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Buccal Mucoadhesive Systems for Antihypertensive Drugs: A Comprehensive Review of Formulation and Therapeutic Applications

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ABSTRACT

Background: Hypertension is a major health burden globally despite the development of effective pharmacotherapy. Conventional oral administration of antihypertensives may be associated with poor bioavailability because of extensive first-pass metabolism as well as degradation in the gastrointestinal tract. A buccal patch using mucoadhesive technology has been recognized as an innovative approach to multidrug therapy for hypertension.

Purpose: The review highlights the status of research in buccal mucoadhesive patches as a delivery system for antihypertensives.

Methods: The relevant literature was scrutinized for formulation methods, choice of polymers and excipients, physicochemical characterization, and advances that have occurred in patch design. The critical focus was also on permeation enhancers, nanoenabled patch systems, multilayered patch systems, and issues related to their preparation, stability, packaging, and regulatory concerns.

Results: Buccal mucoadhesive patches showed improved drug bioavailability, controlled and sustained drug release, and enhanced therapeutic efficiency. Advanced designs, such as those incorporating permeation promoters, nano formulations, and layered structures, demonstrated enhanced performance in terms of drug permeation and control of release, with reduced dosing frequencies and minimized side effects.

Conclusion: Buccal mucoadhesive patch technology is a promising and innovative drug delivery technology for antihypertensive medications. By providing a controlled and consistent level of the drug and improving patient compliance, this technology has the potential to greatly alter the approach to treating this condition.

1. Introduction

Hypertension is a condition that affects approximately 1.28 billion adults worldwide and remains one of the most important modifiable causes of cardiovascular diseases, stroke, and premature death (Al-Makki *et al.*, 2022). While a plethora of effective antihypertensive drugs exists, problems regarding delivery efficacy, patient compliance, and side effects are yet to be fully overcome in clinical settings. The conventional oral route of administration, though convenient, subjects antihypertensive drugs to the harsh gastrointestinal milieu and first-pass hepatic metabolism, which reduces their bioavailability and thus often necessitates the use of higher doses that increase the risk of adverse effects (Al Ragib *et al.*, 2022). Also, the kinetic profile of many antihypertensive drugs shows a short half-life, and multiple daily administrations may be needed, which can further affect patient compliance (Turgeon *et al.*, 2021).

Buccal mucoadhesion has been one of the routes of choice for the delivery of antihypertensive drugs. Buccal mucosa has several features that make it ideal for drug delivery. It possesses good vascularization with higher permeability, a higher surface area, is easily accessible, and does not have a first-pass effect (Morales & McConville, 2011). Moreover, absorption in the

buccal part of the system takes place quickly, due to which the rapid attainment of higher concentrations in cases of hypertensive emergencies can be achieved (Swarup & Agrawal, 2021).

Among all the drug delivery systems via the buccal mucous membrane, buccal mucoadhesive patches are perhaps the most promising systems for antihypertensive drugs. Buccal mucoadhesive patches are devices with mucoadhesive polymer matrices of drugs that adhere to the buccal mucous membrane to deliver drugs with sustained-release action (Remuñán-López *et al.*, 1998). Due to their non-invasive nature, ease of application and removal, possibility of self-administration, and sustained drug release capability, they appear more attractive than other dosage forms (Jeong *et al.*, 2021).

In the present context, this review article highlights different formulations, methods of characterization, and different applications of buccal mucoadhesive patches in connection with delivery systems for antihypertensive drugs. A critical evaluation of recent advancements in designing different patches, mechanisms involved in drug permeation, efficacy of these devices in medical treatments, and translation-related difficulties associated with different buccal mucoadhesive patches is discussed. Moreover, this article highlights important future directions that can bring further advancement in the medical usability of advanced buccal mucoadhesive devices in controlling different hypertensive disorders.

Nanotechnology has presently emerged as an enabling arena in contemporary drug delivery, offering excellent control over drug distribution, release rates, and targeting. In recent years (2022–2025), there have been substantial breakthroughs in the development of multifunctional nanocarriers incorporating targeting ligands, responsive modules, and imaging functionalities into a single platform, thus ushering in a new age of precision medicine. Next-generation nanocarriers have exhibited improved therapeutic potency and minimized systemic toxicities by targeted delivery of drugs to pathological tissues, mainly in oncological, cardiometabolic, and metabolic diseases (Zhu *et al.*, 2026).

Notably, there has been an evolution from proof-of-concept to translational medicine. The approval of lipid nanoparticle (LNP)-based mRNA approaches and their subsequent use in various clinical settings have set the stage for nanomedicine to demonstrate translational efficiency in treating various diseases. FDA-approved nanoformulations have underscored several important points, such as translational efficiency, safety, and acceptability of nanotechnology, thus accelerating the bench-to-bedside translation of nanotechnology-based delivery platforms for treating various conditions. Recent studies have also underscored the role of nanocarriers in increasing bioavailability, target-specific therapies, and personalized medicine approaches, thereby establishing nanotechnology as an important area of pharmaceutical sciences for the future (Zhang *et al.*, 2025).

Buccal mucoadhesive drug delivery systems have recently been identified as a potential substitute for conventional oral drug preparations for antihypertensive therapy, mainly because of their ability to circumvent first-pass metabolism and improve patient compliance. Previous reviews have addressed various aspects of buccal delivery systems for cardiovascular drugs; however, due to recent advances in drug delivery and mucoadhesive technology, a critical reappraisal is essential. The current review not only aims to provide a comprehensive synthesis of recent literature focusing on specific buccal mucoadhesive delivery systems for antihypertensive drugs but also addresses recent advances in drug delivery and mucoadhesive technologies that have not been covered in previous reviews. Furthermore, it provides a critical reappraisal of current delivery systems and upcoming challenges in designing potential buccal mucoadhesive delivery systems for antihypertensive drugs (Southward *et al.*, 2025).

2. Inclusion Criteria

The literature search encompassed research articles in refereed journals, studies, patents, and authoritative scientific literature concerning buccal mucoadhesive drug delivery systems, with a focus on systems developed for antihypertensive drugs. Studies including descriptions of polymer properties, formulation technology, and fundamental understanding related to polymer interaction and mucoadhesion effects, physicochemical analysis, in vitro and ex vivo mucoadhesion parameters, permeation methods, pharmacokinetic modifications, and therapeutic benefits were considered for evaluation. Literature

published in English from reputed databases was included to ensure scientific credibility, along with studies reporting challenges and innovations in buccal delivery for systemic hypertension management.

3. Exclusion Criteria

Publications were excluded if they lacked experimental data, scientific rigor, or relevance to buccal mucoadhesive technology or antihypertensive therapy. Articles based purely on non-mucoadhesive buccal dosage forms, non-systemic oral formulations, or unrelated therapeutic classes were also excluded. Papers published in non-English languages, conference abstracts without full texts, commentaries, and studies without explicit methodological descriptions were not considered. Investigations involving outdated polymers or non-standardized test methodologies that did not conform to the state of the art in buccal delivery were excluded.

4. Research Gap

Although significant strides have been made in mucoadhesive buccal delivery, there remains a considerable gap between laboratory findings and their translation into clinical applications, especially for antihypertensive drugs. Most reports remain limited to in vitro or ex vivo studies, with scarce in vivo and/or human clinical data to establish therapeutic validity. Variability in polymer selection, formulation approaches, and evaluation parameters makes direct comparison between studies difficult. Furthermore, long-term mucosal safety, variability in patient acceptability, and inter-individual differences in buccal permeability have rarely been reported. Few studies have examined the effects of disease states, salivary flow, and variations in mucosal physiology on drug absorption. These gaps indicate a need for more standardized, clinically oriented research.

5. Exploring Buccal Mucosa for Enhanced Drug Delivery

5.1. Anatomical and Physiological Considerations

The buccal mucosa, on the inner surface of the cheek, is composed of about 40 to 50 layers of stratified squamous epithelial cells, with a thickness of about 500 to 800 µm in total (Caon *et al.*, 2015). Unlike the gastrointestinal mucosa, the buccal epithelium is not keratinized, which increases its permeability to drug molecules (Dawson *et al.*, 2013). Underlying the buccal mucosa are the basement membrane, the lamina propria, and the submucosa, which house an extensive network of vessels draining directly into the jugular vein, thus bypassing hepatic first-pass metabolism (Breslin *et al.*, 2018). The buccal mucosa has a neutral pH of 6.8–7.4, which provides a consistent environment for drug delivery, unlike that presented throughout the gastrointestinal tract, since its pH varies from very low in the stomach to appreciably high in the intestines (He & Mu, 2023). The total surface area available for drug absorption is about 50 cm^2, with a blood flow of 2.4 mL/min/cm^2, allowing rapid and efficient drug entry into the systemic circulation (Laitinen *et al.*, 2025).

5.2. Permeation Pathways and Barriers

Drug permeation across the buccal mucosa takes place primarily by passive diffusion via two routes: transcellular, through the cells, and paracellular, between the cells (Alqahtani *et al.*, 2021). The first pathway represents transport across the cell membrane and cytoplasm, with preferential permeation through cell membranes by lipophilic drugs, while the second pathway represents transport via intercellular spaces and tight junctions and is mostly utilized by hydrophilic ones (Webb, 2013). Several barriers impede drug permeation across the buccal mucosa.

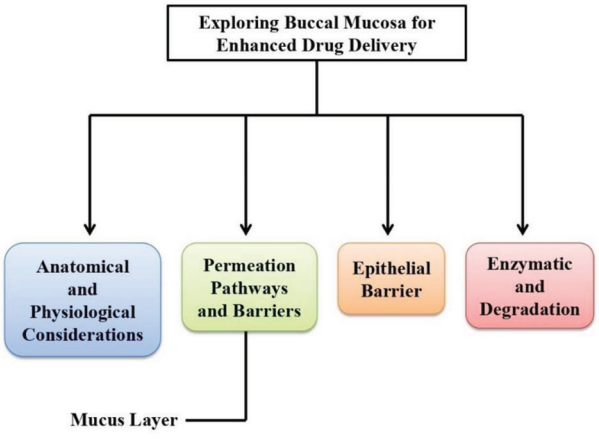

Figure 1: Overview of Major Anatomical, Physiological, and Biological Barriers Influencing Drug Delivery through the Buccal Mucosa

5.2.1. Mucus Layer

A viscoelastic gel of the glycoproteins, mucins, forms the basis for trapping drug molecules within its network. Under physiological pH, mucin bears a negative charge and can interact electrostatically with positively charged drugs. This facilitates retention at the site of application, thereby enhancing residence time and probably improving therapeutic efficacy. The sticky and flexible nature of the gel further provides sustained release by slowing down the diffusional process. Due to these properties, mucin gels are being widely explored in formulation science to achieve targeted and controlled drug delivery applications (Connor *et al.*, 2016).

5.2.2. Epithelial Barrier

Lipid-rich cell membranes and intercellular lipid layers provide natural barriers that slow down many drug molecules, particularly hydrophilic molecules. Due to their water-loving nature, these drugs have difficulty crossing the oily, lipid-dominated pathways in the skin or across other biological membranes. This creates high diffusional resistance to entry, limiting the extent of drug absorption. Therefore, hydrophilic molecules tend to exhibit poor permeability unless formulation strategies such as penetration enhancers, nanoparticles, or lipid-based carriers are employed. This barrier function is an important consideration in designing effective drug delivery systems to help ensure that such limitations can be overcome (Lindner *et al.*, 2025).

6. Enzymatic Degradation

The buccal mucosa also expresses various metabolic enzymes, such as aminopeptidases, carboxypeptidases, and esterases, which can degrade certain drug types. These enzymes are more active against peptide-based molecules and drugs possessing ester linkages and hence make them more prone to degradation before systemic absorption. Thus, many therapeutic agents may demonstrate poor bioavailability after administration via the buccal route. Knowledge of the enzymatic environment of the buccal mucosa is therefore important when designing stable formulations, such as enzyme inhibitors, protective coatings, or advanced drug delivery systems, to improve drug survival and enhance therapeutic effectiveness (Kumar *et al.*, 2025).

The buccal cavity is in constant contact with saliva, with daily secretions ranging from 0.5 to 2 liters. This phenomenon, although necessary for the well-being of the oral cavity, inevitably leads to dilution of drug concentrations at the site of absorption; therefore, higher doses may be required. Saliva may also eject or displace the dosage form from its placement site because of salivary flow. This could decrease the residence period, limiting the amount of time the drug can remain in contact with the mucosa. Consequently, adequate absorption may not be achieved. Therefore, formulation strategies using mucoadhesive systems, controlled-release polymers, or protective matrices are needed to retain the drug in the buccal cavity and allow improved therapeutic outcomes (Patel *et al.*, 2015). Knowledge of these anatomical and physiological factors is essential in developing effective buccal mucoadhesive patches for antihypertensive drug delivery.

7. Antihypertensive Drugs Suitable for Buccal Delivery

Selection Criteria for Buccal Delivery: Not all antihypertensive agents are suitable candidates for buccal delivery. The ideal characteristics of drugs amenable to buccal administration include:

Table 1: Antihypertensive Drugs Explored for Buccal Drug Delivery (Kurćubić *et al.*, 2021)

Drug Class	Drug Name	Buccal Dosage Form Studied	Key Findings from Studies	Advantages of the Oral Route
β-Blockers	Propranolol	Buccal patch, film	Comparable antihypertensive efficacy at half the oral dose; reduced systemic side effects	Avoids first-pass metabolism; improved tolerability
	Metoprolol	Buccal patch	Sustained BP control during long-term use; improved patient compliance	Reduced dosing frequency; consistent plasma levels
	Atenolol	Buccal film	Improved bioavailability compared to oral tablets	Reduced variability in absorption

Calcium Channel Blockers	Nifedipine	Buccal patch	Prolonged drug release and improved BP control	Bypasses hepatic metabolism; reduced dose
	Diltiazem	Buccal film	Sustained plasma levels and controlled release	Reduced gastrointestinal adverse effects
ACE Inhibitors	Enalapril maleate	Buccal patch	Improved pharmacokinetics; reduced incidence of dry cough	Lower systemic exposure to metabolites
	Captopril	Buccal tablet/film	Rapid onset and enhanced bioavailability	Suitable for hypertensive emergencies
ARBs	Valsartan	Buccal patch	Therapeutic plasma levels within 2 h, maintained up to 12 h	Improved bioavailability; sustained effect
	Losartan	Buccal film	Controlled drug release and stable BP reduction	Reduced dosing frequency
α-Adrenergic Blockers	Prazosin	Buccal film	Improved absorption and reduced first-pass effect	Lower dose requirement

7.1. Physicochemical Properties

A drug should satisfy certain physicochemical criteria to be effectively absorbed through the buccal mucosa. Ideally, the molecule should have a moderate molecular weight, preferably below 500 Da, to easily pass through the mucosal barrier. It needs the right balance between lipophilicity and water solubility, usually expressed by a log P value in the range of 1.6 to 3.2. This balance allows the drug to dissolve in saliva while still penetrating the lipid layers. Furthermore, the compound must remain stable at the slightly acidic to neutral pH of the buccal environment for reliable absorption (Yu *et al.*, 2021).

7.2. Pharmacokinetic Considerations

Drugs that undergo extensive first-pass metabolism, have short biological half-lives, or require maintenance of steady therapeutic levels are good candidates for buccal drug delivery. Most drugs administered orally undergo liver metabolism before reaching systemic circulation, which may reduce their activity. Administering them through the buccal mucosa circumvents this phenomenon and enhances their availability (Scholz *et al.*, 2008). Similarly, drugs with short half-lives benefit from this route, as it may provide more controlled and sustained absorption. For medications that require consistent plasma levels, buccal delivery offers a practical means of achieving prolonged therapeutic action with improved patient compliance (de Vries *et al.*, 1988).

7.3. Potency

Drugs of high potency require only small doses, normally less than 50 mg, making them ideal for buccal delivery systems. Low-dose medicines keep the patch or dosage form small, comfortable, and non-irritating to the patient. If a large quantity of a drug is required for therapeutic effectiveness, the patch size becomes bulky, reducing patient acceptability and limiting practical use. Thus, selecting potent drugs leads to effective formulations with manageable sizes, promoting better patient compliance and favoring the development of effective buccal delivery systems with consistent therapeutic performance (Thakkar *et al.*, 2020).

7.4. Taste Aspects

For buccal drug delivery systems, a pleasant or easily maskable taste is highly desirable for patient comfort and acceptance. The dosage form resides in the mouth for a reasonable length of time; therefore, an unpleasant or bitter taste may cause discomfort, irritation, decreased compliance, or early removal of the patch or tablet. Drugs possessing intrinsically mild or neutral taste profiles are preferred; however, when bitterness cannot be avoided, formulation approaches such as flavoring agents, sweeteners, or taste-masking polymers can be employed. Good palatability enhances user acceptability and facilitates consistent and effective therapy (Chinna Reddy *et al.*, 2011).

8. Commonly Explored Antihypertensive Drugs

Several classes of antihypertensive medications have been investigated for buccal mucoadhesive delivery.

8.1. Angiotensin-Converting Enzyme (ACE) Inhibitors

ACE inhibitors, such as captopril, enalapril, and lisinopril, have been widely investigated for buccal delivery due to pharmacokinetic drawbacks such as extensive first-pass metabolism, poor oral bioavailability, and relatively short biological half-lives (Tian *et al.*, 2023). Among these, captopril has attracted the most interest because of its favorable physicochemical and pharmacological properties. Captopril exhibits a relatively low oral bioavailability of about 60–75% due to extensive hepatic metabolism and enzymatic degradation within the gastrointestinal tract. Buccal delivery avoids the hepatic first-pass effect and significantly improves systemic absorption, with reported bioavailability as high as 95% (Kim *et al.*, 2024).

This route of delivery is further supported by the molecular characteristics of captopril. Its relatively low molecular weight of 217.3 Da and moderate log P value of 0.34 favor diffusion across epithelial lipophilic membranes while maintaining sufficient aqueous solubility at the administration site. Collectively, these attributes facilitate efficient buccal permeation and ensure a rapid onset of action. Additionally, the buccal mucosa has a rich blood supply, relatively low enzymatic activity compared with the gastrointestinal tract, and ease of administration, further enhancing its therapeutic potential (Chetty *et al.*, 2001).

8.2. Calcium Channel Blockers

Dihydropyridine calcium channel blockers such as nifedipine, amlodipine, and felodipine are widely prescribed anti-anginal and antihypertensive drugs. However, their therapeutic efficacy is often compromised by extensive first-pass metabolism, resulting in low and variable oral bioavailability (Whelton *et al.*, 2018). This pharmacokinetic limitation makes them suitable candidates for alternative routes of administration.

Nifedipine, when administered orally, exhibits extremely low bioavailability due to extensive first-pass metabolism, with approximately 80% cleared by the liver, rendering frequent administration impractical (Rashid *et al.*, 1995). Buccal delivery circumvents first-pass metabolism, enhances bioavailability, and reduces side effects.

A major advantage favoring buccal delivery of dihydropyridine calcium channel blockers is their high lipophilicity. These molecules typically possess log P values greater than 3, which facilitates efficient transcellular diffusion across buccal mucosal membranes (Preeti *et al.*, 2024). Additionally, their relatively low molecular weights further support diffusion and qualify them as suitable candidates for buccal administration (Malhotra *et al.*, 2025a).

8.3. Beta-Blockers

Beta-adrenergic receptor antagonists, commonly referred to as β-blockers, including propranolol, metoprolol, and atenolol, have attracted significant attention in buccal delivery systems due to pharmacokinetic limitations and high therapeutic relevance in hypertensive emergencies, arrhythmias, and ischemic heart disease (Taddei *et al.*, 2024).

Propranolol, in particular, exhibits an extensive first-pass effect, with more than 90% metabolized after oral administration, resulting in low systemic bioavailability of approximately 10–30% (Kurcubic *et al.*, 2020). Buccal delivery bypasses this effect and increases bioavailability to 60–90%. Enhanced absorption also results in more consistent plasma concentrations with reduced variability, thereby optimizing therapeutic efficacy.

An important consideration in buccal delivery of β-blockers is variability in lipophilicity among drugs in this class (Beckett & Hossie, 1971). Atenolol, for example, has a low log P value of 0.16, making it highly hydrophilic and significantly limiting its transcellular diffusion across the buccal mucosa (Telange *et al.*, 2023).

8.4. Angiotensin II Receptor Blockers (ARBs)

Angiotensin II receptor blockers such as losartan, valsartan, and telmisartan have also been explored for buccal administration as an alternative approach to overcome their low and variable oral bioavailability. Losartan, the first ARB introduced into clinical practice, exhibits limited bioavailability of approximately 33% due to significant first-pass metabolism and irregular gastrointestinal absorption. Buccal administration bypasses hepatic metabolism, resulting in improved pharmacoeconomic efficiency and more consistent systemic availability, thereby enhancing efficacy (Rothlin *et al.*, 2023).

Despite their therapeutic efficacy, certain limitations restrict the buccal delivery of ARBs.

Their relatively high molecular weights, generally exceeding 400 Da, hinder passive diffusion across buccal epithelia. For instance, valsartan (MW 435.5 Da) and telmisartan (MW 514.6 Da) are considerably larger and less permeable than smaller antihypertensive agents such as captopril or propranolol. In addition, most ARBs exhibit poor aqueous solubility, further limiting dissolution and absorption at the buccal site (Salim & Jones, 2022).

9. Mucoadhesive Polymers for Buccal Patches

9.1. Mechanisms of Mucoadhesion

The performance of buccal mucoadhesive patches is essentially based on their ability to adhere to the mucosal surface, a phenomenon regulated by various interrelated theoretical mechanisms. According to the electronic theory, mucoadhesion is the result of the exchange of electrons between the polymer matrix and the mucus, leading to the generation of an electrical double layer at the interface with attractive electrostatic forces (Gilhotra *et al.*, 2013). Augmenting this, adsorption theory posits that adhesion is mainly facilitated by secondary intermolecular interactions such as hydrogen bonding, van der Waals forces, and hydrophobic forces that form between mucin glycoproteins in the mucosal layer and polymer chains. The wetting theory is concerned with the spreading capability of the polymer over the mucosal surface, where adhesion strength depends on the contact angle and surface tension interactions between the patch material and the biological substrate, as illustrated in Figure 2 (Smart, 2005).

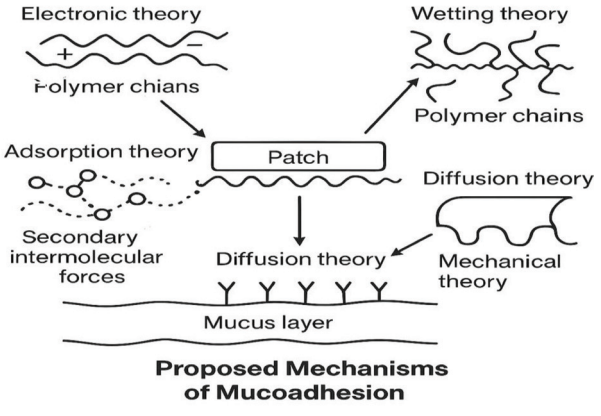

Figure 2: Proposed Theories Explaining Mucoadhesive Interactions between Polymeric Patches and the Mucus Layer (Shaikh *et al.*, 2011)

At a molecular level, mucoadhesion is described by diffusion theory as the interpenetration and physical entanglement of polymer chains with mucin glycoproteins, resulting in semipermanent adhesive bonds and sustained attachment (Vigani *et al.*, 2023). Finally, mechanical theory accounts for the physical mechanism of adhesion by which polymers enter and occupy microscopic unevennesses and crevices that exist on the generally rough mucosal surface, thereby optimizing the contact area available to support intermolecular forces and overall adhesive strength. Such theoretical models explain the therapeutic efficacy of mucoadhesive patches based on several concurrent mechanisms of adherence to the buccal mucosa (Packham, 2003).

9.2. Classification of Mucoadhesive Polymers

Mucoadhesive polymers used in buccal patch formulations can be broadly classified as:

9.2.1. Natural Polymers

Natural polymers exhibit biocompatibility, biodegradability, and generally low toxicity, which are highly desirable for buccal applications. Chitosan is a naturally occurring cationic polysaccharide and derivative of chitin; due to electrostatic interactions between its positively charged amino groups and the negatively charged sialic acid residues in mucin, it exhibits high mucoadhesive performance. Its ability to facilitate permeation provides considerable usefulness in buccal delivery systems.

Sodium alginate is an anionic polysaccharide that forms strong hydrogen bonds with mucin, resulting in good mucoadhesion in the hydrated state (Parhi, 2019). Its gelation upon the addition of calcium ions allows for controlled drug release profiles. Gelatin is a protein polymer containing multiple functional groups capable of forming hydrogen bonds with the mucosa. Due to its amphoteric nature, it interacts with both positively and negatively charged molecules. Hyaluronic acid, a glycosaminoglycan, demonstrates good biocompatibility and mucoadhesion through hydrogen bonding and chain entanglement.

Overall, natural polymers exhibit multiple effective modes of mucoadhesion while maintaining biological compatibility with the buccal mucosa (Shatabayeva *et al.*, 2024).

Table 2: Classification of Mucoadhesive Polymers, Example Drugs, and QbD-Based Selection Rationale for Buccal Patch Formulations (Bayer, 2022)

Polymer Class	Polymer Examples	Example Drugs Used in Buccal Systems	Mechanism of Mucoadhesion	Key Functional Attributes (CQAs)	ICH Q8/Q9 (QbD) Selection Rationale
Natural Polymers	Chitosan	Propranolol, Metoprolol, Insulin, Enalapril	Electrostatic interaction between cationic amino groups and anionic mucin residues	High mucoadhesion, permeation enhancement, and biocompatibility	Selected when bioavailability enhancement and permeation improvement are critical CQAs for BCS II/III drugs
	Sodium alginate	Nifedipine, Atenolol, Ketorolac	Hydrogen bonding; Ca^{2} -induced gel formation	Controlled drug release, hydration-dependent adhesion	Suitable for controlled release CQAs and risk mitigation of dose dumping
	Gelatin	Lidocaine, Benzocaine	Hydrogen bonding; amphoteric interactions	Flexible films, rapid hydration	Used when rapid onset of action is a key QTPP attribute
	Hyaluronic acid	Insulin, Nicotine, Salbutamol	Hydrogen bonding and chain entanglement	High tissue affinity, biocompatibility	Preferred for patient safety and mucosal compatibility risk control.
Semi-synthetic Polymers	HPMC, CMC-Na, HPC	Propranolol, Metformin, Diltiazem	Hydrogen bonding and chain interpenetration	Film integrity, controlled hydration	Selected to ensure robust mechanical CQAs and batch-to-batch reproducibility
	Thiolated chitosan, thiolated hyaluronic acid (Thiomers)	Insulin, Calcitonin, Enalapril	Covalent disulfide bonding with mucus glycoproteins	Strong, prolonged mucoadhesion	Used when extended residence time is a critical CQA and risk of premature detachment must be minimized
Synthetic Polymers	Carbopol®, Polycarbophil	Propranolol, Metoprolol, Valsartan	Hydrogen bonding via carboxyl groups; swelling	Strong adhesion, sustained release	Suitable for high-risk formulations requiring tight control of release kinetics
	Poly Vinyl Alcohol (PVA)	Nicotine, Fentanyl	Hydrogen bonding; film formation	Mechanical strength, flexibility	Used to meet mechanical robustness CQAs in patch handling
	Poly Vinyl Pyrrolidone (PVP)	Midazolam, Diazepam	Hydrogen bonding via carbonyl groups	Solubility, film clarity	Supports content uniformity and dose accuracy
	Poly Ethylene Oxide (PEO)	Morphine, Buprenorphine	Polymer chain entanglement	Swelling-based adhesion, sustained contact	Selected to reduce risk of adhesion failure during use[138].
Novel / Modified Polymers	Preactivated thiomers	Insulin, Peptides, Proteins	Stable covalent bonding with mucin	Improved stability and adhesion	Selected for high-risk APIs requiring risk mitigation for oxidation and instability
	Lectin-modified polymers	Insulin, Vaccines	Specific carbohydrate-lectin binding	Targeted adhesion, site specificity	Supports QTPP targeting requirements and enhanced local residence
	Chitosan-catechol conjugates	Propranolol, Peptides	Covalent bonding via oxidized catechol groups	Strong wet-state adhesion	Suitable for harsh oral environments and high saliva flow risk
	Polyelectrolyte complexes (Chitosan–alginate)	Metoprolol, Nifedipine	Synergistic electrostatic interactions	Improved mechanical strength, controlled release	Used to balance competing CQAs such as adhesion strength vs. release rate.

9.2.2. Semi-synthetic Polymers

Semi-synthetic polymers balance the biocompatibility of natural polymers with superior physical and mechanical properties. Cellulose derivatives such as hydroxypropyl methylcellulose (HPMC), carboxymethylcellulose sodium (CMC-Na), and hydroxypropyl cellulose (HPC) offer a range of hydrophilicity and mucoadhesive strength (Ciolacu *et al.*, 2020). Part of their adhesive nature can be explained by their ability to form hydrogen bonds with mucin.

Thiolated polymers, or thiomers, are chemically modified polymers that bear thiol groups which crosslink with the cysteine-rich subdomains of mucus glycoproteins, resulting in significantly enhanced mucoadhesion (Szilágyi *et al.*, 2017). This chemical modification has been found to produce a remarkable enhancement in adhesive properties, whereby thiolated hyaluronic acid and thiolated chitosan have shown a 140-fold and 20-fold increase, respectively, in mucoadhesive strength compared with their non-thiolated counterparts. The addition of thiol groups is an ingenious method to increase the mucoadhesive capacity of currently used biocompatible polymers while preserving their desirable biological properties (Nakipoglu *et al.*, 2023).

9.2.3. Synthetic Polymers

Synthetic polymers offer advantages such as uniform quality, assured availability, and properties that can be tailored for buccal mucoadhesive applications. Poly acrylic acid derivatives, including Carbopol® and polycarbophil, possess carboxylic acid groups that interact with mucin via hydrogen bonding (Nouban & Abazid, 2017). Due to their high molecular weight and cross-linked nature, these polymers exhibit strong mucoadhesion and extended drug-release characteristics.

Polyvinyl alcohol (PVA) is a water-soluble synthetic polymer with good film-forming ability and mucoadhesion through hydrogen bonding. Similarly, poly vinyl pyrrolidone (PVP) can establish strong hydrogen bonds with mucin via its carbonyl group, exhibiting moderate mucoadhesion along with good film-forming ability (Brough *et al.*, 2016). High-molecular-weight chains of poly ethylene oxide function through entanglement within the mucus network, resulting in entanglement-based mucoadhesion. Overall, synthetic polymers represent a wide range of engineered materials capable of achieving desired mucoadhesive functions while offering uniform manufacturing quality and predictable performance characteristics (Serra *et al.*, 2008).

9.2.4. Novel and Modified Polymers

Recent advances in polymer science have led to the development of novel mucoadhesive materials with improved properties, addressing limitations of traditional polymers. Preactivated thiomers possess protected thiol groups that resist oxidation during storage, thereby exhibiting improved stability and enhanced mucoadhesive properties (Kali *et al.*, 2023).

Lectin-modified polymers incorporate lectins that bind specifically to carbohydrate residues of the mucosa, enabling targeted and improved mucoadhesion through biological recognition mechanisms. Chitosan–catechol conjugates, which are synthetic analogues of mussel adhesive proteins, form strong covalent attachments with mucin upon oxidation of catechol groups, resulting in enhanced mucoadhesion even under harsh physiological conditions (Kaur & Singh, 2020).

Polyelectrolyte complexes formed between oppositely charged polymers, such as chitosan and alginate, exhibit superior mechanical properties and mucoadhesion compared with individual polymers due to synergistic electrostatic interactions. The selection of appropriate mucoadhesive polymers is influenced by several factors, including the physicochemical properties of the antihypertensive drug, desired release kinetics, and characteristics of the target patient population (Hoseinifar *et al.*, 2025). Polymer blends are commonly employed to optimize patch performance, allowing fine-tuning of adhesion strength, drug-release profiles, and overall therapeutic efficacy. A comparison of different mucoadhesive polymers is presented in Table 1 (Manna *et al.*, 2022).

Table 3: Comparative Evaluation of Mucoadhesive Polymers Used in Buccal Drug Delivery Systems (Authimoolam *et al.*, 2014)

Polymer	Mucoadhesion Strength	Drug Release Control	Compatibility	Justification for Ranking
Chitosan	High	Moderate	High	Exhibits strong electrostatic interaction with negatively charged mucin due to its cationic nature; provides moderate control over drug release and demonstrates good biocompatibility and biodegradability.

HPMC (Hydroxypropyl Methylcellulose)	Moderate	High	Moderate	Forms a robust gel matrix that enables sustained drug release; mucoadhesion is primarily via hydrogen bonding, which is moderate compared to ionic polymers.
Alginate	Moderate	Moderate	Moderate	Mucoadhesion occurs through hydrogen bonding and swelling; release control is dependent on ionic crosslinking with divalent cations; compatibility varies with formulation conditions.
PAA (Polyacrylic Acid)	High	High	High	Strong mucoadhesion due to extensive hydrogen bonding with mucin glycoproteins; excellent swelling and controlled-release properties; widely reported compatibility with diverse drugs.
Carbopol	Very High	High	Moderate	Cross-linked PAA derivative with superior mucoadhesive strength due to high density of carboxyl groups; effective release control, though compatibility may be affected by formulation pH and drug properties.
Pectin	Moderate	Moderate	High	Natural polysaccharide with good biocompatibility; mucoadhesion arises from hydrogen bonding; drug release depends on degree of esterification and swelling behavior.
CMC (Carboxymethylcellulose)	Moderate	Moderate	Moderate	Provides mucoadhesion via hydrogen bonding and chain interpenetration; offers balanced release characteristics and acceptable compatibility across formulations.

10. Formulation Strategies for Buccal Mucoadhesive Patches

10.1. Patch Design Considerations

The design of buccal mucoadhesive patches for antihypertensive drug delivery requires careful consideration of several factors:

10.1.1. Single-Layer vs. Multi-Layer Systems

Buccal patches for the delivery of antihypertensive drugs can be classified as single-layer and multi-layer systems, with different design characteristics and functions. Single-layer (matrix) patches are uniform dispersions of drug within a mucoadhesive polymer matrix. Although these devices are easy to produce and inexpensive, they tend to have difficulty achieving controlled drug delivery and may permit partial drug leakage into the oral cavity, consequently decreasing delivery efficiency (Salamat-Miller *et al.*, 2005).

Conversely, multi-layer patches are more advanced in design, consisting of a drug-loaded mucoadhesive layer directly attached to the buccal mucosa and an impermeable backing layer that prevents drug leakage into the oral cavity and provides unidirectional drug release. In some cases, a second drug reservoir layer is incorporated between the two, allowing increased drug loading and sustained release over extended durations (Cheng *et al.*, 2023). These multi-layer designs have proven to be more effective for delivering antihypertensive drugs such as propranolol and nifedipine, with clinical and preclinical studies indicating significantly increased bioavailability compared with traditional single-layer designs (Ryu *et al.*, 1999).

10.1.2. Drug Loading Capacity

Maximal drug loading in buccal patches requires a careful balance between formulation stability and therapeutic activity. Several factors determine loading capacity, including the dose required to achieve the desired pharmacological response, size limitations of the patch (typically restricted to 1–3 cm^2 to remain unobtrusive), and drug solubility within the polymeric matrix (Jacob *et al.*, 2021).

In addition, drug concentration can significantly influence the mechanical properties of the patch, and excessive loading may result in brittleness, reduced flexibility, or diminished mucoadhesive strength. For

antihypertensive drugs, loading capacities are generally reported in the range of 5–30% w/w; however, higher loading levels are often associated with compromised adhesive and mechanical properties, thereby limiting formulation performance (Stenzel, 2021).

10.1.3. Controlled Release Mechanisms

Various release mechanisms are employed in buccal patch formulations to achieve desired drug-release profiles, depending on the physicochemical characteristics of the drug and properties of the polymer matrix. In diffusion-controlled systems, drug release primarily occurs through diffusion within the polymer, with factors such as drug solubility, matrix tortuosity, and effective diffusion path length governing the release rate (Sanopoulou & Papadokostaki, 2017a).

Swelling-controlled systems rely on water uptake, which induces polymer chain relaxation, swelling, and pore formation that permit drug diffusion. In erosion-controlled systems, drug release occurs as the polymer matrix degrades or undergoes slow erosion in the buccal environment. Stimuli-responsive systems have become increasingly sophisticated, with triggers such as pH, temperature, or enzymatic activity initiating drug release for site-specific or controlled delivery. For antihypertensive therapy, extended release over 8–24 hours is generally preferred to maintain steady plasma drug levels, minimize fluctuations, and reduce dosing frequency, thereby improving patient compliance (Freiberg & Zhu, 2004).

10.2. Manufacturing Methods

10.2.1. Solvent Casting

The solvent casting technique is the most commonly employed method for preparing buccal patches due to its simplicity and scalability for laboratory and industrial use. In this process, polymers are initially dissolved in appropriate solvents, followed by the addition of the drug and other excipients to obtain a uniform solution or suspension. The resulting mixture is cast onto a suitable substrate and allowed to undergo solvent evaporation under controlled conditions to yield a uniform film (Semalty *et al.*, 2008).

After drying, the film is cut into patches of the desired size using a slicing device operating at a uniform speed. Although this technique is relatively simple to implement, certain limitations exist, including challenges related to achieving uniform drug dispersion within the polymer matrix. Solvent selection is critical, as incomplete solvent removal may result in residual toxicity within the patch, rendering it unsuitable for patient use (Tirumkudulu & Punati, 2022).

10.2.2. Hot-Melt Extrusion

Hot-melt extrusion (HME) is a widely used solvent-free method for preparing buccal patches, offering several advantages over conventional solvent-based techniques. In this process, the drug is blended with thermoplastic polymers and other excipients, and the mixture is heated above the polymer's glass transition temperature. The softened material is then forced through a die to form thin films, which are subsequently cooled and cut into patches of defined dimensions (Nayak & Nayak, 2025).

HME eliminates the need for organic solvents, thereby avoiding issues related to solvent toxicity, residual solvent traces, and environmental exposure. This technique typically yields patches with superior physical stability, homogeneous drug distribution, and improved mechanical properties. However, its application is limited to thermostable drugs and polymers, as heat-sensitive compounds may degrade during processing (Maniruzzaman *et al.*, 2012).

10.2.3. Electrospinning

Electrospinning is an advanced fabrication technique used to produce ultrafine polymeric nanofibers for buccal drug delivery. In this method, a polymer–drug solution is prepared and subjected to a high electric field, generating a charged jet that elongates and solidifies into nanofibers. These nanofibers are collected on a grounded collector and subsequently fabricated into patch forms.

Electrospun buccal patches exhibit unique structural advantages, including a high surface-area-to-volume ratio, interconnected porosity, and tunable fiber morphology (Concha *et al.*, 2025). These properties enhance drug dissolution, rapid wetting, and permeation through the buccal mucosa. Such features are particularly beneficial for poorly water-soluble antihypertensive drugs such as felodipine and telmisartan, for which conventional formulations often fail to achieve adequate bioavailability. Consequently, electrospinning represents a promising approach

for developing next-generation buccal drug delivery systems with enhanced therapeutic efficacy (Birer & Acartürk, 2021).

10.2.4. 3D Printing

Additive manufacturing technologies such as fused deposition modeling (FDM), stereolithography (SLA), and selective laser sintering (SLS) have been explored for the fabrication of buccal drug delivery systems. Three-dimensional printing offers precise control over geometry, drug loading capacity, and drug distribution within the polymer matrix, enabling the development of highly customized drug-release profiles.

This approach provides an innovative platform for producing personalized buccal patches capable of maximizing therapeutic outcomes through tailored material selection and design (Zhang *et al.*, 2019). Recent studies have demonstrated the feasibility of incorporating antihypertensive drugs using these technologies, resulting in improved bioavailability and advancing the concept of personalized medicine (Bird & Ravindra, 2020).

10.3. Permeation Enhancement Strategies

Enhancing drug permeation across the buccal mucosa is often necessary to achieve therapeutic plasma concentrations.

10.3.1. Chemical Enhancers

Various permeation enhancers temporarily modify properties of the mucosal barrier to improve drug permeation across the buccal mucosa. These include fatty acids and their derivatives, such as oleic acid, sodium caprate, and lauric acid (Maher & Brayden, 2021), which disrupt intercellular lipid structures to create transient permeation pathways.

Surfactants such as sodium dodecyl sulfate, polysorbates, and benzalkonium chloride can remove lipids and proteins from cellular membranes, thereby increasing drug transport via both transcellular and paracellular pathways (Albakr *et al.*, 2024). Bile acids and salts, including sodium deoxycholate and sodium taurocholate, form mixed micelles and interact with membrane lipids, enhancing drug solubilization and membrane permeation. Terpenoids such as d-limonene, menthol, and cineole increase drug partitioning and disrupt intercellular lipids, further improving permeability (Pavlović *et al.*, 2018).

Clinical studies have demonstrated the applicability of these permeation enhancers in formulations containing beta-blockers and calcium channel blockers, with reported enhancements of 2–5-fold in drug permeation. The strategic use of such enhancers represents an important step toward optimizing antihypertensive drug bioavailability via controlled and reversible modulation of the buccal mucosal barrier, while maintaining safety and efficacy (Gupta *et al.*, 2013).

Table 4: Permeation Enhancement Strategies in Buccal Drug Delivery and Associated Safety Concerns (Marwah *et al.*, 2016)

Enhancement Strategy	**Examples**	**Mechanism of Action**	**Benefits**	**Potential Safety Concerns / Risks**
Chemical permeation enhancers	Fatty acids, bile salts, surfactants	Disrupt lipid bilayers; increase membrane fluidity	Improved drug permeation	Mucosal irritation; reversible epithelial damage
Enzyme inhibitors	Protease inhibitors	Reduce enzymatic degradation	Improved peptide/ protein stability	Possible alteration of local enzyme balance
Mucoadhesive polymers	Chitosan, Carbopol®, thiomers	Prolong residence time; open tight junctions	Sustained drug absorption	Excessive adhesion may cause discomfort
Thiolated polymers (Thiomers)	Thiolated chitosan, thiolated HA	Covalent bonding with mucus glycoproteins	Strong, prolonged mucoadhesion	Long-term mucosal safety data limited
Ion-pairing agents	Organic acids, counter-ions	Increase lipophilicity of drug	Enhanced transcellular transport	Risk of altered drug stability
Nanocarriers	Nanoparticles, liposomes	Improve mucosal penetration and protection	Targeted and efficient delivery	Potential toxicity and accumulation risk
Physical methods	Iontophoresis, microneedles (experimental)	Increase membrane permeability	Rapid drug transport	Patient discomfort; tissue damage risk

10.3.2. Physical Enhancement Methods

Physical methods can supplement or replace chemical enhancers to improve drug permeation across the buccal mucosa through noninvasive, mechanical, or energy-related mechanisms. Iontophoresis is a process in which a small electric current is applied to drive ionized drug molecules across the mucosa and has been found particularly useful for charged antihypertensive agents such as atenolol and captopril (Nayak *et al.*, 2019). This electrokinetic enhancement method includes electrophoresis and electroosmosis principles, which facilitate drug passage across the mucosal barrier.

Sonophoresis uses ultrasonic waves to transiently disrupt mucosal structure by creating aqueous channels that increase drug permeation due to cavitational effects and acoustic streaming (Marathe *et al.*, 2024). Microneedle technology is an innovative technique that employs arrays of micrometer-sized needles to penetrate the outer layers of the mucosa painlessly without invading nerve endings, forming direct entry points for drug delivery while ensuring patient comfort (Zafar *et al.*, 2025).

Such physical enhancement approaches offer the advantage of controlled and reversible barrier modification without the potential systemic effects associated with chemical penetration enhancers. Consequently, they are particularly desirable for chronic antihypertensive therapy, where repeated administration is required (Liu *et al.*, 2025).

10.3.3. Nanocarrier Systems

Nanocarriers incorporated within buccal patches can significantly enhance drug permeation through multiple mechanisms that overcome conventional delivery limitations. Liposomes—phospholipid vesicles that enhance drug solubility, protect drugs from enzymatic degradation, and fuse with mucosal membranes—represent a well-established strategy for improving bioavailability (Priya *et al.*, 2023).

Polymeric nanoparticles are submicron-sized carriers that stabilize drugs and regulate release kinetics while enhancing mucosal uptake via endocytotic processes. Solid lipid nanoparticles combine the advantages of polymeric nanoparticles with high drug entrapment efficiency and improved permeation of lipophilic antihypertensive drugs through enhanced interactions with cellular membranes. Nanoemulsions are thermodynamically stable dispersions that improve drug solubility and increase membrane fluidity, thereby facilitating drug transport across the buccal mucosa (Akbari *et al.*, 2022).

Although nanotechnology-based approaches have shown substantial progress, they have also demonstrated effective practical application. For instance, valsartan-loaded chitosan nanoparticles incorporated into buccal patches increased drug permeation by 3.2-fold compared with conventional patches (Patel *et al.*, 2019). Moreover, these nanocarriers hold considerable promise as multifunctional platforms capable of addressing the key challenges of antihypertensive drug delivery, namely solubility, stability, and permeation (Mehta *et al.*, 2023).

11. Characterization of Buccal Mucoadhesive Patches

Comprehensive characterization is essential to ensure quality, efficacy, and reproducibility.

11.1. Physical and Mechanical Characterization

11.1.1. Thickness, Weight Variation, and Surface pH

To ensure precision and ease of use, the thickness and weight of buccal preparations should be uniform. Buccal patches or films are typically manufactured within a thickness range of 0.1–0.5 mm, ensuring uniformity and consistent drug distribution. Deviations in thickness may lead to variability in drug content and performance (Borges *et al.*, 2015).

Surface pH is another critical formulation parameter. Ideally, the surface pH should be close to neutral, typically between 6.5 and 7.5, to match the physiological pH of the buccal mucosa. Excessive acidity or alkalinity may cause irritation, burning sensations, or discomfort, reducing patient acceptability (Zaman *et al.*, 2024). Flat-surface pH electrodes are generally recommended for accurate surface pH measurement. Proper control of thickness, weight, and surface pH enhances therapeutic precision, mucosal compatibility, and overall patient experience (Carias & Hope, 2018).

11.1.2 Folding Endurance and Tensile Strength

Folding endurance refers to the number of times a patch can be folded repeatedly at the same location without breaking. A folding endurance value exceeding 300 is generally considered acceptable, indicating that

the patch can withstand routine handling and intraoral movements without tearing (Laffleur & Egeling, 2020).

Tensile strength is another critical mechanical property that ensures dosage form stability. It is typically measured using instruments such as a texture analyzer or universal testing machine and represents the maximum force the patch can withstand before rupture (Krishnasamy & Ramadoss, 2025). Adequate tensile strength is essential, as buccal patches must tolerate stretching, application pressure, and normal oral movements. Insufficient strength may result in tearing during administration or adhesion, leading to compromised dosing performance.

Collectively, appropriate folding endurance and tensile strength ensure optimal performance, safety, and patient comfort (Sudarjat *et al.*, 2025).

11.1.3. Swelling Behavior and Erosion Studies

The swelling index is a critical parameter that reflects the increase in weight or size of a buccal patch upon hydration. Swelling directly influences drug release and patient comfort. Moderate swelling promotes intimate contact with the buccal mucosa, enhancing adhesion and enabling controlled drug diffusion (Kraisit *et al.*, 2018). Ideally, swelling should be sufficient to ensure effective attachment without becoming excessive and uncomfortable within the oral cavity. Most well-designed formulations exhibit swelling values in the range of 50–200%, depending on the polymers used.

In addition to swelling, erosion is another important characteristic. Erosion studies evaluate the rate at which a water-erodible patch dissolves, disintegrates, or degrades in simulated saliva (Cionca *et al.*, 2015). Controlled erosion plays a vital role in modulating drug release and provides insight into the duration of patch integrity during application. Together, swelling and erosion profiles inform the design of safe, effective, and patient-friendly buccal delivery systems (Sirolli *et al.*, 2024).

11.2. Mucoadhesion Studies

11.2.1. In Vitro Methods

The mucoadhesive strength of buccal patches is conventionally studied using various experimental techniques that provide complementary information on adhesive performance. Generally, texture analyzer–based methods are employed, in which the quantitative force required to detach the patch from either a mucosal substrate or a mucin-coated surface is measured with good precision and reproducibility (Nair *et al.*, 2013a). Modified balance methods represent a less sophisticated alternative and involve measuring the weight required to detach the patch from mucous tissue.

Rheological methods are also employed, wherein viscoelastic changes are evaluated following the interaction of mucoadhesive polymers with mucin solutions, indirectly demonstrating the presence of adhesive forces at a molecular level (Asane *et al.*, 2008). In addition, flow-through methods aim to mimic physiological conditions by testing the retention time of patches on mucosal surfaces under controlled salivary flow, thereby assessing in situ stability and adhesion. Collectively, these methods enable detailed characterization of mucoadhesive performance, which is essential for the optimization of buccal formulations (Łysik *et al.*, 2025).

11.2.2. Ex Vivo Methods

Measurement of mucoadhesive performance using excised animal buccal mucosa—commonly porcine tissue due to its close structural similarity to human oral mucosa—provides a more physiologically relevant assessment compared to synthetic substrates. A range of methodologies is available for such evaluations (Zielińska *et al.*, 2025).

Wash-off tests determine the time required for a patch to detach from mucosal tissue following exposure to mechanical agitation, simulating dynamic oral conditions. Retention tests assess the residence time of patches on vertical or inclined mucosal surfaces under gravitational forces and artificially generated salivary flow, approximating in vivo conditions (Milionis *et al.*, 2020). Additionally, adhesion force may be quantitatively measured using excised tissue and patches mounted on modified balances or tensile testers that directly determine detachment force.

Together, these approaches provide valuable information on adhesive strength and residence time, enabling optimization of buccal patches for improved retention and therapeutic efficacy (Gao *et al.*, 2025).

11.3. Drug Content and Release Studies

11.3.1. Drug Content Uniformity

Drug content uniformity is a critical quality parameter for buccal patches and typically involves complete dissolution of the dosage form in an appropriate solvent

to ensure full extraction of the active pharmaceutical ingredient (Koirala *et al.*, 2021a). The resulting solution is analyzed using validated techniques such as UV–visible spectrophotometry, HPLC, or advanced methods including LC–MS analysis. These methods confirm the actual drug content per patch and ensure uniform drug distribution within the polymer matrix (Igbokwe *et al.*, 2025).

`According to official guidelines, drug content in individual patches should fall within 90–110% of the labeled amount to ensure accurate dosing without exceeding safety limits. Additionally, the relative standard deviation (RSD) should be below 5%, indicating minimal variability among patches. Such uniformity is crucial not only for dose accuracy but also for patient safety and consistent therapeutic performance (Rohani Shirvan *et al.*, 2021).

11.3.2 In Vitro Release Testing

In vitro drug release studies of buccal patches are commonly conducted using modified dissolution apparatus designed to simulate the physiological oral environment. USP dissolution apparatuses are frequently adapted by employing reduced volumes of phosphate buffer (pH 6.8) to mimic salivary conditions, providing a standardized approach for evaluating release kinetics (Mane *et al.*, 2014).

Franz diffusion cells are also widely used, with the buccal patch positioned between donor and receptor compartments to enable controlled sampling of the receptor medium for quantitative drug analysis. Alternatively, dialysis-based methods involve placing patches in dialysis bags immersed in release medium with periodic sampling to assess drug diffusion through the membrane (Berben & Borbás, 2024).

Release profiles of antihypertensive drugs from these systems commonly follow established kinetic models such as Higuchi, Korsmeyer–Peppas, and zero-order kinetics. An optimal release profile ensures sustained therapeutic drug levels throughout the intended application period (Al Shawakri *et al.*, 2025).

11.3.3. Ex Vivo Permeation Studies

Excised buccal mucosa obtained from porcine or ovine sources is widely used in permeation studies to evaluate the ability of drugs to cross biological barriers. This model closely approximates the anatomical and physiological properties of the human buccal membrane, making it suitable for laboratory evaluation (Kulkarni *et al.*, 2010).

These studies allow determination of key permeation parameters, including flux (J), which represents the rate of drug diffusion across the tissue, and the permeability coefficient (Kp), which reflects the ease of drug transport through the membrane. The enhancement ratio is also calculated to assess the effectiveness of permeation enhancers or specific formulation strategies (Shaik *et al.*, 2015).

Collectively, these parameters provide insight into drug transport mechanisms and support optimization of buccal delivery systems for enhanced absorption and therapeutic efficiency.

11.4. Stability Studies

Stability testing of buccal patches is essential to confirm physical integrity and chemical stability throughout the product's shelf life, in accordance with ICH guidelines. Stability studies are typically conducted under long-term conditions (25 °C ± 2 °C/60% ± 5% RH), accelerated conditions (40 °C ± 2 °C/75% ± 5% RH), and stress conditions such as photostability and freeze–thaw cycles that simulate environmental extremes encountered during storage and transportation (Baertschi *et al.*, 2010).

Critical parameters evaluated during stability testing include visual appearance, drug content uniformity, in vitro release profile, mucoadhesive strength, and microbial contamination, all of which directly influence product safety and therapeutic efficacy. Antihypertensive drugs present unique stability challenges; for instance, nifedipine is highly photosensitive and requires light-protective packaging, whereas moisture-sensitive ACE inhibitors such as enalapril necessitate moisture-resistant packaging to preserve potency (Stanisz, 2003).

Comprehensive stability evaluation and appropriate protective formulation strategies are therefore vital for maintaining the quality and effectiveness of buccal patches throughout their intended shelf life (Shipp *et al.*, 2022).

12. Clinical Aspects and Therapeutic Efficacy

12.1. Pharmacokinetics and Bioavailability

A pharmacokinetic comparison of blood concentration–time profiles following buccal and conventional oral administration is presented in Figure

3. Unlike the abrupt decline in plasma drug levels caused by first-pass metabolism after oral dosing, the buccal route exhibits a more sustained concentration profile with a lower peak, indicating more gradual and controlled absorption (Desai *et al.*, 2012).

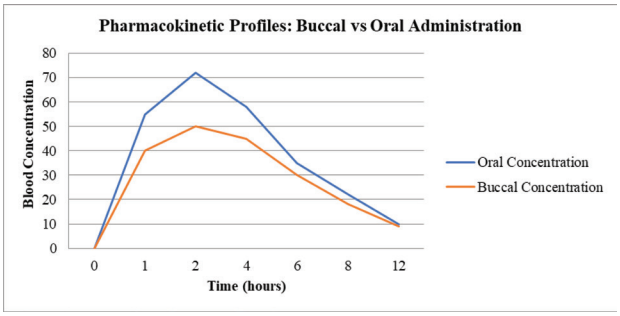

Figure 3: Pharmacokinetic Comparison of Buccal vs Conventional Oral Administration(Sudhakar *et al.*, 2006).

(Blood concentration profiles illustrating the avoidance of first-pass metabolism in buccal drug delivery) Anti-hypertensive medication delivered buccally has clear pharmacokinetic benefits:

- Improved bioavailability: It has been observed in various studies that many antihypertensive drugs have remarkably enhanced bioavailability when administered through alternative routes, especially through the buccal mucosa. Their bioavailability is increased by 1.5 to 3 times compared to oral administration (Abd Elrady *et al.*, 2026). This increase is mainly because they bypass first-pass metabolism, wherein a large amount of the drug is metabolized in the liver and is therefore not presented into systemic circulation. Thus, a higher amount of the active drug is present in the blood, which enhances the therapeutic response and may also lower the required dose (Kajal *et al.*, 2023).
- Decreased first-pass metabolism: More stable therapeutic levels can be maintained with lower doses of drugs if the route of administration offers access, at least directly, to systemic circulation. For instance, the buccal route avoids the drug passing through the gastrointestinal tract and bypasses first-pass liver metabolism. A higher proportion of active molecules reaches the bloodstream intact (Bahraminejad & Almoazen, 2025). Smoother, more consistent plasma concentrations reduce fluctuations commonly caused by oral dosing. Improved efficacy and fewer side effects may result for the patient, offering better overall stability of treatment. The use of lower doses while maintaining steady drug levels increases safety and supports better long-term therapeutic outcomes (Simon & von Fabeck, 2025).
- Modified pharmacokinetic profiles: Controlled drug release from mucoadhesive buccal patches helps maintain steady therapeutic levels by slowing the rate at which the drug enters systemic circulation. This gradual release usually leads to a longer time for the drug to reach its peak concentration (Haddadzadegan *et al.*, 2025). This avoids rapid spikes in drug levels. Meanwhile, the ratio between peak and trough concentrations decreases significantly, reflecting lower fluctuations in blood drug levels throughout the day. In return, the drug maintains a steadier presence within the system for longer periods. Such steadiness contributes to improved treatment success (Gao *et al.*, 2023) and reduces the occurrence of side effects. In addition, more reliable dosing in patients is achieved through this manner of administration.

One study examined hypertensive patients using buccal patches containing 25 mg of metoprolol tartrate. These elicited effects almost similar to the administration of 50 mg of the immediate-release oral form (Narendra *et al.*, 2005). The lower dose was considered sufficient because the buccal route bypassed hepatic first-pass metabolism, allowing a higher amount of the drug to reach systemic circulation directly. Blood level fluctuations were notably lower in patch users (Stillhart *et al.*, 2020), maintaining smoother plasma concentrations throughout the dosing period. Such steady control may be highly beneficial in disease management and may also decrease the risk of side effects associated with higher oral doses (Adepu & Ramakrishna, 2021).

12.2. Clinical Efficacy Studies

12.2.1. Antidiabetic Drugs

Clinical studies on buccal delivery of antidiabetic drugs have shown encouraging results in terms of therapeutic efficacy, particularly in improving bioavailability and patient compliance. Buccal insulin preparations have been tested in early-stage clinical studies, wherein rapid absorption through buccal tissues significantly shortened onset time and remained unaffected by gastrointestinal degradation and first-pass elimination compared to traditional subcutaneous injections (Vaidya & Mitragotri, 2020). These studies demonstrated better control of postprandial blood glucose levels with reduced fluctuation in blood insulin concentrations, indicating benefits for glycemic control.

Furthermore, buccal delivery systems for metformin have been explored to address its low oral bioavailability. Buccal administration of metformin appeared to minimize gastrointestinal side effects, primarily by reducing the required dose while permitting sufficient drug levels to reach systemic circulation (Moreno-Cabañas *et al.*, 2023).

12.2.2. Analgesics and Anti-Inflammatory Drugs

Buccal drug delivery formulations of analgesics, particularly for managing acute and chronic pain, have also undergone clinical evaluation. Buccal fentanyl formulations are well established and have achieved clinical success in managing breakthrough cancer pain. Clinical trials demonstrated rapid systemic absorption with effective pain relief compared to oral opioids, along with minimal gastrointestinal side effects (Fallon *et al.*, 2018).

Similarly, buccal patches containing non-steroidal anti-inflammatory drugs (NSAIDs), such as ketorolac, have shown promising results in pain management due to their prolonged duration of action. Clinical trials indicated effective analgesia with reduced dosing frequency and minimal gastric irritation (Nesseem *et al.*, 2011).

12.2.3. Central Nervous System (CNS) Drugs

The potential of buccal delivery systems to avoid hepatic first-pass metabolism and provide rapid onset of action has led to increased interest in CNS-active drugs. Clinical trials investigating buccal administration of benzodiazepines, such as midazolam, demonstrated effective seizure control during emergency situations, particularly in pediatric patients, with rapid absorption and greater ease of administration compared to intravenous routes (Kutlu *et al.*, 2003).

Buccal formulations of antipsychotic drugs, including risperidone, have also been explored in pilot clinical trials. These studies reported consistent plasma drug levels, improved patient compliance, and fewer extrapyramidal side effects due to controlled drug release and elimination of peak plasma fluctuations commonly associated with oral dosing (Çelik, 2017).

12.3. Patient Acceptability and Compliance

Patient acceptance of buccal patches for antihypertensive therapy is influenced by several factors, with handling convenience and comfort being of primary importance. Good acceptance has been demonstrated for appropriately sized patches (< 2 cm^2), with minimal awareness of their presence. Taste masking is an important consideration for bitter antihypertensive drugs and can be achieved through isolation of the backing layer or the addition of flavoring agents (Zhou *et al.*, 2025).

Ease of application, including insertion and removal, significantly affects patient satisfaction. Extended residence times of 8–24 hours contribute to improved patient compliance, and preference questionnaires have demonstrated a marked preference for once-daily buccal dosing over multiple daily oral doses (Nieuwlaat *et al.*, 2014). Local irritation has been reported in 5–15% of patients, primarily due to the use of chemical permeation enhancers. Importantly, preference surveys indicate that approximately 68–75% of patients with hypertension would be willing to switch from conventional oral therapy to buccal patches if recommended by their physician (Abstracts of the European Association of Poisons Centres and Clinical Toxicologists XXVI International Congress, 2006).

13. Future Prospects

Future research should be directed toward the development of patient-oriented buccal formulations, supported by adequate clinical testing to establish bioavailability enhancement and therapeutic superiority to traditional routes. Possible future directions in polymer science include smart, stimuli-responsive, and biodegradable mucoadhesive materials. Permeation and long-term drug release could be further enhanced using nanotechnology combined with buccal systems (Solanki & Parmar, 2025). Pharmacogenomics combined with mucosal variability may lead to personalized buccal delivery platforms for better therapeutic outcomes in hypertensive patients. Regulatory harmonization, standardized protocols for evaluation, and long-term safety assessment will also be necessary for accelerating clinical and commercial translation of buccal mucoadhesive antihypertensive systems (Nourazarain & Vaziri, 2025).

14. Limitations

The current review is limited by the heterogeneity of the studies published so far, given the variability in the models of drugs, combinations of polymers,

protocols of assessment, and forms of reporting. Most of the formulations described in the literature are not advanced beyond preliminary laboratory testing; thus, findings cannot easily be generalized to clinical practice. Exclusion of non-English publications might have led to the omission of potentially relevant data. Another limitation is that there are few clinical studies on buccal mucoadhesive antihypertensives, which limits comprehensiveness regarding evidence on therapeutic outcomes, pharmacokinetics, and patient compliance. This review is based on published data alone and hence is also prone to publication bias (Choi *et al.*, 2025).

15. Conclusions

Buccal mucoadhesive patches present a promising non-traditional route for oral delivery of antihypertensive drugs. Such systems, by avoiding first-pass metabolism and gastrointestinal degradation, offer the potential for improved bioavailability, extended therapeutic plasma levels, and lowered dosing intervals. Key factors related to formulation controlling the success of such delivery systems are proper polymer choice, optimization of mucoadhesion, controlled release kinetics, and efficient permeation enhancement measures. Improvements in material science, manufacturing processes, and permeation enhancement have considerably increased the efficacy of buccal patches for antihypertensive therapy. Clinical trials have shown these systems can offer equal or better control compared with conventional oral therapies, with fewer side effects. Moreover, easier compliance with fewer side effects and shorter dosing intervals may be an added bonus with a system like this for the treatment of a chronic disease like hypertension.

While very encouraging, there are still a number of challenges that remain to be addressed for these successes at the laboratory level to find implementation at higher magnitudes, such as scale-up production, cost-effectiveness, and addressing safety concerns. Looking ahead, apart from researching new avenues, some of which include stimulus-responsive systems and patches for combination therapies and associated digital health technologies, addressing some challenges would be imperative. The fact that hypertension is still increasing in the global landscape creates an imperative for new and better avenues for therapies. The buccal mucoadhesive patches have been extremely encouraging and very promising for improving antihypertensive therapies and helping improve patient responses within this very serious domain of cardiovascular disease therapies.

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Authorship Contribution

Divyanshu and Jatin Agarwal have contributed to the work through the process of conceptualization, investigation, curation of the data, and preparation of the original draft. Km. Pinki has assisted in the organization, presentation, and critical comparison of the formulation strategy. Harpreet Singh has contributed to the supervision, validation, and critical comparison of the manuscript for editing purposes. Arun Kumar Mishra has provided the supervision, methodology, and editing of the manuscript.

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The authors of the manuscript confirm it to be original, not published anywhere earlier, and not under consideration for publication elsewhere. There were no financial or non-financial conflicts of interest related to the manuscript, and no funding had been provided for the same. Since the work is based on literature already available, the ethical issues do not apply to the manuscript. Permissions have been taken wherever necessary from the available data, and the same data is used to support the results of the manuscript. The final manuscript had been approved by all the authors.

Conflict of Interest

There is no conflict of interest between the authors regarding this paper.

Data Availability Statement

Data sharing is not applicable as no new data were generated or analyzed.

AI Usage Statement

During the preparation of this manuscript, the author(s) used Grammarly for language editing and grammar improvement. After its use, the author(s) thoroughly reviewed, verified, and revised all AI-assisted content to ensure accuracy and originality. The author(s) take full responsibility for the integrity and final content of the published article.

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