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Recent Advances in Buccal Patch Drug Delivery Systems: Formulation Strategies and Therapeutic Applications - A Review

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ABSTRACT

Buccal drug delivery has gained considerable attention as an alternative approach for improving the delivery of therapeutic agents that may exhibit limitations following conventional oral administration. Buccal patches provide intimate contact with the oral mucosa and can facilitate localized or systemic drug delivery while potentially reducing gastrointestinal degradation and hepatic first-pass metabolism. This review provides a comprehensive overview of the formulation, manufacturing and evaluation of buccal patch drug-delivery systems. The fundamental characteristics of the buccal mucosa and the principles underlying mucoadhesive drug delivery are discussed, followed by consideration of the major formulation components, including active pharmaceutical ingredients, film-forming and mucoadhesive polymers, plasticizers, permeation enhancers and backing materials. Different patch architectures, including single-layer, bilayer, multilayer, matrix, reservoir and unidirectional systems, are examined. Conventional and emerging manufacturing approaches, such as solvent casting, direct compression, hot-melt extrusion, lyophilization, continuous film formation, slot-die coating, electrospinning, two-dimensional and three-dimensional printing, and nanocarrier-loaded film fabrication, are also highlighted. Particular emphasis is placed on systematic evaluation of buccal patches through physical, mechanical, physicochemical, mucoadhesive and functional characterization. Parameters including thickness, weight variation, drug content, folding endurance, mechanical properties, moisture behaviour, swelling, surface pH, morphology, drug–excipient compatibility, mucoadhesive strength, residence time, in-vitro drug release, release kinetics, ex-vivo permeation, mucosal safety and stability are discussed. Finally, current formulation and translational challenges and emerging opportunities for patient-centric and advanced buccal delivery systems are considered. Overall, rational integration of polymer science, advanced manufacturing, nanotechnology and physiologically relevant evaluation may facilitate the development of more effective, reproducible and clinically translatable buccal patches.

Keywords: Buccal drug delivery; Buccal patches; Mucoadhesive polymers; Buccal films; Drug permeation; Controlled drug release.

1. INTRODUCTION

The oral route continues to be the most widely accepted route for administration of therapeutic agents because of its convenience, ease of administration, patient acceptability and relatively low cost. Conventional oral dosage forms such as tablets and capsules, however, are not universally optimal for achieving predictable systemic drug exposure. The absorption of an orally administered drug is influenced by a complex sequence of processes involving dissolution, gastrointestinal stability, membrane permeation, intestinal and hepatic metabolism, efflux transport and subsequent distribution into the systemic circulation. Consequently, drugs with extensive gastrointestinal degradation, poor permeability, low aqueous solubility or substantial first-pass metabolism may exhibit inadequate or highly variable bioavailability following conventional oral administration. These limitations have stimulated continuing interest in alternative transmucosal delivery routes capable of improving drug exposure while maintaining the convenience of non-invasive administration [1–4].

Mucosal drug delivery represents an important strategy for addressing some of the limitations associated with conventional oral administration. Drug administration through mucosal surfaces can provide either localized therapy or systemic absorption depending on the anatomical site and formulation design. The nasal, ocular, pulmonary, rectal, vaginal and oral mucosa has therefore been investigated as alternative portals for drug delivery. Among these, the oral mucosa possesses several characteristics that make it particularly attractive for pharmaceutical administration. It is readily accessible, relatively robust, richly vascularized and capable of supporting both local and systemic therapeutic applications. Importantly, transmucosal absorption through selected regions of

the oral cavity can reduce exposure of the drug to the gastrointestinal environment and partially or substantially circumvent hepatic first-pass metabolism [2, 3, 5].

Within the oral cavity, the buccal mucosa has received considerable attention as a site for controlled drug administration. Buccal formulations are positioned against the inner surface of the cheek, where the dosage form can remain in contact with the mucosa for a predetermined period and release the incorporated drug. Unlike rapidly dissolving sublingual systems, which are generally designed to provide rapid drug liberation and absorption, buccal systems can be engineered to provide prolonged residence and controlled drug release. This distinction has encouraged the development of mucoadhesive tablets, patches, films, wafers, hydrogels and other polymeric systems for buccal administration [1, 3, 6].

Recent research has shifted the concept of buccal delivery from a relatively simple alternative route toward a sophisticated formulation platform. Advances in polymer science, nanotechnology, permeation enhancement, multilayer film architecture, electrospinning, hot-melt extrusion, printing technologies and quality-by-design approaches have created opportunities for tailoring drug release, mucosal residence, mechanical performance and transmucosal transport according to therapeutic requirements [1, 7–10]. Recent literature further indicates that the field is increasingly concerned not only with obtaining satisfactory laboratory drug-release profiles but also with establishing meaningful relationships between formulation characteristics, mucosal permeation and in-vivo pharmacokinetics.

1.1 Oral Route and Need for Alternative Drug Delivery Approaches

Although oral administration is convenient and generally preferred by patients, conventional oral dosage forms are associated with several biopharmaceutical and physiological limitations. Following ingestion, the dosage form enters the gastrointestinal tract and encounters variations in pH, digestive enzymes, bile components, intestinal motility and microbial activity. Depending on the physicochemical properties of the drug, these conditions can influence dissolution, degradation and absorption. Furthermore, drugs that are absorbed from the gastrointestinal tract may undergo presystemic metabolism in the intestinal wall and liver before reaching systemic circulation. This phenomenon can substantially reduce the fraction of administered drug that becomes systemically available [3, 7].

First-pass metabolism is particularly important for drugs having high hepatic extraction. Increasing the oral dose may compensate for reduced systemic exposure in some circumstances, but this approach can simultaneously increase gastrointestinal exposure, adverse effects and interindividual variability. Consequently, modification of the administration route may provide a more rational strategy than simply increasing the oral dose. Transmucosal systems have been investigated within this context because they can place the active pharmaceutical ingredient in close proximity to a highly vascularized epithelial surface and reduce dependence on gastrointestinal dissolution and absorption processes [3, 5].

Another limitation of conventional oral dosage forms concerns patient populations for whom swallowing tablets or capsules is difficult. Dysphagia may occur in elderly individuals, pediatric patients and patients with neurological or other disorders. A flexible buccal film can be administered without requiring the patient to swallow a conventional solid dosage form and can therefore provide a potentially more patient-centric dosing option [6, 8]. Recent reviews have emphasized that patient acceptability, ease of administration, portability and the ability to customize film dimensions are among the principal reasons for renewed interest in buccal films [6, 11].

The development of alternative delivery routes should nevertheless not be interpreted as a complete replacement for oral therapy. Instead, the objective is to identify drugs and patient populations for which the physiological characteristics of a particular alternative route provide a meaningful therapeutic advantage. In the case of buccal delivery, the most appropriate candidates generally include drugs for which first-pass metabolism, gastrointestinal instability, difficulty in swallowing or the need for controlled systemic exposure represents a significant limitation to conventional oral therapy [1, 3, 6].

1.2 Mucosal Drug Delivery and the Buccal Route

Mucosal drug delivery involves administration of therapeutic substances across a mucous membrane. Depending on the anatomical location, a formulation may produce a local effect at the mucosal surface or allow the active ingredient to cross the mucosal barrier and enter systemic circulation. The oral cavity is particularly interesting because it contains several anatomically and physiologically distinct mucosal regions. The buccal mucosa is composed of a stratified, non-keratinized squamous epithelium supported by connective tissue and an underlying vascular network. Its accessibility and relatively favorable permeability have contributed to its investigation as a site for systemic drug delivery [1, 5, 7].

The buccal mucosa is not simply a passive membrane. It represents a biological barrier whose protective functions can simultaneously limit pharmaceutical absorption. The epithelial structure, mucus layer, salivary environment, enzymatic activity and continuous mechanical movement of the oral cavity all influence the fate of a buccally administered dosage form. Therefore, successful formulation development requires a balance between sufficient adhesion and controlled drug release on one hand, and adequate drug partitioning and permeation through the mucosal barrier on the other [1, 5, 12].

Compared with the sublingual region, the buccal mucosa generally provides a less permeable but more suitable environment for prolonged retention. This difference is important from a formulation perspective. A highly permeable membrane may facilitate rapid drug absorption, but rapid absorption is not always synonymous with prolonged therapeutic control. Buccal systems can instead exploit the relatively robust nature of the buccal mucosa to maintain a formulation at the administration site for an extended period while releasing drug at a controlled rate [1, 7].

The blood supply underlying the buccal mucosa also contributes to its usefulness for systemic delivery. Once a drug crosses the epithelial barrier and enters the local microcirculation, it can reach systemic circulation without first passing through the gastrointestinal lumen. This can reduce the contribution of gastrointestinal degradation and hepatic first-pass metabolism, although the extent of first-pass avoidance depends on the precise site and route of absorption and should not be considered absolute for every buccal formulation [1, 3].

Recent research has also expanded the potential of buccal delivery beyond conventional small-molecule drugs. Polymeric films incorporating nanoparticles, lipid-based carriers, nanostructured systems and other advanced carriers are being explored to address poor aqueous solubility and limited permeability. Such approaches are particularly relevant for drugs and biological macromolecules that otherwise exhibit inadequate transport across the oral mucosa [7, 9, 13].

1.3 Buccal Mucosa as a Drug-Delivery Barrier

A rational buccal formulation requires an understanding of the mucosal barrier through which the drug must pass. The buccal epithelium consists of multiple layers of epithelial cells and contains lipid-rich domains that contribute to its barrier properties. Consequently, passive diffusion is generally more favorable for relatively small and appropriately lipophilic molecules than for highly hydrophilic compounds or macromolecules. The physicochemical characteristics of the drug—including molecular size, ionization, lipophilicity, hydrogen-bonding capacity and aqueous solubility—therefore strongly influence buccal permeation [1, 5, 7].

The mucus layer represents an additional dynamic interface between the formulation and epithelial surface. Mucins contain glycoprotein structures capable of interacting with polymers through hydrogen bonding, electrostatic interactions and other intermolecular forces. These interactions form the basis of mucoadhesion, which can increase the residence time of a dosage form at the absorption site [7, 14]. However, excessive interaction or excessively strong adhesion is not necessarily desirable because a formulation must eventually be removed without causing mucosal damage.

Saliva presents another important formulation challenge. Continuous salivary secretion can hydrate, dilute, erode or displace a buccal dosage form. Tongue movement, chewing, swallowing and facial movement further impose mechanical stresses on the formulation. Thus, a buccal patch must possess sufficient flexibility and mechanical integrity while simultaneously undergoing appropriate hydration and drug release. These competing requirements explain why polymer selection and polymer blending are central to buccal formulation development [6, 7].

The limited absorptive surface area of the buccal cavity also places practical constraints on dose loading. Unlike gastrointestinal administration, in which large quantities of formulation can be delivered, a buccal film must remain small, thin and comfortable enough for placement inside the cheek. This makes buccal delivery particularly suitable for potent drugs requiring relatively low doses rather than high-dose active ingredients [1,6].

1.4 Mucoadhesive Drug Delivery Systems

Mucoadhesive drug delivery systems are designed to establish prolonged contact between a pharmaceutical formulation and a mucosal surface. In buccal delivery, mucoadhesion is particularly important because the formulation must withstand the continuous washing and mechanical forces of the oral cavity long enough to achieve meaningful drug release and absorption. A mucoadhesive system can therefore be viewed as an interface-engineering approach in which formulation components are selected to establish adequate interaction with the mucus layer while preserving drug-release functionality [6, 14].

The process of mucoadhesion is commonly described in terms of an initial contact stage followed by consolidation of the interaction between the formulation and mucosal surface. During hydration, polymer chains can become sufficiently mobile to establish hydrogen bonds, electrostatic interactions, van der Waals forces and other intermolecular interactions with mucin. Interpenetration of polymer and mucin chains can further strengthen the adhesive interface. The extent of these interactions is affected by polymer molecular weight, chain flexibility, and degree of hydration, functional-group density, concentration and environmental conditions [7, 14].

Recent research has moved toward designing polymers that simultaneously provide mucoadhesion and improve drug solubilization or permeation. Amphiphilic polymer systems are particularly interesting because their hydrophilic segments can interact with the aqueous/mucosal environment while hydrophobic segments may accommodate poorly water-soluble molecules. A 2026 review identified this combination of mucoadhesive and amphiphilic characteristics as a promising strategy for overcoming simultaneous solubility, residence-time and permeability limitations [14].

Natural polymers such as chitosan, alginate, pectin, carrageenan, cellulose derivatives and other polysaccharides have received substantial attention because of their biocompatibility, biodegradability and functional groups capable of interacting with mucosal surfaces. Synthetic polymers, including cellulose derivatives and acrylic polymers, offer more reproducible physicochemical characteristics and can be selected to achieve specific mechanical and release properties. Consequently, modern buccal films frequently employ either individual polymers or combinations of natural and synthetic polymers rather than relying on a single material [7, 10, 14].

1.5 Advantages of Buccal Drug Delivery

1.5.1 Avoidance or Reduction of First-Pass Metabolism

One of the principal attractions of buccal administration is the possibility of reducing exposure of the absorbed drug to gastrointestinal degradation and hepatic first-pass metabolism. For suitable drugs, this can increase systemic exposure and potentially permit reduction of the administered dose. However, the magnitude of the benefit depends on the fraction of drug actually absorbed transmucosally rather than swallowed [1, 3, 7].

1.5.2 Improved Patient Acceptability

Buccal films and patches are generally thin, lightweight and non-invasive. Their small size can make administration more convenient than injections and may be particularly useful for patients who have difficulty swallowing tablets. The flexibility of polymeric films can also improve intraoral comfort when an appropriate formulation is selected [6,11].

1.5.3 Controlled Drug Release

The composition and architecture of a buccal film can be manipulated to regulate drug liberation. Polymer concentration, molecular weight, degree of hydration, plasticizer content, cross-linking, multilayer architecture and incorporation of release-controlling components can all influence the release profile. Consequently, formulations may be designed for rapid, sustained or more complex release patterns [1, 3, 6].

1.5.4 Prolonged Residence at the Absorption Site

Mucoadhesive polymers can prolong the contact between a formulation and the buccal mucosa. Increased residence time may improve the opportunity for drug absorption and can also support localized therapy when the therapeutic target is within the oral cavity [6, 7].

1.5.5 Rapid Onset for Appropriate Drug Candidates

Because the buccal mucosa is directly accessible and highly vascularized, appropriately permeable drugs can enter systemic circulation without passing through the gastrointestinal lumen. This may contribute to a faster onset compared with conventional oral administration for selected drugs [3, 7].

1.5.6 Suitability for Patients with Swallowing Difficulties

A thin film that is placed on the buccal mucosa may provide a useful alternative for patients unable or unwilling to swallow tablets or capsules. This advantage has particular relevance to pediatric and geriatric populations and has become an important consideration in patient-centric formulation development [6, 11].

1.5.7 Possibility of Local and Systemic Therapy

Buccal formulations can be designed for either local action within the oral cavity or systemic delivery. Local applications can reduce the need for systemic exposure, whereas systemic formulations can exploit transmucosal absorption to improve drug availability. Thus, the buccal route represents a versatile platform rather than a single therapeutic strategy [1, 3].

1.5.8 Easy Discontinuation

A mucoadhesive patch or film can generally be removed from the buccal surface if treatment needs to be discontinued. This can be advantageous compared with dosage forms that cannot be readily retrieved after administration.

1.6 Limitations and Disadvantages of Buccal Drug Delivery

Despite its advantages, buccal delivery is not universally applicable. The most important limitation is that the oral mucosa is itself a biological barrier. Improving residence time does not automatically improve systemic absorption; the drug must additionally possess adequate physicochemical characteristics or require appropriate formulation-based enhancement to cross the epithelium [1, 5].

1.6.1 Limited Absorptive Area

The available buccal surface area is considerably smaller than the gastrointestinal absorptive surface. This restricts the amount of formulation that can be comfortably administered and consequently limits the dose of many potential drugs [6, 7].

1.6.2 Salivary Washout

Continuous saliva production can hydrate and gradually remove or dilute the dosage form. Salivary flow varies among individuals and can also change with hydration, food intake, disease and medications. This variability may contribute to differences in residence time and drug absorption [6, 7].

1.6.3 Mechanical Stress

The tongue, teeth, chewing movements and normal facial activity impose repeated mechanical forces on a buccal formulation. A film that is excessively brittle may fracture, whereas one that is excessively soft may lose structural integrity. Mechanical properties therefore need to be balanced with hydration, adhesion and drug-release requirements [6, 10].

1.6.4 Limited Drug Loading

Because buccal films must remain thin and comfortable, they are generally more suitable for potent drugs administered at relatively low doses. Drugs requiring gram-level doses are unlikely to be suitable for conventional buccal film systems [1, 6].

1.6.5 Taste and Irritation

Drug molecules released into the oral cavity may produce unpleasant taste or sensory irritation. This can reduce patient acceptability and increase salivary secretion, potentially accelerating formulation erosion. Therefore, taste masking and appropriate excipient selection may become important components of formulation design.

1.6.6 Mucosal Irritation

Permeation enhancers, strongly acidic or alkaline materials and certain active ingredients may damage the mucosal barrier when used at excessive concentrations. An effective formulation must therefore improve drug transport without compromising mucosal integrity [5, 7].

1.6.7 Interindividual Variability

Differences in saliva composition, mucosal condition, blood flow, epithelial thickness, salivary flow rate and oral physiology can affect drug delivery. Recent work has consequently emphasized the need for physiologically relevant in-vitro and ex-vivo models before advancing buccal formulations toward clinical studies [12].

1.7 Composition of Buccal Patches and Films

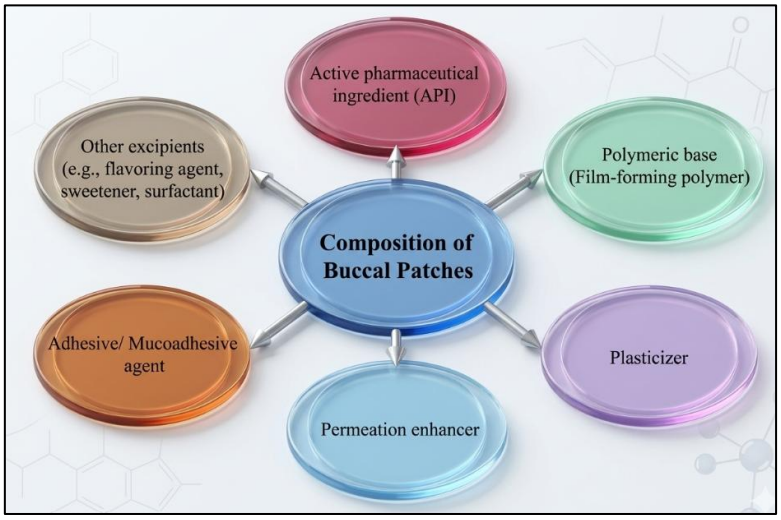


Figure 1: Composition of buccal patches.

A buccal patch is a multifunctional dosage form in which each component contributes to the overall performance of the formulation. The principal components include the active pharmaceutical ingredient, film-forming/mucoadhesive polymers, plasticizers, permeation enhancers and, where required, a backing layer or other structural components.

1.7.1 Active Pharmaceutical Ingredient

The API should possess physicochemical and biopharmaceutical properties compatible with transmucosal delivery. Drug candidates with relatively high potency, moderate molecular size and sufficient membrane permeability are generally more favorable. However, formulation technologies can modify the apparent performance of compounds that otherwise exhibit poor aqueous solubility or permeability. Nanocarriers, cyclodextrins, lipid systems, pH modifiers and permeation-enhancing strategies have therefore been investigated to broaden the range of drugs suitable for buccal administration [1, 7, 9].

The dose is an especially important consideration. Since a buccal patch has limited physical dimensions, highly potent compounds requiring comparatively small doses are generally more practical than drugs requiring large quantities. Drug stability in saliva, taste, mucosal tolerability and the desired duration of therapy should also be considered during candidate selection.

1.7.2 Mucoadhesive and Film-Forming Polymers

Polymers constitute the structural foundation of most buccal films. They provide film formation, mechanical integrity, hydration, adhesion and control of drug liberation. Polymer selection is therefore not based solely on mucoadhesive strength; the formulation scientist must simultaneously consider flexibility, tensile strength, swelling, drug compatibility, permeability, stability and release kinetics [6, 7].

Hydroxypropyl methylcellulose, hydroxypropyl cellulose, sodium alginate, chitosan, carbomers, polyacrylic acid derivatives, pectin and other cellulose-based materials have been explored extensively. Recent work on cellulose ether-based films emphasizes that polymer grade and viscosity can be deliberately selected to create rapidly dissolving systems or longer-retaining mucoadhesive films [10].

The use of polymer blends can provide properties that cannot readily be achieved using one polymer alone. For example, one polymer may contribute adhesion while another improves film strength or regulates hydration. Recent research using

HPMC/polyacrylic acid interpolymer systems for insulin delivery demonstrates the continuing movement toward rational polymer combinations for improving adhesion, release and mucosal transport of challenging therapeutic molecules [15].

1.7.3 Plasticizers

Plasticizers are incorporated to reduce polymer-chain rigidity and improve film flexibility. Glycerol, polyethylene glycol and propylene glycol are among the materials investigated for this purpose. The concentration of plasticizer can substantially influence mechanical properties, moisture uptake, and mucoadhesion and drug release. Therefore, plasticizer concentration should be optimized rather than simply increased to improve flexibility.

A recent study involving slot-die-coated pectin films demonstrated that increasing glycerol content altered film mechanical behavior, mucoadhesion and drug-release characteristics. Higher glycerol concentration produced stronger mucoadhesive behavior and modified paracetamol release and ex-vivo permeation, illustrating how a conventional excipient can act as a critical formulation variable rather than merely an inactive processing aid [16].

1.7.4 Permeation Enhancers

The epithelial barrier is one of the principal determinants of buccal drug delivery. Permeation enhancers are therefore incorporated in some formulations to temporarily increase drug transport through the mucosa. Depending on their chemistry, enhancers may alter membrane lipids, increase drug partitioning, modify epithelial structure or influence intercellular transport.

Potential enhancer categories include bile salts, fatty acids, surfactants, certain chelating agents and other membrane-modifying substances. Their concentration must be carefully controlled because excessive disruption of the epithelial barrier can produce irritation or tissue damage. Modern formulation research is therefore increasingly focused on achieving an appropriate balance between enhanced permeability and preservation of mucosal integrity [7, 14].

1.7.5 Backing Layer

A backing layer can be incorporated when directional drug release is desired. An impermeable or relatively low-permeability backing material reduces drug loss toward the oral cavity and promotes drug movement toward the mucosal surface. Bilayer and multilayer architectures can consequently improve drug utilization and allow more precise control over release [1, 3, 7].

1.8 Types of Buccal Patches

Buccal patches can be classified according to their structural organization, drug-release mechanism and direction of drug transport. The classifications overlap to some extent because a single formulation may simultaneously be described as multilayered, matrix-type and unidirectional.

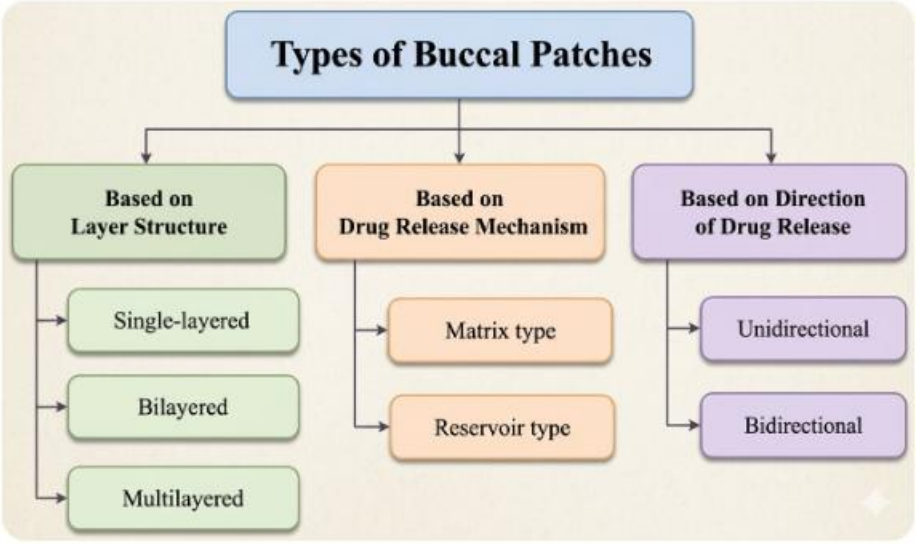


Figure 2: Types of buccal patches

1.8.1 Single-Layer Buccal Patches

A single-layer patch incorporates the drug and polymeric matrix within one principal film layer. The system is relatively simple to manufacture and can provide either local or systemic drug delivery. Drug release depends on hydration, polymer swelling, dissolution, diffusion and/or erosion of the polymeric matrix.

The major advantage of the single-layer architecture is formulation simplicity. However, when the formulation releases drug in both directions, some fraction of the dose may be lost into saliva rather than being absorbed across the mucosa. This has stimulated the development of multilayer and backing-layer systems.

1.8.2 Bilayer Buccal Patches

Bilayer systems generally consist of a drug-containing mucoadhesive layer and a backing layer. The mucoadhesive layer establishes contact with the buccal surface, whereas the backing layer restricts drug diffusion toward the oral cavity. Such an arrangement promotes more directional drug delivery.

Bilayer systems also allow the formulator to independently modify the properties of the adhesive/drug layer and the backing layer. This can improve drug utilization while providing additional control over release kinetics. Three-dimensional printing and other advanced manufacturing approaches have further expanded the possibility of creating geometrically controlled bilayer buccal systems [1, 7].

1.8.3 Multilayer Buccal Patches

Multilayer systems contain three or more functional layers and can incorporate a drug reservoir, mucoadhesive layer, rate-controlling layer and backing membrane. Their principal advantage is the ability to separate different formulation functions spatially.

For example, one layer may be responsible for adhesion, another for drug storage, another for controlling release and an outer layer for protection. Recent advances in film architecture have highlighted multilayer designs as an important strategy for achieving more predictable release and pharmacokinetic control [7, 17].

1.8.4 Matrix-Type Buccal Patches

In matrix systems, the drug is distributed throughout a polymeric network. When the formulation encounters saliva, polymer hydration or swelling facilitates drug diffusion. Depending on the polymer and formulation composition, erosion or dissolution may also contribute to drug release.

Matrix systems are comparatively straightforward to formulate and are suitable for sustained or controlled delivery. Their performance, however, depends strongly on polymer concentration, molecular weight, drug loading, drug-polymer interactions and hydration behavior.

1.8.5 Reservoir-Type Buccal Patches

In reservoir systems, the drug is concentrated in a defined compartment and surrounded or covered by a rate-controlling membrane. The membrane regulates movement of drug from the reservoir toward the mucosal surface.

Compared with simple matrix systems, reservoir designs may provide greater control over release kinetics. However, their structural complexity can increase manufacturing requirements and may introduce additional quality-control considerations.

1.8.6 Unidirectional Buccal Patches

Unidirectional systems are designed to favor drug movement toward the mucosal surface. A backing layer is commonly employed to reduce drug diffusion into saliva. This architecture can improve the fraction of the administered drug available for transmucosal absorption.

Unidirectional delivery is particularly attractive for systemic administration because it can minimize drug wastage into the oral cavity. It can also reduce exposure of taste-sensitive drugs to taste receptors.

1.8.7 Bidirectional Buccal Patches

Bidirectional systems permit drug movement toward both the mucosa and the oral cavity. They may be useful when local oral action is desired or when a formulation does not require strict directional control.

For systemic delivery, however, bidirectional release may reduce delivery efficiency because some drug can be lost through saliva and subsequent swallowing. The choice between uni- and bidirectional architecture should therefore be based on the intended therapeutic target and drug properties rather than on structural preference alone.

1.9 Recent Evolution of Buccal Patch Technology

The contemporary development of buccal patches is increasingly moving beyond conventional solvent-cast polymer films. Solvent casting remains important because it is relatively simple and permits incorporation of a wide variety of polymers and active ingredients. Nevertheless, limitations associated with solvent removal, film thickness uniformity, residual solvent, scale-up and reproducibility have encouraged exploration of alternative manufacturing technologies [1, 6, 7].

Hot-melt extrusion is one such technology and is particularly attractive because it can eliminate organic solvents and provide a continuous manufacturing process. Recent work has demonstrated the use of hot-melt extrusion combined with a Quality-by-Design framework for development of extended-release buccal films, emphasizing the increasing integration of process parameters, critical material attributes and critical quality attributes in buccal formulation development [18].

Printing technologies are another emerging area. Inkjet and three-dimensional printing can potentially provide greater control over drug distribution, dose personalization, film geometry and multilayer architecture. These technologies may be especially relevant for individualized dosing and complex formulations, although their scalability, regulatory acceptance and process validation remain important considerations [1, 6, 7].

Electrospinning provides another strategy for producing fibrous structures with high surface area. Such systems can be designed to incorporate drugs or nanocarriers within polymeric fibers and may offer opportunities for modifying dissolution, mucoadhesion and drug release. Nanocarrier-loaded buccal films are similarly being investigated to address poor aqueous solubility and limited mucosal permeability of challenging drugs [7, 9, 17].

Thus, contemporary buccal delivery research is increasingly characterized by the convergence of **polymer engineering, nanotechnology, advanced manufacturing and physiologically relevant evaluation**. The objective is no longer simply to produce a film that adheres to the cheek, but to develop a dosage form in which adhesion, mechanical behavior, drug release, permeation and pharmacokinetics are deliberately coordinated [7,17].

1.10 Current Research Perspective and Future Significance

The future development of buccal drug delivery will depend on overcoming the biological and formulation barriers that currently limit clinical translation. One important challenge is the development of predictive in-vitro and ex-vivo models. Conventional release testing alone cannot adequately predict mucosal permeation because drug transport depends on the interaction between the formulation and a living biological barrier. Recent reviews have therefore emphasized the importance of physiologically relevant oral mucosa models and standardized permeability methods [12].

Another major research direction is the delivery of macromolecules. Conventional passive diffusion across buccal epithelium is generally less efficient for peptides, proteins and other large molecules than for small, appropriately lipophilic drugs. Consequently, successful delivery of biologics may require combinations of mucoadhesion, permeation enhancement, nanocarriers and other transport-enhancing technologies [1, 7, 9].

Polymer engineering is also expected to remain central to future developments. Smart polymers, amphiphilic polymers, polymeric nanoparticles and stimuli-responsive systems may allow the formulation to respond to the local mucosal environment and provide controlled drug liberation. Recent research on amphiphilic mucoadhesive polymers illustrates the potential of integrating adhesion and drug-solubilization functions into a single material platform [14].

The application of Quality-by-Design principles is another important development. Instead of optimizing formulations solely through trial and error, QbD approaches identify the desired quality target product profile, critical quality attributes, critical material attributes and critical process parameters. This can improve formulation understanding and may facilitate reproducibility and scale-up [18].

The most important future transition, however, will be from promising laboratory formulations toward reproducible clinical products. A recent 2026 review emphasizes that the field is increasingly concerned with linking formulation design to pharmacokinetic outcomes, including drug exposure, maximum plasma concentration and time to maximum concentration, rather than relying solely on in-vitro release data [17].

Consequently, the next generation of buccal patches is likely to be characterized by **patient-specific dosing, engineered polymer matrices, directional drug delivery, nanocarrier incorporation, advanced manufacturing, improved permeability and stronger formulation–pharmacokinetic correlations**. These developments could establish buccal films as more than an alternative dosage form and instead position them as a rational platform for controlled and patient-centric drug delivery.

2. FORMULATION AND MANUFACTURING STRATEGIES OF BUCCAL PATCHES

The successful development of a buccal patch requires simultaneous consideration of drug properties, polymer characteristics, mucosal physiology, desired residence time, drug-release kinetics, mechanical performance and manufacturing feasibility. Unlike conventional tablets, a buccal patch must function at the interface between a solid polymeric dosage form and a continuously hydrated, mobile biological surface. Consequently, formulation development involves balancing several apparently competing requirements: sufficient flexibility and mechanical integrity, rapid or controlled hydration, adequate mucoadhesion, predictable drug release, acceptable mouthfeel and, where systemic delivery is intended, efficient drug permeation through the buccal epithelium [18–20].

The formulation strategy also depends on whether the intended product is a rapidly dissolving buccal film, a prolonged-residence mucoadhesive patch, a unidirectional system, a multilayer patch or a more sophisticated nanocarrier-loaded film. Modern research has therefore moved away from considering manufacturing as an isolated processing step. Instead, formulation composition and manufacturing conditions are increasingly treated as interconnected variables that determine critical quality attributes such as thickness, drug content uniformity, mechanical properties, adhesion, swelling, dissolution and permeation [18, 20, 23].

2.1 Formulation Design Considerations

Before selecting a manufacturing process, the physicochemical and biopharmaceutical characteristics of the drug should be evaluated. Molecular size, aqueous solubility, lipophilicity, pKa, melting point, dose requirement, stability and ability to cross the buccal epithelium can strongly influence formulation feasibility. Drugs requiring a relatively small dose are generally more suitable because the physical dimensions of a buccal patch restrict drug-loading capacity. In addition, the drug should preferably be non-irritant and should not produce an unacceptable taste when exposed to saliva [18–20].

Drug–polymer compatibility is another fundamental consideration. Interactions between the active pharmaceutical ingredient and film-forming polymer can influence crystallinity, molecular mobility, drug diffusion and stability. A drug may remain molecularly dispersed within an amorphous polymeric matrix, form crystalline domains or interact chemically or physically with functional groups of the polymer. Such changes can significantly alter release and permeation. Therefore, preformulation investigations such as Fourier-transform infrared spectroscopy, differential scanning calorimetry, X-ray diffraction and microscopic examination may be useful when developing a new buccal system [18, 20].

The polymeric system should be selected according to the desired product profile rather than solely on the basis of its reported mucoadhesive strength. A polymer that produces strong adhesion but forms a brittle film may not be appropriate for practical use. Conversely, a highly flexible film with inadequate adhesion may be rapidly displaced by saliva. Polymer molecular weight, concentration, degree of substitution, chain flexibility, hydrophilic/hydrophobic balance and functional-group availability can influence adhesion, swelling, mechanical strength and drug release [18–20].

Polymer blending is consequently common in buccal formulation development. A hydrophilic polymer may provide rapid hydration and mucoadhesion, whereas a second polymer can increase mechanical strength or retard drug diffusion. Similarly, incorporation of a hydrophobic polymer can reduce water penetration and prolong release. Recent work using combinations of release-controlling and bioadhesive polymers in hot-melt-extruded films demonstrates how polymer ratios can be deliberately manipulated to obtain a specific balance between release, adhesion and mechanical characteristics [23].

Plasticizers represent another important formulation variable. Glycerol, polyethylene glycol and propylene glycol can increase polymer-chain mobility and reduce brittleness. However, excessive plasticization can decrease tensile strength, increase moisture sensitivity or modify drug diffusion. A 2025 study using slot-die-coated pectin films demonstrated that glycerol concentration influenced mechanical behavior, mucoadhesion, drug release and ex-vivo permeation, emphasizing that plasticizer concentration can function as a critical formulation variable rather than simply a processing aid [24].

Permeation enhancers may be incorporated when passive transport through the buccal epithelium is insufficient. Their role is particularly relevant for drugs with low intrinsic mucosal permeability. However, enhancement should occur without causing irreversible epithelial disruption. The selection and concentration of permeation enhancers should therefore be guided by both permeability improvement and mucosal safety [19, 20].

The backing layer is particularly important in unidirectional patches. An impermeable or relatively low-permeability backing layer can reduce drug loss into saliva and increase the proportion of the dose directed toward the mucosal surface. Ethyl cellulose and other suitable film-forming or impermeable materials have been used for this purpose. The choice of backing material should consider flexibility, adhesion between layers, moisture resistance and compatibility with the drug-containing layer [18, 19].

2.2 Selection of Film-Forming and Mucoadhesive Polymers

Polymers constitute the structural framework of most buccal patches. More than thirty different mucoadhesive polymers have been reported in buccal-film formulations, reflecting the large number of possible material combinations and formulation architectures [18].

2.2.1 Natural Polymers

Natural polymers including chitosan, pectin, sodium alginate, starch derivatives, gelatin, hyaluronic acid and various gums have attracted considerable attention because of their biocompatibility, biodegradability and functional groups capable of interacting with mucin.

Chitosan is particularly interesting because its amino groups can participate in electrostatic interactions with negatively charged mucosal components. It can also influence epithelial permeability and has therefore been investigated both as a mucoadhesive polymer and as a functional permeation-enhancing material [19, 20].

Pectin has also been investigated for buccal-film development. Its abundant hydroxyl and carboxyl groups facilitate hydration and interaction with mucosal surfaces. Recent slot-die-coated pectin films demonstrated that modification of glycerol concentration could simultaneously alter mechanical properties, mucoadhesion and drug permeation, illustrating the potential of natural-polymer platforms for tunable buccal delivery [24].

2.2.2 Synthetic and Semisynthetic Polymers

Synthetic and semisynthetic polymers such as hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyvinyl alcohol, polyvinylpyrrolidone, carbomers and acrylic polymers are widely investigated because of their reproducible physicochemical properties and established pharmaceutical use.

HPMC is particularly useful because different viscosity grades can be selected to modify film strength, hydration and drug release. Carbomer-type materials can provide strong mucoadhesion because of their high density of ionizable functional groups. Combining these polymers may allow the formulator to compensate for the limitations of individual materials.

Recent research has increasingly focused on engineered polymer combinations rather than single-polymer systems. The objective is to generate a multifunctional matrix in which adhesion, hydration, mechanical performance and release can be controlled simultaneously [19, 20, 23].

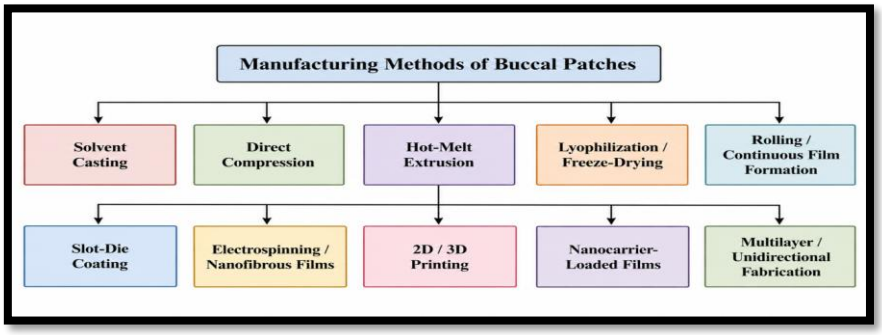


Figure 3: Manufacturing methods for Buccal Patches.

2.3 Solvent Casting Method

Solvent casting remains the most extensively investigated method for preparing buccal films because of its relative simplicity, versatility and compatibility with a wide range of polymers and active ingredients [18–20].

In this approach, the selected polymer or polymer mixture is dissolved or dispersed in an appropriate solvent system. Water, ethanol, hydroalcoholic mixtures and other pharmaceutically acceptable solvents may be selected according to polymer solubility and drug stability. The drug is subsequently incorporated into the polymeric solution or dispersion, followed by addition of plasticizers and other functional excipients.

The resulting film-forming liquid, commonly referred to as a **film-forming solution or film dope**, must possess suitable viscosity and homogeneity. Entrapped air should be minimized because air bubbles can produce thickness variation, weak regions and non-uniform drug distribution. The prepared solution is then cast over a suitable flat substrate, followed by controlled drying to remove the solvent. After drying, the resulting film is peeled from the substrate and cut into predetermined dimensions [18, 19].

The basic sequence can therefore be represented as:

Polymer selection → Polymer dissolution/dispersion → Drug incorporation → Excipient addition → Homogenization → De-aeration → Casting → Controlled drying → Film removal → Cutting → Packaging

The major advantage of solvent casting is its flexibility. It can accommodate polymers with relatively low processing temperatures and is therefore suitable for thermolabile drugs. It is also useful when multiple polymers or functional excipients need to be incorporated into a homogeneous film.

However, solvent casting has limitations. The final film can be affected by solvent evaporation rate, drying temperature, humidity, casting volume, solution viscosity and substrate characteristics. Rapid solvent removal can cause surface defects or internal stresses, whereas slow drying may prolong processing time and influence polymer morphology. Residual solvent can also become a quality and safety concern when organic solvents are used [18, 19].

Another important limitation is scale-up. A formulation that produces uniform films in a laboratory Petri dish may not automatically translate to large-scale manufacturing. Film thickness, drying conditions and drug distribution must remain controlled across the entire production width. Continuous coating technologies have therefore been investigated as a means of improving reproducibility and manufacturing efficiency [18,29,30].

2.4 Direct Compression Method

Direct compression is more appropriately associated with **mucoadhesive buccal tablets and compressed buccal systems** rather than flexible polymeric patches. Nevertheless, because buccal dosage-form literature frequently discusses tablets and patches together, it is relevant to include this technique when describing the broader manufacturing landscape.

In direct compression, the API, mucoadhesive polymer and other excipients are blended and compressed directly using suitable punches and dies. No wet granulation or solvent evaporation step is required. The technique is therefore comparatively simple and economical.

Mucoadhesive polymers such as HPMC, Carbopol and sodium carboxymethylcellulose can serve as matrix-forming materials. Depending on the design, an impermeable backing layer may be incorporated to produce directional release.

For example, mucoadhesive buccal tablets containing aceclofenac have been prepared using direct compression with Carbopol, HPMC and sodium carboxymethylcellulose, followed by assessment of hardness, thickness, friability, drug content, swelling, surface pH, mucoadhesion and drug release [31].

The principal advantage of direct compression is process simplicity and the absence of solvent evaporation. It is particularly useful for drugs and excipients that exhibit adequate powder flow and compressibility. However, conventional compression does not produce the thin, flexible geometry characteristic of a polymeric buccal film. Excessive hardness may also affect hydration and drug release, while inadequate mechanical strength may cause premature erosion.

Therefore, in the context of this review, direct compression should be regarded as a **manufacturing route for compressed mucoadhesive buccal dosage forms**, whereas solvent casting, hot-melt extrusion, printing and related technologies are more directly relevant to thin buccal patches and films.

2.5 Hot-Melt Extrusion

Hot-melt extrusion (HME) has emerged as an important solvent-free manufacturing approach for polymeric buccal films. In this process, drug and thermoplastic polymeric components are mixed and conveyed through an extruder under controlled temperature and shear. The material undergoes melting or softening and is subsequently forced through a die to form a continuous film or sheet [19, 20].

The major advantage of HME is that it can eliminate the need for volatile organic solvents. It is also inherently compatible with continuous manufacturing, making it attractive for scale-up. The applied thermal and mechanical energy can facilitate intimate mixing of drug and polymer and may modify drug distribution within the polymeric matrix [19].

However, HME requires careful assessment of thermal stability. The API, polymer and other excipients must tolerate the processing temperature and residence time without significant degradation. Drug–polymer interactions and changes in the solid state must also be considered.

A recent 2024 study demonstrated the application of HME and a Quality-by-Design approach to extended-release buccal films containing adipic acid. Eudragit® RS PO, Carbopol® 971P and PEG 1500 were systematically varied, while extrusion temperature and speed were considered critical process variables. The optimized system exhibited extended release over 8 h, demonstrating how HME can be combined with systematic formulation optimization rather than used simply as a processing technique [23].

The HME process can be broadly represented as:

Feeding → Powder blending → Melting/softening → Mixing and shear → Extrusion through die → Film formation → Cooling → cutting.

The process offers an important opportunity for continuous manufacturing, but the relationship between barrel temperature, screw speed, residence time, melt viscosity and film thickness must be understood to obtain reproducible product quality.

2.6 Lyophilization or Freeze-Drying

Lyophilization provides a different approach to buccal dosage-form manufacturing. Instead of producing a dense polymeric film through solvent evaporation, the process creates a porous matrix by freezing an aqueous formulation followed by sublimation of ice under reduced pressure.

A typical process involves preparation of a drug-polymer solution or suspension, filling into suitable molds, freezing and subsequent primary and secondary drying. Removal of ice produces a highly porous structure. The resulting dosage form may exhibit rapid wetting and disintegration because saliva can penetrate the porous matrix quickly.

Lyophilized buccal matrices can be particularly useful when rapid drug liberation is required. However, the process can also be adapted to produce mucoadhesive matrices capable of remaining in contact with mucosa for an extended period.

A study of freeze-dried buccal matrices containing propranolol investigated polymers including gum tragacanth, pectin, HPMC, hyaluronic acid, gelatin and chitosan. The resulting systems were evaluated for solid-state characteristics, morphology, water uptake, mucoadhesion, drug release and permeation through porcine epithelium [32].

Lyophilization is also important in the development of buccal/oral wafers. The porous architecture generated during freeze-drying can provide rapid disintegration without requiring conventional compression forces. However, the process is relatively energy intensive and requires careful control of freezing conditions, formulation solids content, drying temperature and residual moisture [33].

A major limitation is the potential fragility of highly porous matrices. Consequently, the formulation may require protective packaging and appropriate polymer reinforcement. Moisture uptake during storage must also be controlled because water can collapse or soften the porous structure.

2.7 Rolling and Continuous Film Formation

The rolling method is a manufacturing approach in which a polymeric solution or suspension is continuously transferred onto a moving carrier or roller system. The wet film is subsequently dried and converted into a continuous sheet that can be cut into individual dosage units.

This approach is particularly relevant to scale-up because it transforms the batchwise casting process into a more continuous operation. The conventional laboratory casting process can produce excellent films but is relatively difficult to scale while maintaining consistent thickness across large areas. Continuous coating and rolling technologies address this limitation by controlling the flow of film-forming material and the movement of the substrate [18, 29].

The basic sequence involves:

Preparation of film-forming mass → Metered application onto moving carrier → Controlled spreading → Drying → Continuous film formation → Slitting/cutting → Packaging

The viscosity and rheological behavior of the film-forming solution are particularly important. If viscosity is too low, spreading may be uneven and edge effects may occur. Excessively viscous formulations may be difficult to pump and spread uniformly.

The drying zone must also be controlled carefully. Temperature, air velocity and residence time influence solvent removal and final film characteristics. Continuous film manufacturing literature emphasizes the importance of controlling coating thickness, drying conditions and process parameters to maintain uniformity during scale-up [29,30].

The rolling approach described in the original draft is therefore best understood as part of a broader family of **continuous film-forming processes**, rather than simply a laboratory rolling operation.

2.8 Slot-Die Coating: An Emerging Continuous Manufacturing Approach

Slot-die coating is a relatively recent development with considerable potential for scalable buccal-film manufacturing. In this technique, a controlled volume of polymeric formulation is delivered through a narrow slot onto a moving substrate. The process can generate highly uniform continuous films while allowing control over wet-film thickness.

The technology is particularly interesting because it can bridge the gap between laboratory-scale film casting and industrial continuous production. A recent study investigated slot-die-coated pectin films containing different concentrations of glycerol and demonstrated that the process could produce buccal films with controlled physicochemical and functional characteristics [24].

The major advantages include:

- Continuous film production;
- Improved control over film thickness;
- Reduced dependence on manual casting;
- Potential for process automation;
- Compatibility with scalable production; and
- Possibility of integrating online process monitoring.

Slot-die coating may therefore be particularly useful when formulation development has progressed beyond laboratory proof-of-concept and manufacturing reproducibility becomes a priority.

2.9 Electrospinning and Nanofibrous Buccal Films

Electrospinning is an advanced technique capable of generating nanoscale or microscale polymeric fibers from a polymer solution or melt. Under a high electric field, the polymer solution is stretched into fine fibers and collected as a fibrous membrane.

Electrospun structures possess a high surface-area-to-volume ratio and interconnected porosity. These characteristics can influence hydration, drug release and interaction with biological surfaces. The technology is particularly attractive for incorporation of poorly soluble drugs, nanocarriers or combinations of active substances.

Recent research has demonstrated the potential of electrospun fibrous buccal films for sustained delivery. A 2024 study reported Janus electrospun fibrous buccal films loaded with LAAM for opioid-use-disorder treatment, illustrating the possibility of engineering the architecture of a fibrous film to achieve controlled drug delivery [28].

Electrospinning also offers the possibility of producing multilayer or core–shell structures. Such structures can separate incompatible ingredients or provide differential release characteristics.

However, the process involves several variables, including polymer concentration, solvent properties, applied voltage, flow rate, collector distance and environmental humidity. Reproducibility and scale-up remain important challenges. Furthermore, residual solvent and the safety of the selected polymers must be carefully evaluated.

2.10 Two-Dimensional and Three-Dimensional Printing

Printing technologies represent one of the most promising directions for personalized buccal drug delivery. Unlike conventional casting, where the entire film generally possesses a relatively uniform drug distribution, printing can provide spatial control over drug deposition.

Two-dimensional printing approaches can be used to deposit predetermined quantities of drug-containing formulation onto a substrate. Inkjet printing, for example, can potentially provide accurate dosing and enable the preparation of films containing multiple active ingredients or spatially separated drug regions [19, 20].

Three-dimensional printing provides an even greater degree of structural control. Film geometry, thickness, internal architecture and drug-loading patterns can potentially be modified according to the intended therapeutic requirements.

A 2023/2024 study combined nanostructured lipid carriers with pressure-assisted 3D printing to prepare cannabidiol-loaded buccal films. The optimized nanocarrier-loaded film demonstrated sustained in-vitro release and illustrated the possibility of combining nanotechnology with personalized additive manufacturing [25].

Another study used fused deposition modelling to manufacture personalized dexamethasone acetate buccal patches. Ethyl cellulose was incorporated as a barrier material to achieve unidirectional drug release [26].

These studies demonstrate an important conceptual transition: 3D printing can be used not merely to manufacture a film but to **engineer its geometry and drug-release direction**.

Nevertheless, 3D printing presents challenges related to printer resolution, feed-material rheology, thermal stability, dose reproducibility and manufacturing speed. The technology is therefore highly promising for personalized or small-batch production, but further development is required before widespread industrial implementation.

2.11 Nanocarrier-Loaded Buccal Films

Nanotechnology can be integrated into buccal films to address the limitations of conventional polymeric systems. Nanoparticles, nanostructured lipid carriers, polymeric nanoparticles and other nanosystems may improve apparent solubility, protect labile drugs, modify drug release and potentially enhance mucosal transport [19, 20].

A major advantage of this approach is the possibility of separating the functions of the **nanocarrier** and the **film matrix**. The nanocarrier can be designed to improve drug solubilization or permeability, while the polymeric film provides residence, mechanical integrity and site-specific delivery.

The CBD-NLC 3D-printed buccal film described above is an example of this integrated strategy [25]. The study combined a nanostructured lipid carrier with a hydroxyethyl cellulose-based printable matrix, thereby integrating nanoscale drug formulation with macroscopic dosage-form engineering [25].

Similarly, electrospun and nanofiber-based systems can be used to incorporate advanced drug carriers while maintaining a flexible dosage form [28].

Despite these advantages, nanocarrier-loaded films require additional characterization. Particle size, polydispersity, surface charge, drug-loading efficiency and carrier stability must be evaluated in addition to conventional film properties. Therefore, such systems are more complex than traditional polymeric patches and require a broader quality-control strategy.

2.12 Multilayer and Unidirectional Film Fabrication

A major objective in systemic buccal delivery is to minimize drug loss into saliva and maximize the fraction available for transmucosal absorption. Multilayer manufacturing can address this requirement by combining a drug-containing adhesive layer with a backing or rate-controlling layer.

The basic architecture may consist of:

Backing layer → Drug-containing matrix → Mucoadhesive interface → Buccal mucosa

The backing layer limits drug movement toward the oral cavity, while the adhesive layer maintains contact with the mucosa. Additional intermediate layers can be incorporated to regulate drug diffusion.

Modern additive manufacturing technologies have increased the design possibilities for these systems. For example, FDM-based 3D printing has been used to produce personalized buccal patches in which ethyl cellulose was applied to the upper and side surfaces to achieve unidirectional drug release [26].

Multilayer systems therefore represent an important link between **formulation composition and drug-release direction**. Their principal limitation is increased manufacturing complexity and the requirement for reliable interlayer adhesion.

2.13 Quality by Design Approach in Buccal Patch Development

Quality by Design (QbD) represents an important advancement in modern pharmaceutical formulation development. Instead of optimizing a formulation through repeated trial-and-error experiments, QbD begins by defining the desired **Quality Target Product Profile (QTPP)** and then identifying the **Critical Quality Attributes (CQAs)** that must be controlled to achieve the desired performance.

For a buccal patch, potential CQAs may include:

- Film thickness;
- Weight uniformity;
- Drug content;
- Mechanical strength;
- Elongation;
- Folding endurance;
- Moisture content;
- Surface ph;
- Swelling;
- Mucoadhesive strength;
- Residence time;
- Drug-release rate;

- Permeation rate; and
- Stability.

The formulation variables that influence these attributes can be considered **Critical Material Attributes (CMAs)**. Examples include polymer type and concentration, polymer ratio, plasticizer concentration, permeation enhancer concentration and drug loading.

Similarly, process variables such as mixing time, casting speed, drying temperature, extrusion temperature, screw speed, printing parameters or coating rate can function as **Critical Process Parameters (CPPs)**.

The interaction between these variables can be investigated using Design of Experiments (DoE). This allows the formulator to determine not only the effect of individual variables but also interactions between them.

A particularly relevant recent example is the 2024 HME study by Elkanayati et al., in which a patient-centered QTPP was developed and CQAs, CMAs and CPPs were identified for extended-release buccal films. A D-optimal mixture design was then employed to optimize the proportions of Eudragit®, Carbopol® and PEG 1500 [23].

The significance of QbD in buccal systems extends beyond formulation optimization. It can improve understanding of how material properties and manufacturing conditions affect film performance, thereby facilitating scale-up, reproducibility and eventual regulatory development.

2.14 Critical Manufacturing Variables Affecting Buccal Patch Quality

Regardless of the manufacturing technique selected, several variables can significantly influence the final quality of buccal patches.

2.14.1 Polymer Concentration

Increasing polymer concentration can improve film strength and viscosity but may also increase thickness and retard drug release. Excessively high polymer concentration can make casting or extrusion difficult.

2.14.2 Plasticizer Concentration

Plasticizer concentration affects flexibility, elongation, moisture uptake and drug diffusion. Insufficient plasticizer may produce brittle films, whereas excessive amounts may reduce mechanical strength and alter release.

2.14.3 Drying Conditions

Drying temperature and duration determine residual moisture, polymer morphology and film integrity. Excessively rapid drying may generate cracks or internal stress, whereas inadequate drying may result in residual solvent or excessive moisture.

2.14.4 Film Thickness

Thickness influences drug loading per unit area, mechanical properties and diffusion distance. Uniform thickness is therefore particularly important for dose accuracy.

2.14.5 Solution Rheology

For casting, coating and printing processes, viscosity and viscoelasticity affect spreading, film thickness and content uniformity. This becomes increasingly important in continuous and automated manufacturing.

2.14.6 Processing Temperature

Temperature is particularly critical for hot-melt extrusion. It must be sufficiently high to process the polymer but low enough to avoid degradation of the API or excipients.

2.14.7 Residence Time

Residence time affects solvent evaporation, thermal exposure and polymer transformation. In continuous processes, residence time must remain sufficiently controlled to maintain batch-to-batch consistency.

2.15 Scale-Up and Manufacturing Considerations

One of the major limitations in buccal-film research is the transition from laboratory-scale preparation to reproducible commercial manufacturing. A large proportion of published studies rely on small-area solvent casting, which is useful for early formulation screening but does not necessarily reproduce the challenges associated with continuous manufacturing.

At larger scale, parameters such as solution viscosity, pumping behavior, coating speed, dry kinetics, substrate characteristics and environmental humidity become increasingly important. Variations in these factors can produce changes in thickness, drug content and mechanical performance.

Continuous manufacturing technologies such as slot-die coating, continuous casting and related coating systems offer potential solutions. Recent research in pharmaceutical continuous film processing emphasizes the importance of process monitoring and control for achieving consistent film quality [30].

The development of continuous buccal-film manufacturing may also facilitate integration with process analytical technology (PAT). Online measurements of wet-film thickness, temperature, moisture and other variables could permit real-time process control rather than relying exclusively on end-product testing.

This represents a significant change from conventional laboratory-scale formulation development:

- **Traditional approach:**

Formulation → Batch preparation → Drying → Evaluation.

- **Modern manufacturing approach:**

QTPP → CQAs → CMAs/CPPs → DoE → Controlled continuous processing → PAT → Real-time quality assurance.

Such integration is likely to become increasingly important as buccal formulations progress toward commercial translation.

2.16 Packaging and Storage Considerations

Although manufacturing determines the initial quality of a buccal patch, packaging plays a major role in maintaining that quality during storage. Buccal films are often sensitive to moisture because many film-forming polymers are hydrophilic and may absorb water from the environment.

Excessive moisture uptake can alter flexibility, adhesion, drug diffusion and physical appearance. Conversely, excessive drying may increase brittleness and reduce handling characteristics. Therefore, packaging must maintain an appropriate moisture environment.

Individual unit-dose packaging is particularly desirable because it minimizes repeated exposure to atmospheric humidity. Depending on the formulation, moisture-barrier laminates, aluminum-based packaging or other protective materials may be appropriate.

Stability evaluation should examine physical appearance, drug content, mechanical properties, mucoadhesion, moisture content and drug release over the intended storage period. The stability of nanocarrier-containing or thermolabile systems may require additional parameters such as particle size and solid-state characterization.

2.17 Integrated Manufacturing Strategy for Buccal Patches

The choice of manufacturing technology should ultimately be based on the desired product profile rather than the novelty of the technology itself. Solvent casting remains highly useful for early formulation development because of its simplicity and broad polymer compatibility. Hot-melt extrusion is attractive for solvent-free and continuous processing, particularly when the drug and polymers are thermally stable. Lyophilization is valuable when highly porous, rapidly hydrating matrices are required. Rolling and

slot-die coating offer pathways toward continuous manufacturing, whereas 2D/3D printing provides opportunities for personalized dosing and complex architectures [18–20, 23–26].

2.18 Emerging Direction of Buccal Patch Manufacturing

The field is progressively moving from simple polymeric films toward **multifunctional, personalized and process-controlled buccal delivery platforms**. Recent developments demonstrate integration of nanocarriers with 3D printing, electrospun fibrous architectures, continuous coating, QbD-guided HME and engineered multilayer structures [19, 23–26, 28].

The next generation of buccal patches is therefore expected to emphasize four interconnected characteristics:

- **Functional formulation design** – polymers and excipients selected for defined roles in adhesion, release and permeation.
- **Advanced manufacturing** – continuous coating, extrusion, printing and electrospinning for improved control.
- **Personalization** – adjustment of dose, dimensions, drug combinations and release behavior according to individual requirements.
- **Translational quality** – incorporation of physiologically relevant permeation models and pharmacokinetic assessment during development.

Importantly, technological complexity should not be pursued for its own sake. A technologically advanced buccal patch is valuable only when the additional complexity produces a clinically meaningful improvement in dose accuracy, patient acceptability, drug exposure, release control or therapeutic outcome.

3. EVALUATION AND CHARACTERIZATION OF BUCCAL PATCHES

Evaluation of buccal patches is a critical step in establishing the quality, performance and suitability of a formulation for mucosal drug delivery. Unlike conventional oral solid dosage forms, a buccal patch must simultaneously satisfy several requirements: adequate dose uniformity, mechanical integrity, and controlled hydration, intimate contact with the mucosal surface, sufficient residence time, predictable drug release and, when systemic delivery is intended, effective permeation across the buccal epithelium. Consequently, characterization should not be restricted to conventional physical tests but should progressively connect the properties of the patch with its intended biological performance.

There is still no single universally standardized evaluation protocol applicable to all buccal films and patches. Differences in film composition, thickness, drug loading, intended release profile, direction of drug release and experimental model can influence the results. Therefore, a meaningful evaluation strategy should combine **physical, mechanical, physicochemical, mucoadhesive, drug-release, permeation, and safety and stability assessments**.

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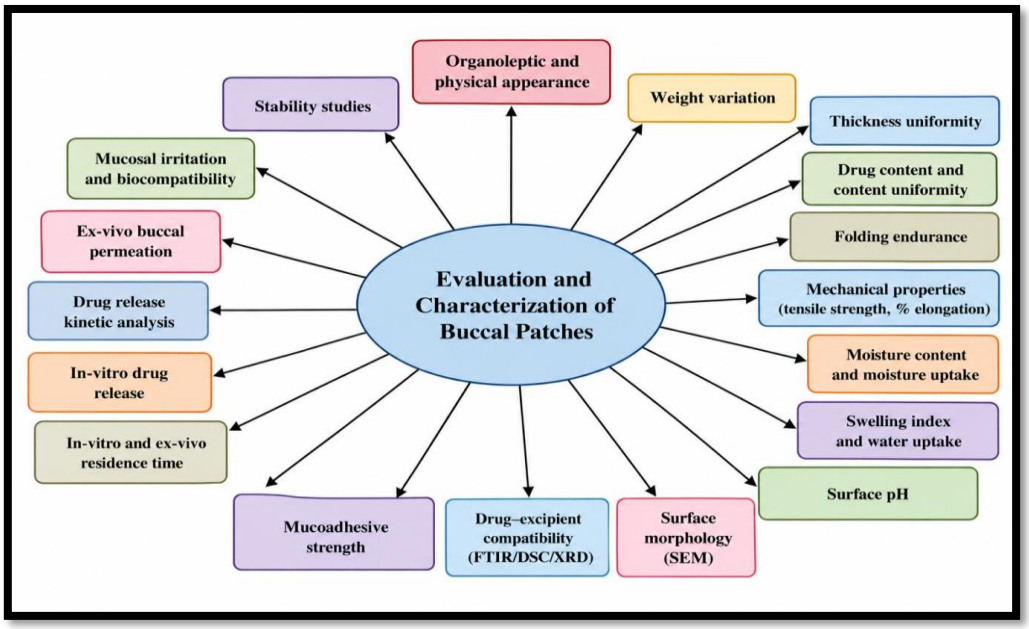


Figure 4: Evaluation Parameters for Buccal Patches.

3.1 Organoleptic and Physical Appearance

The preliminary assessment of a buccal patch includes visual examination of its colour, surface appearance, transparency or opacity, flexibility and overall physical uniformity. The patch should preferably possess a smooth and homogeneous surface without visible cracks, air bubbles, pinholes, crystals, phase separation or other manufacturing defects.

Appearance is particularly important because surface imperfections can influence hydration, drug release, mechanical strength and mucosal contact. A patch intended for buccal administration should also be sufficiently thin and flexible to minimize discomfort during application and movement of the cheek. In addition, the presence of visible drug crystals may indicate inadequate drug dispersion or precipitation during drying and may subsequently produce dose non-uniformity or altered dissolution behaviour [34].

3.2 Weight Variation

Weight variation provides an initial indication of the consistency of the manufacturing process and, indirectly, the uniformity of formulation components within individual patches. Randomly selected patches of identical dimensions are weighed individually using a sensitive analytical balance, and the mean weight and percentage deviation are calculated.

For a homogeneous film produced by solvent casting or another continuous process, relatively low variation in individual patch weight is expected. Excessive variation may indicate non-uniform spreading of the casting solution, variation in film thickness, inadequate mixing or inconsistent cutting of the final film.

Although weight uniformity does not directly establish drug-dose uniformity, it remains a useful preliminary quality-control parameter and should be interpreted together with thickness and drug-content measurements [34].

3.3 Thickness Uniformity

Film thickness is an important quality attribute because it can influence mechanical strength, flexibility, hydration, and drug diffusion distance and release behaviour. Thickness is generally measured at several predetermined locations on each patch using a digital micrometer, screw gauge or calibrated thickness gauge, followed by calculation of the mean and variation.

Uniform thickness indicates effective control of the casting, drying or film-forming process. Considerable variation may suggest uneven distribution of the polymeric solution or non-uniform drying. For multilayer patches, thickness measurements may additionally be performed separately for individual layers when technically feasible.

Importantly, thickness should not be considered merely as a physical dimension. Changes in thickness can alter the path length for drug diffusion and may therefore contribute to differences in dissolution and permeation performance [35].

3.4 Drug Content and Content Uniformity

Drug-content analysis determines whether the intended amount of active pharmaceutical ingredient is incorporated into individual patches. A known area or complete patch is dissolved or extracted using an appropriate solvent or buffer, followed by quantitative analysis using a validated analytical technique such as UV-visible spectrophotometry or HPLC.

The percentage drug content may be calculated as:

$$\textbf{Drug Content}\ (\%) = \frac{\text{Measured amount of drug}}{\text{Theoretical amount of drug}} \times 100$$

Multiple individual patches should be analysed rather than relying solely on a pooled sample. This is particularly important for low-dose formulations, where small differences in drug distribution can have a relatively large effect on the delivered dose.

Content uniformity is closely associated with formulation homogeneity and manufacturing reproducibility. In solvent-cast systems, inadequate mixing, sedimentation, crystallization or uneven drying may result in dose variability. Therefore, drug-content testing should preferably be correlated with microscopic/morphological examination and process variables [35].

3.5 Folding Endurance

Folding endurance evaluates the flexibility and resistance of a buccal patch to repeated mechanical deformation. A patch is repeatedly folded at the same location until visible cracking or breakage occurs, and the number of folds tolerated is recorded.

A higher folding-endurance value generally indicates greater flexibility; however, an excessively flexible film is not necessarily optimal because excessive plasticization may compromise mechanical strength or alter drug-release behaviour. Conversely, a brittle patch may fracture during cutting, packaging, handling or placement in the oral cavity.

Thus, folding endurance should preferably be interpreted together with tensile strength and percentage elongation rather than being used as an isolated indicator of mechanical quality [36].

3.6 Mechanical Properties

Mechanical characterization is particularly important for patches because the dosage form must withstand handling, packaging, application and continuous movement within the oral cavity without premature rupture.

3.6.1 Tensile Strength

Tensile strength represents the maximum stress that a film can withstand before breaking. It is commonly determined using a texture analyser or universal testing machine.

$$\textbf{Tensile Strength} = \frac{\text{Force at Break}}{\text{Initial Cross} - \text{sectional Area}}$$

Adequate tensile strength provides structural integrity during manufacturing and administration. However, very high strength accompanied by low elasticity may produce a rigid film that is uncomfortable for buccal application [37].

3.6.2 Percentage Elongation

Percentage elongation indicates the ability of the patch to deform before rupture. It can be calculated as:

$$\textbf{Elongation}\ (\%) = \frac{\text{Increase in length at break}}{\text{Original length}} \times 100$$

A suitable buccal patch generally requires a balance between strength and flexibility. Polymer type, molecular weight, plasticizer concentration, moisture content and drug loading can all influence this balance. Mechanical testing based on tensile measurements has therefore become an important component of contemporary buccal-film characterization [37].

3.7 Moisture Content and Moisture Uptake

Moisture-related properties are particularly relevant for hydrophilic polymeric patches because water can alter polymer mobility, flexibility, swelling, and adhesion and drug diffusion.

Moisture content describes the amount of residual water present in the dried formulation, whereas **moisture uptake** evaluates the tendency of the patch to absorb environmental moisture under controlled humidity conditions.

Excessive moisture may promote microbial growth, polymer relaxation, stickiness and instability, whereas extremely low moisture content can make certain polymeric films brittle. Consequently, an appropriate moisture balance is necessary for maintaining mechanical and functional properties during storage.

Moisture behaviour should also be considered during packaging selection because buccal films may be sensitive to atmospheric humidity [37].

3.8 Swelling Index and Water Uptake

Swelling behaviour is a particularly important parameter for mucoadhesive buccal patches. After contact with simulated saliva or an appropriate aqueous medium, hydrophilic polymers absorb water and undergo hydration. The extent of swelling can be determined by measuring the weight increase of the patch over a defined period.

$$\textbf{Swelling Index}\ (\%) = \frac{\mathrm{Wt} - \mathrm{Wo}}{\mathrm{Wo}} \times 100$$

Where,

- Wo is the initial weight and;
- Wt is the weight after hydration for a specified period.

Moderate hydration can facilitate polymer-chain mobility and promote interaction with mucus. It can also influence drug diffusion from the hydrated matrix. However, excessive swelling may weaken the film, accelerate erosion or cause premature detachment from the mucosa. Therefore, the optimal swelling behaviour depends on whether the formulation is designed for rapid, sustained or prolonged drug delivery [38].

3.9 Surface pH

Surface-pH determination is performed to assess the likelihood of local irritation after application. A patch with a strongly acidic or alkaline surface may cause discomfort or mucosal irritation and can potentially affect polymer behaviour and drug release.

The patch is generally allowed to hydrate or swell under controlled conditions, after which its surface pH is measured using a suitable pH electrode or indicator method. Ideally, the formulation should remain close to the physiological environment of the oral mucosa.

Surface pH should therefore be considered a **mucosal compatibility parameter**, rather than simply another physical test [38].

3.10 Surface Morphology

Surface morphology provides information about the physical structure and quality of the patch. **Scanning electron microscopy (SEM)** is commonly employed to examine surface roughness, cracks, pores, voids, polymer distribution and visible drug crystals.

A relatively homogeneous surface may indicate effective mixing and film formation, whereas cracks or large pores can influence mechanical integrity, water penetration and drug release. Cross-sectional SEM can also provide information about film thickness and internal structure, which becomes particularly useful for multilayer or reservoir-type systems.

Morphological characterization is therefore complementary to conventional measurements such as thickness, drug content and mechanical strength [39].

3.11 Drug–Excipient Compatibility and Solid-State Characterization

The incorporation of a drug into a polymeric matrix can modify its physical state, molecular interactions and stability. Therefore, compatibility and solid-state studies are important, particularly when new polymer combinations or processing conditions are introduced.

Fourier-transform infrared spectroscopy (FTIR) can be used to investigate characteristic functional groups and identify major chemical interactions between the drug and formulation components. **Differential scanning calorimetry (DSC)** provides information about melting behaviour, glass transitions and possible changes in the physical state of the drug. **X-ray diffraction (XRD)** is useful for determining whether the drug remains crystalline or undergoes partial or complete amorphization during formulation.

These studies should not be interpreted solely on the basis of disappearance or shifting of a single peak. Instead, the results should be considered alongside drug assay, dissolution, morphology and stability data. Changes in drug crystallinity may substantially influence apparent solubility and release behaviour. Freeze-dried buccal systems, for example, have demonstrated that polymer composition and processing can influence drug solid state as well as release and permeation characteristics [39].

3.12 Mucoadhesive Strength

Mucoadhesion is one of the defining characteristics of a buccal patch. The formulation must establish sufficient interaction with the mucus layer to resist displacement caused by saliva, tongue movement, swallowing and normal oral activity.

Mucoadhesive strength can be evaluated using texture analysers, modified balance methods, detachment-force measurements or other experimentally validated approaches. The measured force represents the resistance to separation between the patch and mucosal substrate.

An appropriate mucoadhesive strength should provide adequate retention without causing excessive adhesion that could make removal difficult or damage the mucosal surface. Polymer molecular weight, concentration, degree of hydration, functional groups, plasticizer level and mucosal condition can all influence the measured adhesion.

Importantly, **mucoadhesive strength and residence time are related but not interchangeable parameters**. A formulation may exhibit high detachment force but relatively short practical residence under dynamic oral conditions. Both parameters should therefore be assessed where prolonged retention is claimed [39].

3.13 In-Vitro and Ex-Vivo Residence Time

Residence-time studies determine how long a patch remains attached to a mucosal surface under experimental conditions. The patch is generally attached to freshly isolated animal buccal tissue or an appropriate mucosal model and exposed to a controlled aqueous flow or agitation environment.

Residence time is especially important for sustained-release and unidirectional systems because premature detachment can prevent the formulation from delivering the intended dose.

However, experimental residence time should not automatically be interpreted as equivalent to clinical residence. The human oral cavity involves continuously changing saliva flow, tongue movement, chewing, food intake and mucosal turnover. Consequently, physiologically relevant residence models are desirable for improving the predictive value of laboratory testing [40].

3.14 In-Vitro Drug Release

In-vitro dissolution or drug-release testing determines the rate and extent at which the active ingredient is liberated from the patch. Depending on formulation design, suitable dissolution or release apparatus and media can be selected to reproduce the intended environment.

For a **unidirectional patch**, the backing layer may be oriented away from the release medium so that drug release primarily occurs from the adhesive side. Sampling is performed at predetermined intervals and the released drug is quantified using an appropriate analytical method.

Release data should be plotted as cumulative drug released versus time. The resulting profile can help differentiate immediate, sustained, delayed or controlled-release behaviour. Experimental conditions such as medium composition, pH, temperature, agitation and exposed surface area should be reported clearly because variations in these parameters can substantially affect results and limit comparison between studies [40].

3.15 Drug-Release Kinetic Analysis

Mathematical modelling can provide additional insight into the mechanism governing drug release. Depending on the formulation, experimental data may be fitted to models such as **zero-order, first-order, and Higuchi and Korsmeyer–Peppas models**.

The purpose of kinetic modelling should not simply be to identify the model producing the highest correlation coefficient. The selected model should be interpreted in relation to the physical structure of the patch, polymer hydration, swelling, erosion and drug diffusion.

For example, matrix systems may exhibit diffusion-controlled behaviour, whereas polymer relaxation, swelling or erosion may contribute to more complex release profiles. Therefore, release kinetics provides mechanistic information that complements, rather than replaces, experimental dissolution data [40].

3.16 Ex-Vivo Buccal Permeation

For formulations intended to provide systemic drug delivery, ex-vivo permeation studies represent a critical bridge between dissolution testing and biological performance. Excised buccal mucosa from suitable animal sources can be mounted in a **Franz diffusion cell** or an equivalent diffusion system, with the formulation positioned on the mucosal side.

During the experiment, samples are withdrawn from the receptor compartment at predetermined intervals and analysed for drug concentration. Important parameters may include cumulative amount permeated per unit area, steady-state flux and apparent permeability coefficient.

$$\mathbf{J} = \frac{\mathrm{dQ}}{\mathrm{A\ dt}}$$

Where **J** is steady-state flux, **dQ/dt** is the rate of drug transfer and **A** is the exposed mucosal area.

Ex-vivo models provide useful information regarding the interaction between the formulation and biological tissue. Nevertheless, tissue viability, source of mucosa, thickness, storage conditions and experimental temperature can influence the results. Standardized oral mucosa models are therefore still an important research need [40].

3.17 Mucosal Irritation, Biocompatibility and Safety

A formulation that provides high drug permeation but damages the mucosal barrier cannot be considered an acceptable buccal delivery system. Therefore, mucosal safety should be incorporated into evaluation whenever a permeation enhancer, novel polymer, nanocarrier or other potentially irritating component is used.

Assessment may include histopathological examination of exposed mucosa, cell-viability studies using relevant buccal epithelial cell models and, where appropriate, inflammatory or cytotoxicity measurements.

Cell-based oral mucosa models can provide useful information about cytocompatibility and permeability while reducing dependence on animal experiments. Recent research has highlighted the importance of more physiologically relevant oral mucosa models because conventional cell culture and excised tissue models each have limitations [40].

3.18 Stability Studies

Stability testing determines whether the patch maintains its critical quality attributes throughout the proposed storage period. Parameters that may be monitored include appearance, thickness, drug content, moisture, mechanical strength, mucoadhesive behaviour, drug release and chemical stability.

Accelerated and long-term stability studies should be performed according to appropriate stability protocols, with storage conditions selected according to the intended product and packaging system. Packaging is particularly important because moisture and oxygen exposure can modify polymer properties and drug stability.

A stability study should therefore evaluate not only chemical assay but also **functional stability**. A patch may retain acceptable drug content while experiencing significant changes in flexibility, mucoadhesion or release behaviour. Such changes can compromise therapeutic performance even when chemical degradation is minimal. Studies on buccal films have demonstrated the usefulness of monitoring physical properties, mucoadhesion, API content, permeability and cytotoxicity during stability assessment [41].

3.19 Integrated Evaluation Strategy for Buccal Patches

The evaluation of buccal patches should ultimately be viewed as an interconnected quality-assessment process rather than a collection of independent tests. **Physical properties** establish uniformity and handling characteristics; **mechanical testing** establishes robustness; **swelling and surface-pH studies** provide information regarding hydration and mucosal compatibility; **mucoadhesion and residence-time studies** indicate retention; while **drug-release and permeation studies** determine the functional performance of the dosage form.

For advanced formulations, particularly nanocarrier-loaded, multilayer, unidirectional or 3D-printed patches, conventional tests alone may be insufficient. Morphological analysis, solid-state characterization, permeability studies, biological safety assessment and stability testing become increasingly important. Recent reviews consequently emphasize physiologically relevant evaluation approaches and improved correlation between laboratory performance and actual buccal conditions.

A rational evaluation sequence can therefore be represented as:

Physical quality → Mechanical integrity → Hydration behaviour → Surface compatibility → Mucoadhesion → Residence time → Drug release → Buccal permeation → Mucosal safety → Stability

This integrated approach is particularly relevant to the future development of patient-centric buccal patches, where formulation performance must be demonstrated not merely by acceptable laboratory values but by the ability of the dosage form to remain functional under the dynamic conditions of the oral cavity [41].

4. CONCLUSION

Buccal patch drug delivery has emerged as a promising mucosal drug-delivery strategy capable of addressing several limitations associated with conventional oral administration. The buccal mucosa provides a relatively accessible and vascularized site for drug absorption and offers the potential to reduce gastrointestinal degradation and hepatic first-pass metabolism. The ability to maintain a formulation at the site of administration through mucoadhesion further provides opportunities for prolonged drug residence, controlled drug release and improved therapeutic performance. These characteristics make buccal patches particularly attractive for drugs requiring improved bioavailability, controlled systemic exposure or localized action within the oral cavity.

The performance of a buccal patch is strongly dependent on rational formulation design. Selection of an appropriate film-forming and mucoadhesive polymer, plasticizer, permeation enhancer, backing material and other functional excipients must be carefully balanced to achieve flexibility, mechanical integrity, adequate hydration, mucosal adhesion and desirable drug-release characteristics. The development of single-layer, bilayer, multilayer, matrix, reservoir and unidirectional systems has further expanded the ability to tailor drug-release behaviour according to therapeutic requirements. Recent advances have also demonstrated the potential of nanocarrier-loaded films and advanced architectures for addressing the solubility and permeability limitations of challenging drug molecules and biologics.

Manufacturing technology represents another major determinant of buccal patch quality. Conventional solvent casting remains an extensively investigated approach because of its simplicity and adaptability; however, hot-melt extrusion, freeze-drying, continuous film formation, electrospinning, slot-die coating and two-dimensional/three-dimensional printing are increasingly expanding the

technological landscape. These approaches provide opportunities for improved process control, multilayer construction, dose personalization and incorporation of advanced drug-delivery carriers. Nevertheless, successful translation of these technologies requires careful control of critical material attributes and process parameters together with appropriate scale-up and packaging strategies.

Comprehensive evaluation is equally important because no single parameter can adequately predict the performance of a buccal patch. Physical appearance, weight, thickness, drug content, folding endurance, mechanical properties, moisture behaviour, swelling and surface pH provide information about formulation quality, while morphology and solid-state characterization help establish structural and physicochemical integrity. Mucoadhesive strength and residence time provide information regarding retention at the mucosal site, whereas in-vitro drug release, release kinetics and ex-vivo permeation provide progressively more meaningful information about drug-delivery performance. Assessment of mucosal irritation, biocompatibility and stability is also essential for establishing the safety and reliability of the final formulation. The need for physiologically relevant evaluation models and improved correlation between in-vitro, ex-vivo and in-vivo performance remains an important research consideration.

Despite considerable scientific progress, the translation of buccal patch systems from laboratory research to commercially successful and clinically established products remains challenging. Variability in oral physiology, saliva-mediated drug clearance, limited absorption area, mucosal permeability, patient-specific factors and difficulties in reproducing in-vivo conditions can influence therapeutic performance. Therefore, future development should increasingly integrate Quality by Design (QbD), physiologically relevant testing, advanced manufacturing, nanotechnology, patient-centric formulation design and predictive pharmacokinetic approaches. Recent research is also moving towards personalized and structurally complex buccal systems capable of controlling drug release and improving transmucosal delivery.

Overall, buccal patches represent a versatile platform that connects conventional mucoadhesive drug delivery with emerging technologies such as nanocarriers, electrospinning and additive manufacturing. Continued integration of formulation science, manufacturing engineering, mucosal biology and pharmacokinetic evaluation may facilitate the development of safer, more reproducible and clinically relevant buccal delivery systems. The future success of this approach will ultimately depend not only on achieving desirable laboratory characteristics but also on demonstrating consistent therapeutic benefit, patient acceptability, manufacturing scalability and regulatory feasibility.

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