Formulation and Evaluation of Mucoadhesive Buccal Tablets of Naratriptan: A Strategic Review

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ABSTARCT

Mucoadhesive buccal drug delivery systems have gained significant attention as a non-invasive and patient-friendly alternative to conventional oral and parenteral routes, particularly for drugs with poor gastrointestinal stability and extensive hepatic first-pass metabolism. Naratriptan, a selective 5-HT1B/1D receptor agonist used in the acute treatment of migraine, exhibits limited oral bioavailability (~56%) and delayed onset of action due to gastric stasis during migraine episodes. Buccal administration offers a promising route to overcome these limitations by enabling direct systemic absorption through the richly vascularized buccal mucosa, thereby enhancing bioavailability and therapeutic efficacy. This review provides a comprehensive analysis of the formulation strategies, polymeric systems, and evaluation methodologies employed in the development of mucoadhesive buccal tablets of Naratriptan. Various natural and synthetic polymers—such as hydroxypropyl methylcellulose (HPMC), chitosan, sodium alginate, and carbopol—are discussed in terms of their mucoadhesive properties, swelling behavior, and influence on drug release kinetics. The review also explores the physicochemical and pharmacokinetic rationale for buccal delivery, mechanisms of mucoadhesion, and the impact of formulation variables on bioadhesive strength and drug permeation. A critical appraisal of recent preclinical studies and formulation trials is presented, along with insights into regulatory considerations and marketed analogues. Future directions, including the integration of nanocarriers, bioresponsive polymers, and 3D printing technologies, are also

discussed. Overall, buccal mucoadhesive delivery of Naratriptan represents a viable and innovative approach to improving patient outcomes in migraine therapy.

Keywords: Naratriptan, Buccal drug delivery, Mucoadhesive tablets, Bioavailability enhancement, Migraine therapy.

1. INTRODUCTION

A persistent neurovascular condition, migraine is characterized by recurring bouts of moderate to severe headaches that are often accompanied by phonophobia, photophobia, and nausea. [1] It is one of the top 10 causes of years lived with disability and impacts more than 1 billion people worldwide. Because they selectively agonize 5-HT1B/1D receptors, triptans—including naratriptan—are the cornerstone of acute migraine treatment, causing cranial vasoconstriction and inhibiting the production of pro-inflammatory neuropeptides [2].

Despite their efficacy, the oral administration of triptans is often compromised by several pharmacokinetic limitations. Naratriptan, in particular, exhibits a relatively limited oral bioavailability (around 56%) as a result of first-pass metabolism in the liver and variable gastrointestinal absorption, especially during migraine attacks when gastric stasis is common [3,4]. These limitations necessitate alternative delivery strategies that can bypass the gastrointestinal tract and both the digestive system and hepatic metabolism.

Buccal Systems for mucoadhesive drug delivery offer a compelling solution. By adhering to the buccal mucosa, these systems facilitate direct Absorption of drugs into the bloodstreamvia the rich vascular network of the oral cavity, thereby circumventing first-pass metabolism and enzymatic degradation [5] the oral mucosa, avoiding enzymatic breakdown and first-pass metabolism [5]. Moreover, buccal delivery allows for sustained and controlled drug release,

improved patient adherence and simplicity of use, especially in patients experiencing nausea or vomiting during migraine episodes [6].

This review aims to provide a comprehensive analysis of the formulation and evaluation of mucoadhesive buccal tablets of Naratriptan. It explores the anatomical and physiological basis of buccal drug delivery, the mechanisms of mucoadhesion, the role of various polymers, and the impact of formulation variables on drug release kinetics and mucoadhesive strength. The goal of this study is to provide a thorough examination of the production and assessment of naratriptan mucoadhesive buccal tablets. It investigates the physiological and anatomical underpinnings of buccal drug administration, mucoadhesion processes, the function of different polymers, and how formulation factors affect mucoadhesive strength and drug release kinetics. Additionally, it synthesizes findings from recent literature and discusses future directions for optimizing buccal delivery systems for antimigraine therapy.

2. Buccal Mucoadhesive Drug Delivery: Fundamentals

2. 1 Buccal Mucosa Anatomy and Physiology

A lamina propria and submucosa support the non-keratinized, stratified squamous epithelium that lines the inner cheek, known as the buccal mucosa. Its extensive vascularization and thickness of 500–800 μm allow for quick systemic medication absorption without going through the liver's first-pass metabolism [7]. The buccal cavity, in contrast to the gastrointestinal system, has a pH of 6.2–7.4, little enzymatic activity, and a constant salivary flow (~0.5–2 L/day), which collectively favor drug stability and mucosal residence [8].

2.2 Advantages of Buccal Mucoadhesive Systems

Buccal drug delivery offers several clinical and pharmaceutical advantages:

- Keeping first-pass hepatic metabolism at bay
- Quick start of action and improved bioavailability
- Sustained and controlled drug release
- Ease of administration and termination
- Suitability for patients with dysphagia or nausea
- Potential for peptide and protein delivery [9,10]

However, limitations include restricted surface area, salivary washout, and potential for mucosal irritation or taste masking challenges.

2.3 Mechanisms of Mucoadhesion

Mucoadhesion refers to the adhesion between a polymeric formulation and the mucosal surface. It involves two sequential stages: (7) contact and wetting of the mucosa, and (8) interpenetration and bonding between polymer chains and mucin glycoproteins [11]. The strength and duration of mucoadhesion depend on polymer characteristics such as molecular weight, charge, flexibility, and hydration capacity.

2.4 Theories of Mucoadhesion

Multiple physicochemical foundation of mucoadhesion has been explained by a number of ideas. Each theory emphasizes different molecular interactions or structural phenomena [12-14]:

Theory	**Principle**	**Mechanism**	**Relevance to buccal system**
Wetting Theory	Adhesion occurs if the adhesive spreads well over the mucosal surface	Surface tension, contact angle	Important for liquid/semi-solid formulations
Diffusion Theory	Polymer chains interpenetrate with mucin chains to form entangled layers	Chain entanglement, diffusion depth	Crucial for hydrophilic polymers like HPMC
Electronic Theory	Electron transfer creates an electrical double layer at the interface	Electrostatic attraction	Relevant for charged polymers like chitosan
Adsorption Theory	Adhesion due to secondary chemical bonds after initial contact	Hydrogen bonding, van der Waals, hydrophobic forces	Explains reversible adhesion in hydrated systems
Fracture Theory	Adhesion strength is proportional to the force required to separate layers	Fracture mechanics, detachment force	Used in mechanical testing of mucoadhesive tablets

Mechanical Theory	Adhesion due to interlocking of polymer into mucosal surface irregularities	Micromechanical interlocking	Relevant for rough or porous mucosal surfaces

Table 1: Captures the comparative theoretical insights on mucoadhesion mechanisms

2.5 Ideal Mucoadhesive Polymer Properties

The following qualities should be present in the perfect mucoadhesive polymer:

- Biocompatibility and non-toxicity
- High molecular strength and flexibility of the chain
- The capacity to create hydrogen bonds
- Hydrophilicity and swelling capacity
- Resistance to enzymatic degradation
- pH compatibility with buccal mucosa [15]

Commonly used polymers include hydroxypropyl methylcellulose (HPMC), chitosan, sodium alginate, carbopol, and polycarbophil—each offering distinct advantages in terms of adhesion strength, swelling behavior, and drug release modulation.

3. Naratriptan: Pharmacological and Biopharmaceutical Profile

3.1 Pharmacological Overview

A selective zoloft receptor agonist, naratriptan is a the second-generation drugs triptan that is used to treat acute migraines with or without aura. It works by causing dilated cranial blood arteries to contract, preventing neurogenic inflammation, and preventing the production of vasoactive neuropeptides such substance P and CGRP, which stands calcitonin gene-related

[16,17]. Naratriptan is appropriate for people who need long-lasting treatment since it has a longer half-life and a better adverse effect profile than first-generation triptans like the drug [18].

3.2 Biopharmaceutical Challenges

Despite its clinical efficacy, Naratriptan suffers from several pharmacokinetic limitations when administered orally:

- Hepatic first-pass metabolism is mainly responsible for the around 63% oral bioavailability [19].
- Peak plasma concentration (Tmax) is delayed (2–3 hours), which is suboptimal during acute migraine attacks where rapid onset is desired [20].
- Gastric stasis during migraine episodes further impairs drug absorption [21].

These limitations necessitate alternative delivery strategies that can bypass the gastrointestinal tract and hepatic metabolism while offering rapid and sustained therapeutic action.

3.3 Rationale for Buccal Delivery

Buccal administration of Naratriptan offers several advantages:

- By evading hepatic first-pass metabolism, it enters the systemic circulation directly via the jugular vein.
- Rapid onset action due to high vascularity of the buccal mucosa.
- Improved patient compliance, especially in migraine patients experiencing nausea or vomiting.
- Potential for sustained drug release through mucoadhesive systems, reducing dosing frequency and side effects [22].

3.4 Pharmacokinetic Profile of Naratriptan

Parameter Group	Oral Administration	Buccal Delivery (Expected)
Bioavailability & Metabolism	~63% bioavailability; extensive first-pass hepatic metabolism [16,19]	>80% estimated bioavailability; bypasses hepatic metabolism [22]
Onset & Peak Concentration	Delayed onset (Tmax: 2–3 h); Cmax ≈ 8.3 ± 3.4 ng/mL [18,20]	Faster onset (Tmax: 0.5–1.5 h); higher Cmax due to direct absorption [22]
Half-life & Absorption Rate	t½ ≈ 5–6 h; absorption affected by gastric stasis and pH variability [18,21]	Similar or slightly prolonged t½; stable absorption via buccal mucosa [22]
Clinical Implications	Moderate compliance; reduced efficacy during migraine-induced gastric delay [17,21]	Improved compliance; effective during acute attacks with nausea [22]

Table 2: Highlights polymer classification, functionality, and formulation relevance

These pharmacokinetic advantages make Naratriptan an ideal candidate for buccal mucoadhesive delivery systems aimed at improving therapeutic outcomes in migraine management.

4. Mucoadhesive Polymers in Buccal Formulations

By evading hepatic first-pass metabolism, it enters the systemic circulation directly via the jugular vein. The ideal polymer should be biocompatible, non-toxic, hydrophilic, and capable of forming strong non-covalent interactions with mucin glycoproteins [23].

4.1 Classification of Mucoadhesive Polymers

Mucoadhesive polymers are broadly classified into:

- **Natural polymers**: gum acacia
- **Semi-synthetic**: hydroxypropyl methylcellulose, sodium carboxymethylcellulose
- **Synthetic polymers**: carbopol, polycarbophil, Eudragit

Each class offers unique advantages in terms of swelling behavior, mucoadhesive strength, and drug release modulation [24].

4.2 Functional Roles in Buccal Tablets

These polymers serve multiple roles:

- Enhance mucoadhesion via hydrogen bonding or electrostatic interactions
- Control drug release through swelling and gel formation
- Improve mechanical integrity and tablet cohesion
- Facilitate unidirectional drug diffusion when paired with backing layers [25]

Polymer	Type	Key Properties	Functional Role in Formulation
HPMC (K4M/K15M/K100M)	Semi-synthetic	Hydrophilic, forms viscous gel, pH-independent swelling [26]	**Sustained drug release, moderate mucoadhesion, matrix formation**

Chitosan	Natural	Cationic, bioadhesive, permeation enhancer, biodegradable [27]	**Enhances mucosal permeability, strong mucoadhesion, pH-sensitive**
Sodium Alginate	Natural	Anionic, forms hydrogels in presence of divalent ions, biocompatible [28]	**Swelling-controlled release, moderate adhesion, stabilizes matrix**
Carbopol 974P	Synthetic	High mucoadhesive strength, pH-sensitive, forms strong hydrogen bonds [29]	**Strong adhesion, prolonged residence time, synergistic with HPMC**

Table 3: Organizes key ADME parameters and their impact on therapeutic outcomes

These polymers are often used in combination to balance adhesion, drug release, and mechanical strength. For example, HPMC with Carbopol enhances both swelling and mucoadhesive strength, while chitosan with sodium alginate improves permeation and matrix stability [29].

5. Emerging Innovations in Buccal Mucoadhesive Drug Delivery

With growing interest in personalized and precision drug delivery, conventional buccal tablets are being reimagined using advanced pharmaceutical technologies. These innovations aim to improve drug loading, mucosal retention, targeting efficiency, and patient acceptability — especially for potent molecules like triptans.

5.1 Nanocarriers and Mucoadhesive Nanoparticles

Nanostructured carriers such as liposomes, solid lipid nanoparticles, and polymeric nanospheres have shown promise in enhancing transmucosal permeation. When surface-functionalized with mucoadhesive ligands (e.g., lectins or thiolated polymers), these nanoparticles can adhere strongly to the buccal mucosa and provide sustained release [30].

Notably, chitosan-based nanoparticles loaded with antimigraine drugs demonstrated increased permeability, reduced dosing frequency, and enhanced Cmax in animal studies [31]. This approach also facilitates co-delivery of absorption enhancers and targeting moieties.

5.2 Bioresponsive and Smart Polymers

Recent advances include bioresponsive polymers that adapt to stimuli like pH, temperature, or enzyme presence. Thermosensitive gels (e.g., based on Pluronic F127 or Poloxamers) undergo sol-gel transition upon contact with mucosal heat, forming intimate contact and sustained release systems [32]. Similarly, thiolated carbopol can form covalent disulfide bonds with mucins, enhancing residence time [33].

These smart materials hold particular value for triptan delivery, where rapid onset and reliable mucosal contact are key.

5.3 3D Printing of Buccal Tablets

Additive manufacturing (3D printing) allows for customized geometry, layered structures, and personalized dosing profiles. Using semi-solid extrusion and fused deposition modeling, researchers have printed buccal films and tablets with precise drug loading and release gradients [34].

In migraine therapy, this enables patient-specific triptan regimens based on severity, age, or comorbidities — potentially improving efficacy while minimizing side effects.

5.4 Patient-Centric and Sensory-Optimized Formulations

Taste masking, flexible dosage formats (e.g., wafers, films, discs), and saliva-triggered disintegration are now essential in buccal design. Innovations such as micro-adhesive patches with built-in permeation enhancers or moisture-activated release layers offer superior comfort and compliance [35].

These advances align with the industry's shift toward user experience as a factor in therapeutic success.

6. Clinical and Regulatory Perspectives on Buccal Mucoadhesive Triptan Delivery

6.1 Clinical Relevance in Migraine Management

Migraine attacks often involve gastrointestinal dysfunctions like vomiting — compromising efficacy in oral triptans. Buccal delivery circumvents this by ensuring rapid drug absorption even during emetic episodes [36]. Clinical studies have shown that transmucosal triptan formulations may reduce onset time, avoid dosing delays, and enhance patient satisfaction [37].

In addition, buccal mucoadhesive tablets offer improved therapeutic consistency across age groups and physiological states by minimizing intersubject variability in absorption. For migraine sufferers with drug sensitivity or comorbid conditions, personalized buccal systems may offer a safer, more tolerable route compared to injectables or high-dose oral options [38].

6.2 Regulatory Considerations and Excipients Approval

Mucoadhesive excipients used in buccal [39]. Most have established monographs in USP and Ph. Eur., supporting their inclusion in immediate and modified release dosage forms.

However, when developing novel buccal systems:

- **Permeation enhancers**, flavoring agents, and solubilizers must be evaluated for mucosal toxicity
- **Bioequivalence studies** are required if replacing conventional triptan dosage forms
- **In vitro–in vivo correlation (IVIVC)** validation is essential for scale-up approval [40]

To meet regulatory expectations, robust characterization of mucoadhesive strength, disintegration time, and microbial stability is needed — especially for buccal tablets designed for sustained release.

6.3 Marketed Buccal and Transmucosal Triptan Products

While Naratriptan buccal tablets are yet to be commercialized, other triptans offer lessons:

Product Name	API	Delivery Type	Manufacturer	Clinical Feature
ZolmistNasal Spray	Zolmitriptan	Intranasal	Cipla Ltd.	Fast onset; used during vomiting episodes [41]
ACTIQ Lozenge	Fentanyl citrate	Oral transmucosal	Cephalon Inc.	Rapid relief in cancer breakthrough pain [42]

Zydis® Ondansetron	Ondansetron	Fast-dissolving oral film	Catalent Pharma	Taste-masked; used for nausea & migraine [43]

Table 4: Offers regulatory insight and benchmark comparisons.

These products demonstrate that transmucosal systems can be successfully regulated and adopted when formulation, patient compliance, and absorption dynamics are optimized.

7. Conclusion

Mucoadhesive buccal drug delivery systems represent a clinically and pharmaceutically promising approach for managing acute migraine attacks, particularly through the delivery of Naratriptan. This review highlights the multifaceted advantages of buccal administration, compliance — factors essential during migraine episodes where gastrointestinal absorption is compromised.

The evolving landscape of buccal delivery — enriched by nanotechnology, bioresponsive systems, and 3D printing — opens new frontiers in personalized and patient-centric therapy, extending beyond conventional drug design.

As regulatory frameworks increasingly acknowledge the importance of transmucosal delivery, future development of Naratriptan buccal tablets will benefit from robust characterization studies, safety profiling of excipients, and innovations in sensory optimization. The integration of smart materials and scalable manufacturing technologies may soon transform buccal mucoadhesive platforms from niche solutions to mainstream migraine therapies.

Overall, Naratriptan buccal delivery is not only a formulation challenge but a therapeutic opportunity — merging science, innovation, and patient empathy in the journey toward more effective and accessible migraine relief.

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