6.50 $\pm$ 0.08 (n = 3). This value lies within the physiological pH range of human saliva (6.5 to 7.2), indicating excellent biocompatibility.

This near-neutral surface pH is achieved by the balanced integration of the slightly acidic Carbopol 934 polymer (which contains carboxylic acid functional groups) and the non-ionic HPMC E15 matrix, adjusted with a trace concentration of anhydrous citric acid (5.0 mg per plate). Citric acid serves a dual role: it functions as a localized pH modifier and acts as a salivary stimulant, which promotes localized salivary flow upon application, accelerating the initial hydration and mucoadhesion of the patch. The clinical implication of this physiological compatibility is that the film can be safely maintained on the buccal mucosa for hours without triggering inflammatory tissue responses or painful burning sensations, even over denuded ulcerative lesions.

3.5. Hydration and Swelling

The swelling behavior of a mucoadhesive polymeric delivery system is a critical biophysical parameter that controls both the rate of mucoadhesive bond consolidation and the diffusion-controlled release of the encapsulated bioactive molecules. Upon contact with Simulated Saliva Fluid (SSF, pH 6.8), the hydrophilic polymer networks of HPMC and Carbopol undergo rapid hydration, transitioning from a dry, glassy state to a highly swollen, rubbery gel matrix. The swelling kinetics of the optimized formulation, evaluated on an agar gel plate substrate, showed a progressive increase in water absorption over time. The calculated Swelling Index (SI) was 30.4 $\pm$ 1.8% (n = 3) after a hydration period of 60 minutes.

This controlled swelling profile is governed by the structural synergy between HPMC E15 and Carbopol 934. HPMC, a non-ionic hydrophilic cellulose ether, undergoes rapid water uptake and physical swelling due to the fast hydration of its methoxyl and hydroxypropyl substituent groups. However, un-cross-linked HPMC matrices can undergo rapid erosion and dissolution. The integration of Carbopol 934, a highly cross-linked polyacrylic acid polymer, stabilizes the hydrated structure. Carbopol undergoes significant swelling in pH 6.8 environments due to the ionization of its carboxylic acid groups (-COOH) into negatively charged carboxylate ions ($-COO^-$). The resulting electrostatic repulsion between the ionized polymeric chains forces the network to expand,

absorbing large volumes of water within its cross-linked voids [14, 22]. This controlled swelling creates a highly viscous, cohesive gel barrier that regulates the diffusion rate of the dissolved phytoconstituents while preventing the premature physical disintegration of the patch.

3.6. Moisture Content and Moisture Uptake

The equilibrium moisture profile of a buccal film influences both its physical stability during long-term storage and its initial mechanical performance. The percentage moisture content of the freshly fabricated polyherbal patches was quantified as 2.45 ± 0.18% (n = 3). This low level of residual moisture is highly desirable as it restricts molecular mobility within the dry matrix, preventing chemical degradation or oxidation of the active phytoconstituents (such as eugenol and glycyrrhizinic acid). Maintaining low moisture content effectively prevents opportunistic microbial or fungal contamination within the package during its shelf life.

The moisture uptake analysis, which evaluates the physical stability of the formulation under high-humidity stress (75 ± 5% Relative Humidity), revealed a controlled moisture absorption value of 5.12 ± 0.34% (n = 3) over 72 hours. This restricted hygroscopicity is critical; excessive moisture absorption under environmental storage conditions can cause premature plasticization, leading to sticky, deformed films that are difficult to handle. The results indicate that wrapping the patches in aluminum foil and storing them in a desiccator containing activated silica gel is sufficient to maintain their dry, flexible state and preserve their mechanical characteristics over extended periods.

3.7. *In Vitro* Disintegration and Dissolution

The *in vitro* disintegration time of the polyherbal patches was evaluated in simulated saliva fluid (pH 6.8) at 37 ± 0.5∘C to determine the duration required for the film to undergo complete structural breakdown. The formulation exhibited a disintegration time of 4.15 ± 0.32 minutes (n = 6). This rapid structural disintegration is highly suitable for localized oral ulcer management.

Upon application, the film rapidly hydrates to form a protective, highly mucoadhesive gel layer. The fast structural transition of HPMC and Carbopol allows the mechanical release of the active ingredients within the first few minutes, providing rapid clinical relief from localized pain via the anesthetic activity of eugenol. This is followed by the slower, sustained diffusion of glycyrrhizin and acemannan from the gel layer onto the ulcerated epithelial tissues, ensuring continuous anti-inflammatory and wound-healing action.

Table 2. Physicochemical Evaluation Results

Sr. No.	Parameter Evaluated	Quantitative Value (Mean ± SD)	Reference/Standard Range
1.	Color Uniformity	Reddish brown, highly uniform (n=10)	Visually consistent across casting area
2.	Surface Texture	Smooth, non-tacky, crack-free (n=10)	Physically defect-free structural matrix
3.	Average Thickness	0.42 ± 0.03 mm (n=6)	0.2 to 0.7 mm (Buccal target)
4.	Mass Uniformity	45.2 ± 1.2 mg (n=10)	Within ± 5% pharmacopoeial limit
5.	Individual Mass Deviation	-3.44 ± 0.52% (n=10)	Meets USP specifications
6.	Folding Endurance	112 ± 8 folds (n=6)	>100 folds (Indicates high flexibility)
7.	Surface pH	6.50 ± 0.08 (n=3)	6.5 to 7.2 (Compatible with saliva)
8.	Swelling Index	30.4 ± 1.8% (n=3)	Controlled swelling without erosion
9.	Percentage Moisture Content	2.45 ± 0.18% (n=3)	Low moisture to prevent microbial spoilage
10.	Percentage Moisture Uptake	5.12 ± 0.34% (n=3)	Highly stable under humid conditions
11.	*In Vitro* Disintegration Time	4.15 ± 0.32 minutes (n=6)	Rapid initial breakdown for quick relief
12.	*Ex Vivo* Mucoadhesive Force	0.38 ± 0.04 N (n=3)	Prolonged retention at mucosal interface
13.	Glycyrrhizin Content Uniformity	98.12 ± 1.45% (n=6)	85% to 115% (Dose uniformity target)
14.	Eugenol Content Uniformity	97.45 ± 1.82% (n=6)	85% to 115% (Dose uniformity target)

3.8. *Ex Vivo* Mucoadhesive Strength

Mucoadhesion is the key biophysical mechanism that prevents salivary washout and keeps the active ingredients localized at the target site. The *ex vivo* mucoadhesive strength of the polyherbal film was quantified on freshly excised porcine buccal mucosa using

a modified physical balance system. The minimum weight required to detach the hydrated 2 × 2 cm^2 patch from the mucosal surface was 38.7 ± 4.2 g (n = 3). The corresponding Mucoadhesive Force (F) was calculated to be 0.38 ± 0.04 N.

This robust mucoadhesive force is driven by the physical and chemical interactions between the hydrated polymeric blend and the mucus gel layer coating the buccal mucosa. Carbopol 934 is widely recognized as an exceptional mucoadhesive polymer due to its high density of carboxylic acid groups. Upon initial hydration (contact phase), these carboxyl groups form strong hydrogen bonds with the oligosaccharide chains of mucin glycoproteins [22]. Similarly, the flexible, linear chains of HPMC interpenetrate into the mucus network (consolidation phase), establishing physical entanglements. The combination of chemical hydrogen bonding and physical chain entanglement prevents the displacement of the patch by salivary flow or mechanical tongue movements, ensuring localized therapeutic action.

3.9. Drug Content Uniformity

To ensure dosage accuracy and therapeutic consistency, the content uniformity of key bioactive marker compounds within the polyherbal matrix was validated using double-beam UV-Visible spectrophotometry. Eugenol from *Syzygium aromaticum* and glycyrrhizinic acid from *Glycyrrhiza glabra* were selected as the analytical index markers. Quantitative analysis of individual 2 ×2 cm^2 film units revealed an exceptionally high degree of content uniformity, with a glycyrrhizinic acid content of 98.12 ± 1.45% and a eugenol content of 97.45 ± 1.82% (n = 6) relative to the theoretical loading. These values conform to the strict pharmacopoeial requirements for dosage uniformity (85% to 115%). This confirms that the solvent casting methodology and premixing steps successfully prevented precipitation or localized crystallization of the active herbal constituents during the casting and drying processes.

3.10. *In Vitro* Microbiological Inhibition

The localized antimicrobial efficacy of the developed polyherbal mucoadhesive buccal films was evaluated using the agar well diffusion method against two opportunistic oral pathogens: *Streptococcus mutans* (a primary cariogenic bacterium) and *Candida albicans* (an opportunistic fungal pathogen that causes oral candidiasis in immunocompromised or ulcerated patients). The results of the microbiological assays are summarized in Table 3.

Table 3. *In Vitro* Microbiological Inhibition of Polyherbal film in comparison with Blank and Standard

Test Organism	Test Group (Polyherbal Film) Zone (mm)	Positive Control (0.2% w/v CHX) Zone (mm)	Negative Control (Blank Film) Zone (mm)
Streptococcus mutans (MTCC 497)	16.2 ± 0.8	22.4 ± 1.1	0.0 ± 0.0
Candida albicans (MTCC 3017)	14.5 ± 0.6	20.1 ± 0.9	0.0 ± 0.0

Mean ± Standard Deviation with n = 3. *CHX - chlorhexidine gluconate.*

The microbiological evaluation showed that the optimized polyherbal buccal patch possesses significant, broad-spectrum antimicrobial activity. The zone of inhibition against *Streptococcus mutans* was 16.2 ± 0.8 mm, and the zone against *Candida albicans* was 14.5 ± 0.6 mm. The blank polymeric film (negative control) showed no zone of inhibition (0.0 mm), confirming that the HPMC and Carbopol base has no inherent antimicrobial activity and verifying that the observed therapeutic effect is entirely due to the encapsulated herbal extracts.

This powerful antimicrobial action is driven by the synergistic mechanisms of the active phytoconstituents. Eugenol, the primary phenylpropanoid in *Syzygium aromaticum*, partition into the lipid bilayer of microbial cell membranes, increasing membrane permeability and causing the leakage of vital intracellular components. Eugenol also deactivates critical membrane-bound enzymes, disrupting cellular respiration and proton-motive force generation [23]. Glycyrrhizinic acid from *Glycyrrhiza glabra* contributes to this effect by disrupting bacterial cell wall synthesis and inhibiting microbial adhesion to mucosal surfaces. The mucilaginous polysaccharides of *Aloe vera* gel, particularly acemannan, enhance this activity by forming a localized protective layer that prevents microbial colonization and biofilm formation. Although the positive control (0.2% w/v chlorhexidine) produced larger zones of inhibition (22.4 mm and 20.1 mm), chlorhexidine is known to cause mucosal staining, taste alterations, and localized tissue toxicity upon prolonged use. The polyherbal patch offers a safer, highly effective, and natural alternative with minimal risk of mucosal irritation.

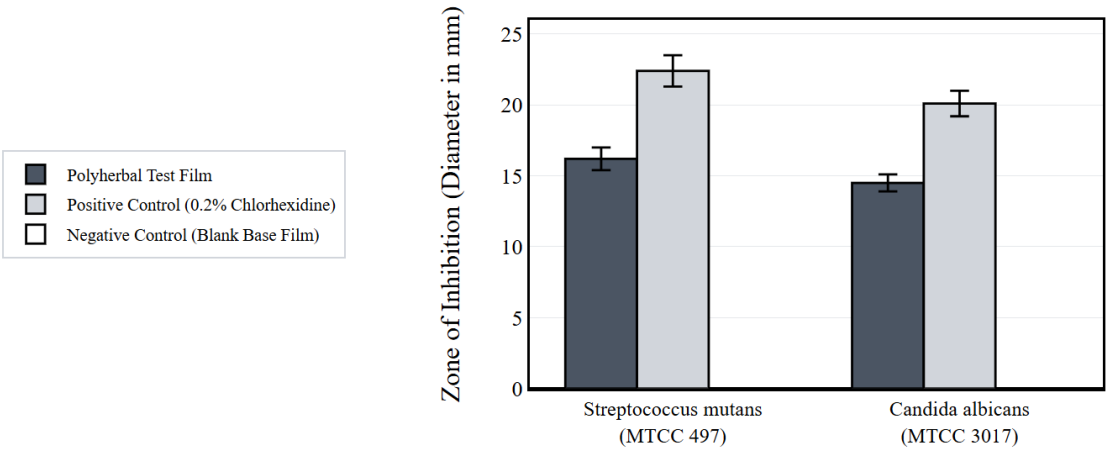

Figure 2. *In Vitro* Microbiological Inhibition of Polyherbal film in comparison with Blank and Standard

4. Discussion

The primary clinical advantage of the formulated polyherbal mucoadhesive buccal film is its ability to provide localized, site-specific delivery of active phytoconstituents directly to the damaged oral mucosa. The HPMC and Carbopol matrix serves as a localized drug depot by adhering to the mucosal interface. This depot releases the active principles directly into the surrounding extracellular fluid, achieving high local concentrations with a very small total dose. This targeted delivery route completely bypasses the gastrointestinal tract, protecting the active herbal molecules from enzymatic degradation in the stomach and avoiding first-pass hepatic metabolism. Therefore, therapeutic efficacy is maximized, and the risk of systemic side effects is minimized.

Recurrent aphthous stomatitis and oral ulcers are characterized by the loss of the protective epithelial layer, exposing the highly sensitive nerve endings of the lamina propria to thermal, chemical, and mechanical irritants. The developed buccal film addresses this clinical challenge by acting as a protective physical barrier. Upon contact with saliva, the hydrophilic polymers hydrate to form a soft, protective cohesive gel layer that covers the ulcerated bed. This physical shield protects the exposed nerves from friction during speech and chewing, as well as irritation from acidic, spicy, or hot foods, providing immediate symptomatic relief. Similarly, the steady release of eugenol from the clove extract provides localized anesthetic action, numbing the pain receptor pathways without causing the localized tissue necrosis or burning sensations associated with synthetic topical anesthetics.

Apart from providing physical protection and pain relief, the polyherbal buccal patch actively promotes tissue repair. The concentrated *Aloe vera* gel within the matrix contains high concentrations of acemannan, a polysaccharide that stimulates localized macrophages and fibroblasts. This stimulation triggers the secretion of growth factors, including Epidermal Growth Factor (EGF) and Fibroblast Growth Factor (FGF), which accelerate cell proliferation, collagen deposition, and wound contraction. This regenerative process is supported by the cytoprotective effects of glycyrrhizinic acid from *Glycyrrhiza glabra*, which downregulates pro-inflammatory cytokines such as TNF-α and IL-1β. The film prevents further tissue destruction, shortens the recovery phase, and accelerates mucosal re-epithelialization by reducing localized inflammation.

The moist, nutrient-rich environment of the oral cavity makes open ulcerative lesions highly vulnerable to secondary opportunistic infections by bacteria (such as *Streptococcus mutans*) and fungi (such as *Candida albicans*). This secondary microflora colonize the damaged tissues, forming resilient biofilms that delay healing and exacerbate localized inflammation. The polyherbal film addresses this complication through its broad-spectrum antimicrobial activity. The continuous release of eugenol and glycyrrhizinic acid from the mucoadhesive patch inhibits microbial adhesion and disrupts biofilm formation. This antimicrobial protection helps maintain a hygienic environment around the lesion, preventing secondary complications and supporting optimal physiological healing.

5. Conclusion

The development and systematic characterization of the polyherbal mucoadhesive buccal film show the viability of integrating therapeutic botanical extracts into a modern, site-specific polymeric delivery device. A highly uniform, flexible, and cohesive matrix was successfully casted by utilizing a binary polymeric blend composed of hydroxypropyl methylcellulose E15 and Carbopol 934, optimized with a 30% w/w concentration of glycerol as a plasticizer. The results achieved, including a localized surface pH of 6.50 ± 0.08 and a dimensional thickness of 0.42 ± 0.03 mm, align with the physiological parameters of the human oral cavity, confirming

that the formulation is highly biocompatible and non-irritating to the sensitive oral mucosa. The mechanical durability of the film is highlighted by a folding endurance value exceeding 100 folds (112 ± 8 folds), ensuring that the patch can withstand the physical stresses of speech and mastication. Biophysical evaluation confirmed that the controlled swelling index of 30.4 ± 1.8% and an *ex vivo* mucoadhesive force of 0.38 ± 0.04 N work together to resist rapid salivary washout, enabling prolonged retention at the targeted mucosal site. The spectrophotometric validation of content uniformity (98.12 ± 1.45% for glycyrrhizinic acid and 97.45 ± 1.82% for eugenol) proves the consistency and reliability of the solvent casting methodology. *In vitro* microbiological assays confirmed that the encapsulated active principles retain their therapeutic potency, producing distinct zones of inhibition of 16.2 ± 0.8 mm against *Streptococcus mutans* and 14.5 ± 0.6 mm against *Candida albicans*. These values show significant localized antimicrobial action when compared to the inactive negative control films. This multi-component polymeric device succeeds in combining immediate physical shielding with sustained pharmacological action, indicating a major advancement over conventional semi-solid gels and mouthwashes.

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