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Review Article

Advances in Buccal Films: A Promising Platform for Oral Mucosal Drug Delivery: An updated review

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Abstract

The buccal route offers a non-invasive method for drug administration that improves systemic absorption by bypassing hepatic first-pass metabolism. This article summarises recent innovations, including the incorporation of nanoparticles and 3D printing technologies, with a particular focus on challenges in biologics delivery and clinical translation. The discussion encompasses anatomical considerations, mechanisms of adhesion, formulation design, and evaluation procedures, with applications ranging from local therapies to systemic treatments for conditions such as chronic pain, neurological disorders, and immunisation. Limitations such as reduced drug-loading capacity and saliva-induced erosion are critically examined, alongside potential solutions offered by novel polymer systems. The paper also explores emerging prospects, including the role of artificial intelligence in design optimisation and evolving regulatory frameworks that could accelerate the clinical adoption of buccal films.

Keywords: Buccal films, mucoadhesive drug delivery, nanotechnology, 3D printing, therapeutics, regulatory guidelines.

1. Introduction

The oral cavity serves as a versatile site for drug delivery, with the buccal mucosa standing out due to its vascular absorption and ability to bypass first-pass metabolism [2]. Clinical studies in 2024 demonstrated fentanyl achieving about 71% bioavailability through buccal delivery [21], surpassing oral routes (~35%)[32], highlighting it's utility for patients who struggle with swallowing [24]. The transition from tablets to films has gained momentum since 2021, driven by 3D printing technology[19], expanding applications from local antifungals[14] to systemic treatments like hypertension management[10]. Market growth is projected at 8.5% CAGR to 2032[12], yet commercialization remains limited (e.g., Suboxone®[1]). This review integrates 2021-2025 insights on nanoparticles[18], regulatory challenges[20], and clinical outcomes[27], building on prior works[1],[15]. Building upon recent insights, this review provides a comprehensive overview of anatomical, mechanistic, and formulation aspects, along with evaluation protocols, therapeutic applications, limitations, and future perspectives.

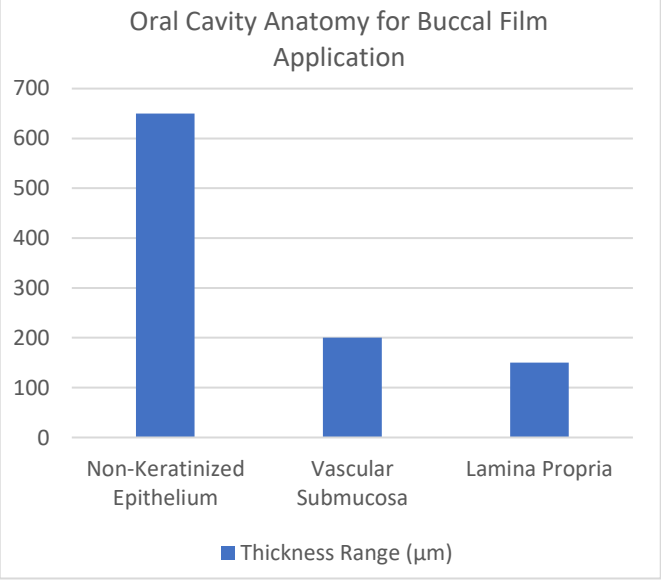

Figure 1: Bar chart of buccal layer thicknesses (non-keratinised epithelium 500-800 µm, vascular submucosa, lamina propria) [2].

2. Anatomy and Physiology of the Buccal Mucosa:

The buccal lining is composed of a stratified squamous epithelium supported by an underlying connective tissue framework, together spanning an approximate surface area of 170 cm^2. Within this structure, the non-keratinised zones are comparatively thinner and therefore more favourable for drug penetration than keratinised regions, which serve as stronger protective barriers[18]. For hydrophilic compounds, absorption tends to occur predominantly through paracellular pathways [2], and this process is strongly affected by the local environment, including the mucus layer (typically with a pH between 6.0 and 7.5) and the continuous secretion of saliva, which can reach volumes of (0.5-2 L/day) per day [2]. The rich vascularization of the buccal tissues allows for direct drug uptake into the systemic circulation, largely via the jugular venous system [3], although enzymes present in the mucosa pose challenges to the delivery of proteins and peptides [29]. Recent 2024 Recent experimental evidence suggests that the incorporation of nanoparticulate carriers can substantially increase permeation efficiency, in some cases doubling transport rates across the mucosal barrier. The relatively rapid turnover of epithelial cells, which occurs within a few days, may help to minimize long-term irritation from dosage forms [18], The relatively rapid turnover of epithelial cells, which occurs within a few days, may help to minimize long-term irritation from dosage forms [2].

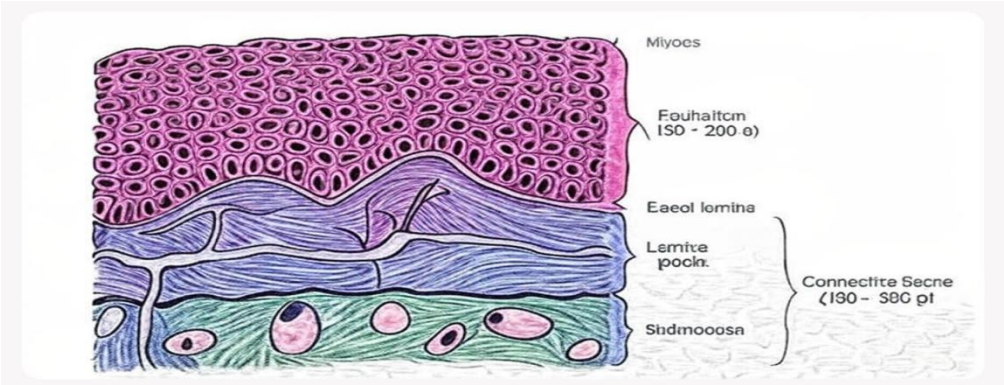

Figure 2: permeation gradient across buccal layers (epithelium to submucosa) [2].

3. Mechanisms of Mucoadhesion

Mucoadhesion describes the ability of a formulation to remain attached to the mucosal surface for extended periods, thereby improving drug absorption. This phenomenon is often explained by multiple theoretical models, including diffusion of polymer chains into the mucus layer, the creation of intermolecular bonds, and mechanical interlocking or consolidation at the interface [4]. The extent of adhesion is highly dependent on the chemical nature of the excipients used. For instance, negatively charged polymers such as pectin [3] tend to exhibit strong adhesive performance within the mildly acidic to neutral pH range. Increasing the molecular weight of polymers can further improve performance, as longer chains are more likely to entangle with mucin glycoproteins. More recent innovations have focused on chemically modifying polymers—for example, thiolation, which introduces sulfhydryl groups capable of forming disulfide bonds with mucus components. Such approaches have been shown to significantly prolong retention [4],with some experimental data indicating up to a threefold improvement compared with conventional materials [26]. Computational and biomimetic models developed in recent years now provide predictions of how long buccal formulations may remain attached, typically suggesting residence times of several hours under optimal conditions[23].

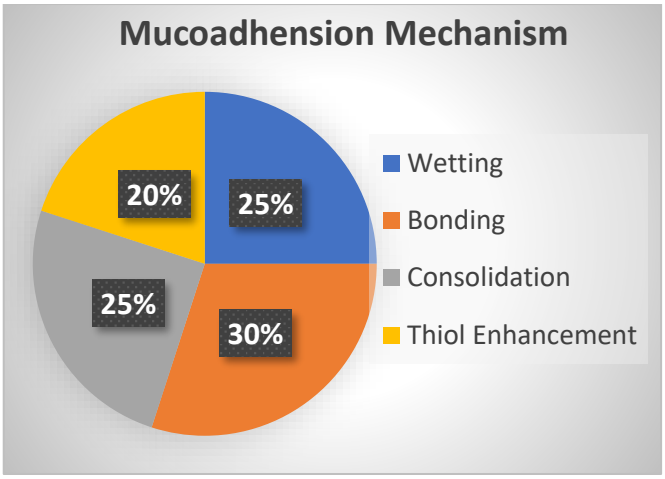

Figure 3: Pie chart of mucoadhesion contributions (Wetting 25% , Bonding 30% , Consolidation 25% , Thiol Enhancement 20%) [26].

4. Advantages and Disadvantages of Buccal Films

Buccal films enhance patient compliance by avoiding the need to swallow [24], improving bioavailability (e.g., 71% for fentanyl[21]), and support a broad range of therapeutic applications [2]. They are cost-effective[13] and suitable for pediatric use[24]. However, limitations include a restricted surface area of ~50 cm^2 (limiting drug loads to <20 mg^3), saliva dilution[2], and barriers to biologics delivery[29].

Aspect	Advantages	Disadvantages
Bioavailability	Bypasses first-pass (71% fentanyl[21])	Limited by ~50 cm^2 area[3]
Compliance	Easy placement, no swallowing[24]	Potential for irritation[2]
Stability	Protects against enzymatic degradation[29]	Erosion by saliva and enzymes[2]
Customization	Tailored release via 3D printing[19]	Restrictions due to meals
Scalability	Cost-effective extrusion[13]	Regulatory challenges[20]

5. Formulation Aspects

Buccal film formulations typically include 5-30% active pharmaceutical ingredient (API), along with mucoadhesive polymers (e.g., HPMC, chitosan[3]), plasticizers (e.g., PEG[5]), and permeation enhancers (e.g., bile salts[39]). Polymer options include natural (xanthan[5]) and synthetic (PVA[11]) types. Fabrication methods encompass solvent casting[1], hot-melt extrusion[13], and 3D printing[19]. Recent 2024 innovations feature lipid nanoparticles, increasing drug loading by approximately threefold[18]. Permeation is enhanced with cyclodextrins[39] and peptide inhibitors[29].

Evaluation Methods:

Thickness: The thickness of buccal films is an important parameter influencing both comfort and drug release. It is commonly determined using precision tools such as micrometers or digital calipers. Formulations are usually engineered to remain within the range of 50–1000 µm, as excessively thin films may compromise mechanical stability, while thicker ones may reduce patient acceptability or interfere with adhesion [7] .

Weight Variation: Weight uniformity testing is carried out by individually weighing several film samples to confirm consistency across a batch. Minimal variation in weight indicates that the drug and excipients have been evenly distributed during preparation, which is essential for achieving reproducible dosing [8].

Folding Endurance: Mechanical flexibility of buccal films is assessed through folding endurance tests, where a film is repeatedly bent at the same point until visible cracking or breakage occurs. A higher number of folds tolerated before failure reflects superior flexibility and durability. In most studies, values above 300 folds are considered adequate for handling and administration [9].

Tensile Strength: Tensile strength measurements are performed to evaluate how much force a film can withstand before breaking. Using instruments such as universal testing machines, the films are subjected to controlled stretching until rupture occurs. Optimal values usually fall within the range of 16–24 MPa, which is sufficient to maintain integrity during storage and placement in the oral cavity [10].

Swelling Index: The swelling behaviour of films is quantified by immersing them in simulated saliva and monitoring the increase in mass over time. The percentage change, often referred to as the swelling index, is calculated by comparing hydrated weight to the original dry weight. This parameter reflects the hydration capacity of the polymers, which is critical for mucoadhesion but must be balanced to prevent premature erosion [11].

pH: To ensure patient comfort and avoid irritation, the surface pH of the films is assessed by dissolving them in small volumes of distilled water, followed by measurement with pH paper or digital meters. Values close to neutrality (around 6.0–7.5) are preferred, as they align with the physiological conditions of the oral cavity [11].

Mucoadhesion: Adhesive strength is usually determined using ex vivo tissues, such as porcine buccal mucosa, in combination with texture analyzers. The detachment force required to separate the film from the mucosal surface provides a measure of adhesive capacity, while residence time can also be monitored to estimate clinical performance [12].

Content Uniformity: Drug content is quantified by analyzing multiple film samples using spectrophotometric or chromatographic techniques. The results are compared to the labelled claim, with most pharmacopeial guidelines requiring that the active content falls within 95–105% of the intended dose. This ensures dose precision across units [13].

Dissolution: Dissolution testing is carried out in vitro using USP-approved apparatus containing simulated salivary fluid, typically at pH 6.8. The rate and extent of drug release from the films are monitored over time, providing insights into their in vivo performance and onset of action [6].

Permeation: The ability of drugs to cross the buccal mucosa is often studied using Franz diffusion cells, in which excised animal or human mucosal tissues serve as the barrier. The flux of drug across the tissue is measured over time, offering predictive data for systemic absorption [1].

In Vivo: In vivo evaluations involve human volunteers or animal models and focus on determining the residence time of the films within the oral cavity as well as the pharmacokinetic profiles of the delivered drug. Such studies are vital for linking in vitro performance to clinical outcomes [32].

Stability: Stability studies are conducted to evaluate how the films withstand long-term storage and environmental stresses. These tests often involve accelerated conditions [30] of temperature and humidity, as outlined in regulatory guidelines, to predict shelf-life. Additional analyses, such as rheological testing and

imaging, may be used to verify uniformity and integrity during storage [8].

6. Applications in Pharmaceuticals

Buccal films have been investigated for both localised treatment and systemic delivery. On the local level, antifungal agents such as azoles have been incorporated into thin films to treat oral infections effectively [14]. In systemic therapy, strong evidence supports their use in pain management, as seen with fentanyl buccal films that offer rapid onset of action and higher bioavailability compared with conventional oral administration [21]. Beyond analgesics, other drugs such as domperidone have demonstrated improved pharmacokinetic profiles when delivered through this route. Recent years have also seen experimental formulations targeting more complex therapeutic areas [6] For example, buccal films are being studied as vehicles for insulin delivery [22]. Emerging applications explored in 2024 includes mucosal vaccines[33], neurodegeneration management with pramipexole[38], and combined formulations such as candesartan- based therapies for hypertension [10]. Market applications extend to polypill formulations[10] and improved pediatric compliance[42].

7. Challenges

Limited Drug Loading Capacity:

The buccal mucosa provides only about 50 cm^2 of effective surface area. This restricts films to relatively low-dose medications, making them unsuitable for drugs requiring higher quantities [3].

Saliva Interference:

Continuous saliva secretion (0.5–2 L per day) can dilute the drug or gradually erode the film. This reduces residence time and may compromise consistent drug release [2].

Barriers to Biologics Delivery:

Large molecules such as peptides and proteins are degraded by mucosal enzymes. Tight junctions between epithelial cells further limit the passage of macromolecules [29].

Regulatory hurdles:

Agencies such as FDA and EMA demand rigorous testing for safety stability and efficacy, so scaling up production and meeting international regulatory standards remains an obstacle. For example, FDA 2024 guidelines[20] and EMA stability criteria requires strict compliance [43], while 2023 biocompatibility standards[36] add further complexity.

8. Future Prospects

Nanotechnology Integration:

Lipid-based carriers such as liposomes and nanoparticles can enhance drug permeability and stability. These systems may help overcome enzymatic barriers and improve delivery of biologics [18].

Advancements in 3D Printing:

Additive manufacturing enables precise control over film dimensions, drug distribution, and release kinetics. Personalized dosing becomes possible, allowing adjustments based on individual patient needs [19] and ensures stability[40].

Innovative Polymers:

Development of novel mucoadhesive materials, including thiolated and chitosan derivatives, shows promise for stronger and longer adhesion. Such polymers may also improve drug protection against enzymatic degradation [26 41] .

Artificial Intelligence and Modelling:

AI-based tools can optimize formulation design by predicting pharmacokinetics [37], and drug–polymer interactions.

Computational models may reduce trial-and-error in laboratory development, saving time and resources . They also help in formulating vaccines for targeting respiratory pathogens [33].

Conclusion

Buccal films have emerged as a versatile platform that can significantly enhance drug delivery by improving bioavailability and patient adherence. Evidence from recent studies, such as the high systemic absorption achieved with fentanyl, highlights their clinical potential. Progress in formulation technologies—including nanoparticles, advanced polymers, and 3D printing—has addressed several limitations, although challenges remain in delivering biologics and ensuring consistent large-scale production. Moving forward, closer alignment with international regulatory requirements and the application of computational tools such as artificial intelligence may accelerate the development of clinically viable products. Overall, buccal films are well positioned to become an important component of precision medicine, offering flexible, patient-friendly solutions for a wide range of therapeutic areas.

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Author Contributions:

Zubair Khan*[1] : Conceptualization, original draft preparation, and visualization.

Dr. S.M. Shahidulla*[2] : Supervision and review-editing.

Mohammed Imtiyaz [3] : Data curation and investigation.

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