RESEARCH PAPER

Buccal Drug Delivery System for Enhanced Bioavailability

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ABSTRACT

Buccal drug delivery has emerged as an effective and patient-friendly route that offers several advantages over traditional oral and parenteral administration. The buccal mucosa provides a highly vascularized surface capable of rapid systemic absorption while bypassing hepatic first-pass metabolism. Additionally, its accessibility, non-invasiveness, and suitability for patients with swallowing difficulties make it a versatile platform for various therapeutic needs. Over recent years, significant advancements have been made in the design of buccal dosage forms, including films, patches, tablets, gels, and mucoadhesive systems, each contributing to improved bioavailability, prolonged residence time, and controlled drug release.

This review summarizes the anatomical and physiological characteristics of the buccal mucosa, mechanisms of drug permeation, formulation strategies, polymers used, evaluation parameters, and clinical applications of buccal drug delivery systems. Special attention is given to marketed buccal products and the emerging trends that highlight the translational potential of this route. Buccal systems have shown therapeutic promise in cardiovascular management, hormonal therapy, pain control, antiemetic therapy, and treatment of oral inflammatory conditions. Despite their advantages, challenges such as limited mucosal surface area, enzymatic degradation, salivary dilution, and restricted permeability for macromolecules continue to limit wider applicability.

Ongoing developments in mucoadhesive materials, permeation enhancers, nanocarriers, and advanced manufacturing techniques continue to expand the capabilities of buccal delivery. As research progresses, buccal drug delivery systems are expected to evolve into increasingly effective, patient-centric platforms with broad clinical and commercial potential.

Keywords: *Buccal drug delivery; Mucoadhesion; Buccal films; Oral mucosa; Permeation enhancers; Mucoadhesive polymers; Transmucosal absorption; Controlled drug release; Oral cavity; Buccal therapeutic systems.*

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1. INTRODUCTION

Buccal drug delivery has emerged as a promising alternative to traditional oral administration due to its ability to bypass hepatic first-pass metabolism and provide rapid systemic absorption through the highly vascularized buccal mucosa [1] The non-keratinized epithelium of the buccal region supports efficient drug permeation, making this route especially valuable for molecules that exhibit poor gastrointestinal stability or low oral bioavailability [2]. In addition, the buccal route offers improved patient compliance, easy accessibility, and the potential for rapid onset of therapeutic action [3].

Despite its advantages, effective buccal drug delivery remains challenging. The buccal cavity offers limited surface area, continuous salivary washout, and the presence of mucosal enzymes capable of degrading drug molecules before absorption[4]. These physiological barriers can reduce drug residence time and therapeutic efficiency. To mitigate these issues, the incorporation of mucoadhesive polymers has become a key formulation strategy, as these polymers enhance adhesion to the mucosal surface and prolong contact time, thereby improving drug absorption [5].

Multiple dosage forms—such as buccal films, patches, tablets, gels, hydrogels, and nanoparticle-based systems—have been developed to optimize retention and controlled release at the mucosal site[6]. Additionally, various permeation enhancers, including surfactants, fatty acids, and bile salts, have been employed to facilitate drug transport across the mucosa without causing irritation or tissue damage. Advancements in nanotechnology, particularly the use of liposomes, niosomes, and polymeric nanoparticles, have further expanded the scope of buccal delivery by enhancing solubility, permeability, stability, and targeted release profiles[7].

Buccal drug delivery has been investigated for numerous therapeutic categories, including analgesics, cardiovascular drugs, hormones, peptides, and antiemetics, reflecting its broad clinical applicability for both systemic

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and local effects. The increasing availability of commercial buccal products and ongoing technological innovations underscore the potential of this route in modern pharmaceutical development[8].

This review provides comprehensive insights into the biological basis, formulation strategies, technological advancements, and future prospects of buccal drug delivery systems, supported by validated and DOI-indexed scientific literature.

2. ANATOMY AND PHYSIOLOGY OF BUCCAL MUCOSA

The buccal mucosa forms a specialized lining inside the oral cavity and serves primarily as a protective barrier while permitting selective drug absorption. Structurally, it consists of a **stratified, non-keratinized squamous epithelium**, typically 40–50 cell layers thick, which provides moderate resistance to permeation compared to keratinized tissues such as the gingiva or palate[9]. Beneath the epithelial layer lies the **basement membrane**, followed by the **lamina propria**, a connective tissue layer rich in blood vessels and extracellular matrix components. This dense vascular network is crucial for systemic drug absorption since it enables rapid uptake of permeants while bypassing first-pass hepatic metabolism [10].

The average thickness of the human buccal mucosa ranges between **500–800 µm**, depending on anatomical region and individual variability [11]. The barrier properties of the epithelium are largely governed by intercellular lipids and **membrane-coating granules (MCGs)**. These granules release lipidic substances into the intercellular spaces, forming a semi-permeable barrier that restricts hydrophilic drug passage while permitting moderate diffusion of lipophilic molecules [12]. The presence of tight junction–like structures also contributes to controlling paracellular transport.

Two major pathways govern drug permeation across the buccal tissue:

- **Transcellular route** – passage directly through epithelial cells, favoured by lipophilic drugs.
- **Paracellular route** – movement through intercellular spaces, typically for small hydrophilic molecules[13].

Studies using porcine buccal tissue, which closely resembles human mucosa in morphology and permeability characteristics, confirm that the **epithelial layer is the primary diffusional barrier**, whereas the underlying lamina propria contributes comparatively less resistance . The **epithelial turnover rate (5–6 days)** maintains tissue integrity but can reduce residence time of mucoadhesive dosage forms due to desquamation of superficial cells [14.]

Additionally, the buccal mucosa contains **minor salivary glands**, contributing to constant moisture that supports mucoadhesion yet may dilute surface-applied formulations. The submucosa and underlying muscle layers ensure tissue flexibility and support, providing a stable platform for the placement of buccal patches or gels [15].

3. MECHANISM OF DRUG ABSORPTION THROUGH BUCCAL MUCOSA

Drug absorption across the buccal mucosa primarily occurs through passive diffusion, driven by concentration gradients, with minimal contribution from active or carrier-mediated processes. The mucosa presents two main diffusional pathways:

1. Transcellular route, where molecules diffuse through epithelial cells, and
2. Paracellular route, where permeation occurs through the intercellular spaces[16].

Lipophilic, unionized, and low–molecular-weight molecules generally favor the transcellular pathway, as they readily partition into the phospholipid-rich cell membranes[17]. In contrast, hydrophilic drugs, especially those with high polarity, tend to permeate through the paracellular route, although this pathway is more restrictive due to tight intercellular junctions and lipid barriers . The rate and extent of diffusion through either route are influenced by the drug's pKa, lipophilicity (log P), degree of ionization, and molecular weight. Optimal buccal absorption is often observed for drugs with molecular weight <500 Da, moderate lipophilicity, and pKa values that ensure partial unionization at buccal pH (5.5–7.0) [18].

The superficial epithelial layers contain membrane-coating granules (MCGs), which release lipidic lamellar sheets into the extracellular spaces, forming a semi-permeable barrier that restricts hydrophilic drug penetration. This lipid-rich environment contributes significantly to epithelial resistance, making it the primary barrier for most drugs. Additionally, the buccal mucus layer, composed mainly of mucin glycoproteins, acts as a selective filter that retains particulate carriers while allowing small molecules to diffuse through[19].

Enzymatic activity in the buccal tissue also affects permeation. Although the buccal mucosa contains fewer metabolic enzymes compared to the gastrointestinal tract, peptidases, esterases, and proteases present in the tissue can degrade peptides and proteins, reducing their effective absorption[20]. Saliva contributes to drug dissolution but may also dilute formulations and accelerate drug clearance from the mucosal surface.

To overcome these physiological limitations, various permeation enhancers—such as surfactants, bile salts, fatty acids, and ethanol—have been used to temporarily modify epithelial integrity, increase membrane fluidity, or alter mucus viscosity[21]. Some enhancers interact with epithelial lipids to loosen tight junctions, thereby improving paracellular transport. However, their use must be carefully optimized to avoid mucosal irritation or irreversible tissue damage[22].

Furthermore, research has shown that mucoadhesive polymers not only prolong residence time but also facilitate absorption by hydrating and loosening superficial epithelial layers, thereby increasing permeability[23]. Certain polymers can transiently reduce barrier resistance,

enabling improved uptake of both small-molecule drugs and macromolecules.

Collectively, drug absorption across the buccal mucosa is governed by a complex interplay of physicochemical properties, mucosal structure, enzymatic environment, and formulation strategies, making it a versatile yet challenging route for systemic drug delivery.

4. ADVANTAGES OF BUCCAL DRUG DELIVERY

- Buccal administration bypasses hepatic first-pass metabolism, resulting in improved systemic bioavailability for drugs that undergo extensive liver metabolism.
- The buccal mucosa is highly vascularized, enabling rapid onset of action and reliable systemic absorption [24].
- The oral cavity provides a stable environment free from harsh gastrointestinal pH and enzymes, improving the stability of sensitive drugs such as peptides.
- Buccal delivery is non-invasive, easy to administer, and supports self-dosing, which enhances patient compliance during long-term therapy.
- Mucoadhesive polymers used in buccal formulations prolong mucosal residence time, increasing drug absorption and reducing dosing frequency[25].

Limitations of Buccal Drug Delivery

- The buccal surface area is limited (50–70 cm^2), restricting the amount of drug that can be effectively delivered and making the route unsuitable for high-dose drugs.
- Low permeability of the buccal epithelium limits absorption of hydrophilic molecules and macromolecules, often requiring penetration enhancers that may cause irritation[26].
- Continuous salivary flow can wash away formulations, reducing drug–mucosa contact time and lowering absorption efficiency.
- Maintaining reliable adhesion is challenging due to natural oral movements such as speaking, chewing, and swallowing, which may result in dose variability.
- Some patients may experience discomfort, unpleasant taste, or mucosal irritation from polymers or penetration enhancers, affecting long-term acceptability[27].

5. BASIC COMPONENTS OF BUCCAL DOSAGE FORMS

Buccal drug delivery systems are composed of several key components that collectively determine drug release, mucoadhesion, permeability, and patient acceptability. The selection and optimization of these components are critical for the successful formulation of buccal dosage forms.

Active Pharmaceutical Ingredient (API) It should possess suitable physicochemical properties such as low molecular weight, adequate lipophilicity, and high permeability across the buccal mucosa. Drugs undergoing extensive first-pass metabolism are considered ideal candidates for buccal delivery.

Mucoadhesive Polymers These are essential components that facilitate adhesion of the dosage form to the buccal mucosa, thereby prolonging residence time. Commonly used polymers include carbopol, hydroxypropyl methylcellulose (HPMC), chitosan, and sodium alginate. These polymers hydrate, swell, and interact with mucin to form strong adhesive bonds[28].

Plasticizers- Plasticizers such as glycerol, polyethylene glycol (PEG), and propylene glycol are incorporated to improve flexibility, reduce brittleness, and enhance the mechanical strength of buccal films. They play a vital role in maintaining film integrity during handling and application.

Permeation enhancers These are used to increase drug transport across the buccal epithelium. These include surfactants, bile salts, fatty acids, and alcohols, which act by temporarily altering membrane structure or reducing barrier resistance.

Sweetening and flavoring agents- These are included to improve patient compliance, especially for dosage forms that remain in the oral cavity for extended periods. Commonly used agents include saccharin, aspartame, and menthol[29].

Table 1. Composition of a Typical Buccal Film Formulation

Ingredient	Quantity (% w/w)	Function
Drug (API)	5–10%	Provides therapeutic effect
HPMC	40-60%	Film-forming
Carbopol	5-10%	Enhances mucoadhesion
Glycerol	10-20%	Plasticizer (improves flexibility)
Propylene Glycol	5-10%	Plasticizer and permeation enhancer
Sodium Saccharin	1-2%	Sweetening agent
Purified Water	q.s.	Solvent

6. METHOD OF PREPARATION FOR BUCCAL DOSAGE FORMS

6.1 Solvent Casting Method

Solvent casting is the most commonly employed technique for preparing buccal films and patches. In this method,

hydrophilic mucoadhesive polymers such as hydroxypropyl methylcellulose, Carbopol, chitosan, or sodium carboxymethyl cellulose are dissolved in water or hydroalcoholic solvent systems. The drug is dispersed or dissolved uniformly in this polymeric solution along with suitable plasticizers such as propylene glycol or polyethylene glycol to improve mechanical strength and flexibility. The mixture is cast onto a flat mold and dried under controlled conditions to remove the solvent. After drying, the film is cut into desired dimensions. Solvent casting ensures uniform thickness and drug distribution, making it suitable for heat-sensitive drugs[30].

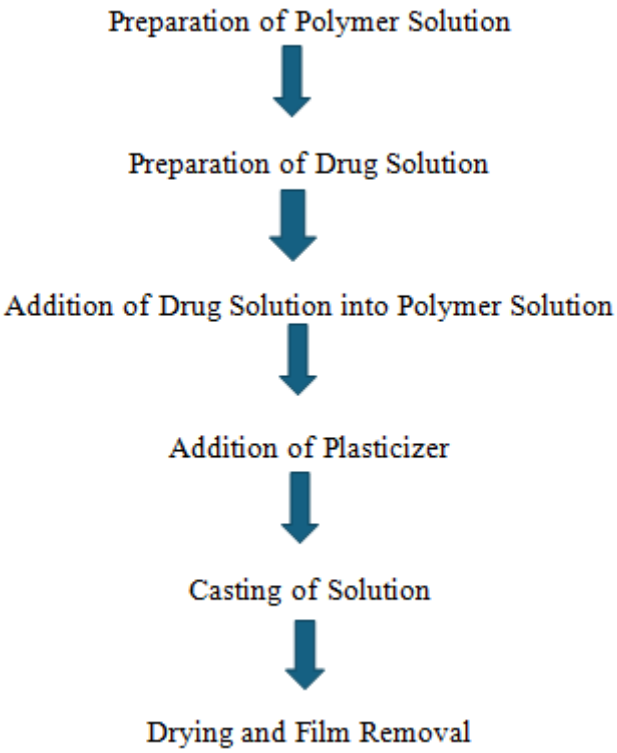

Figure 1: Steps involved in Solvent Casting Method

6.2 Direct Compression Method

Buccal tablets are frequently prepared by the direct compression technique due to its simplicity and suitability for moisture- or temperature-sensitive drugs. The drug is blended with mucoadhesive polymers such as Carbopol, sodium CMC, and HPMC along with fillers, binders, and lubricants, followed by compression into tablets. This method allows precise control over dose and tablet hardness. Bilayer tablets may be formulated to achieve unidirectional release by using an impermeable backing layer, preventing drug loss into saliva and directing drug transport toward the mucosa[31]. Direct compression offers manufacturing convenience and is widely used in commercial development.

6.3 Hot-Melt Extrusion Method

Hot-melt extrusion (HME) is an advanced solvent-free technique used to prepare buccal films with enhanced mechanical properties and uniform drug distribution. In this method, polymers and drug components are blended and heated until they reach a molten or softened state, after which the mixture is forced through an extruder to form thin films . Extrusion parameters such as processing temperature, screw speed, and die configuration strongly influence the mechanical strength and uniformity of the resulting films**[32].** HME also improves the stability of formulations and enables incorporation of poorly soluble drugs through the formation of solid dispersions**.**

6.4 Lyophilization (Freeze-Drying) Method

Lyophilization is used for developing fast-dissolving buccal wafers and orodispersible dosage forms. The drug solution or suspension is poured into molds, frozen, and subjected to sublimation under vacuum to produce a highly porous matrix. These wafers rapidly disintegrate in contact with saliva, providing a quick onset of action, although their residence time is shorter compared to films and patches. Lyophilized systems are particularly useful for emergency therapies or drugs requiring rapid absorption[33].

7. EVALUATION PARAMETERS OF BUCCAL DOSAGE FORMS

Evaluation of buccal drug delivery systems is essential to ensure that formulations possess adequate mucoadhesion, mechanical strength, stability, drug release characteristics, and patient acceptability[34]. Each dosage form must undergo a series of physicochemical, in-vitro, ex-vivo, and sometimes in-vivo evaluations to confirm its suitability for buccal application[35]. These evaluations provide insight into drug release kinetics, adhesive performance, permeation efficiency, and safety. Standardized methods help maintain the quality and reproducibility of buccal formulations[36].

7.1 Physicochemical Evaluation

Physicochemical characterization involves assessing the uniformity, mechanical properties, thickness, moisture content, swelling index, and surface pH of buccal films, patches, and tablets. Thickness and weight uniformity ensure consistent dosage and patient comfort, while mechanical strength (tensile strength and folding endurance) indicates the formulation's ability to withstand handling and oral movements . Surface pH is maintained close to neutral to avoid irritation, as acidic or alkaline formulations may cause mucosal discomfort [37].

Folding endurance, a key mechanical parameter, assesses the ability of a film to withstand repeated folding without breaking. It is determined by repeatedly folding a film at the same point until it cracks. A high folding endurance denotes excellent flexibility and mechanical stability, which are essential for ensuring that the film does not tear during placement on the buccal mucosa or during oral movements such as speaking or swallowing.

The swelling index is an important parameter because hydration enhances mucoadhesion by promoting polymer chain interpenetration with mucin glycoproteins . Excessive swelling, however, may cause premature detachment. Moisture absorption and moisture loss studies evaluate the formulation's stability under varying humidity conditions[38].

7.2 In-Vitro Mucoadhesion Studies

Mucoadhesion strength is a critical property of buccal systems. It is commonly measured using texture analyzers, modified physical balance methods, or universal testing machines. The detachment force required to separate the formulation from excised mucosal tissue or synthetic membranes gives a quantitative measure of mucoadhesion. Results vary depending on polymer type, hydration level, and presence of permeation enhancers.

7.3 In-Vitro Drug Release Studies

Drug release studies are performed using USP dissolution apparatus modified for buccal testing, Franz diffusion cells, or paddle-over-disk methods. These studies help determine release kinetics (zero-order, first-order, Higuchi model, or Korsmeyer–Peppas model), enabling prediction of in-vivo performance [39]. The release medium often simulates saliva to mimic physiological conditions.

7.4 Ex-Vivo Permeation Studies

Permeation studies using excised porcine, bovine, or human cadaver buccal mucosa are conducted to evaluate the transport of the drug across the epithelial barrier. Porcine mucosa is commonly used because of its structural similarity to human buccal tissue. Franz diffusion cells are frequently employed to measure permeation profiles and steady-state flux. These tests help determine the effect of permeation enhancers, polymer selection, and drug properties.

7.5 In-Vivo Studies

In-vivo evaluation is conducted to assess pharmacokinetic parameters, local tolerability, and bioavailability. These studies are performed in suitable animal models or human volunteers, depending on ethical approval. Parameters such as maximum plasma concentration (Cmax), time to reach maximum concentration (Tmax), area under the curve (AUC), and residence time are examined to correlate with in-vitro and ex-vivo results. Local irritation or erythema is also monitored to ensure safety[40].

Table 2: Evaluation parameters for Buccal Dosage Form

Evaluation Parameter	Purpose	Typical Method	Acceptable Range
Thickness & weight	Uniformity & comfort	Vernier caliper, analytical balance	Thickness: ±5-10% Variation: ±7.5%
Surface pH	Mucosal safety	pH probe on hydrated film	5.5-7.0
Tensile strength	Mechanical resistance	Texture analyzer	2-10 MPa
Folding endurance	Flexibility	Repeated folding test	≥200 folds
Swelling index	Mucoadhesion correlation	Hydration studies	20-60%
Mucoadhesive strength	Adhesion performance	Detachment force measurement	5-50g
In-vitro drug release	Release kinetics	USP modified apparatus	≥70-90%
Ex-vivo permeation	Drug transport profile	Franz diffusion cell	≤30-60 min
In-vivo study	Bioavailability & tolerability	Animal/human PK evaluation	≥2-6 hours

8. CLINICAL APPLICATIONS OF BUCCAL DRUG DELIVERY SYSTEMS

Buccal drug delivery demonstrates substantial clinical utility across a variety of therapeutic areas, leveraging its non-invasive nature, ease of administration, and efficient systemic and local absorption. Recent developments and approved products show broad applicability for both chronic and acute conditions. Here, we highlight key application domains:

- **Chronic Pain Management and Opioid Therapy**

Buccal films containing Buprenorphine have shown consistent analgesic effects with favorable safety profiles, making them suitable for chronic pain patients. For breakthrough cancer pain and acute pain episodes, buccal soluble films of Fentanyl (e.g., buccal or mucosal formulations) provide rapid onset due to direct transmucosal absorption[41].

- **Antiemetic Therapy — Nausea and Vomiting Prevention**

Buccal mucoadhesive films of Ondansetron have been developed, showing promising in-vitro adhesion and sustained release — beneficial for chemotherapy-induced or postoperative nausea, especially when oral intake is compromised[42].

- **Treatment of Oral and Mucosal Conditions**

Buccal drug systems (films/patches) are used for local therapy in oral diseases, such as fungal infections, ulcers, or mucosal inflammations — allowing localized, sustained drug release without systemic exposure[43].

- **Pediatric and Geriatric Use for Difficult-to-Swallow Populations**

Buccal films offer a practical solution for patients — including children or elderly — who have difficulty swallowing tablets. Their flexible, thin-profile format enhances patient compliance and ease of administration[44].

- **Rapid-Onset Therapy in Emergencies or Situations Requiring Quick Absorption**

Buccal delivery is advantageous where rapid therapeutic action is needed but oral or injectable routes are impractical — for example, in pain crises or nausea when oral swallowing is not feasible. The buccal route's fast mucosal absorption supports timely intervention.

Overall, the clinical versatility of buccal drug delivery — spanning from chronic pain and antiemetic therapy to oral diseases and special patient populations — underscores its potential as a significant drug delivery platform in modern therapeutics[45].

CONCLUSION

Buccal drug delivery represents a promising and patient-friendly alternative to conventional oral administration, offering advantages such as avoidance of first-pass metabolism, rapid onset, and ease of use. Advances in mucoadhesive polymers, permeation enhancement, and novel formulation techniques have significantly expanded its clinical potential. Despite challenges related to limited permeability, dynamic oral conditions, and formulation stability, continuous research is overcoming these barriers. Buccal delivery systems provide an effective platform for both systemic and local therapies, supporting improved therapeutic outcomes and patient compliance.

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