REVIEW

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Advances and Challenges in Buccal Drug Delivery Systems: A Comprehensive Review of Muco-

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ABSTRACT

Buccal drug delivery offers a non-invasive route that bypasses first-pass metabolism and enhances patient compliance. This review highlights recent progress in mucoadhesive polymers, including both traditional and stimuli-responsive materials that improve drug retention and controlled release. Various dosage forms such as tablets, films, sprays, and advanced systems like microneedles and nanofibers are examined for their design and clinical potential. Nanocarrier integration has expanded buccal delivery to include peptides, proteins, and nucleic acids. Key challenges—such as enzymatic degradation, limited permeability, and patient adherence—are discussed alongside regulatory and market considerations. Future directions point toward smart, personalized systems and AI-driven formulation strategies.

KEYWORDS: Buccal drug delivery, Mucoadhesive polymers, Nanocarriers, Smart drug delivery, Controlled release

INTRODUCTION

In recent years, buccal drug delivery systems have gained significant attention as an alternative route for the administration of various therapeutic agents. The buccal mucosa, lining the inside of the cheek, presents a unique anatomical and physiological site for drug absorption. Its rich vascularization, relatively low enzymatic activity compared to the gastrointestinal tract, and ease of access make it a promising portal for both local and systemic drug delivery. Importantly, drugs administered via the buccal route can bypass the hepatic first-pass metabolism, which often significantly reduces the bioavailability of orally ingested medications. This offers a major advantage, especially for drugs that are extensively metabolized in the liver or those with low gastrointestinal stability.(1)

The structure of the buccal mucosa plays a critical role in its suitability for drug delivery. Composed of non-keratinized stratified squamous epithelium, connective tissue, and an underlying vascular network, the mucosa allows for effective drug permeation while offering a certain degree of mechanical and enzymatic protection. Additionally, the relatively neutral pH of saliva (ranging from 5.5 to 7.5) creates a favorable environment for the stability of many drugs. Despite its smaller surface area compared to other routes like the gastrointestinal tract, the buccal cavity compensates with a direct and rapid absorption pathway into the systemic circulation.(2)

Various dosage forms have been developed to exploit this route, including buccal tablets, films, patches, gels, and sprays. These formulations often incorporate mucoadhesive polymers that enable the drug system to adhere to the mucosal surface for extended periods, enhancing residence time and improving drug absorption. Advances in material science and pharmaceutical technology have further enabled the design of buccal systems with controlled release properties, taste-masking features, and enhanced drug penetration capabilities.(3)

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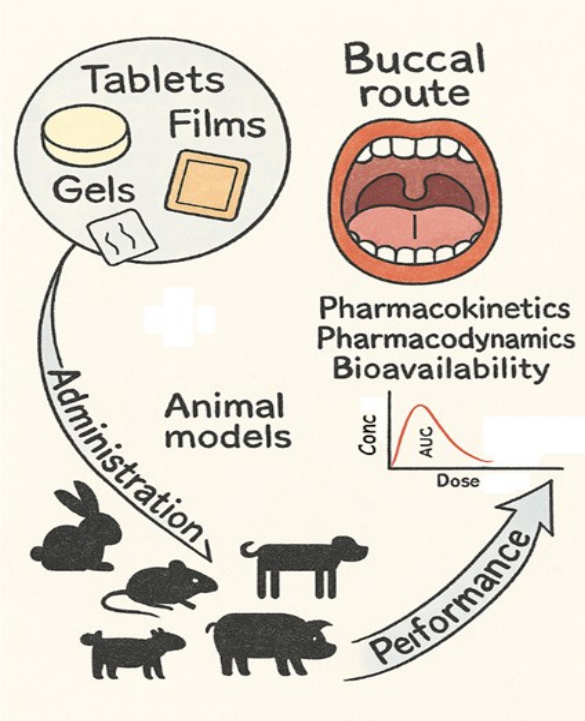

Figure 1: Clinical study of buccal route

buccal route also shows considerable promise in delivering

macromolecules such as peptides, proteins, and even vaccines, although challenges such as enzymatic degradation, limited permeation, and mucosal turnover still need to be addressed. With the integration of nanotechnology, novel polymers, and smart delivery platforms, there is increasing potential for this route to accommodate a wider range of therapeutic molecules, including biologics and gene-based treatments.

Given the growing interest and expanding research in this field, it is important to review the current state of buccal drug delivery systems. This paper aims to provide a comprehensive overview of the advancements, challenges, and future directions in buccal drug delivery, with a particular focus on mucoadhesive technologies, innovative formulations, and clinical applications. By examining both the opportunities and limitations of this route, this review seeks to highlight the evolving role of buccal drug delivery in modern pharmaceutical science.

MUCOADHESIVE POLYMERS IN BUCCAL DELIVERY

Buccal drug delivery systems rely heavily on mucoadhesive polymers, which enable formulations to adhere to the mucosal surface for extended periods. This prolonged residence time not only improves the absorption of the drug through the buccal mucosa but also enhances patient compliance by reducing the frequency of administration. Mucoadhesive polymers, whether of natural or synthetic origin, interact with the mucus layer coating the buccal cavity through physical or chemical means, allowing for sustained and controlled drug delivery.(4)

2.1 Mechanism of Mucoadhesion

The process of mucoadhesion generally unfolds in two main stages: the contact stage and the consolidation stage. In the contact stage, the polymer-containing dosage form comes into physical contact with the buccal mucosa. For successful contact, the polymer must be sufficiently wettable and capable of spreading over the moist mucosal surface. Hydrophilic polymers are particularly useful in this context, as they absorb water from the surrounding environment, swell, and increase surface contact with the mucosa.

Following initial contact, the consolidation stage begins. This phase involves deeper interactions at the molecular level between the polymer chains and the mucin glycoproteins present in the mucus layer. One of the primary mechanisms facilitating this adhesion is polymer chain entanglement, wherein the long, flexible chains of the polymer interpenetrate with mucin strands. This physical interlocking enhances the mechanical strength of the adhesive bond. In addition to chain entanglement, hydrogen bonding plays a critical role in mucoadhesion. Polymers that contain functional groups such as hydroxyl, carboxyl, and amino groups are particularly effective, as they can form hydrogen bonds with complementary groups in the mucin. The extent of hydrogen bonding is influenced by the polymer's molecular weight, degree of cross-linking, and hydration level. Overall, the combined effects of physical entanglement and chemical bonding determine the strength, durability, and performance of mucoadhesive systems used in buccal drug delivery.(5)

TYPES OF MUCOADHESIVE POLYMERS

Mucoadhesive polymers used in buccal drug delivery are broadly categorized into natural and synthetic polymers. Each type offers distinct advantages in terms of biocompatibility, mechanical properties, and ease of formulation.

Natural Polymers

Natural polymers have the inherent advantage of being biocompatible, biodegradable, and generally well-tolerated by mucosal tissues. Among them, chitosan**,** gelatin**,** pectin, and alginate are frequently used in buccal drug delivery systems.

- **Chitosan**, derived from chitin found in crustacean shells, is a cationic polysaccharide known for its excellent mucoadhesive properties. Its positive charge allows it to interact electrostatically with the negatively charged mucosal surfaces, improving adhesion. Additionally, chitosan has the unique ability to transiently open tight junctions between epithelial cells, enhancing the paracellular transport of hydrophilic drugs and macromolecules.(6)
- **Gelatin**, a protein obtained by hydrolysis of collagen, exhibits good film-forming capabilities and moderate mucoadhesion. It is particularly useful in combination with other polymers for the preparation of buccal films or gels.
- **Pectin and alginate**, both plant-derived polysaccharides, are favored for their swelling and gelling abilities. Pectin, commonly extracted from citrus fruits, forms hydrogels in the presence of calcium ions, while alginate, sourced from brown seaweed, can form ionically cross-linked gels suitable for sustained release.(7-8)

These natural polymers are non-toxic and can be combined with synthetic polymers to optimize mechanical properties and drug release profiles.

Synthetic Polymers

Synthetic polymers offer greater control over physical properties, such as viscosity, swelling capacity, and degradation rate. They are engineered to meet specific formulation needs and are widely used in commercial mucoadhesive products.

- **Hydroxypropyl methylcellulose (HPMC)** is one of the most widely used synthetic polymers in buccal formulations. It is a semi-synthetic, water-soluble cellulose ether that forms transparent films and hydrogels upon hydration. HPMC provides good mucoadhesion and can be used to modulate the drug release rate by varying its molecular weight and concentration.(7)
- **Polyvinyl alcohol (PVA)** is another commonly used synthetic polymer that exhibits excellent film-forming properties and mechanical strength. Though its mucoadhesive strength is moderate, it is often blended with stronger bioadhesive agents to enhance performance.(9)
- **Carbopol**, a high molecular weight polyacrylic acid derivative, is known for its high viscosity and superior mucoadhesive capabilities. It swells considerably in aqueous environments, forming a gel-like structure that adheres strongly to mucosal surfaces. Due to its high water absorption capacity, Carbopol is often used in formulations requiring prolonged residence time.
- **Polyacrylic acid (PAA)** and its copolymers have also demonstrated significant mucoadhesive strength. These polymers contain a large number of carboxyl groups, which contribute to extensive hydrogen bonding with mucin and result in strong adhesion.

Synthetic polymers can be chemically modified or combined with other materials to fine-tune their performance in buccal delivery systems. Their mechanical robustness and consistent quality make them ideal for commercial scale-up and manufacturing.

EMERGING SMART POLYMERS

The evolution of drug delivery technologies has led to the emergence of smart polymers an advanced class of mucoadhesive materials that respond to specific physiological or environmental stimuli. These polymers are particularly promising for buccal drug delivery, where precise control over drug release is crucial for achieving targeted therapeutic effects and reducing systemic side effects. Unlike conventional mucoadhesive polymers, smart polymers are designed to undergo physical or chemical changes in response to triggers such as temperature, pH, or enzymatic activity, allowing them to release drugs in a controlled and predictable manner.(10)

One major category of smart polymers includes thermo-sensitive polymers, which exhibit a sol-gel transition in response to temperature changes. These polymers remain in a liquid state at room temperature, facilitating easy administration, but gel upon contact with body temperature (approximately 37°C), forming a mucoadhesive depot at the site of application. Poloxamers, also known as Pluronics, are well-known thermo-sensitive polymers used in buccal formulations. Their gelation ability enhances mucosal retention and provides a sustained release of the active pharmaceutical ingredient (API), especially useful in conditions requiring prolonged drug exposure to the buccal mucosa.(11)

pH sensitive polymers represent another important class. These materials alter their swelling behavior or solubility depending on the pH of their surrounding environment. The buccal cavity, with its relatively stable pH range (5.5 to 7.5), offers an ideal site for the deployment of such systems. Polyacrylic acid (PAA) and its derivatives are examples of pH-sensitive polymers that expand and release their drug load in response to neutral or slightly basic pH conditions. The ability of pH-sensitive systems to protect acid-labile drugs or enable site-specific release makes them valuable in the design of mucoadhesive platforms for drugs with narrow absorption windows. (12)

In addition, enzyme-responsive polymers are being increasingly explored in buccal drug delivery for their potential to trigger drug release in response to specific enzymes present in the saliva or oral mucosa. These polymers are designed to degrade or modify their structure upon contact with target enzymes, such as amylases or proteases, thereby facilitating the release of encapsulated drugs. This strategy is particularly beneficial for the delivery of biomolecules like peptides, proteins, and nucleic acids, which require protection from premature degradation but benefit from a responsive release mechanism when at the target site.

The integration of these smart polymers into stimuli-triggered delivery systems provides several advantages, including precise control of dosing, protection of sensitive drug molecules, and minimization of dosing frequency. Smart polymers can be engineered to incorporate multiple triggers, resulting in multi-responsive systems that respond to combinations of pH, temperature, and enzymatic activity for even greater control. Furthermore, they can be used in combination with nanotechnolo-

gy-based carriers such as nanoparticles or liposomes to improve mucosal penetration and drug loading capacity.(10)

In summary, the advancement of smart polymers represents a significant step forward in the field of buccal drug delivery. These innovative materials offer the potential to overcome several limitations of traditional delivery systems, including low bioavailability, poor mucosal retention, and lack of controlled release. As research in material science and polymer chemistry continues to progress, smart mucoadhesive polymers are likely to play a central role in the future development of sophisticated buccal drug delivery platforms.(4, 9)

TYPES OF BUCCAL DRUG DELIVERY SYSTEMS

Buccal drug delivery systems have evolved significantly, offering a variety of dosage forms tailored to specific therapeutic needs. These systems are designed to exploit the buccal mucosa as a route for both local and systemic drug delivery, leveraging its rich vascularization and ease of access. Depending on the drug's properties, target action, and patient convenience, several delivery formats are available, ranging from conventional tablets to advanced microneedle and nanofiber-based systems. Each system comes with its own mechanism for drug release, mucoadhesion strength, and manufacturing complexity.

Buccal Tablets and Lozenges

Buccal tablets and lozenges represent some of the earliest and most widely studied forms of buccal drug delivery. These solid dosage forms are placed between the gum and cheek, where they slowly dissolve or erode, releasing the drug over time. There are generally two main design types: matrix-type and reservoir-type tablets.

In matrix-type systems, the drug is uniformly dispersed within a mucoadhesive polymer matrix. As the tablet hydrates upon contact with saliva, the polymer swells, gradually releasing the drug through diffusion and erosion mechanisms. This design is simple and cost-effective, often suitable for drugs with good mucosal permeability.

In contrast, reservoir-type tablets contain a distinct drug-loaded core surrounded by a mucoadhesive layer or coating. This setup allows for more controlled, unidirectional drug release toward the mucosa, minimizing drug loss into the oral cavity. The slow disintegration characteristic of both types supports sustained release, enhancing therapeutic efficacy, particularly for chronic conditions that require prolonged drug exposure. (13, 2)

Buccal Patches and Films

Buccal patches and films are thin, flexible dosage forms designed to adhere closely to the mucosal surface, offering improved comfort and extended residence time compared to tablets. These systems can be classified as single-layered or multilayered, depending on their structure and function. Single-layered films release the drug in all directions, which may lead to partial loss into saliva. In contrast, multilayered patches are engineered with an impermeable backing layer to direct drug release solely toward the mucosa. This targeted release enhances bioavailability while reducing the amount of drug swallowed. These patches may consist of an adhesive layer, a drug-containing layer, and a backing layer, offering both mechanical stability and controlled release characteristics. Depending on the formulation, buccal films can be designed for fast dissolving applications-where immediate drug release is required—or for extended release, suitable for sustained therapeutic action. Fast-dissolving films are often used for analgesics or antiemetics, while extended-release patches may deliver hormones or cardiovascular drugs. In terms of manufacturing, the most common methods include solvent casting and hot-melt extrusion. Solvent casting involves dissolving the polymer and drug in a solvent, casting it into molds, and evaporating the solvent to form a film. This method allows for precise control over film thickness and drug content. Hot-melt extrusion, on the other hand, involves melting the polymer and incorporating the drug at high temperatures, eliminating the need for solvents and offering better scalability for industrial production.(14-15)

Gels and Sprays

Gels and sprays provide a non-solid alternative for buccal drug delivery, often preferred for their ease of administration and rapid onset of action. In-situ forming gels are particularly innovative; they are applied in liquid form and undergo a sol-to-gel transition upon contact with the buccal mucosa. This transformation can be triggered by physiological factors such as temperature, pH, or ion concentration. The resulting gel adheres to the mucosal surface, forming a mucoadhesive depot that releases the drug over a defined period. This is especially beneficial for pain management, hormone therapy, or local antiseptic delivery. The gel's consistency can be tailored to modulate release kinetics and improve patient retention time. Buccal sprays offer another convenient platform, particularly for drugs

requiring rapid onset of action, such as nitroglycerin or midazolam. These formulations are typically aqueous or ethanol-based and are delivered via metered-dose pumps to ensure dosing accuracy. Their non-invasive nature, ease of use, and fast mucosal absorption make them ideal for emergency treatments or on-demand therapies.(16)

Microneedle and Electrospun Systems

Recent advancements in material science have introduced microneedle arrays and electrospun nanofiber films as cutting-edge approaches for buccal drug delivery. These systems are designed to overcome the natural barrier properties of the buccal epithelium and enhance drug penetration without causing significant discomfort. Microneedles are tiny, minimally invasive projections that create microchannels in the mucosal tissue, facilitating the direct transport of drugs into systemic circulation. These can be solid, coated, or dissolving microneedles, each tailored for specific applications. The buccal mucosa's relative thinness and accessibility make it a promising site for such delivery, especially for biomolecules like insulin, peptides, or vaccines that typically struggle with mucosal absorption.(17)

In parallel, electrospun nanofiber films are gaining attention for their high surface area-to-volume ratio, which allows for enhanced drug loading and controlled release profiles. These fibers, typically made from polymers like polyvinyl alcohol (PVA) or polylactic acid (PLA), are engineered to form ultrathin, breathable films that adhere tightly to the mucosal surface. Drugs can be embedded within the fibers or coated onto them, offering flexibility in design. The resulting films are lightweight, nearly invisible upon application, and suitable for both fast and prolonged drug delivery.(9)

These advanced systems, while still under active research and development, hold tremendous promise for the future of buccal drug delivery. They offer innovative solutions to existing challenges, such as low permeability and short residence time, and may pave the way for personalized, minimally invasive therapies with enhanced patient compliance.

Nanotechnology and Novel Carriers

The integration of nanotechnology into buccal drug delivery systems has opened new avenues for improving therapeutic outcomes. Traditional buccal formulations often face limitations such as short residence time, low permeability of certain drugs, and enzymatic degradation. Nanocarrier-based systems offer enhanced bioavailability, sustained release, targeted delivery, and protection of labile drugs. These nanoscale platforms—ranging from liposomes and polymeric nanoparticles to dendrimers and lipid-based carriers—have demonstrated significant potential in overcoming physiological barriers associated with buccal administration.(18)

Liposomes and Niosomes

Liposomes are spherical vesicles composed of one or more phospholipid bilayers surrounding an aqueous core. Their amphiphilic nature allows them to encapsulate both hydrophilic and lipophilic drugs, making them versatile carriers in buccal drug delivery. The incorporation of lipophilic drugs into the lipid bilayer enhances their solubility and bioavailability, particularly for molecules that exhibit poor aqueous solubility. Additionally, liposomes can be engineered to interact with the mucosal surface through surface charge modifications or by incorporating mucoadhesive polymers, thereby improving retention at the buccal site and enhancing absorption.(19)

Niosomes, which are structurally similar to liposomes, are composed of non-ionic surfactants instead of phospholipids. They offer several advantages, including improved stability, lower production costs, and reduced oxidative degradation. Like liposomes, niosomes can encapsulate both hydrophilic and lipophilic drugs and have shown promise in enhancing the buccal delivery of various therapeutics. Their ability to interact with the buccal epithelium and form a depot at the site of application contributes to sustained and localized drug release**.** (20)

Nanoparticles and Microparticles

Polymeric nanoparticles and microparticles are among the most studied carriers for buccal delivery due to their ability to encapsulate drugs within biodegradable matrices, providing sustained and controlled drug release. Polymers such as poly (lactic-co-glycolic acid) (PLGA) and Eudragit are commonly used for this purpose, owing to their biocompatibility, tunable degradation rates, and regulatory approval for human use. These particles can be designed to remain adhered to the buccal mucosa for extended periods, minimizing the need for frequent dosing. The particle size plays a crucial role in determining the residence time and the penetration capability through the mucosal epithelium. Nanoparticles, due to their smaller

size, can more effectively interact with mucosal tissues and facilitate paracellular or transcellular transport of the encapsulated drug. Moreover, surface modification of nanoparticles with ligands such as lectins, antibodies, or peptides enables targeted delivery to specific cell types or receptors on the mucosal surface. This targeted approach not only improves drug uptake but also reduces systemic exposure and potential side effects. Such functionalized nanoparticles are particularly useful for site-specific therapies, including the localized treatment of oral infections or the targeted delivery of anticancer agents in the oral cavity.(21)

Dendrimers, Cyclodextrins, and Solid Lipid Nanoparticles (SLNs)

Dendrimers are highly branched, tree-like macromolecules with a central core, interior layers (generations), and multiple surface functional groups. Their well-defined structure and multivalency make them ideal for drug delivery applications. In buccal systems, dendrimers can be functionalized to enhance mucoadhesion and drug loading capacity. Additionally, they can facilitate the transport of drugs across the buccal epithelium by temporarily disrupting tight junctions or enhancing membrane fluidity.

Cyclodextrins are cyclic oligosaccharides that form inclusion complexes with hydrophobic drug molecules, thereby enhancing solubility and stability. These complexes protect the drug from degradation in the oral cavity and promote better permeation through the mucosa. Cyclodextrins have been incorporated into buccal films and gels to improve the delivery of poorly soluble drugs, such as certain antifungal agents or corticosteroids, offering a more efficient route for systemic delivery.(22)

Solid Lipid Nanoparticles (SLNs) are another promising class of nanocarriers composed of solid lipids stabilized by surfactants. They combine the advantages of both liposomes and polymeric nanoparticles, such as high drug loading, protection against enzymatic degradation, and sustained drug release. SLNs provide a stable delivery platform for sensitive drugs like peptides and proteins, which are otherwise prone to degradation in the buccal environment. Their lipidic nature also enhances interaction with the mucosal membrane, facilitating better drug absorption.

The ability of these novel nanocarriers to improve solubility, enhance mucosal retention, and offer site-specific targeting significantly expands the scope of buccal drug delivery beyond conventional small-molecule drugs. As research progresses, the integration of nanotechnology with buccal systems is expected to enable the delivery of more complex therapeutics, including gene therapies, vaccines, and personalized medicine approaches.(23-22)

Challenges in Buccal Drug Delivery

Despite the significant advantages of buccal drug delivery, including its non-invasiveness and potential for bypassing hepatic first-pass metabolism, several challenges still hinder its widespread clinical adoption. These limitations arise from physiological conditions within the oral cavity, inherent properties of the drug, and patient-related factors that can affect the efficacy and acceptability of the dosage form. Understanding and addressing these challenges is critical for the successful design and optimization of buccal delivery systems.

Physiological Barriers

The buccal mucosa presents multiple physiological barriers that can limit the performance of drug delivery systems. One major issue is salivary dilution, where the continuous flow of saliva—ranging from 0.5 to 2 liters per day—can wash away the drug or carrier system from the site of application. This dilution effect not only reduces drug concentration at the absorption site but also decreases contact time with the mucosal membrane, negatively impacting bioavailability.

Drug-Related Limitations

The physicochemical properties of the drug itself often dictate the suitability for buccal delivery. Molecules with high molecular weight or poor aqueous solubility face difficulty diffusing through the mucosal barrier. Although the buccal mucosa is more permeable than skin, it is considerably less permeable than intestinal epithelium, which limits the absorption of macromolecules such as peptides, proteins, and nucleic acids.

5.3 Patient-Related Factors

Patient-centric issues also influence the effectiveness and marketability of buccal drug delivery systems. One such factor is taste masking. The buccal region is in direct contact with the oral cavity's taste buds, making it essential for the formulation to avoid unpleasant flavors or aftertaste, which can significantly impact patient compliance. Drugs with bitter or metallic taste profiles require effective masking techniques, such as flavoring agents, sweeteners, or taste-neutral encapsulation.(2, 24)

CLINICAL APPLICATIONS

The evolution of buccal drug delivery has progressed from conceptual research into tangible clinical applications. Several buccal formulations have already received regulatory approval, while others are under development, particularly for the delivery of complex biomolecules such as peptides, proteins, vaccines, and genetic material. The buccal route offers unique clinical advantages for managing both acute and chronic conditions by enabling non-invasive, rapid, and controlled drug administration. This section outlines current buccal formulations in clinical use, explores innovative approaches to macromolecular and vaccine delivery, and highlights emerging trends such as personalized buccal therapy.(25)

Current Approved Buccal Formulations

A number of pharmaceutical products using the buccal route have gained approval and are commercially available, demonstrating the route's viability for systemic drug delivery. One notable example is Fentora®, a buccal tablet formulation of fentanyl citrate used for managing breakthrough pain in cancer patients. The formulation is designed to rapidly disintegrate and deliver fentanyl directly into the systemic circulation via the buccal mucosa, bypassing the gastrointestinal tract and hepatic metabolism. It provides a fast onset of action, making it suitable for episodes of acute pain.(26)

Prochlorperazine buccal tablets are another clinically approved example. Marketed under various trade names, these tablets are used to manage nausea and vertigo. The buccal route is particularly advantageous for patients who cannot tolerate oral medication due to vomiting, offering therapeutic benefit through systemic delivery without the need for gastrointestinal absorption.(27)

Peptide and Protein Delivery

Delivering peptides and proteins via the buccal route poses significant challenges due to their large molecular size, hydrophilicity, and susceptibility to enzymatic degradation. However, this has not deterred research and development efforts. Molecules like insulin, calcitonin, and interferons have been investigated extensively for buccal administration. These macromolecules typically require protection from proteolytic enzymes and enhancement of their permeability across the mucosal barrier. To address these challenges, researchers have employed enzyme inhibitors to reduce degradation within the buccal cavity. Concurrently, permeation enhancers such as bile salts, surfactants, and fatty acids are incorporated to facilitate the translocation of these large molecules through the tight junctions of the epithelium. Advances in nanoparticle-based carriers and mucoadhesive systems have further improved the pharmacokinetics of buccally delivered peptides. Although no buccal insulin formulation has yet achieved full market approval, several are in advanced clinical trials, showing promise for non-invasive diabetes management.(28)

Vaccines and Gene Delivery

The buccal route is increasingly recognized for its potential in mucosal vaccination and gene therapy. The oral mucosa is rich in immune cells, including dendritic cells and macrophages, which can initiate a strong mucosal and systemic immune response. This makes it an attractive site for delivering vaccines without needles. Several preclinical studies have demonstrated successful buccal delivery of antigens leading to effective immunization against pathogens like influenza and hepatitis.

Recent developments in DNA and RNA-based therapeutics, such as those used in mRNA vaccines, have led to interest in nanocarrier-mediated buccal delivery of genetic material. Nanoparticles made from lipids, polymers, or hybrid materials can encapsulate genetic payloads, protecting them from enzymatic degradation and facilitating their uptake into target cells via transcytosis or endocytosis. These innovations offer a platform for non-invasive gene therapy and vaccination, particularly for populations where injectable routes are less practical.(29)

Personalized Buccal Therapy

The concept of personalized medicine has gained momentum across various therapeutic domains, and buccal delivery systems are being adapted to support individualized dosing and treatment regimens. One of the most promising tools in this area is 3D printing. This technology allows the creation of buccal films and tablets with precise drug loading, customized geometries, and layered drug release profiles, all tailored to the specific needs of the patient. For example, drug-polymer films can be printed in varying thicknesses and shapes to control disintegration time and release kinetics, enhancing therapeutic outcomes while minimizing side effects.

Additionally, the integration of buccal systems with wearable health devices presents new opportunities for real-time monitoring and controlled drug release. Smart buccal patches with embedded sensors can potentially adjust drug delivery in response to physiological parameters such as salivary pH, temperature, or biomarkers. This convergence of digital health and

drug delivery is paving the way for dynamic, responsive, and patient-specific therapy, especially valuable in managing chronic diseases like hypertension or diabetes.(30)

Regulatory and Market Considerations

The successful development and commercialization of buccal drug delivery systems require careful navigation through complex regulatory frameworks and competitive market environments. Regulatory oversight ensures the safety, efficacy, and quality of buccal formulations, while market considerations influence innovation, intellectual property strategies, and commercial success. This section discusses the critical aspects of regulatory guidelines and market dynamics relevant to buccal drug delivery technologies.

Regulatory Guidelines

Buccal drug delivery systems fall under the purview of major global regulatory agencies such as the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). These organizations provide specific guidance on the development of mucosal products, encompassing safety evaluations, formulation standards, and clinical performance requirements. For buccal products intended for systemic absorption, the FDA mandates comprehensive evaluations of bioavailability and bioequivalence. Products must demonstrate that their pharmacokinetic profiles are comparable to either existing formulations or defined reference standards. In some cases, particularly for novel delivery systems or complex molecules, pharmacodynamic or clinical endpoint studies may be required in lieu of traditional bioequivalence trials. The EMA similarly requires justification of local or systemic delivery mechanisms and emphasizes the need for detailed pharmacokinetic modeling and in vitro–in vivo correlation (IVIVC) data.(31)

Stability testing is a critical regulatory requirement for buccal formulations, especially given their vulnerability to environmental factors such as moisture, temperature, and enzymatic degradation. ICH guidelines, including ICH Q1A(R2), outline the protocols for conducting long-term and accelerated stability studies. These evaluations ensure that the product retains its intended strength, integrity, and therapeutic efficacy over its shelf life. Packaging materials, such as moisture-resistant blisters or multilayered sachets, are also assessed to prevent degradation and ensure product safety.(32)

Future Perspectives

Buccal drug delivery systems are evolving beyond conventional formulations, with future developments aiming to enhance precision, responsiveness, and compatibility with complex biological therapeutics. Emerging technologies including smart polymers, nanocarrier systems, and gene delivery platforms are poised to redefine the therapeutic potential of the buccal route. Furthermore, translational research and scalable manufacturing approaches are essential to ensure these innovations reach clinical and commercial realization. This section outlines the prospective advancements shaping the future of buccal drug delivery.

Smart and Responsive Buccal Systems

One of the most exciting directions in buccal drug delivery is the development of smart, stimuli-responsive delivery platforms. These systems are engineered to respond dynamically to physiological cues in the buccal environment such as pH fluctuations, temperature variations, or glucose levels to trigger drug release in a controlled and on-demand manner. Advanced polymeric materials are being synthesized to exhibit environmental sensitivity, making them ideal for diseases requiring precise or pulsatile dosing. For example, glucose-responsive buccal films are being explored for the self-regulated release of insulin, helping to maintain glycemic balance without patient intervention. Similarly, temperature-sensitive hydrogels can remain in a semi-solid state at room temperature and become more permeable at body temperature, enhancing mucosal retention and release kinetics. Moreover, the incorporation of artificial intelligence (AI) and machine learning algorithms is expected to revolutionize formulation design. AI can assist in optimizing polymer compositions, predicting drug release profiles, and tailoring delivery systems to individual patient needs, potentially paving the way for personalized buccal therapy.(10, 33)

Integration with Nanomedicine and Biologics

The integration of buccal delivery systems with nanotechnology and biologic therapeutics represents a transformative leap in drug delivery science. While conventional small molecules are commonly administered via the buccal route, there is growing interest in extending this modality to complex biologics, such as mRNA therapies, CRISPR-Cas gene editing components, and therapeutic proteins.

Nanocarriers including lipid nanoparticles, polymeric micelles, and dendrimers—are being adapted for buccal application to protect fragile biologic payloads from enzymatic degradation and facilitate mucosal penetration. These nanocarrier-buccal hybrid systems offer the dual benefit of localized action and potential systemic absorption, depending on the therapeutic target.

For example, mRNA-based vaccines or gene therapies, which currently rely on injectable administration, could one day be delivered through the buccal mucosa using mucoadhesive nano-formulations. This approach may reduce the need for cold chain logistics, simplify administration, and improve patient compliance—especially in pediatric or needle-phobic populations.(34)

Conclusion

Buccal drug delivery offers a non-invasive, patient-friendly alternative to traditional routes, enabling rapid onset and avoiding hepatic first-pass metabolism. Advances in mucoadhesive polymers both natural and synthetic have improved drug retention and release profiles, while smart polymers responsive to pH, temperature, or enzymes offer precise, on-demand dosing. Various dosage forms, including tablets, films, gels, sprays, and innovative systems like microneedles and nanofibers, have expanded the therapeutic scope to include peptides, proteins, and genetic material. Nanocarriers such as liposomes, nanoparticles, and dendrimers further enhance solubility, stability, and mucosal absorption. Despite significant promise, challenges remain, including salivary dilution, enzymatic degradation, formulation barriers for biologics, and user compliance. Regulatory frameworks and scalable manufacturing are crucial for clinical translation. As the field moves toward AI-assisted design and personalized therapies, interdisciplinary research and patient-centered development will be key to unlocking the full potential of buccal drug delivery in modern therapeutics.

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