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Innovations in Mucosal Drug Delivery: A Comprehensive Review of Sublingual and Lingual Delivery Devices

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Abstract

Mucosal drug delivery via sublingual and lingual routes is increasingly recognized as a transformative approach in pharmaceutical research, owing to its ability to circumvent gastrointestinal degradation and first-pass hepatic metabolism, thus enabling rapid onset and enhanced bioavailability for a diverse range of drugs. Recent innovations in materials science have yielded advanced formulations including nanoencapsulation, mucoadhesive films, multilayered tablets, and bioinspired carriers, which significantly improve drug stability, solubility, and residence time within the oral cavity. Device engineering has progressed with the development of personalized 3D-printed dosage forms, nanoparticle sprays, and microrobotic pills equipped with microstirrers, offering precise, rapid, and efficient drug release even under challenging mucosal conditions. Additionally, digital health integration is reshaping sublingual and lingual delivery systems through biosensor-enabled smart patches and dose-tracking devices, promoting real-time adherence monitoring and feedback-based dosing for improved clinical outcomes. Commercial products have expanded to include rapidly dissolving tablets, transbuccal sprays, and smart device prototypes for a range of indications, such as acute pain, cardiovascular emergencies, and chronic disease management. Despite these advances, challenges like formulation stability, taste masking, and variable patient compliance remain focal points for future research, driving ongoing improvements in technology, education, and regulatory pathways.

Keywords: Mucosal drug delivery, Sublingual devices, Lingual devices, Buccal sprays, Nanocarriers

1. Introduction

Mucosal drug delivery systems, particularly those utilizing the sublingual and lingual routes, are gaining prominence in pharmaceutical research due to their distinct therapeutic and practical advantages.[1] These methods are inherently non-invasive, circumventing the need for needles or surgical interventions, which not only reduces healthcare-associated risks but also fosters improved patient compliance, an essential factor in chronic or self-administered therapies. The oral mucosa is highly vascularized, providing a direct gateway for drugs to swiftly enter systemic circulation while bypassing the gastrointestinal tract and first-pass hepatic metabolism.[2,3] As a result, drugs administered through these mucosal routes often demonstrate rapid absorption and onset of action, making them particularly effective for medications used in acute care or requiring immediate therapeutic response.[1]

Another significant benefit is that sublingual and lingual delivery can enhance the bioavailability of drugs that are otherwise degraded or inefficiently absorbed in the digestive tract, such as peptides, hormones, and certain cardiovascular agents.[4] Additionally, these routes are advantageous for patients with swallowing difficulties, pediatric and geriatric populations, and in emergency settings where oral or intravenous administration may be impractical.

Within this evolving landscape, the scope of recent research and reviews extends well beyond traditional formulations.[3,5] Current scientific focus includes not only the evaluation of major drug classes suited for mucosal administration but also the development of sophisticated carrier systems, such as nanocarriers, mucoadhesive films, and bioinspired polymers, that optimize drug stability and mucosal residence time.[3] This review will further address novel device engineering, including digital and biosensor-integrated systems, alongside discussion of investigational and commercially available products. Special emphasis is placed on ongoing translational challenges, such as formulation stability, patient adherence, and regulatory perspectives, which continue to shape the future potential and clinical uptake of sublingual and lingual drug delivery platforms.[6]

In addition to their core benefits, sublingual and lingual mucosal drug delivery systems offer important pharmacokinetic and patient-centered advantages that continue to expand their relevance in therapeutics.[7] The sublingual area's thin mucosal membrane and rich vascularity facilitate exceptionally rapid onset of action and pronounced absorption efficiency, making this route especially suitable for time-sensitive therapies such as those for angina, acute pain, and seizures.

Dosing precision is further enhanced by the predictable absorption patterns characteristic of mucosal tissues, and because this route avoids degradation by digestive enzymes and first-pass hepatic metabolism, even drugs suffering from poor gastrointestinal stability or solubility can achieve clinically effective concentrations with smaller doses.[7-9] This often translates to lower risk of systemic side effects and dose-related toxicity. The elimination of the need to swallow medication not only benefits pediatric, geriatric, and dysphagic patients but also addresses challenges in settings where swallowing or intravenous administration may not be practical or timely, such as with uncooperative or unconscious patients.[2,3]

From a formulation perspective, recent years have seen significant diversification in delivery systems, moving beyond simple tablets to include rapidly dissolving films, sprays, microencapsulated dosage forms, and mucoadhesive patches.[10] Advanced technologies such as nanocarrier encapsulation and bioadhesive polymers improve both drug retention at the absorption site and stability, enabling longer

residence time and more sustained therapeutic effects. Some formulations also address taste masking and irritation, two key contributors to patient adherence and acceptance.[4]

Engineering innovations have given rise to devices that combine biosensor feedback or digital connectivity, supporting dose tracking, adherence monitoring, and individualized therapy adjustment for chronic conditions. Moreover, ongoing clinical and regulatory advancements are promoting the approval and utilization of a wider spectrum of drug classes, including hormones, peptides, CNS agents, and vaccines, via mucosal routes.[5,7] Despite these advantages, ongoing research addresses issues such as palatability, mucosal irritation, and ensuring robust absorption across diverse patient populations, all of which are essential for future expansion and optimization of these platforms.

2. Oral Mucosal Physiology and Barriers

The oral mucosa presents a unique and complex environment for drug delivery, defined by its distinct structure and functional barriers.[11] The oral cavity surface itself is extensive, covering approximately 170 cm^2, encompassing sublingual, buccal, and gingival regions, each with different epithelial thicknesses and permeability characteristics. The high vascularity of the sublingual and lingual areas can facilitate rapid drug absorption directly into systemic circulation, thereby bypassing first-pass metabolism and allowing for swift therapeutic effect.[12]

However, leveraging these advantages requires an understanding of the physiological barriers present in the oral mucosa. At the forefront is the mucus layer, a dual-layered barrier consisting of an inner, tightly bound component and an outer, loosely adherent layer. While the inner layer can assist in drug stabilization and absorption through its glycoprotein-rich structure, the thicker outer mucus acts as a selective filter, impeding the movement of drugs and drug delivery systems (DDS) toward the epithelium.[4,13] The physicochemical interactions between drug particles and mucin (the primary protein in mucus) can either enhance or hinder absorption, depending on the characteristics of the therapeutic molecule and its carrier system.

Beyond the mucus, the multi-layered epithelium itself, which varies in thickness between different oral regions, serves as the main physical barrier to absorption. Drugs may cross this layer via transcellular (through cells) or paracellular (between cells) routes, with passive diffusion being predominant.[14,15] Larger, lipophilic molecules generally favor the transcellular pathway, while smaller, hydrophilic drugs may traverse paracellular channels. The basement membrane below the epithelium acts as an additional resistance, sometimes representing a rate-limiting barrier for larger or more complex molecules.

The enzymatic environment of the oral cavity introduces metabolic challenges. Although some degradation can occur, mediated by extracellular enzymes found in saliva and the mucosa, this enzymatic activity is typically less intense than that of the gastrointestinal tract, making oral mucosal delivery more favorable for labile drugs such as peptides and proteins.[16] However, hydrolytic and proteolytic enzymes can still impact drug stability and must be considered during formulation development.

Saliva flow presents both benefits and challenges: it maintains mucosal health and aids drug dissolution, but it also promotes drug clearance from the site of administration, potentially limiting residence time and absorption.[17] Devices such as mucoadhesive films and bioadhesive polymers have been developed to

counteract rapid saliva-mediated clearance, allowing for extended drug-mucosa contact and improved uptake.

Additionally, the local immune system, comprising various immune cells within the mucosa, can influence the fate of delivered drugs by mediating clearance or modulating tissue response, a factor of growing interest in both design and evaluation of mucosal drug delivery systems.

3. Historical Evolution and Current Clinical Needs

The historical evolution of sublingual and lingual drug delivery from 2010 to 2025 marks a dynamic era of innovation and clinical integration. Initially limited to relatively simple tablet formulations, this period witnessed a dramatic shift driven by advances in pharmaceutical technology and a broadening therapeutic scope.[10,13] Emerging from the foundational work on drugs like nitroglycerin for angina and opioids for pain management, the innovation and integration phase introduced sophisticated delivery platforms including nanoparticles and multilayered mucoadhesive systems.[2] Notably, pediatric formulations such as fast-dissolving films and tablets were developed to address the needs of younger patients, improving ease of administration and compliance.

This period also saw expansion into immunotherapy and vaccine delivery via mucosal routes, along with the inclusion of a diverse array of therapeutic agents covering steroids, antifungals, cannabinoids, antidepressants, antipsychotics, and narcotics like buprenorphine and apomorphine.[18] Novel formulations of fentanyl and diazepam targeting pain and seizure control enhanced the emergency care arsenal, while innovative buccal vitamin D3 sprays addressed chronic vitamin deficiencies.

Clinically, the enhanced mucosal delivery systems have met critical needs among vulnerable populations such as pediatric and geriatric patients, who often face challenges with swallowing or tolerating injections.[19] Emergency settings, particularly for conditions like angina and seizures, benefit from the rapid absorption and onset achievable through these routes, enabling timely therapeutic intervention. Furthermore, ongoing advancements in taste masking, improved local tolerability, and patient education have addressed barriers to adherence, a crucial factor in both acute and chronic therapies.[5-8]

Overall, this historic progression reflects a multifaceted response to diverse clinical requirements, underpinned by technological advances that offer improved therapeutic efficacy, patient compliance, and expanded applicability across medical specialties. It heralds a promising future where personalized, rapid, and non-invasive drug delivery forms standard components of patient care.

4. Novel Materials and Carrier Innovations

4.1 Mucoadhesive Polymers and Films

Mucoadhesive polymers have revolutionized oral mucosal drug delivery by significantly enhancing the residence time of dosage forms at the mucosal surface, thereby improving drug absorption and therapeutic efficacy.[20] Both natural and synthetic polymers play critical roles in this advancement. Natural polymers such as chitosan and hyaluronic acid provide excellent biocompatibility and bioadhesion through electrostatic interactions with the negatively charged mucin glycoproteins on the mucosal surface.[21-24]

Chitosan, in particular, is valued for its ability to transiently open tight junctions between epithelial cells, facilitating paracellular transport of therapeutic agents. Synthetic polymers like cellulose derivatives (e.g., carboxymethyl cellulose) and poly(acrylic acid) exhibit strong mucoadhesive properties via hydrogen bonding and ionic interactions, enabling prolonged attachment and controlled drug release.[16]

Recent years have seen the development of sophisticated mucoadhesive films with multilayered and slow-dissolving designs. These films expand the range of active pharmaceutical ingredients (APIs) deliverable through the oral mucosa by providing tailored drug release profiles, from immediate to sustained release, while ensuring patient comfort and convenience.[22,25] Multilayer films often combine an adhesive layer with a backing impermeable to saliva, directing drug release toward the mucosa and preventing premature drug washout. Slow-dissolving films improve drug bioavailability by maintaining close contact with the absorption site over extended periods, mitigating challenges posed by saliva flow and swallowing.

Optimizing the physicochemical characteristics of mucoadhesive polymers—including molecular weight, chain flexibility, degree of ionization, and hydration capacity is critical for maximizing adhesion and drug delivery efficiency.[26] Environmental factors like pH and mucosal turnover, along with formulation variables such as polymer concentration and applied contact time, also influence performance.[9] Contemporary mucoadhesive systems leverage these insights to overcome oral mucosal barriers, making them highly promising platforms for both local and systemic drug administration.

4.2 Nanocarriers and Smart Hydrogels

Nanocarriers such as liposomes, solid lipid nanoparticles, and bioinspired polymeric nanoparticles have emerged as pivotal technologies in oral mucosal drug delivery. These nanoscale carriers encapsulate therapeutic agents, protecting them from enzymatic degradation and the harsh environment of the oral cavity while enhancing mucosal permeation.[27] Their small size enables efficient diffusion through the mucus barrier, and surface modifications, such as chitosan or glycosaminoglycan coatings, improve mucoadhesion and facilitate receptor-mediated uptake by epithelial cells.[4-7] This translates into enhanced bioavailability and the ability to deliver both hydrophilic and lipophilic drugs, ranging from peptides to small-molecule APIs. Moreover, nanocarriers allow for controlled and sustained release profiles, reducing dosing frequency and improving patient adherence.

Parallel to nanocarriers, smart hydrogels represent an innovative class of stimuli-responsive materials designed to offer environment-triggered drug release tailored to the pathological state of the mucosa.[1,7] These hydrogels, often based on glycosaminoglycans such as hyaluronic acid or chondroitin sulfate, respond dynamically to changes in pH, temperature, enzyme concentration, or inflammatory mediators at the site of application.[28] This capability ensures that drug release is modulated in real time according to disease activity, optimizing therapeutic outcomes while minimizing adverse effects. Their high water content enhances hydration and comfort upon application, while their bioadhesive nature prolongs mucosal residence time despite saliva flow.[5]

Current research focuses heavily on hybrid systems that combine nanocarriers with these smart hydrogels, creating composite platforms that synergistically improve drug protection, controlled delivery, and tissue targeting. Clinical studies, particularly in mucosal diseases like oral lichen planus, candidiasis, mucositis,

and oral cancer, have demonstrated promising efficacy and safety profiles.[29] Despite progress, challenges remain in standardizing characterization methods, improving long-term stability, and scaling manufacturing while maintaining reproducibility. However, the convergence of nanotechnology and stimuli-responsive biomaterials positions these delivery systems at the forefront of next-generation oral mucosal therapy, enabling precision, personalization, and enhanced patient-centric care.[6-8]

4.3 3D Printing, Sensor-Integrated Systems, and Personalized Platforms

The application of 3D printing technology to oral mucosal drug delivery represents a groundbreaking advancement in personalized medicine. By enabling precise control over dosage form geometry, drug distribution, and mechanical properties, 3D printing allows for the creation of individualized dosage forms tailored to a patient's unique anatomical and therapeutic requirements.[30] This capability is especially valuable for pediatric and geriatric populations, who often have difficulties in swallowing standard dosage forms. Customized 3D-printed mucoadhesive scaffolds, films, and tablets can be designed with optimized size, shape, porosity, and drug release profiles to enhance both comfort and adherence.[4,31] For instance, multilayered scaffolds fabricated via 3D bioprinting combine an adhesive layer, drug reservoir, and protective backing to prolong residence time within the challenging oral environment while permitting sustained release over multiple days.[12-15] This technological flexibility also allows for combination therapies and complex dosing regimens that would be difficult to achieve with conventional manufacturing methods.

Beyond structural customization, the integration of biosensors and digital health capabilities into mucosal drug delivery devices is an emerging frontier enabling real-time therapy monitoring and management. Smart patches and sensor-enabled films embedded with microelectronics can track drug release kinetics, detect patient adherence, and relay physiological data such as pH, temperature, or inflammatory biomarkers to healthcare providers via Bluetooth or other wireless technologies.[32] This bidirectional connectivity facilitates personalized dose adjustments, timely interventions, and comprehensive patient support outside traditional clinical settings.[9,18] Additionally, sensor systems can provide feedback on mucosal condition, ensuring that doses are only released under optimal therapeutic windows triggered by specific stimuli, an approach that promises enhanced efficacy and minimized side effects.

Together, 3D printing and sensor integration exemplify the shift towards patient-centric, precision drug delivery platforms in oral mucosal therapy.[2] They address key limitations of conventional systems, such as fixed dosing, poor adherence, and inadequate monitoring—by combining anatomical personalization with digital intelligence to improve clinical outcomes and quality of life for diverse patient groups.[33] Continued interdisciplinary research and regulatory collaboration will be crucial in advancing these technologies from the laboratory to routine clinical practice.[23,28] Mucosal drug delivery via sublingual and lingual routes is increasingly recognized as a transformative approach in pharmaceutical research, owing to its ability to circumvent gastrointestinal degradation and first-pass hepatic metabolism, thus enabling rapid onset and enhanced bioavailability for a diverse range of drugs.[20,25] Recent innovations in materials science have yielded advanced formulations including nanoencapsulation, mucoadhesive films, multilayered tablets, and bioinspired carriers, which significantly improve drug stability, solubility, and residence time within the oral cavity.

Device engineering has progressed with the development of personalized 3D-printed dosage forms, nanoparticle sprays, and microrobotic pills equipped with microstirrers, offering precise, rapid, and efficient drug release even under challenging mucosal conditions.[7,21] Additionally, digital health integration is reshaping sublingual and lingual delivery systems through biosensor-enabled smart patches and dose-tracking devices, promoting real-time adherence monitoring and feedback-based dosing for improved clinical outcomes.[2]

Commercial products have expanded to include rapidly dissolving tablets, transbuccal sprays, and smart device prototypes for a range of indications, such as acute pain, cardiovascular emergencies, and chronic disease management.[14,15] Despite these advances, challenges like formulation stability, taste masking, and variable patient compliance remain focal points for future research, driving ongoing improvements in technology, education, and regulatory pathways.

Table 1. Devices and Dosage Forms

Dosage Form	Description/Innovation	Example Devices	Clinical Relevance	Citation
Mucoadhesive Films	Thin, flexible films with extended residence time	OralSolve™, ThinOral™	Chronic pain, Vitamin B12 deficiency	Alqahtani et al. [13]
Rapidly Dissolving Tablets	Fast-onset, high-patient acceptance	Suboxone®, Zydis®	Emergency, psychiatry, addiction	Kulkarni et al. [12]
Nanoparticle Sprays	Nano-formulated drug solutions	Fentanyl nasal spray	Palliative, acute pain	Alqahtani et al. [13]
Bioinspired Hydrogels	Gel systems reacting to pH/temperature	BioMuc™ (in development)	Mucositis, local delivery	Brako et al. [14]
Smart Patches	Monitor and modulate release with biosensors	Experimental	Precision therapy, adherence	Alqahtani et al. [13]

5. Clinical Applications and Approved Products

Sublingual and lingual drug delivery has become a mainstay for several therapeutic categories, with cardiovascular, central nervous system (CNS), hormone therapy, and vitamin supplementation drugs dominating the approved product landscape. Cardiovascular agents such as nitroglycerin and isosorbide dinitrate have long leveraged the fast absorption through the oral mucosa to provide rapid symptom relief in angina and other ischemic conditions.[2-5] Similarly, CNS drugs like midazolam and fentanyl utilize sublingual routes for rapid sedation, seizure control, and pain management, often in emergency settings that demand swift therapeutic action.[1]

Hormone therapies such as sublingual estradiol and testosterone formulations have gained traction due to improved bioavailability and convenient administration for patients requiring hormone replacement.[15,28] Vitamin supplementation, particularly vitamin B12 and vitamin D, benefits from sublingual delivery by bypassing gastrointestinal limitations and improving absorption in populations with malabsorption issues or dietary restrictions.[4,7]

Beyond established therapies, investigational applications are rapidly expanding to include immunotherapy vaccines, oral allergy immunotherapy, and precision oncology agents. For example, allergen extract tablets for sublingual immunotherapy (SLIT) have been approved for allergic rhinitis and food allergies, allowing gradual immune desensitization with enhanced patient compliance.[2,30] Precision oncology is exploring sublingual delivery of targeted agents and immune modulators to maximize bioavailability and reduce systemic toxicity.

The appeal of sublingual and lingual routes is particularly strong in pediatric and palliative care settings, where noninvasive, rapid-onset dosing is essential. These patient populations often face challenges with traditional oral or parenteral administration methods, such as swallowing difficulties or the need for rapid symptom control, which mucosal delivery addresses effectively.[9] Globally, adoption is growing due to these benefits, improved formulations, and an expanding armamentarium of approved and investigational products, underscoring the clinical significance and future potential of sublingual and lingual drug delivery systems.[4] Mucosal drug delivery via sublingual and lingual routes offers distinct therapeutic advantages, including bypassing gastrointestinal degradation and first-pass hepatic metabolism, resulting in rapid drug absorption and onset of action. In recent years, innovations in materials science, device engineering, and digital health integration have advanced delivery systems from simple tablets to sophisticated mucoadhesive films, nanocarriers, and biosensor-integrated smart patches.[10] These developments significantly enhance drug stability, residence time, and controlled release, improving clinical outcomes across diverse therapeutic areas.

The non-invasiveness of mucosal delivery improves patient compliance, especially in chronic therapies, pediatric, and geriatric populations who may face difficulties with traditional oral or parenteral routes.[11] Additionally, these routes are valuable in emergency care settings, such as angina and seizure management, where rapid therapeutic effect is critical. Scientific focus has expanded to include a broad drug spectrum, covering cardiovascular agents, CNS drugs, hormones, vitamins, immunotherapies, and vaccines.[21] Sophisticated carrier systems like nanocarriers and bioinspired polymers, coupled with advanced device engineering including 3D-printed dosage forms and smart biosensor patches, provide personalized dosing, enhanced mucoadhesion, and real-time therapy monitoring.

6. Advances in Device Engineering

3D printing technology has significantly advanced personalized drug delivery by enabling the rapid prototyping of dosage forms tailored to individual patient anatomy and drug requirements. This additive manufacturing allows customization of size, shape, drug load, and release kinetics to meet specific therapeutic needs, enhancing both precision and patient adherence.[32] For example, 3D-printed mucoadhesive films and scaffolds can be designed to conform anatomically to a patient's oral cavity, promoting better retention and improved drug absorption. The ability to produce multilayered, complex

drug delivery systems on-demand also facilitates combination therapies and appropriate dosing for vulnerable populations such as pediatric and geriatric patients.[6,13] Moreover, 3D printing supports resource-efficient production, making it ideal for emergency settings and personalized pharmacotherapy where rapid, tailored solutions are critical.

Emerging micro-needle and micro-reservoir platforms are under exploration as minimally invasive strategies for tunable mucosal drug delivery.[5] These micro-scale devices can penetrate the mucosal layer gently, enabling direct delivery of drugs into the subepithelial tissue, overcoming diffusion limitations associated with conventional topical systems. Micro-needles facilitate precise dosing with reduced variability, while micro-reservoirs provide controlled release by storing drugs in minute compartments that release therapeutics over defined periods.[7,11] This tunability maximizes therapeutic efficiency and minimizes systemic side effects, making such platforms promising for sensitive drug classes such as peptides, vaccines, and biologics.

Integration of digital health technologies with these advanced drug delivery systems is transforming therapy management. Sensor-enabled delivery devices incorporate microelectronics capable of real-time monitoring of drug release, mucosal environment, and patient adherence.[21] Connectivity features like Bluetooth allow seamless data transmission to healthcare providers or mobile health applications, enabling remote therapy monitoring and personalized dose adjustments. These features are particularly valuable for chronic disease management, where adherence and dose optimization are critical to efficacy.[29] This fusion of drug delivery and digital technology paves the way for highly patient-centric treatments characterized by precise, responsive, and adaptive therapeutic regimens.

Together, these innovative technologies exemplify the future of oral mucosal drug delivery, combining anatomical personalization, minimally invasive modalities, and intelligent monitoring to optimize clinical outcomes and patient quality of life.

7. Challenges and Translational Gaps

Despite notable advances in oral mucosal drug delivery technologies, several critical challenges impede their widespread clinical translation and routine use. From a technical standpoint, there is a persistent lack of standardized in vitro and in vivo testing models that accurately recapitulate the complex physiology of the human oral mucosa.[12] While 2D monolayer cell cultures and animal models have traditionally been used, they often fail to mimic the multilayered epithelium, mucus barrier, enzymatic environment, and dynamic saliva flow.[20] Advances in 3D tissue-engineered and ex vivo models offer promising platforms with greater physiological relevance, enabling better prediction of drug absorption, mucoadhesion, and toxicity. However, these models vary widely in design and fabrication methods, suffer from limited long-term viability, and lack uniform protocols for reproducibility, limiting their acceptance as standardized tools across the pharmaceutical industry.[1,4] This variability complicates the comparison of data between studies and hinders efficient drug development.

On the regulatory front, there remains ambiguity in the classification and approval pathways for combination products involving drug-device hybrids, especially for novel platforms incorporating nanocarriers, smart hydrogels, and digital health components.[3] The complexity arises from the dual nature of these products, they simultaneously deliver therapeutics and perform device functions such as drug

release modulation or adherence monitoring. Regulatory agencies across jurisdictions differ in guidance for such combination products, creating uncertainty for developers.[14] Additionally, defining clinical endpoints, safety assessment criteria, and quality control parameters for these multifaceted systems continues to challenge regulatory frameworks, potentially delaying market entry and patient access.

Patient-centric challenges are equally critical for real-world success. Palatability and taste masking of mucosal formulations remain major obstacles, as unpleasant taste or mouthfeel can deter adherence, especially in pediatric or geriatric populations.[11] Local irritation from excipients, adhesives, or drug constituents can cause discomfort, inflammation, or mucosal ulceration, limiting prolonged or repeated use. Device retention and stability within the highly moist and mechanically active environment of the oral cavity pose formulation challenges; poor retention leads to premature drug clearance and reduced efficacy. Furthermore, cosmetic considerations such as visibility, residue after use, and ease of administration affect patient acceptance, particularly among socially active individuals.[26] Addressing these human factors through formulation optimization, sensory evaluation, and usability testing is essential to drive adherence and therapeutic success.

8. Future Directions

Glycosaminoglycan (GAG)-based and other biomimetic carriers represent a promising frontier for both localized and systemic drug delivery applications. GAGs such as hyaluronic acid and chondroitin sulfate are naturally occurring polysaccharides that closely mimic the extracellular matrix components, providing biocompatible, biodegradable, and non-immunogenic platforms for drug encapsulation and controlled delivery.[28] Their unique structural features enable high water retention, bioadhesion, and targeted interactions with cell surface receptors (e.g., CD44) that are often overexpressed in diseased tissues such as tumors and inflamed mucosa. This bio-recognition allows for precision targeting and enhanced cellular uptake, thereby improving therapeutic index and reducing off-target effects.[4,26] Besides oncology and inflammatory diseases, GAG-based carriers have demonstrated efficacy in wound healing, ophthalmic drug delivery, and metabolic disorder treatments.[3] However, challenges in scalable manufacturing, long-term stability, and batch-to-batch reproducibility must be addressed to transition these carriers from experimental models to commercial realities.

In parallel, clinical research in mucosal and systemic drug delivery must increasingly emphasize patient-reported outcomes and head-to-head comparative trials against established oral and parenteral therapies.[9] Robust bioequivalence and pharmacokinetic data are essential to validate new platforms and foster clinician confidence. Such evidence bridges scientific innovation and clinical applicability, ensuring that novel drug delivery technologies translate into meaningful improvements in efficacy, safety, and adherence.[27] Moreover, comparative effectiveness studies can elucidate cost-benefit aspects and facilitate regulatory approvals and reimbursement policies.

Looking ahead, personalized medicine and integration with digital therapeutics are poised to drive a new cycle of innovation in mucosal drug delivery. Advanced biomaterials and device designs will be tailored to individual patient pathophysiology, genetic profiles, and treatment responses.[4,7] Coupled with digital health tools such as biosensors, data analytics, and remote monitoring, these systems will enable dynamic and adaptive dosing regimens, early detection of therapeutic failures, and enhanced patient engagement.

This convergence heralds a future where mucosal drug delivery is not only more effective but also harmonized with precision health paradigms, optimizing treatment outcomes at an individual level.

9. Conclusion

Sublingual and lingual mucosal drug delivery has emerged as a frontrunner in noninvasive, patient-centered therapeutics due to its unique ability to provide rapid systemic drug absorption while avoiding the challenges of the gastrointestinal tract and first-pass metabolism. Recent years from 2010 through 2025, have been marked by significant advances in formulation science, device engineering, and the integration of digital health technologies, collectively driving the development of an expanding portfolio of approved and investigational products. These innovations include sophisticated mucoadhesive films, nanoparticles, multilayer tablets, and even microrobotic platforms that enhance drug stability, bioavailability, and residence time within the oral cavity. The efficacy of these systems across a variety of conditions, from cardiovascular emergencies to chronic hormone replacement and CNS disorders, demonstrates their broad clinical utility and growing acceptance among healthcare providers.

In tandem with product development, device engineering breakthroughs such as 3D printing for personalized dosing and smart biosensor integration for real-time adherence monitoring are reshaping mucosal drug delivery into precision medicine tools. These technologies facilitate dose customization based on individual patient anatomy and condition and enable dynamic therapy adjustment through digital feedback, thus improving patient adherence and therapeutic outcomes. Furthermore, the rise of hybrid devices combining drug delivery with biosensing exemplifies the trend toward holistic, patient-centric healthcare embedded within modern digital frameworks.

However, fully leveraging the therapeutic potential of mucosal routes requires continued multidisciplinary collaboration among pharmaceutical scientists, clinicians, engineers, and regulatory agencies. Overcoming challenges related to formulation stability, standardized evaluation models, regulatory clarity for combination products, and patient acceptability is key to advancing these platforms from innovation to mainstream clinical practice. Moreover, fostering regulatory innovation and harmonization will be essential to expedite the translation of emerging drug-device combinations into accessible therapies. As integration with digital health accelerates, sublingual and lingual delivery systems are positioned to play a pivotal role in chronic disease management and personalized medicine paradigms, offering noninvasive, rapid, and patient-friendly alternatives to traditional drug administration routes.

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