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REVIEW ARTICLE

Current Technological Advances in Mucoadhesive Buccal Drug Delivery Systems and Their Therapeutic Applications

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Abstract: Buccal drug delivery has emerged as a promising route of administration, offering distinct advantages over conventional oral delivery systems. The unique physiological characteristics of the buccal mucosa, including rich vascularity and relatively high permeability, make it an attractive site for both local and systemic drug administration. Bioadhesive formulations have revolutionized buccal drug delivery by ensuring prolonged contact with the mucosal surface, thereby enhancing drug absorption and bioavailability. Recent developments in polymer science have introduced novel mucoadhesive materials, including thiolated polymers, lectins, and stimuli-responsive systems, which demonstrate superior adhesion properties and controlled release characteristics. Various formulation approaches, such as films, tablets, patches, and hydrogels, have been developed to optimize drug delivery through the buccal route. These systems incorporate permeation enhancers, enzyme inhibitors, and novel drug carriers to overcome the biological barriers associated with buccal delivery. The application of nanotechnology has further advanced the field, introducing nanostructured formulations that exhibit enhanced mucoadhesion and improved drug permeation. Current research focuses on developing intelligent delivery systems that respond to physiological triggers and maintain therapeutic drug levels. Understanding the critical factors affecting bioadhesion, including polymer characteristics, environmental conditions, and physiological variables, has led to the development of more effective formulations. The integration of modern analytical techniques and quality control measures ensures the development of stable and efficient buccal delivery systems and improves patient compliance and therapeutic outcomes.

Keywords: Mucoadhesion; Buccal delivery; Polymeric systems; Permeation enhancement, Bioavailability.

1. Introduction

Buccal drug delivery has gained significant attention in pharmaceutical research due to its unique advantages in delivering therapeutic agents both locally and systemically [1]. The buccal mucosa, with its robust blood supply and relatively large surface area, presents an attractive site for drug administration, bypassing hepatic first-pass metabolism and enzymatic degradation in the gastrointestinal tract [2]. Bioadhesive formulations represent a breakthrough in buccal drug delivery by enabling prolonged contact between the drug delivery system and the mucosal surface [3]. These formulations utilize specific polymers that interact with the mucin layer of the buccal mucosa, ensuring enhanced drug absorption and improved therapeutic efficacy [4]. The mechanism of bioadhesion involves various physicochemical interactions, including hydrogen bonding, electrostatic forces, and hydrophobic interactions [5].

The evolution of buccal drug delivery systems has been marked by significant technological advancements in formulation design and polymer science [6]. Traditional formulations have evolved from simple adhesive tablets to sophisticated delivery systems incorporating novel polymeric materials and advanced drug carriers [7]. The incorporation of permeation enhancers and enzyme inhibitors has further improved the delivery of drugs through the buccal route [8]. Recent developments in nanotechnology have introduced innovative approaches to enhance the performance of buccal delivery systems [9]. Nanostructured formulations offer advantages such as increased surface area, improved mucoadhesion, and enhanced drug permeation [10]. The application of stimuli-responsive polymers has enabled the development of smart delivery systems that respond to environmental changes, optimizing drug release patterns [11].

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The selection of appropriate polymers plays a crucial role in developing effective buccal formulations [12]. Natural polymers, synthetic polymers, and their modifications have been extensively studied for their mucoadhesive properties and biocompatibility [13]. The development of novel polymer derivatives, particularly thiolated polymers and lectin-modified systems, has significantly enhanced the potential of buccal drug delivery [14].

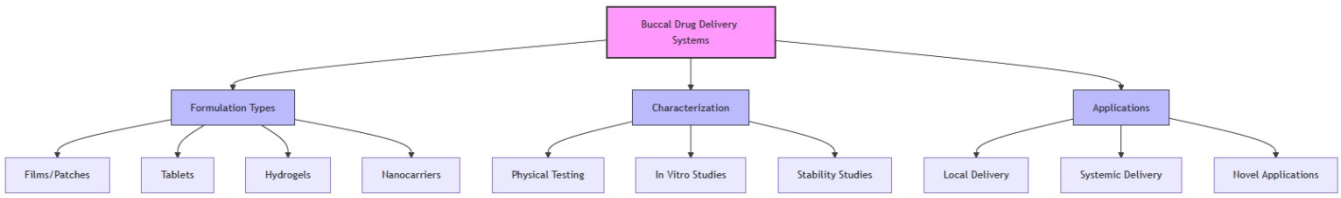

Figure 1. Buccal drug delivery systems (BDDS) and their components

2. Anatomy of Buccal Cavity

2.1. Structure and Components of Buccal Mucosa

The buccal mucosa consists of multiple layers that play crucial roles in drug absorption and distribution [15]. The epithelium, comprised of approximately 40-50 cell layers, serves as the primary barrier for drug permeation [16]. The basement membrane, lamina propria, and submucosa contribute to the structural integrity and vascular supply of the tissue [17]. The presence of specialized tight junctions between epithelial cells regulates paracellular transport of drugs [18].

2.2. Physiological Factors Affecting Drug Absorption

2.2.1. Salivary Characteristics

Salivary secretion represents a primary physiological factor influencing drug absorption through the buccal mucosa. The continuous flow of saliva, ranging from 0.5 to 2.0 mL/min, creates a dynamic environment that directly impacts drug dissolution kinetics and residence time within the buccal cavity. The maintenance of pH between 6.2 to 7.4 by salivary buffering systems significantly influences drug ionization states, affecting their solubility profiles and overall absorption characteristics. This controlled pH environment also plays a crucial role in determining the stability of drug molecules and the performance of mucoadhesive delivery systems [19].

2.2.2. Vascular Supply

The buccal mucosa possesses an extensive vascular network, characterized by a remarkable blood flow rate of approximately 2.4 mL/min/cm^2. This rich blood supply provides direct access to the systemic circulation, enabling drugs to bypass hepatic first-pass metabolism. The high perfusion rate facilitates rapid drug distribution throughout the body, leading to enhanced bioavailability and accelerated onset of therapeutic action. This vascular advantage often translates to reduced dose requirements compared to conventional oral administration routes [20].

2.2.3. Enzymatic Environment

The buccal cavity demonstrates a notably lower enzymatic activity compared to the gastrointestinal tract, particularly regarding peptidase presence. This relative absence of degradative enzymes creates an advantageous environment for the delivery of sensitive therapeutic molecules, especially proteins and peptides. The reduced enzymatic barrier results in enhanced stability of macromolecular drugs, minimizing their degradation and consequently improving their bioavailability. This characteristic makes the buccal route particularly attractive for the administration of biotechnology-derived therapeutic agents [21].

3. Mechanisms of Bioadhesion

3.1. Theories of Mucoadhesion

3.1.1. Electronic Theory

The electronic theory provides a fundamental framework for understanding mucoadhesion at the molecular level. This theory postulates that adhesion occurs through electronic transfer between the mucoadhesive polymer system and the mucus layer, resulting in the formation of an electrical double layer at the interface. The electron transfer process arises from differences in electronic structures between the adhesive polymer and mucus substrate, leading to the development of attractive forces. These electronic

interactions contribute to the overall adhesive strength and are particularly significant when considering polymers with distinct electronic characteristics [22].

3.1.2. Adsorption Theory

The adsorption theory explains mucoadhesion through the formation of various chemical bonds between the polymer and mucus surfaces. This mechanism involves both primary and secondary bonding. Primary bonds, which are relatively rare in mucoadhesion, include covalent bonds that provide strong adhesion. Secondary bonds, which are more prevalent, encompass hydrogen bonds, van der Waals forces, and electrostatic interactions. The cumulative effect of these multiple weak bonds creates significant adhesive strength. The theory emphasizes the importance of surface chemistry and functional group availability in determining the extent of mucoadhesion [23].

3.1.3. Wetting Theory

The wetting theory focuses on the physical aspects of polymer-mucus interactions, particularly in liquid or low-viscosity systems. This theory emphasizes the crucial role of surface tension and contact angle in establishing and maintaining adhesive bonds. The ability of a mucoadhesive system to spread across the mucosal surface is directly related to the surface energies of both the polymer and mucosal substrate. Lower contact angles and higher surface energy facilitate better spreading and consequently stronger adhesion. The theory provides insights into optimizing formulation parameters to enhance mucoadhesive performance through improved wetting characteristics [24].

3.1.4. Diffusion Theory

The diffusion theory describes the interpenetration and entanglement of polymer chains with mucin molecules. The depth of interpenetration depends on the diffusion coefficient and contact time. Greater chain flexibility, similar chemical structures, and optimal environmental conditions enhance this interpenetration process, leading to stronger adhesive bonds.

3.1.5. Mechanical Theory

The mechanical theory addresses the role of surface roughness and physical interlocking in mucoadhesion. The irregular surface features of both the mucosa and the adhesive system contribute to increased contact area and mechanical interlocking, enhancing the overall adhesive strength.

3.1.6. Fracture Theory

The fracture theory analyzes the forces required to separate two surfaces after adhesion has occurred. This theory is particularly useful in understanding the mechanical strength of mucoadhesive bonds and helps in quantifying the adhesive strength of different formulations.

3.2. Factors Influencing Bioadhesion

3.2.1. Polymer-Related Factors

The structural and chemical properties of polymers play a fundamental role in determining bioadhesive strength. Molecular weight serves as a critical parameter, with optimal adhesion typically observed in polymers of intermediate molecular weight ranges. Higher molecular weights provide stronger adhesion through enhanced chain entanglement, while excessive molecular weight can inhibit chain interpenetration. Chain flexibility enables better interdiffusion and entanglement with mucin molecules, promoting stronger adhesive bonds. The concentration and spatial distribution of functional groups, particularly those capable of hydrogen bonding, directly correlate with adhesion strength by facilitating chemical interactions with mucosal surfaces [25].

3.2.2. Environmental Conditions

The surrounding environment significantly impacts bioadhesive performance. pH variations affect the ionization state of both polymer and mucin molecules, thereby influencing their interaction potential. The magnitude of applied force during initial contact determines the degree of polymer spreading and interpenetration into the mucosal layer. Initial contact time is crucial as it determines the extent of polymer hydration and chain relaxation, processes necessary for establishing strong adhesive bonds. Temperature influences polymer chain mobility and the rate of interpenetration, while moisture levels affect polymer hydration and mucin interaction capability [26].

3.2.3. Physiological Factors

The dynamic nature of the physiological environment presents several variables affecting bioadhesion. Mucin turnover rate directly impacts the duration of adhesive bonds, with faster turnover reducing residence time. Saliva production influences the hydration state of both polymer and mucosal surface, affecting polymer chain mobility and mucin interaction. The presence of charged molecules and ions in the physiological environment can either enhance or interfere with electrostatic interactions between polymer

and mucin. Disease states can alter these physiological parameters, potentially affecting bioadhesive performance. The continuous movement of the buccal tissues during speaking and eating also influences the longevity and strength of bioadhesive interactions [27].

3.2.4. Interface-Related Factors

The characteristics of the interface between the polymer and mucosal surface significantly affect bioadhesion strength. Surface roughness influences the total contact area available for interaction. The presence of food debris or other substances can interfere with polymer-mucin contact. The initial spreading coefficient and wetting properties at the interface determine the extent of intimate contact achieved between the adhesive system and mucosal surface.

3.2.5. Application-Related Factors

The method and conditions of application impact bioadhesive performance. The duration of force application during initial contact affects polymer spreading and interpenetration. The surface area of the application site influences the total adhesive strength. The removal rate of the delivery system affects the measured bioadhesive strength and practical performance in clinical settings.

4. Polymers in Buccal Drug Delivery

4.1. Natural Polymers

Chitosan has emerged as a prominent natural polymer due to its excellent mucoadhesive properties and permeation enhancement capabilities [28]. Sodium alginate and hyaluronic acid demonstrate superior biocompatibility and controlled release characteristics [29]. Cellulose derivatives offer versatility in formulation development through various chemical modifications [30].

4.2. Synthetic Polymers

Poly(acrylic acid) derivatives, particularly Carbopol® and polycarbophil, exhibit strong mucoadhesive properties due to their high molecular weight and numerous carboxyl groups [31]. Poly(vinyl pyrrolidone) and poly(vinyl alcohol) provide excellent film-forming properties and compatibility with various drugs [32].

4.3. Modified and Novel Polymeric Systems

Thiolated polymers represent a significant advancement, offering enhanced mucoadhesion through thiol-disulfide exchange reactions [33]. Lectin-modified polymers provide specific binding to sugar residues in the mucus layer, improving targeting efficiency [34]. Stimuli-responsive polymers enable smart drug delivery systems that respond to environmental changes such as pH and temperature [35].

Table 1. Commonly Used Polymers in Buccal Drug Delivery Systems and Their Characteristics

Polymer Category	Examples	Properties	Applications
Natural Polymers	Chitosan	High mucoadhesion, biocompatible	Films, tablets
	Sodium alginate	Good film-forming ability	Hydrogels
	Gelatin	Excellent biodegradability	Films, patches
Synthetic Polymers	Carbopol	Strong mucoadhesion	Tablets, gels
	HPMC	Controlled release properties	Films, matrices
	PVP	Film-forming ability	Films
Modified Polymers	Thiolated chitosan	Enhanced mucoadhesion	Advanced films
	CMC-Na	Good swelling properties	Matrices
	PEGylated polymers	Improved stability	Novel carriers

5. Formulations

5.1. Buccal Films and Patches

Multi-layered films have revolutionized buccal drug delivery by incorporating backing layers that prevent drug loss into the oral cavity [36]. The selection of film-forming polymers and plasticizers significantly influences mechanical properties and drug release characteristics [37]. Advanced manufacturing techniques, including solvent casting and hot-melt extrusion, enable precise control over film thickness and uniformity [38]. Recent innovations include the development of quick-dissolving films for rapid drug release and multi-layered systems for controlled release applications [39].

Table 2. Comparative Analysis of Different Buccal Formulation Types

Formulation Type	Advantages	Limitations	Drug Release Pattern
Films/Patches	- Precise dosing - High patient compliance - Uniform drug distribution	- Complex manufacturing - Storage sensitivity	Sustained/Controlled
Tablets	- Easy manufacturing - Cost-effective - Stability	- Limited residence time - Variable absorption	Immediate/Sustained
Hydrogels	- Easy application - Enhanced contact - Better spreading	- Dose inaccuracy - Limited drug loading	Immediate/Controlled
Nanocarriers	- Enhanced permeation - Improved bioavailability - Targeted delivery	- Complex preparation - Stability concerns - Cost	Modified release

5.2. Buccal Tablets

Matrix tablets incorporating hydrophilic polymers demonstrate controlled swelling behavior and sustained drug release profiles [40]. Double-layered and multi-layered tablet designs prevent drug loss through unidirectional release mechanisms [41]. The incorporation of penetration enhancers and enzyme inhibitors in tablet formulations has improved the bioavailability of poorly absorbed drugs [42].

5.3. Hydrogels and Semi-solid Systems

In-situ forming hydrogels offer advantages of easy application and enhanced retention time [43]. The development of thermosensitive and pH-sensitive hydrogels enables smart drug delivery responding to physiological triggers [44]. Novel crosslinking approaches have improved the mechanical strength and mucoadhesive properties of hydrogel formulations [45].

6. Novel Drug Delivery Approaches

6.1. Nanostructured Delivery Systems

6.1.1. Polymeric Nanoparticles

Polymeric nanoparticles represent a significant advancement in buccal drug delivery technology. Their exceptionally small size, typically ranging from 10-1000 nm, coupled with an expansive surface area-to-volume ratio, facilitates enhanced drug permeation across biological membranes. These nanostructures demonstrate superior cellular uptake and can effectively traverse biological barriers. The versatility of polymeric materials allows for precise control over drug release kinetics, while their modifiable surface properties enable targeted delivery. The incorporation of different polymer types can yield varied degradation profiles and release patterns, making them suitable for diverse therapeutic applications [46].

6.1.2. Lipid-Based Nanocarriers

Lipid-based nanocarriers have revolutionized the delivery of lipophilic drugs through the buccal route. Solid Lipid Nanoparticles (SLNs) offer enhanced stability and controlled release properties, while Nanostructured Lipid Carriers (NLCs) provide improved drug loading capacity and storage stability. These systems demonstrate exceptional biocompatibility and can significantly enhance the bioavailability of poorly water-soluble drugs. Their lipophilic nature facilitates improved interaction with biological membranes, leading to enhanced drug permeation and absorption. The structural organization of lipids in these carriers provides additional advantages in terms of drug protection and controlled release characteristics [47].

6.1.3. Surface-Modified Nanoparticles

Surface modification of nanoparticles with mucoadhesive polymers represents a strategic approach to optimize buccal drug delivery. This modification strategy substantially extends residence time in the buccal cavity and enhances interaction with mucin layers, ultimately improving drug absorption efficiency. The selection of appropriate mucoadhesive polymers and modification techniques significantly influences the performance of these delivery systems. The modified surface characteristics enable prolonged contact with the buccal mucosa, leading to sustained drug release and improved therapeutic outcomes [48].

6.2. Advanced Carrier Systems

6.2.1. Microspheres and Microparticles

Microspheres and microparticles offer sophisticated control over drug delivery through precise release kinetics and enhanced drug stability during storage and administration. The versatility of microsphere formulation allows for customization based on specific drug properties and therapeutic requirements. Their larger size compared to nanoparticles can provide extended release profiles while maintaining adequate mucoadhesion. The manufacturing process can be optimized to achieve desired particle size distributions and drug loading capacities, making them suitable for various therapeutic applications [49].

6.2.2. Dendrimer-Based Systems

Dendrimers represent a unique class of delivery vehicles characterized by their highly branched, tree-like structures and uniform size distribution. Their architectural design enables the simultaneous delivery of both hydrophilic and hydrophobic drugs, making them versatile carriers for combination therapy. The controlled synthesis process allows for precise manipulation of size and surface properties. The presence of multiple functional groups facilitates drug loading through various mechanisms, including physical entrapment and chemical conjugation [50].

6.2.3. Hybrid Delivery Systems

The development of hybrid systems, combining multiple carrier types, has demonstrated remarkable advantages in drug delivery efficiency. These systems integrate the beneficial properties of different carriers to overcome individual limitations and achieve optimal therapeutic outcomes. The rational design of hybrid systems considers the complementary properties of various carriers, resulting in synergistic enhancement of drug delivery, improved control over release patterns, and better stability characteristics. This approach has shown particular promise in addressing complex therapeutic challenges and improving patient compliance [51].

7. Characterization and Evaluation

7.1. Physical Characterization

7.1.1. Surface Morphology Analysis

Advanced microscopic techniques, including scanning electron microscopy (SEM), atomic force microscopy (AFM), and transmission electron microscopy (TEM), provide detailed insights into the structural characteristics of buccal formulations. These techniques reveal critical surface features such as particle size distribution, surface roughness, porosity, and structural homogeneity. The high-resolution imaging capabilities enable the visualization of nano-scale features and interface properties between different components. This morphological information proves invaluable in understanding drug distribution patterns and predicting formulation behavior in physiological conditions [52].

7.1.2. Mechanical Properties Assessment

The evaluation of mechanical properties forms a crucial aspect of formulation development, particularly for films and patches. Tensile strength measurements quantify the maximum stress that the formulation can withstand before failure, while elongation studies determine flexibility and elasticity. These parameters are essential for ensuring that the formulation maintains its integrity during handling and application. The measurement of Young's modulus and other mechanical parameters helps in optimizing formulation composition to achieve desired physical properties that enhance patient compliance and therapeutic efficacy [53].

7.1.3. Swelling Behavior Studies

Swelling studies provide fundamental understanding of the hydration kinetics and dimensional stability of buccal formulations. The analysis includes measurement of swelling index, water uptake capacity, and erosion characteristics under simulated conditions. These studies reveal crucial information about the mechanism of drug release, polymer chain relaxation, and matrix integrity over time. The relationship between swelling behavior and mucoadhesive properties helps in predicting the residence time and drug release patterns in the buccal cavity [54].

7.2. *In Vitro* Studies

7.2.1. Mucoadhesion Strength Evaluation

Various instrumental methods are employed to quantify mucoadhesive strength, including texture analyzers, modified balances, and tensile testing equipment. These measurements determine the force required to detach the formulation from mucosal tissue or synthetic membranes. Parameters such as work of adhesion, peak detachment force, and adhesion time provide comprehensive insights into the mucoadhesive performance. The data obtained helps in optimizing formulation components to achieve desired residence time in the buccal cavity [55].

7.2.2. Drug Release Studies

Drug release studies conducted under simulated conditions provide critical information about release kinetics and mechanisms. These studies utilize specialized dissolution apparatus and media that simulate the buccal environment. The analysis of release profiles helps in understanding the influence of formulation parameters on drug availability. Mathematical modeling of release data aids in predicting in vivo performance and optimizing formulation composition to achieve desired release patterns [56].

7.2.3. Permeation Studies

Permeation studies employ specialized diffusion cells, including Franz cells and Ussing chambers, to evaluate drug transport across buccal mucosa. These studies assess factors affecting drug permeation, such as membrane barrier properties, drug physicochemical characteristics, and enhancer effects. The analysis of permeation parameters, including flux and permeability coefficients, provides valuable insights into the efficiency of drug delivery through the buccal route. The data obtained guides the selection of appropriate permeation enhancers and optimization of formulation strategies [57].

8. Recent trends

8.1. 3D Printing Technology Integration

Three-dimensional printing technology has revolutionized the development of buccal drug delivery systems by enabling the production of customized dosage forms. This advanced manufacturing approach allows precise control over geometric designs, drug distribution patterns, and release profiles. The technology facilitates the creation of complex multi-layered structures and patient-specific formulations based on individual therapeutic requirements. The ability to modify design parameters rapidly makes it particularly valuable for personalized medicine applications and optimization of drug delivery systems during development stages [58].

8.2. Smart Delivery Systems

The incorporation of biosensors into buccal drug delivery systems represents a significant advancement in therapeutic monitoring. These smart systems provide real-time feedback on drug release patterns, local pH conditions, and other physiological parameters. The integration of responsive polymers and sensor technologies enables adaptive drug release based on physiological triggers. This intelligent approach to drug delivery enhances therapeutic efficiency and patient monitoring capabilities, leading to improved treatment outcomes [59].

8.3. Mucoadhesive Proteins and Peptides

The development of novel mucoadhesive proteins and peptides has opened new avenues in targeted drug delivery. These biomolecular adhesives demonstrate superior specificity and biocompatibility compared to conventional polymeric systems. Their ability to interact with specific cellular receptors enables more precise targeting and enhanced therapeutic efficiency. The integration of these biological components has led to improved residence time and drug absorption characteristics [60].

8.4. Enhanced Protein and Peptide Delivery

Advanced delivery systems for proteins and peptides have shown remarkable progress in clinical studies. These systems incorporate innovative approaches to overcome traditional challenges such as enzymatic degradation and poor permeation. The development of specialized protective mechanisms and permeation enhancers has significantly improved the bioavailability of these macromolecular drugs. Clinical evidence demonstrates the potential of these systems for delivering therapeutic proteins and peptides effectively through the buccal route [61].

8.5. Local Treatment Formulations

Novel formulations designed for local treatment of oral diseases exhibit enhanced therapeutic efficacy. These systems provide improved drug targeting to specific oral sites while minimizing systemic exposure. The incorporation of advanced materials and delivery technologies has resulted in better retention times and drug distribution within the oral cavity. These developments have particular significance in treating conditions such as oral infections, inflammation, and mucosal lesions [62].

8.6. Vaccine Delivery Systems

The exploration of buccal route for vaccine delivery presents promising opportunities for needle-free immunization. These systems utilize the rich immune network of the buccal mucosa to generate effective immune responses. The development of specialized carriers and adjuvants enhances vaccine stability and immunogenic responses. This approach offers advantages in terms of patient compliance and ease of administration, particularly in mass vaccination programs [63].

8.7. Quality by Design Implementation

The adoption of Quality by Design (QbD) principles has significantly improved product development and manufacturing processes. This systematic approach enables better understanding of critical quality attributes and process parameters. The establishment of design space facilitates consistent product quality during scale-up operations. The implementation of QbD principles has led to more robust manufacturing processes and reduced variability in product quality [64].

8.8. Standardized Testing Methods

The development and establishment of standardized testing methods have enhanced regulatory compliance in buccal drug delivery system development. These methods provide consistent approaches for evaluating critical parameters such as mucoadhesion, drug release, and stability. The standardization efforts have improved product characterization and quality assessment procedures. This harmonization facilitates regulatory approval processes and ensures product consistency across different manufacturing sites [65].

8.9. Process Analytical Technology

The implementation of Process Analytical Technology (PAT) has revolutionized manufacturing processes for buccal drug delivery systems. This approach enables real-time monitoring and control of critical process parameters during production. The integration of advanced analytical tools and control systems has improved process understanding and product quality. The application of PAT has resulted in enhanced manufacturing efficiency, reduced waste, and improved product consistency [65].

9. Conclusion

Bioadhesive buccal formulations represent a significant advancement in drug delivery technology, offering numerous advantages for both local and systemic drug administration. The understanding of buccal physiology, coupled with innovations in polymer science and formulation strategies, has led to the development of more effective and patient-friendly delivery systems. The integration of nanotechnology and smart polymeric systems has opened new avenues for improved drug delivery. Although challenges remain in terms of scaling up production and regulatory compliance, continued research and technological advancements suggest a promising future for buccal drug delivery systems. The evolution of these formulations, from simple adhesive systems to sophisticated responsive delivery platforms, shows their potential to mitigate current therapeutic limitations and improving patient outcomes.

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