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Physiological and Biopharmaceutical Perspectives on Orally Disintegrating Buccal Tablets: Mechanistic Insights into Rapid Mucosal Absorption, Drug Transport, and Controlled Release Dynamics

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ABSTRACT

Orally Disintegrating Buccal Tablets (ODBTs) provide a rapid, noninvasive platform for systemic drug delivery by combining fast tablet disintegration with efficient absorption through the highly vascularized buccal mucosa. This review integrates physiological and biopharmaceutical perspectives to explain the mechanistic factors governing drug dissolution, mucosal permeation, and controlled release dynamics. The structural features of the buccal epithelium, minimal keratinization, rich blood supply, and avoidance of first-pass metabolism are examined in relation to rapid systemic drug uptake. Salivary composition, mucosal hydration, and enzymatic activity are analyzed for their influence on disintegration, dissolution rate, and diffusion kinetics. Mechanistic drug transport pathways—including transcellular, paracellular, and carrier-mediated routes are described along with the role of mucoadhesion in maintaining tablet contact and modulating release. Key formulation strategies for ODBTs, such as superdisintegrants, mucoadhesive polymers, permeation enhancers, and nano-enabled systems, are discussed in relation to physicochemical performance and kinetic models like Higuchi and Korsmeyer–Peppas. Emerging tools such as physiologically based pharmacokinetic (PBPK) modeling, artificial intelligence-assisted formulation optimization, and pH- or ion-responsive polymers are highlighted for their ability to tailor drug delivery to mucosal physiology. Clinical applications demonstrate the relevance of ODBTs in cardiovascular, neurological, endocrine, and pain-management therapies owing to their rapid onset and improved patient compliance. Challenges including variability in mucosal barrier properties, saliva-mediated dilution, enzymatic degradation, and regulatory requirements for biocompatibility are also addressed. Overall, the convergence of mucosal physiology and advanced formulation strategies positions ODBTs as a promising next-generation platform for adaptable and patient-centered drug delivery.

KEYWORDS: Orally Disintegrating Buccal Tablets, Rapid Mucosal Absorption, Drug Transport, Controlled Release, Physiological Barriers, Buccal Delivery.

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INTRODUCTION

ement of the prostate gland is a common symptom of benign prostatic hyperplasia (BPH), a condition that affects older men [1]. Alternative drug delivery systems have gained significant attention due to the limitations of conventional oral administration, including enzymatic degradation, first-pass metabolism, and poor bioavailability of certain drugs. The buccal route presents a viable solution by facilitating direct drug absorption into systemic circulation through the highly vascularized buccal mucosa, thereby bypassing hepatic metabolism and improving therapeutic efficacy. Mucoadhesive drug delivery systems further enhance this approach by ensuring prolonged retention at the site of absorption, minimizing dosing frequency, and improving patient compliance. Mucoadhesion is governed by various physicochemical interactions, including hydrogen bonding, van der Waals forces, and electrostatic interactions. The strength and duration of mucoadhesion depend on multiple factors, such as polymer hydration, interfacial bonding, and the mechanical properties of the bioadhesive material. Various mathematical models have been used to describe drug diffusion and bioadhesion behavior, aiding in the optimization of formulation strategies. The ability to control drug release kinetics through polymeric modifications makes mucoadhesive buccal tablets an attractive alternative for sustained and controlled drug delivery. The objective of this review is to comprehensively analyze the formulation strategies, physicochemical properties, evaluation techniques, and recent advancements in mucoadhesive buccal tablets. The discussion also extends to regulatory perspectives, challenges, and future opportunities for improving bioadhesive drug delivery through personalized medicine and AI-driven formulation design. By integrating mathematical modeling with novel drug delivery technologies, mucoadhesive buccal systems hold immense potential in achieving targeted and controlled drug release for various therapeutic applications.

BUCCAL DRUG DELIVERY

Physiology of Buccal Mucosa

The buccal mucosa, located inside the cheeks, consists of non-keratinized stratified squamous epithelium supported by an underlying lamina propria and submucosa. The thickness of this epithelium ranges between 500 and 800 µm, providing a moderate permeability barrier compared to other mucosal sites. The presence of an extensive capillary network in the lamina propria allows for efficient systemic absorption of drugs, provided they exhibit appropriate solubility and permeability characteristics. The buccal mucosa is also relatively less enzymatically active than the gastrointestinal tract, making it suitable for peptide and protein drug delivery. However, the rate and extent of drug absorption depend on mucosal turnover, salivary flow, and enzymatic degradation, which collectively influence the retention and bioavailability of drugs administered via this route. A detailed comparison of the buccal mucosa with other drug delivery routes is presented in Table 1.

Table 1. Comparative Analysis of Buccal, Sublingual, and Gastrointestinal Mucosa

Parameter	Buccal Mucosa	Sublingual Mucosa	Gastrointestinal Mucosa
Thickness (µm)	500–800	100–200	50–4000
Surface Area (cm²)	50–200	20–30	300–400
Permeability	Moderate	High	Low to high
Enzymatic Activity	Low	Low	High
Drug Retention Time	High	Low	Moderate to high
Blood Supply	Rich capillary network	Extensive vascularization	Extensive but variable vascularization
Salivary Clearance	Moderate	High	Minimal
First-Pass Metabolism Avoidance	Yes	Yes	No
pH Environment	Neutral (pH 6.2–7.4)	Neutral to slightly acidic (pH 6.0–7.0)	Acidic (pH 1.5–3.5 in stomach, neutral in intestine)
Suitability for Sustained Release	High	Low	Moderate
Drug Absorption Pathway	Transcellular and paracellular	Transcellular	Transcellular and paracellular
Suitability for Peptide/Protein Drugs	High	Low	Low
Risk of Local Irritation	Low to moderate	Moderate to high	High

Pathways of Buccal Drug Absorption

Buccal drug absorption primarily occurs through two major pathways: transcellular and paracellular absorption. The transcellular route involves drug transport across the epithelial cell membrane via passive diffusion, facilitated diffusion, or active transport mechanisms. This pathway is more favorable for lipophilic drugs with an appropriate partition coefficient, as they can easily permeate the lipid bilayer of epithelial cells. In contrast, the paracellular route involves drug diffusion through intercellular spaces between epithelial cells. However, tight junctions in the buccal epithelium limit the passage of hydrophilic drugs, making this pathway less efficient for systemic drug delivery. Several formulation strategies have been employed to enhance buccal drug absorption, including the use of permeation enhancers such as bile salts, surfactants, and enzyme inhibitors. These agents disrupt the intercellular lipid structure, increase membrane fluidity, or inhibit enzymatic degradation, thereby improving drug permeation across the mucosal barrier. However, careful selection of permeation enhancers is necessary to balance enhanced absorption with minimal mucosal irritation. A detailed representation of the buccal drug absorption pathways is illustrated in Figure 1.

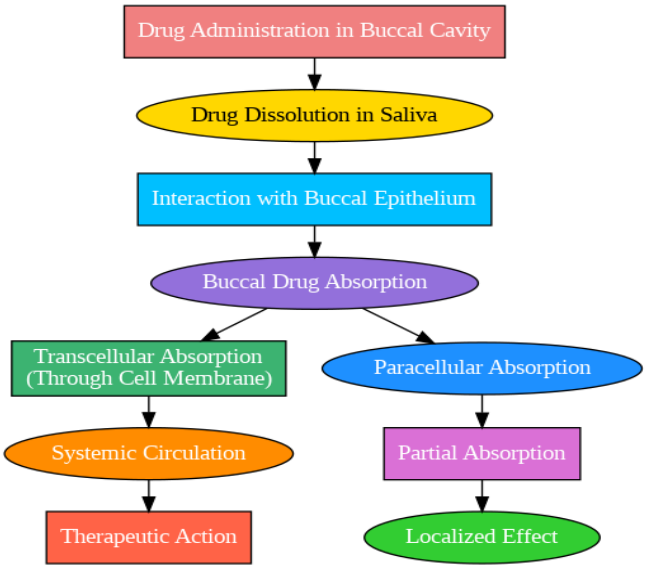

Figure 1. Buccal Drug Absorption Pathways

Advantages and Limitations

Buccal drug delivery provides multiple advantages over conventional routes. One of its most significant benefits is the avoidance of hepatic first-pass metabolism, leading to enhanced bioavailability of drugs that undergo extensive hepatic degradation. This method is particularly advantageous for peptide and protein drugs that degrade in the acidic gastric environment but remain stable in the buccal cavity. Additionally, buccal drug delivery is non-invasive and patient-friendly, making it a preferable alternative to injections or intravenous administration. Sustained and controlled drug release achieved through buccal formulations reduces dosing frequency and enhances patient adherence. Furthermore, this route is suitable for both systemic and local drug delivery, making it useful for treating conditions such as orofacial pain and periodontal diseases.

MUCOADHESIVE DRUG DELIVERY SYSTEMS

Mucoadhesion

Mucoadhesion refers to the ability of a drug formulation to adhere to the mucosal membrane for an extended period, facilitating localized or systemic drug delivery. This process involves an interplay between mucoadhesive polymers and mucosal glycoproteins, particularly mucin, which is a crucial component of mucus secretions. The strength of adhesion depends on polymeric characteristics such as molecular weight, crosslinking density, charge distribution, and hydration ability. When a mucoadhesive formulation is applied to the mucosa, the polymer absorbs water from the mucosal surface, leading to swelling and improved contact between the polymer and mucin. This interaction increases residence time, resulting in prolonged drug retention and improved bioavailability. The effectiveness of mucoadhesion is influenced by multiple factors, including polymer concentration, degree of crosslinking, and environmental conditions such as pH and ionic strength. These factors play a crucial role in determining the adhesion strength, drug diffusion rate, and overall therapeutic efficacy. Mucoadhesive drug delivery systems have shown significant advantages over conventional drug delivery methods by ensuring prolonged therapeutic effects and reducing dosing frequency, making them particularly useful for chronic disease management and localized therapies.

Mechanism of Mucoadhesion

Mucoadhesion is governed by several theories that explain the interaction between the mucoadhesive polymer and the mucosal membrane. The major adhesive theories include the electronic theory, wetting theory, adsorption theory, diffusion theory, and fracture theory. Each of these theories provides a distinct perspective on how adhesion occurs at the molecular and macroscopic levels. A comprehensive comparison of these theories is presented in Table 2.

Table 2. Theories of Mucoadhesion and Their Mechanisms

Theory	Mechanism	Mucoadhesive Polymers
Electronic Theory	Electrostatic attraction between oppositely charged polymer and mucosal membrane	Chitosan, Carbopol
Wetting Theory	Liquid spreadability and reduction of interfacial tension enhance adhesion	Hydroxypropyl methylcellulose (HPMC), Pectin
Adsorption Theory	Secondary bonding forces (hydrogen bonding, van der Waals interactions) lead to adhesion	Sodium alginate, Polyvinyl alcohol (PVA)
Diffusion Theory	Interpenetration of polymer chains into mucosal layer enhances adhesion strength	Polyacrylic acid, Gelatin
Fracture Theory	Mechanical failure at the adhesive interface determines adhesion strength	Polyethylene glycol (PEG), Carbomers

FORMULATION ASPECTS

Selection of Mucoadhesive Polymers

The choice of mucoadhesive polymers is fundamental to the performance of buccal tablets. These polymers facilitate adhesion to the buccal mucosa, ensuring prolonged retention and controlled drug release. Natural polymers, such as chitosan and pectin, offer biocompatibility and biodegradability, while synthetic polymers, such as polycarbophil and Carbopol, provide enhanced adhesion strength and stability. The swelling capacity of the polymer is also a key determinant of adhesion performance, as it influences the extent of contact with the mucosal surface. A comparative analysis of commonly used mucoadhesive polymers is presented in Table 3.

Table 3. Comparison of Mucoadhesive Polymers for Buccal Tablets

Polymer Type	Examples	Mucoadhesive Strength	Swelling Capacity	Application in Buccal Tablets
Natural	Chitosan, Pectin, Gum Arabic	Moderate to High	High	Enhances bioadhesion and biocompatibility
Semi-Synthetic	Hydroxypropyl Methylcellulose (HPMC), Sodium Alginate	Moderate	Moderate	Provides controlled drug release
Synthetic	Carbopol, Polycarbophil, Polyvinyl Alcohol (PVA)	High	Moderate to High	Strong adhesion and prolonged retention

Role of Excipients in Mucoadhesive Buccal Tablets

In addition to mucoadhesive polymers, excipients such as binders, plasticizers, and diluents play a critical role in tablet formulation. Binders, such as microcrystalline cellulose and povidone, enhance tablet cohesion and mechanical strength.

Plasticizers, including polyethylene glycol (PEG) and glycerol, improve tablet flexibility and prevent brittleness. Diluents, such as lactose and mannitol, contribute to tablet bulk and facilitate dissolution. The optimization of excipients ensures the balance between adhesion strength, drug release kinetics, and patient acceptability.

Tablet Design and Types

The design of mucoadhesive buccal tablets significantly impacts their functionality and drug release behavior. Single-layered tablets are the simplest formulation, where the drug and mucoadhesive polymer are combined into one matrix. However, bilayered and multilayered tablets offer greater control over drug release and permeability. In bilayered designs, one layer is formulated for mucoadhesion while the other layer modulates drug release, preventing excessive drug loss due to salivary clearance. Multilayered tablets further enhance this functionality by incorporating additional layers to regulate drug permeation and sustain drug delivery over an extended duration.

Permeation Enhancers and Bioadhesion Enhancers

Permeation enhancers are incorporated into mucoadhesive buccal tablets to facilitate drug transport across the buccal mucosa. These enhancers work by modifying mucosal lipid bilayers, opening tight junctions, or altering enzyme activity to improve drug absorption. Common permeation enhancers include bile salts, surfactants (e.g., sodium lauryl sulfate), and fatty acids (e.g., oleic acid). In addition to permeation enhancers, bioadhesion enhancers such as thiolated polymers (thiomers) can further strengthen adhesion to the mucosal surface, ensuring prolonged drug retention and minimizing premature detachment. The careful selection and combination of mucoadhesive polymers, excipients, permeation enhancers, and bioadhesion enhancers contribute to the successful formulation of buccal tablets with prolonged retention, improved bioavailability, and enhanced therapeutic effects. By optimizing these formulation parameters, mucoadhesive buccal tablets offer an effective platform for sustained and targeted drug delivery, reducing systemic side effects and enhancing patient compliance.

EVALUATION PARAMETERS

Physicochemical Evaluation

Physicochemical evaluation is essential for ensuring that the formulated tablets possess the required mechanical strength, mucoadhesion capability, and structural stability. Various tests such as hardness, friability, swelling index, and surface pH assessment are conducted to determine these properties. Hardness testing ensures that the tablets have sufficient mechanical strength to withstand handling, packaging, and storage without breaking apart. Friability testing evaluates the tendency of tablets to crumble or break under stress, ensuring their durability. The swelling index measures the hydration capacity of the mucoadhesive polymer, which significantly influences adhesion strength and drug release characteristics. Surface pH measurement is crucial to confirm that the formulation does not cause irritation or discomfort in the buccal cavity, ensuring patient compliance.

Mucoadhesive Strength Testing

Mucoadhesive strength testing is performed to evaluate the adhesion properties of the buccal tablet. This parameter is critical as it determines the retention time of the tablet in the buccal mucosa, affecting drug absorption and therapeutic efficacy. The detachment force required to separate the tablet from a mucosal substrate is measured using a texture analyzer. This test provides insights into the strength of adhesion, which depends on factors such as polymer hydration, molecular interactions, and viscosity. A higher detachment force indicates stronger adhesion, which prevents tablet displacement due to saliva and tongue movement. The selection of appropriate mucoadhesive polymers and formulation techniques significantly influences the mucoadhesive strength of buccal tablets.

In Vitro Drug Release and Permeation Studies

In vitro drug release studies are performed to analyze the dissolution profile of the drug from the mucoadhesive buccal tablet. These studies help in understanding the drug release mechanism and optimizing the formulation for controlled or sustained release. The dissolution profile is typically assessed using a dissolution apparatus under simulated buccal conditions, and the drug release rate is monitored over time. An ideal mucoadhesive buccal tablet should exhibit a sustained or controlled drug release pattern to enhance therapeutic efficacy while minimizing dosing frequency. Permeation studies further assess the drug transport across the buccal mucosa. These studies are conducted using a Franz diffusion cell, where the excised buccal mucosa is placed as a barrier between the donor and receptor compartments. The drug permeation rate is measured to determine its bioavailability and systemic absorption potential. The success of a buccal formulation depends on its ability to release the drug in a controlled manner while ensuring sufficient permeation across the mucosal barrier.

***Ex-Vivo* and *In-Vivo* Evaluation Techniques**

Ex vivo studies involve the use of excised animal buccal mucosa to test the mucoadhesive properties and permeation characteristics of buccal tablets under controlled laboratory conditions. These studies help in predicting how the formulation will behave in real biological environments. The mucoadhesive strength, swelling index, and permeation rate are analyzed to optimize the formulation before in vivo testing. In vivo studies are performed on human subjects or animal models to evaluate the pharmacokinetics, bioavailability, and overall therapeutic efficacy of the mucoadhesive buccal tablet. These studies involve measuring drug plasma levels over time to determine the rate and extent of systemic drug absorption. In vivo evaluations also provide data on patient compliance, stability of the formulation, and potential adverse effects. The results obtained from these evaluations are used to optimize the formulation and ensure that the final product meets regulatory standards. A detailed comparison of various evaluation parameters for mucoadhesive buccal tablets is presented in Table 4. This table provides a structured overview of the key evaluation parameters for mucoadhesive buccal tablets, highlighting their significance, standard

ranges, and testing methods. These evaluations are essential for optimizing the formulation and ensuring regulatory approval before clinical use.

Table 4. Comprehensive Evaluation Parameters of Mucoadhesive Buccal Tablets

Evaluation Parameter	Description	Acceptable Range	Test Method
Hardness (kg/cm²)	Measures the mechanical strength of the tablet	3–6 kg/cm²	Monsanto Hardness Tester
Friability (%)	Measures tablet resistance to breaking or crumbling	<1%	Roche Friabilator
Swelling Index (%)	Measures the hydration capacity of the polymer	50–200%	Gravimetric Swelling Study
Surface pH	Determines the pH of the hydrated tablet	5.5–7.5	Digital pH Meter
Mucoadhesive Strength (N)	Measures the adhesion force between the tablet and mucosa	0.2–1.0 N	Texture Analyzer
In Vitro Drug Release (%)	Analyzes drug dissolution profile over time	70–100% within 8 hours	USP Dissolution Apparatus
Permeation Rate (µg/cm²/hr)	Measures drug transport across buccal mucosa	10–50 µg/cm²/hr	Franz Diffusion Cell
Ex Vivo Studies	Conducted using excised animal buccal mucosa	Varies based on formulation	Porcine/Human Buccal Mucosa Study
In Vivo Bioavailability (%)	Determines drug plasma levels post-administration	>50%	Blood Plasma Concentration Analysis

RECENT ADVANCES AND INNOVATIONS

Smart Mucoadhesive Polymers

Smart mucoadhesive polymers have emerged as a promising advancement in buccal drug delivery. These polymers are designed to respond to environmental stimuli such as pH, temperature, or enzymatic activity, enabling site-specific drug release and prolonged adhesion to the buccal mucosa. pH-sensitive polymers, such as polyacrylic acid derivatives and chitosan-based formulations, undergo structural modifications in response to changes in the buccal environment, leading to controlled drug release. Similarly, temperature-responsive hydrogels have been explored to enhance drug retention and absorption by forming gels upon contact with the buccal mucosa. These polymers not only improve drug release kinetics but also provide enhanced mucoadhesion, ensuring sustained therapeutic effects.

Nanoparticle-Loaded Buccal Tablets

The incorporation of nanoparticles into mucoadhesive buccal tablets has revolutionized drug delivery by enhancing drug solubility, stability, and permeability. Various nanoparticulate systems, including liposomes, polymeric nanoparticles, and solid lipid nanoparticles, have been integrated into buccal tablets to facilitate controlled drug release and improved bioavailability. These nanoparticles can encapsulate both hydrophilic and lipophilic drugs, protecting them from enzymatic degradation in the oral cavity while allowing for sustained absorption through the buccal mucosa. Additionally, nanoparticle surface modification using bioadhesive ligands has been explored to improve targeting efficiency and increase retention at the mucosal site. Such advancements offer a promising approach for enhancing the therapeutic efficacy of buccal drug delivery systems.

Nanofiber-Based Buccal Drug Delivery Systems

Nanofiber technology has gained attention in the field of buccal drug delivery due to its high surface area, tunable porosity, and ability to provide rapid drug absorption. Electrospinning techniques have been employed to fabricate mucoadhesive nanofiber mats loaded with drugs, offering enhanced bioadhesion and controlled release properties. These nanofibers can be formulated using biodegradable polymers such as polyvinyl alcohol, chitosan, and polyethylene oxide, ensuring biocompatibility and minimal toxicity. The unique structural properties of nanofibers enable efficient drug loading while facilitating sustained drug diffusion through the buccal mucosa. Recent studies have demonstrated the potential of nanofiber-based buccal formulations for delivering a wide range of therapeutic agents, including analgesics, anti-inflammatory drugs, and hormones.

3D-Printed Buccal Drug Delivery Systems

3D printing technology has introduced a novel approach to the development of personalized buccal drug delivery systems. This technology enables the fabrication of mucoadhesive buccal tablets with precise drug-loading capabilities, customizable release profiles, and patient-specific formulations. Various 3D printing techniques, such as fused deposition modeling and stereolithography, have been utilized to design buccal tablets with controlled porosity, enhanced mucoadhesion, and tailored drug release characteristics. The ability to create multilayered drug delivery systems using 3D printing allows for the incorporation of multiple therapeutic agents in a single formulation, facilitating combination therapy and improved patient compliance. Additionally, the scalability and reproducibility of 3D-printed formulations offer significant advantages for large-scale pharmaceutical manufacturing.

Mucoadhesive Microspheres and Liposomal Buccal Systems

Mucoadhesive microspheres and liposomes have emerged as effective carriers for buccal drug delivery, providing sustained drug release and improved bioavailability. Microspheres composed of bioadhesive polymers such as sodium alginate, Carbopol, and Hydroxypropyl methylcellulose exhibit enhanced mucoadhesion and prolonged residence time in the buccal cavity. These

microspheres facilitate the controlled release of drugs, reducing the frequency of administration and improving therapeutic outcomes. Similarly, liposomal buccal formulations have been developed to encapsulate both hydrophobic and hydrophilic drugs, ensuring their stability and efficient permeation across the buccal mucosa. The lipid bilayer structure of liposomes enhances drug solubility while protecting the active pharmaceutical ingredient from degradation. These advancements offer promising solutions for improving the efficacy and patient acceptability of buccal drug delivery systems. The recent innovations in mucoadhesive buccal drug delivery highlight the growing potential of advanced formulation strategies in improving therapeutic outcomes. The integration of nanotechnology, smart polymers, and 3D printing has paved the way for next-generation buccal drug delivery systems that offer precise, controlled, and patient-centric treatment approaches. As research continues to evolve, these advancements are expected to drive the development of novel buccal formulations with enhanced bioavailability, improved patient compliance, and broader therapeutic applications.

THERAPEUTIC APPLICATIONS

Drugs Delivered via Buccal Route

A wide range of drugs have been successfully formulated into mucoadhesive buccal tablets to enhance their bioavailability and therapeutic effectiveness. Analgesics such as fentanyl and buprenorphine have been delivered via buccal formulations to provide rapid pain relief in patients with chronic pain conditions. Hormonal therapies, including estrogen and testosterone, have been developed as buccal tablets for controlled and sustained release, ensuring consistent hormone levels in the bloodstream. Cardiovascular drugs such as propranolol and nitrates have been explored for buccal delivery to achieve rapid systemic absorption and effective management of hypertension and angina. Additionally, anti-inflammatory drugs, antifungal agents, and local anesthetics have been incorporated into buccal tablets to treat oral infections, periodontal diseases, and mucosal lesions.

Clinical Relevance in Pain Management, Hormonal Therapy, and Cardiovascular Treatment

Mucoadhesive buccal tablets play a crucial role in pain management by providing rapid analgesic effects with prolonged drug action. Opioid analgesics such as fentanyl buccal tablets have been widely used for breakthrough cancer pain, ensuring faster onset of action compared to conventional oral formulations. Hormone replacement therapies delivered via buccal tablets provide steady hormone levels while minimizing gastrointestinal degradation and hepatic metabolism. For instance, testosterone buccal tablets have been developed to treat hypogonadism in men, offering sustained hormone release with improved patient adherence. In cardiovascular treatment, buccal tablets containing nitrates have been utilized for the rapid relief of angina by facilitating immediate drug absorption through the buccal mucosa. These formulations eliminate the need for frequent dosing and improve treatment outcomes in patients with cardiovascular disorders.

Case Studies and Marketed Formulations

Several case studies have demonstrated the clinical efficacy of mucoadhesive buccal tablets in different therapeutic areas. Studies on buprenorphine buccal tablets have shown superior pain relief and longer duration of action compared to conventional opioid formulations, reducing the risk of dose escalation and dependence. Hormone therapy trials using buccal estradiol tablets have reported improved bioavailability and consistent plasma drug levels, ensuring effective treatment for menopausal symptoms. In cardiovascular therapy, clinical studies on buccal propranolol have highlighted its potential in managing hypertension with reduced systemic side effects. Marketed formulations of mucoadhesive buccal tablets have been successfully introduced for various medical conditions. Fentora, a fentanyl buccal tablet, has been approved for the management of breakthrough cancer pain, providing rapid and sustained analgesic effects. Striant, a testosterone buccal tablet, has been developed for testosterone replacement therapy, ensuring prolonged hormone release with minimal fluctuations. Nitrostat, a nitroglycerin buccal formulation, has been widely used for angina relief, offering immediate therapeutic benefits. These commercially available buccal tablets highlight the clinical relevance and market potential of mucoadhesive drug delivery systems in modern medicine. The therapeutic applications of mucoadhesive buccal tablets continue to expand, with ongoing research focusing on developing advanced formulations for personalized medicine and targeted drug delivery. The ability of buccal tablets to provide controlled, sustained, and effective drug release makes them a promising alternative for managing various chronic and acute conditions. Future advancements in formulation strategies, polymer science, and drug delivery technologies will further enhance the efficacy, safety, and patient acceptability of buccal drug delivery systems.

CHALLENGES AND LIMITATIONS

Mucoadhesive buccal tablets offer a promising strategy for drug delivery by enhancing bioavailability and bypassing first-pass metabolism; however, their development and commercialization face several challenges, including formulation complexities, stability issues, patient compliance, regulatory hurdles, and large-scale manufacturing difficulties. Formulating effective tablets requires balancing drug release kinetics with optimal mucoadhesion strength, as excessive adhesion may cause mucosal irritation while inadequate adhesion can lead to premature detachment. The physicochemical properties of the drug—such as solubility, permeability, and molecular weight play a critical role in formulation design, while stability concerns arise due to enzymatic degradation, pH variations, and salivary dilution. Protective strategies like coatings, nanoencapsulation, or prodrug conversion may be needed to maintain stability. Additionally, the compatibility of excipients, including polymers and permeation enhancers, must be thoroughly assessed to prevent adverse interactions and ensure shelf life. Patient compliance remains a key factor, as bitter taste, discomfort, and prolonged buccal retention may lead to poor adherence, especially in pediatric or geriatric populations. Techniques like taste masking using polymer coatings, cyclodextrin complexes, and microencapsulation can improve palatability, while the use of thinner, flexible, and bioerodible tablets can enhance comfort. Regulatory approval is another major challenge, requiring comprehensive studies on safety, efficacy, mucoadhesion, and controlled drug release, in accordance with guidelines from agencies like the USFDA and EMA. Scalability is equally demanding, as conventional manufacturing methods may not guarantee batch consistency; innovative techniques such as 3D printing, electrospinning, and hot-melt extrusion are being

explored for precision and reproducibility. Moreover, prolonged mucosal contact may lead to irritation or allergic reactions, necessitating the use of biocompatible polymers like HPMC or chitosan. The suitability of drugs for buccal delivery is also limited by poor permeability, high molecular weight, or instability in the oral environment, but drug modification approaches such as prodrugs or liposomal carriers can help broaden the scope of eligible candidates. Addressing these multifaceted limitations through advanced formulation strategies and technologies is essential for the clinical and commercial success of mucoadhesive buccal tablets (Table 5).

Table 5. Challenges and Limitations of Mucoadhesive Buccal Tablets

Challenges	Description	Impact on Formulation	Potential Solutions
Formulation Issues	Difficulty in optimizing drug release and mucoadhesion	Inconsistent therapeutic effects	Use of smart polymers, bioadhesive excipients, and sustained-release systems
Drug Stability	Enzymatic degradation, salivary dilution, and pH variations	Reduced bioavailability and loss of therapeutic effect	Nanoencapsulation, protective coatings, and prodrug modification
Patient Compliance	Bitter taste, irritation, excessive salivation	Poor adherence and discomfort	Taste-masking strategies, bioerodible tablets, and mucoadhesive films
Regulatory Constraints	Stringent approval processes for bioavailability and safety	Delays in commercialization	Comprehensive preclinical and clinical studies, adherence to regulatory guidelines
Manufacturing Scalability	Difficulties in ensuring batch-to-batch consistency	High production costs and lower reproducibility	Adoption of 3D printing, electrospinning, and hot-melt extrusion techniques
Mucosal Irritation	Prolonged contact causing local irritation or inflammation	Patient discomfort and withdrawal from therapy	Use of biocompatible polymers and anti-inflammatory excipients
Limited Drug Types	Not all drugs are suitable for buccal delivery due to permeability issues	Restriction in therapeutic applications	Prodrug strategies, nanoparticle-based formulations, and permeability enhancers
Short Retention Time	Tablets may detach prematurely due to salivary flow and movements	Inconsistent drug absorption	Development of mucoadhesive films, multi-layered tablets, and polymeric hydrogels
Moisture Sensitivity	Absorption of moisture affecting stability	Altered tablet properties and reduced efficacy	Use of moisture-resistant packaging and stabilizing agents

REGULATORY PERSPECTIVES

Regulatory approval of mucoadhesive buccal tablets involves stringent guidelines from authorities like the USFDA**,** EMA**,** and ICH, which require detailed studies on pharmacokinetics, drug permeation, bioequivalence, and safety. These tablets are classified as controlled- or modified-release systems, necessitating in vitro, in vivo, and stability testing, along with risk assessments for toxicity. Demonstrating bioequivalence especially for generics is critical, requiring comparative data on absorption, bioavailability, mucoadhesion, and long-term safety. Labeling must clearly instruct patients on dosage, usage duration, and interactions, particularly for controlled-release forms. Compliance with Good Manufacturing Practices (GMP) is essential to ensure quality, sterility, and shelf stability. However, regulatory challenges remain, including complex approval processes, regional variations in requirements, and the difficulty of proving equivalence for certain drugs. Close collaboration with regulatory bodies and adherence to international standards are vital for the successful development and commercialization of buccal drug delivery systems.

FUTURE TRENDS

The future of mucoadhesive buccal drug delivery is being redefined by innovation, personalization, and digital intelligence. A prominent advancement lies in stimuli-responsive **systems**, which represent a leap beyond traditional formulations. These intelligent platforms are designed to react to physiological cues such as shifts in pH, temperature, or enzymatic activity thereby enabling dynamic, on-demand drug release. Imagine a buccal film that senses inflammation and immediately delivers an analgesic, or a hydrogel that adapts to hormonal cycles, offering precision in hormone therapy. This adaptability enhances both therapeutic outcomes and patient responsiveness. Complementing this is the rising wave of personalized medicine via the buccal route, where patient-centric care converges with cutting-edge formulation science. Driven by pharmacogenomics and 3D printing, future buccal tablets could be custom-engineered to align with an individual's genetic makeup, optimizing dosage and minimizing side effects. Especially for sensitive populations like children and the elderly this tailored approach ensures safety, comfort, and therapeutic efficacy.

CONCLUSION

Mucoadhesive buccal tablets have emerged as a promising drug delivery system, offering advantages such as enhanced bioavailability, bypassing first-pass metabolism, and controlled drug release. Their formulation, integrating mucoadhesive polymers and permeation enhancers, has significantly improved therapeutic outcomes and patient compliance. This review has highlighted key formulation strategies, evaluation parameters, and recent advancements, demonstrating their growing clinical

relevance. Despite these advantages, challenges remain in terms of formulation stability, scalability, and regulatory approvals. Addressing these issues through innovative approaches like stimuli-responsive polymers, nanotechnology, and AI-driven formulation design will further enhance their potential. Future research should focus on improving biocompatibility, optimizing drug permeability, and developing cost-effective manufacturing techniques. In conclusion, mucoadhesive buccal tablets offer a valuable alternative to traditional oral drug delivery, with potential applications in personalized medicine and controlled drug administration. Continued advancements in material science and pharmaceutical technology will drive their widespread clinical adoption, making them a cornerstone of next-generation drug delivery systems.

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