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Buccal Delivery System: A Comprehensive Review of an Emerging Drug Delivery Paradigm

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Abstract : The buccal delivery system has emerged as an effective alternative for systemic drug administration, offering unique advantages such as bypassing gastrointestinal (GI) degradation and hepatic first-pass metabolism. The buccal mucosa provides a richly vascularized and accessible site for drug absorption, making it a preferred route for delivering various therapeutic agents. This review discusses the anatomical and physiological basis of the buccal mucosa, formulation strategies, challenges, and advancements in this field, with references for each discussed aspect. Additionally, applications and future trends in buccal delivery are highlighted.
Key words: Buccal delivery, Mucoadhesive polymers, Drug bioavailability, First-pass metabolism avoidance.

I. INTRODUCTION

1. Introduction
Buccal drug delivery involves administering drugs through the mucosal lining of the cheek, which acts as a portal for systemic circulation. This route offers advantages such as non-invasiveness, improved patient compliance, and avoidance of GI and hepatic first-pass effects【1】. It has gained significant attention in delivering drugs with low oral bioavailability, peptides, and vaccines【2】.

2. Anatomy and Physiology of the Buccal Mucosa
The buccal mucosa is composed of a stratified squamous epithelium overlying a connective tissue layer. Its high vascularity and moderate permeability make it suitable for systemic drug delivery. The epithelial thickness (~500–800 μm) and the neutral pH (5.8–7.4) of the mucosa are ideal for many drugs【3】【4】. The permeability of the buccal mucosa is lower than sublingual but higher than skin, providing a balance between protection and absorption【5】.

3. Advantages of Buccal Drug Delivery
The buccal route offers several advantages:

- Avoidance of First-Pass Metabolism: Drugs absorbed through the buccal mucosa directly enter the systemic circulation【6】.
- Patient Compliance: Non-invasive and suitable for individuals with swallowing difficulties【7】.
- Controlled Drug Release: Allows for sustained or immediate release formulations tailored to therapeutic needs【8】.
- Rapid Onset: Drugs such as analgesics achieve quicker therapeutic levels via buccal delivery【9】.

4. Challenges in Buccal Drug Delivery
Despite its potential, buccal delivery faces challenges:

- Limited Permeability: The epithelial barrier restricts drug diffusion, especially for hydrophilic and macromolecular drugs【10】.
- Saliva Clearance: Continuous saliva secretion and mucosal movements can reduce drug contact time【11】.
- Irritation Potential: Some drugs and excipients may cause local irritation or discomfort【12】.
- Limited Absorption Area: The buccal mucosa has a relatively small surface area (~50 cm^2), limiting drug absorption【13】.

5. Formulation Strategies
Various strategies have been developed to optimize buccal drug delivery:
5.1. Mucoadhesive Polymers
Polymers such as chitosan, carbopol, and hydroxypropyl methylcellulose enhance drug retention by adhering to the mucosal surface【14】.
5.2. Permeation Enhancers
Substances like bile salts, surfactants, and fatty acids improve drug permeability by altering the mucosal barrier【15】【16】.
5.3. Sustained Release Systems
Bioadhesive tablets, films, and patches allow for prolonged drug release, reducing the frequency of administration【17】.
5.4. Nanotechnology Approaches
Nanoparticles, liposomes, and microemulsions offer targeted delivery and improved stability for drugs delivered through the buccal route【18】【19】.

6. Recent Advancements
6.1. 3D Printing
The application of 3D printing has enabled the fabrication of customized buccal films and tablets, offering personalized dosing and drug release profiles【20】.
6.2. Microneedle Technology
Microneedles enhance drug delivery through the buccal mucosa by creating microchannels, increasing the absorption of large molecules like peptides【21】.
6.3. Smart Polymers
Stimuli-responsive polymers, which react to pH or temperature changes, have been developed for controlled and on-demand drug release【22】.

7. Applications of Buccal Delivery Systems
7.1. Hormonal Therapies
Buccal delivery systems are used for testosterone and estradiol administration, offering consistent absorption and patient compliance【23】.
7.2. Pain Management
Buccal fentanyl tablets provide rapid relief for breakthrough cancer pain【24】.
7.3. Vaccines and Biologics
The buccal route is being explored for delivering vaccines and biologics due to its ability to bypass the GI tract【25】【26】.

8. Future Perspectives
Future research in buccal delivery focuses on integrating advanced technologies such as biosensors for real-time monitoring and feedback-controlled drug delivery systems. Gene therapy and RNA-based treatments via buccal routes are also emerging as promising areas of exploration【27】【28】.

10. Challenges in Scaling Buccal Drug Delivery Systems
The transition of buccal delivery systems from research to large-scale production and commercialization poses significant challenges.

10.1. Formulation Stability
Maintaining the stability of drugs, especially peptides and proteins, during formulation and storage is a critical challenge. Environmental factors such as temperature, humidity, and pH can compromise the integrity of buccal formulations【29】.

10.2. Regulatory Approvals
Buccal drug delivery systems often require rigorous testing to meet regulatory standards. Demonstrating consistent drug release, efficacy, and safety poses challenges, particularly for novel technologies such as nanocarriers and 3D-printed systems【30】.

10.3. Patient Acceptance
While buccal delivery offers many advantages, patient acceptance can vary based on factors such as taste, texture, and the potential for local irritation【31】. Ensuring user-friendly designs is crucial for widespread adoption.

11. Advanced Technologies in Buccal Delivery

11.1. Hydrogel-Based Systems
Hydrogels have emerged as a promising platform for buccal drug delivery due to their biocompatibility and ability to encapsulate hydrophilic and hydrophobic drugs. They can be designed for sustained release and improved mucoadhesion【32】.

11.2. Edible Films and Dissolving Systems
Fast-dissolving buccal films offer an innovative solution for delivering drugs rapidly without the need for water. These are particularly beneficial for pediatric and geriatric populations【33】.

11.3. Electrospinning
Electrospinning technology has enabled the production of ultra-thin fibers for buccal drug delivery. These fibers have high surface-area-to-volume ratios, allowing for efficient drug loading and rapid dissolution【34】.

12. Economic and Environmental Considerations
Developing cost-effective and sustainable buccal delivery systems is increasingly becoming a priority.

- **Economic Viability**: Ensuring affordability through scalable manufacturing techniques, such as continuous manufacturing, can promote broader accessibility【35】.
- **Sustainability**: Using biodegradable and renewable materials for buccal films and patches minimizes environmental impact, aligning with green pharmaceutical practices【36】.

13. Future Trends

13.1. Integration with Digital Health
Wearable devices with integrated sensors could monitor drug delivery kinetics and physiological responses in real-time. This could enhance the precision and personalization of buccal drug delivery systems【37】.

13.2. Combination Therapies
Buccal systems can be designed for co-delivery of multiple drugs, such as analgesics and anti-inflammatory agents, providing synergistic effects for conditions like cancer pain【38】.

13.3. Expansion to Biologics and Gene Therapy
The buccal route holds potential for delivering biologics, including monoclonal antibodies and nucleic acid-based therapeutics, by incorporating permeation enhancers and advanced nanocarrier systems【39】【40】.

14. Conclusion
Buccal delivery systems are a rapidly evolving field with significant potential to improve drug delivery and patient outcomes. While challenges such as limited absorption and formulation stability remain, advancements in mucoadhesive technologies, nanocarriers, and smart polymers have paved the way for innovative solutions. With ongoing research, buccal drug delivery is set to expand its applications in personalized medicine, biologics, and beyond.

The integration of buccal delivery systems with emerging technologies like 3D printing and biosensors signifies a promising future, offering tailored therapeutic solutions with enhanced efficacy and compliance. By addressing scalability, regulatory, and patient-centered challenges, this approach can redefine non-invasive drug delivery paradigms.

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