REVIEW ARTICLE

Dual-Functional Mucoadhesive Films for Buccal Delivery: Integration of Permeation Enhancers with Smart Polymers for Controlled Release

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ABSTRACT

Buccal drug delivery is ideal for first-pass drugs, enabling systemic delivery through the buccal mucosa while bypassing hepatic metabolism. This review highlights amphiphilic mucoadhesive films that deliver functionalized permeation enhancers and smart polymers for controlled, sustained release in the buccal environment. Buccal tissue's layered structure, permeation barriers, saliva washout, and rapid turnover underscore the need for dual-functional systems. These systems, with mucoadhesive properties for retention and enhancers for absorption, improve drug efficacy against mucosal barriers. Smart polymers responsive to pH, temperature, enzymes, and light adjust release profiles to the local environment, enhancing therapy and reducing dosing. Advances in nanocomposite, multilayer, in situ forming films, and 3D-printed and biosensor-integrated films further boost buccal delivery. Nanocomposite films enhance bioavailability, multilayer films ensure stability, in situ films solidify for snug fit, and 3D printing allows personalized designs. Biosensors enable real-time treatment monitoring and adjustments. This review discusses formulation innovations, showing the promise of mucoadhesive and permeation-enhancing technologies for greater therapeutic efficacy, patient compliance, and clinical potential.

Keyword: clinical potential, 3D printing, Buccal drug delivery, nanocomposite, mucoadhesive

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INTRODUCTION

Overview of Buccal Drug Delivery

Buccal drug delivery is a noninvasive route of administration where drugs are absorbed directly through the buccal mucosa, the inner lining of the cheek. This pathway avoids the gastrointestinal (GI) tract and first-pass metabolism in the liver, such that drugs achieve systemic circulation more directly. The buccal mucosa makes an excellent site for drug absorption in view of its rich vascular supply and relatively high permeability. Drugs are formulated in different dosage forms, including tablets, films, gels, and patches, all of which are designed to adhere to the buccal surface and release the drug slowly. Of course, drugs that have poor absorption in the GI tract or are sensitive to digestive enzyme degradation are also administered beneficially with this technology, since it offers a more direct route of delivery to the bloodstream. This also provides the opportunity for sustained release controlled formulations that may lead to reduced dosing frequency and increased patient compliance[1-6].

Significance and Advantages of Buccal Route

Bypasses First-Pass Metabolism

Buccal drug delivery avoids the liver's first-pass metabolism, significantly improving the drug's bioavailability and enhancing its overall effectiveness.

Direct Systemic Circulation Entry

Drugs administered buccally enter the bloodstream directly through the veins in the oral mucosa, bypassing the gastrointestinal tract and avoiding degradation by stomach acid or digestive enzymes.

Enhanced Bioavailability

Buccal drug delivery bypasses the GI tract and liver, thereby increasing the bioavailability of drugs that would otherwise degrade in the stomach or liver.

Patient-Friendly Administration

The buccal cavity is relatively accessible and therefore more convenient for simple, non-invasive application and removal of the dosage form. Such ease of use may be favoured to increase compliance with therapy, particularly in children and the elderly.

Lower Enzymatic Activity

The buccal area has relatively low enzymatic activity as compared to that in the GI tract; thus, drug degradation is reduced and the area is appropriate for peptide-based or protein drugs, which are generally sensitive to the action of enzymes.

Reduced Dosage and Side Effects

At lower dosages of specific drugs, direct absorption through the buccal mucosa can be used to minimize systemic side effects and improve the safety of treatment for patients.

Non-Invasive and Painless

Buccal drug delivery is pain- free, noninvasive, and an alternative to injections or infusions. It provides patients with a comfort level that avoids the pain of needles or fear of them.

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Extended Contact with Immobile Surface

The relatively immobile nature of the buccal mucosa makes it suitable for mucoadhesive dosage forms meant to be retained in place, allowing a sustained release and absorption of the drug.

Compatibility with Permeation Enhancers

Formulations through the buccal route can have pH modulators, enzyme inhibitors, or permeability enhancers added to bring an optimized penetration of drugs while upping the ante on effectiveness in cases of tough permeability.

Rapid Healing of Mucosa

The buccal mucosa is extremely resistant and heals rapidly after exposure, making it suitable for repeated applications without causing lasting tissue damage.

Controlled and Sustained Release Options

Buccal delivery is highly suited to controlled and sustained release formulations. With this, one obtains an extended therapeutic effect which is available with decreased dosing frequency. It is thus very beneficial in the management of chronic conditions[7-12].

Need for Dual-functional Systems

Although these advantages, buccal drug delivery remains a developing area, essentially associated with two major points: drug permeation and retention time at the mucosal surface. The mucosa acts as a natural barrier for the absorption of drugs in the buccal region, particularly to hydrophilic drugs or larger molecules, thus requiring active enhancement of permeation. These prolonged periods of natural movement of saliva and constant mechanical activities of the mouth may not really allow direct maintenance of mucosa contacts. To overcome these limitations, dual functional systems were developed for integration of mucoadhesive along with permeation-enhancing functionality within a single formulation. Mucoadhesive components retain the drug in place for a longer release, whereas permeation enhancers enhance the transmucosal permeation of the drug by attaining therapeutic levels more efficiently. These are sometimes multi-functional systems that involve sophisticated pH- and temperature-sensitive polymers which, on exposure to environmental stimuli, vary the amount released based on the given conditions. A controlled and sustained release makes this formulation optimize drug bioavailability and therapeutic effect. Incorporation of these functionalities in one dual-functional buccal system meets the challenges unique to buccal delivery and is likely to provide a more efficient targeted or patient-friendly systemic drug administration[1].

Scope and Objectives of the Review

This review covers the developments and formulation strategies for dual-functional buccal films with recent advances. It encompasses key aspects of buccal drug delivery with special emphasis on mucoadhesive polymers and permeation enhancers to form effective drug delivery systems. Material selection, design considerations, and various manufacturing techniques in the formulation of buccal films are also discussed. Simultaneously, it points toward the latest trends of recent technological advancements that have expanded the buccal film potential to comprise nanocomposite films, multilayer systems, and 3D-printed films. The main aim is to provide insights into how developments are shaping an evolving landscape of buccal film technology in terms of improved drug delivery performance and patient-centric solutions.

Anatomy and Physiology of Buccal Mucosa

Structural Characteristics

This mucosa can be seen lining the inner cheeks and forms part of the oral mucosal tissue providing for a protective and absorptive layer in the oral cavity. The buccal mucosa has several structural layers, namely: the epithelium, basement membrane, lamina propria, and submucosa. It has an outermost epithelium that is actually stratified squamous tissue that may be keratinized or non-keratinized. It consists of four layers of keratinocytes basal, spinous, granular (only in keratinized regions), and superficial where keratinocytes differentiate, enlarge, and flatten as they migrate outward. Besides these, several other cell types are present in the epithelium, including Merkel cells, lymphocytes, Langerhans cells, and melanocytes, which work together through desmosomes, a type of junctional complex comprising proteins from desmosomal cadherins and related families, to hold the tissue together. Under this, the basement membrane is a continuous extracellular layer some 1 μm thick which separates the epithelium from the connective tissue, structurally supporting, along with acting as a barrier to certain molecules. Specialized structures known as hemidesmosomes anchor keratinocytes to the basement membrane, thus ensuring stable cohesion with the underlying connective tissue.

The layer under it is referred to as the connective tissue layer, or lamina propria, consisting of collagen fibres, blood vessels, and nerves, giving the mucosa mechanical support. There are fibroblasts present in abundance, producing and sustaining collagen fibres (types I, III, V, VI) and secreting growth factors for proliferation and differentiation of keratinocytes.

The innermost layer, the submucosa, is made of fatty and granular tissue with nerves and blood vessels to add further support to the buccal mucosa. All layers together help in the resilience and functionality of the buccal mucosa thus making it a capable barrier and support member in the oral cavity[13-15].

Permeability Barriers

Although the buccal mucosa is permeable, it does possess a few natural barriers to absorption; one such barrier is virtually permeable: the epithelial layer itself is a semi-permeable membrane. Tight junctions between cells within that epithelial layer prevent the passage of larger molecules, meaning only the smaller, lipid-soluble drugs could make their way through cell membranes; drugs have to cross over either by the transcellular or paracellular routes if they are to be absorbed. The transcellular route, diffusion directly across the cell membrane, would Favor lipophilic compounds because phospholipids constitute cell membranes, whereas hydrophilic drugs would be more suited to the paracellular route, movement through the tight junctions between cells, although this would normally be less efficient[17].

Another significant barrier is the mucus layer formed by the gel-like secretion from mucosal glands, mainly containing water, mucins, enzymes, and ions. The drug penetration can be barred by this mucus layer due to a viscoelastic, impenetrable surface layer above the mucosa, which denies accessibility to the epithelial layer. The salivary glands also contribute to the function of being a barrier because saliva may dilute drugs, wash away dosage forms and reduce the residence time of drugs on the buccal mucosa. These barriers protect the mucosa from harmful substances but are greater challenges toward drug absorption in cases involving larger and hydrophilic molecules. Permeation enhancers are common methods for overcoming such barriers by altering membrane fluidity or transiently opening tight junctions to enhance drug penetration[18].

Factors Affecting Drug Absorption

Drug absorption through the buccal mucosa is affected by both drug-specific factors and buccal environment conditions.

Physicochemical Properties

Molecular Weight: Lower molecular weights enhance absorption.

Lipophilicity: Lipophilic drugs are more easily absorbed, particularly through the transcellular route.

Ionization: Non-ionized molecules cross cell membranes more easily than ionized ones.

Impact of pH on Drug Ionization: The pH of the buccal cavity, ranging from 5.5 to 7.5, influences drug ionization. Adjustments may be needed for pH-sensitive drugs.

Contact Time and Surface Area: Prolonged contact time between the drug and buccal mucosa enhances absorption. Mucoadhesive formulations improve contact time by adhering to the mucosa, resisting saliva clearance.

Hydration Level and Saliva: Saliva maintains mucosal hydration, aiding in the dissolution of solid dosage forms and facilitating drug diffusion.

Blood Flow to Buccal Mucosa: High blood flow in the buccal area supports rapid drug uptake into systemic circulation.

This pathway is suitable for drugs needing quick onset, bypassing the GI tract for faster therapeutic effects[19-21].

Physiological Challenges in Buccal Delivery

Buccal drug delivery poses specific physiological barriers, which may affect either the absorption efficacy of a drug or the reproducibility. Saliva flow and clearance are among the most critical challenges, which results from the continued and constant secretion from the glands, thereby diluting drugs on the buccal mucosa surface, thus reducing their concentration and available amount for absorption. Saliva washes out dosage forms if mucoadhesive properties are not satisfactory, resulting in an extremely short residence time of drugs on the surface. Another reason is that chewing, speaking, and swallowing create mechanical stress that can dislodge dosage forms, hence making difficult to achieve prolonged contact of the drug with the mucosa. For this reason, mucoadhesive systems that firmly attach to the buccal tissue are often preferred to ensure sustained drug release.

Another major issue is that buccal mucosa is relatively less permeable, especially for hydrophilic and larger molecular weight drugs. Although the buccal route offers a medium to excellent permeability level, it is rather less permeable as compared to the sublingual mucosa, often requiring permeation enhancers for drug absorption by formulation. However, caution should be made in the selection of safe and effective enhancers because some enhancers could trigger irritation or damage to the mucosal tissue if used for long periods. The other physiological barrier is mucus turnover. It is critical that only the superficial layer is affected since the mucosal lining is constantly renewing; hence, any drug sticking to or reacting with the surface layer is slowly lost into the system and needs to either penetrate deeper layers or elude the drug from being removed by turnover[22–24].

Smart Polymers in Buccal Drug Delivery

This is called a class of smart or stimuli-responsive or "intelligent" polymers which can undergo significant and reversible physical or chemical changes upon perceived environmental triggers like pH, temperature, ionic strength, electric or magnetic fields, and even light. Their responsiveness makes them highly suited to applications in drug delivery systems, for in which great precision and control over the quantity of the drug released are vital to drug effectiveness and minimizing side effects[25].

The adaptability of smart polymers gives immeasurable advantages in the context of buccal drug delivery. The pH values range from slightly acidic to neutral, close to the body temperature, and create an environment where smart polymers can exploit these environmental factors for the proper control of the process of drug release and proper release only when appropriate.

The mechanism on which smart polymers work in most cases is based on the reversible physical or chemical change within the matrix of the polymer. Application of smart polymers in buccal delivery systems can be of importance for drugs whose release has to be localized, sustained, or time-specific[26].

Classification of Smart Polymers

Smart polymers are categorized based on their responsiveness to specific stimuli or environmental conditions. Their unique ability to undergo reversible changes in response to these stimuli makes them highly adaptable for various applications, particularly in drug delivery.

pH-responsive Polymers

New generations of materials called pH-responsive polymers are designed to change their physical or chemical properties in response to environmental changes in the pH. The unique adaptability is caused by ionizable acidic or basic groups within the polymer structure, which results in the polymer swelling, dissolving, or changing its solubility under local conditions of pH. This sensitivity makes pH-responsive polymers suitable for targeted drug delivery applications as they can be designed to deliver drugs in specific regions with different pH levels, such as the gastrointestinal tract or in the tumour microenvironment. In this scenario, tailoring the responsiveness of the polymer to the pH profile ensures selective drug delivery at the target site, hence maximally leveraging therapeutic efficacy while minimizing the risk of systemic side effects.

Oral drug delivery is one of the prime applications of pH-sensitive polymers as these can be formed as protective carriers of drugs sensitive to gastric fluids and permit the delay of drug release until they reach the higher pH environment of the intestines. This feature is quite handy for enteric-coated tablets: when in the stomach, the drug degrades due to pH-sensitive polymer inhibition of degradation. Bioavailability thus increases. In the context of cancer therapy, pH-responsive polymers are particularly useful because they take advantage of the acidic extracellular environment characteristic of tumor tissues in order to deliver anticancer agents at the tumour location and therefore circumvent off-target toxicity.

In addition, pH-responsive polymers are exploited in buccal and vaginal drug delivery systems. It utilizes the acidic pH of mucosal surfaces like the buccal and vaginal mucosa for local drug release, especially where a condition needs the sustained and controlled drug delivery at that delivery site. For example, chitosan-based formulations exploit its pH sensitivity to control the drug delivery in the oral cavity[27–30].

Summary of pH-Sensitive Polymers and Their Applications in Buccal Film Formulations is given table 1.

Temperature-sensitive Polymers

Temperature-sensitive polymers, also known as thermo-responsive polymers, are a particular class of smart material which changes reversibly in terms of physical properties with temperature. This type of polymer exhibits an exclusive transition at a specific temperature, while sometimes known as the lower critical solution temperature or LCST. Below this temperature, they are hydrophilic and dissolve in an aqueous environment. Above the LCST, they are hydrophobic and cause phase separation and precipitation. This characteristic allows for controlled and predictable release of drugs; thus temperature-sensitive polymers are particularly precious in drug delivery systems where localized or targeted release is desired.

Temperature-sensitive polymers, such as PNIPAAm, are very useful in drug delivery for various biomedical applications. These have undergone a phase transition near body temperature and find use in systemic and localized applications, from wound healing to cancer therapy and tissue engineering. Systems based on PNIPAAm, including gels, coatings, micelles, and mucoadhesive films, respond to natural body warmth or slight externally induced increases. The polymers have shown structural integrity in the ambient temperature of the buccal environment, thereby enhancing drug bioavailability across applications.

This type of polymer is also used in injectable gels and implants. For example, a polymer solution that, at room temperature, is liquid can be injected into the body in which case the polymer would gel up at body temperature and act as depot for sustained drug release over time. This not only reduces patient discomfort but also increases compliance with chronic conditions requiring extended release formulations. Despite these advantages, limitations persist in temperature-sensitive polymers, such as the need to fine tune the LCST for target purposes and biocompatibility and stability in physiological conditions[38-40]. Summary of Temperature-Sensitive Polymers and Their Applications in Buccal Film Formulations have been given in table 2.

Enzyme-responsive Polymers

Enzyme-responsive polymers therefore fall into the class of smart materials, designed to respond toward specific enzymes present in the biological environment towards targeted drug release. In the case at hand, polymers are engineered to respond selectively towards enzymes naturally occurring in saliva, such as amylases, proteases, or esterases. Such specific responsiveness will make for highly localized and specific drug delivery, hence making them particularly well-suited for buccal applications where sustained or site-specific delivery is desired.

The sensitivity of the enzyme-responsive polymers can be tuned in for specific enzymatic activities to design buccal films that release drugs on activation and according to therapeutic needs. That is true in the case of the use of protease-sensitive polymers optimally designed with drug release profiles if the drugs are to function properly under prolonged mucosal exposure. This selectivity is uniquely useful for drugs administered for local effects since such therapy minimizes potential side effects in the systemic environment but maximizes drug absorption at the site of administration[44-46]. Summary of Enzyme-Responsive Polymers and Their Applications in Buccal Film Formulations have been given table 3.

Light-responsive Polymers

Their main characteristics are their response towards specific wavelengths of light, which allows them to act as smart materials that can be controlled for the release of the drug. These characteristics are more than especially useful in buccal applications where on-demand drug release is achieved while allowing for precision control of time and dosage directly at the buccal mucosa.

Photolabile buccal films offer several advantages in terms of administration if used for applications where drug delivery is either fast or time-controlled, like pain treatment or localized infections. Modulation of light type, intensity, and exposure time allows for the control of dosage curve, and therefore, therapeutic areas where therapy may require adaptability as well as patient-specific adaptation come into use of these polymers. Advances in light-emitting devices such as portable LED lights further increase the feasibility of these light-activated buccal films and make the use of these drugs increasingly accessible for both clinical and home care settings. This method of buccal drug delivery creates a new dimension of control and convenience. This non-invasive targeted treatment offers the possibility of better therapeutic outcomes[50,51]. Summary of Light-Responsive Polymers and Their Applications in Buccal Film Formulations.

Mechanism of Smart Polymer Response

pH-responsive Polymers

The pH-sensitive polymers interact with the change in environmental pH because they contain ionizable groups within their structure and are capable of selectively releasing drugs. According to whether they create an acidic or basic environment, such polymers will swell or shrink and change permeability to control the release of the drug.

Table 1: Overview of pH-Sensitive Polymers Applied in Buccal Films for Drug Release Modulation

S. No.	Name of pH-Sensitive Polymer	Buccal Film Application	Reference
1	Poly(acrylic acid) (PAA)	Utilized in buccal films for controlled drug release due to its pH-responsive swelling.	[31]
2	Poly(methacrylic acid) (PMAA)	Employed in buccal films for pH-dependent drug release profiles.	[32]
3	Poly(lactic-co-glycolic acid) (PLGA)	Used in buccal films for sustained drug delivery applications.	[33]
4	Chitosan	Incorporated in buccal films for its mucoadhesive and pH-sensitive properties.	[34]
5	Poly(N-vinyl pyrrolidone-co-methacrylic acid)	Applied in buccal films for controlled drug release.	[35]
6	Poly(ethylene glycol)-co-(lactic acid)	Utilized in buccal films for its biodegradability and pH-responsive behavior.	[36]
7	Poly(acrylamide-co-acrylic acid)	Used in buccal films for pH-sensitive drug delivery systems.	[35]
8	Eudragit® L	Employed in buccal films for targeted drug release in specific pH environments.	[37]
9	Cellulose acetate phthalate (CAP)	Incorporated in buccal films for its enteric coating properties and pH sensitivity.	[35]
10	Polyvinyl alcohol (PVA)	Used in buccal films for its film-forming capabilities and pH-responsive behaviour.	[36]

Table 2: Overview of Some Temperature-Sensitive Polymers Applied in Buccal Films for Controlled Drug Release

S. No.	Name of Temperature-Sensitive Polymer	Buccal Film Application	Reference
1	Poly(N-isopropylacrylamide) (PNIPAAm)	Utilized in buccal films for its thermoresponsive gelation properties, enabling controlled drug release.	[41]
2	Poloxamers (Pluronics)	Employed in buccal films for their reversible thermal gelation, enhancing mucoadhesion and sustained drug delivery.	[42]
3	Poly(ethylene oxide)-poly(propylene oxide) copolymers	Applied in buccal films for temperature-induced sol-gel transitions, facilitating controlled release profiles.	[43]
4	Poly(ethylene glycol)-poly(lactic acid) copolymers	Incorporated in buccal films for their thermosensitive behavior, allowing for responsive drug release mechanisms.	[41]
5	Poly(ethylene glycol)-poly(caprolactone) copolymers	Used in buccal films for temperature-triggered gelation, providing controlled drug delivery systems.	[42]

Table 3: Overview of Some Enzyme-Responsive Polymers Applied in Buccal Films for Controlled Drug Release

S. No.	Name of Enzyme-Responsive Polymer	Buccal Film Application	Reference
1	Chitosan-Based Polymer Blends	Utilized in buccal films for enzyme-triggered drug release, enhancing mucoadhesion and controlled delivery.	[47]
2	Thiolated Polymers (Thiomers)	Employed in buccal films for their enzyme-responsive degradation, facilitating targeted and sustained drug release.	[48]
3	Enzyme-Degradable Polymeric Systems	Applied in buccal films for enzyme-specific drug release, improving therapeutic efficacy and minimizing side effects.	[49]

In anionic polymers, such as poly(acrylic acid), acidic groups become deprotonated under basic conditions and therefore carry a negative charge, resulting in electrostatic repulsion, swelling of the polymer. Cationic polymers, for example chitosan, protonate in acidic conditions and are, therefore hydrophilic and swell in acidic conditions, such as inside the stomach or in other mucosal sites. These changes in volume and structure of polymers make pH-sensitive polymers suitable for all applications where the environment pH varies, thus leading to targeted controlled release in specific regions, like in the gastrointestinal tract or tumour microenvironments[55-57].

Temperature-sensitive Polymers

Temperature-sensitive polymers, also referred to as thermo-responsive polymers, have a lower critical solution temperature (LCST), which determines the solubility conditions in response to temperature changes. Generally, below the LCST, these polymers are hydrophilic, swell and retain drugs inside their structure. Above the LCST, they are hydrophobic and cause the polymer to collapse or phase separate, which ensures release of the encapsulated drug. PNIPAAm is a particularly nice example of such temperature-sensitive material that exhibits this behaviour near body temperature (~32°C), and it finds very broad applications in biomedical applications involving drug delivery triggered by minor increases in temperature, whether by an external source or localized inflammation. The solubility of temperature-sensitive polymers that changes as the temperature is altered can create controlled, site-specific drug delivery-an especially advantageous

Table 4: Overview of Some Light-Sensitive Polymers Applied in Buccal Films for Controlled Drug Release

S. No.	Name of Light-Responsive Polymer	Buccal Film Application	Reference
2	Spiropyran-Containing Polymers	Employed in buccal films for reversible photo-induced switching, facilitating controlled drug release upon light exposure.	[52]
3	Coumarin-Based Photocrosslinkable Polymers	Applied in buccal films for light-induced crosslinking, enhancing drug stability and release control.	[52]
4	Poly(ethylene glycol)-based Photopolymers	Incorporated in buccal films for their light-triggered swelling behavior, enabling on-demand drug release.	[53]
5	Polydopamine-Modified Light-Sensitive Polymers	Used in buccal films for controlled release under light, with improved mucoadhesion properties.	[54]

feature for injectable gels or films that solidify at body temperature for sustained release[58-61].

Enzyme-responsive Polymers

Thus, the enzyme-responsive polymers are designed to respond selectively in those target environments where such specific enzymes reside, such as the site of diseased tissues or the buccal cavity. These polymers consist of cleavable bonds sensitive to proteases, esterases, or amylases and may degrade or swell only in the presence of such enzymes. For example, polymers with peptide linkages are hydrolytically degradable by proteases whereas esters degrade in the presence of esterases. This structural alteration of the polymer after interaction with the target enzyme allows the drug to be gradually released from the matrix of the polymer. This mechanism highly favors the localized and controlled release of drugs, especially where drugs can be released precisely in the place and time of the specific presence of enzymes, thus minimizing their off-target effects and maximizing therapeutic efficacy in enzyme-rich environments[62-64].

Light-responsive Polymers

There are light-sensitive polymers having photo-reactive functions: iropyran, spiroxazine, azobenzene, diarylethene, fulgide whose structure changes upon action by the specific wavelengths of light. In such polymers, it induces photoisomerization, photocleavage or cross-linking which causes changes in polymer permeability or degradation releasing drug within. For instance, azobenzene groups can change their conformational structure from trans to cis by exposure of UV or visible light, which changes the polymer structure to either allowing drug content to release or retain within it. Such a photoresponsive response would control drug release tightly since the timing, intensity, and wavelength of the light could be tailored for on-demand release. Among the promising applications is one involving immediate or localized drug delivery, where light-responsive polymers offer the spatial and temporal control of release. Such an adjustment in dosing can greatly benefit therapies that have an externally controlled dosing requirement[65-67].

Selection Criteria for Buccal Applications

Mucoadhesive Properties

A suitable polymer or material that shows good mucoadhesive properties would have to be used to ensure the formulation stays adherent for a prolonged period on the buccal mucosa. The adhesion helps in reducing drug loss and increases the contact time of the formulation with the mucosa, thereby improving bioavailability and the efficiency of the drug as a whole. Mucoadhesive polymers include hydroxypropyl methylcellulose, carbopol, and chitosan.

Biocompatibility and Safety

Materials used for buccal applications must be biocompatible, non-irritating, and safe for prolonged exposure in the oral cavity. Buccal mucosae are sensitive; therefore, polymers as well as excipients used must not cause irritation, inflammation, or toxicity. A majority of biodegradable and non-toxic polymers are opted for to avoid adverse effects and increase compliance among patients while there is safe breakdown in the body.

Controlled Release Capability

For therapeutic efficacy, especially for chronic diseases, the drug delivery system should provide controlled and sustained release of the active moiety. This can be developed using smart polymers responsive to environmental stimuli, such as pH or temperature, for modulation of the rate of drug release. For instance, combining pH-or enzyme-responsive polymers allows the drug to be released in a sustained and controlled manner relative to the local buccal environment.

Drug Permeability and Absorption

As the buccal mucosa provides with only a moderate barrier function, it becomes important that the formulation chosen for drug delivery enhances the permeability of the drug. The drug should be sufficiently soluble and permeable so that the permeability of the drug through the mucosal barrier into systemic circulation is assured. This is particularly more so for drugs that have low oral bioavailability, for which it requires incorporating permeation enhancers or applying nano-sized drug carriers to enhance drug absorption.

Patient Comfort and Compliance

Ease of use as well as comfort characterizes buccal applications. It should be thin, flexible, and comfortable to wear without eliciting excessive salivation or irritation. Of course, it ought to be the case for tasteless or with pleasant taste for a better acceptance by patients. The comfort and easy application of fast-dissolving or slowly eroding films and patches support patient compliance with the treatment.

Stability and Shelf Life

Any buccal formulation must be stable in the oral environment and during storage. Polymer and excipients chosen for use must be resistant to temperature, pH, and enzymatic activity variation without premature

degradation. Stable formulations mean a predictable drug release profile as well as an extended shelf life-a critical factor for commercially viable buccal drug delivery systems[68-73].

Recent Advances in Polymer Engineering

Recent advances in polymer engineering have significantly broadened the capabilities and applications of polymers, especially in the fields of drug delivery, tissue engineering, and smart material development. Key innovations include:

Stimuli-responsive Polymers

Stimuli-responsive or "smart" polymers have moved from the traditional pH and temperature responses to more complex triggers, including electric fields, magnetic fields, enzymes, and redox conditions. Moreover, multi-response polymers can be devised for response to two or more stimuli at the same time, thereby yielding highly responsive and controlled drug delivery systems for the deliberate release of drugs only when the surrounding physiological condition is appropriate. In view of these developments, more accurate and responsive treatments are possible-the highly cited use of such techniques has been for site-specific delivery in cancer therapy and wound healing[74-76].

Biodegradable and Biocompatible Polymers

Significant emphasis has been put on developing polymers that are biodegradable and biocompatible to make them safer and more sustainable for biomedical applications. One of the biggest advances in polymer chemistry over this period is that it is now possible to design polymers whose degradation is predictable, which is very important in drug delivery systems where drugs need to be released over an extended period of time without any toxic accumulation in the body. Examples include modified polyesters, polyanhydrides, and poly(ortho esters), all of which degrade into nontoxic by-products[77-80].

3D and 4D Printing of Polymers

The advent of 3D printing has revolutionized polymer engineering to actually and customarily create the polymer-based structure, like patient-specific implants and tissue scaffolds. This newest concept, 4D printing, takes this further wherein the printed material can transform or alter its function in changing time properly stimulated by such external parameters as temperature, pH or humidity. The application is particularly suitable for dynamic biomedical devices that may adapt well with changing environments in the body in terms of compatibility and effectiveness[81-86].

Polymers for Nanomedicine

Advances in polymer-based nanomaterials enabled the development of nanoscale carriers such as polymeric nanoparticles, micelles, and dendrimers, that target delivery of drugs at the cellular level. Nanocarriers improve solubility, stability, and bioavailability of drugs while minimizing side effects. Polymers in nanomedicine are increasingly formulated to deliver drugs directly to cancer cells, inflamed tissues, or other targeted areas with higher precision at a lower dose[87-91].

Hydrogel Technology

Hydrogel-based polymers have rapidly advanced and reached highly tenable and functional materials for tissue engineering and wound healing. Hydrogels can be engineered to mimic the properties of the extracellular matrix, providing a three-dimensional scaffold for cell growth and a supportive matrix, thereby supporting tissue regeneration. Advanced hydrogel systems may include bioactive compounds, growth factors, or even living cells, making them suitable candidates for wound care, tissue scaffolds, and regenerative medicine[92-96].

Polymers for Self-healing Materials

The one of the new innovations brought about in polymer science through self-healing polymers is the repair of automatically damage. It has properties that can heal autonomously structural damage to extend longevity and durability for use within biomedical devices, electronics and various layers within their coatings. They are further analysed towards wearable medical device applications including implantable sensors, that require extreme reliability and durability[97-99].

Sustainable and Eco-friendly Polymers

The focus on sustainable and eco-friendly polymers for inclusion into dual-functional mucoadhesive films for buccal delivery can be seen as an important pathway toward greener pharmaceutical products. Biodegradable polymers, such as PLA, PCL, and chitosan, can provide the essential mucoadhesive properties needed for mucous membrane adhesion and, at the same time, give them biodegradable characteristics without any harming residues. For instance, chitosan enhances permeation via the mucosal barriers, whereas PLA has excellent film-forming properties to aid in control release. Use of such environment-friendly materials brings the development of buccal drug delivery systems in line with sustainability goals, meeting demand for safe, effective, and environmentally responsible healthcare solutions[100-102].

Permeation Enhancers: Modern Approaches

Permeation enhancers are specialized agents or techniques used to improve the transport of drugs across biological barriers, such as skin or mucosal membranes, which naturally limit drug absorption. Modern approaches in permeation enhancement aim to increase drug bioavailability safely and efficiently, particularly for drugs with low permeability[103].

Classification of Permeation Enhancers

Permeation enhancers can be classified into several major categories based on their mechanism of action and type:

Chemical Enhancers

Chemical permeation enhancers: chemicals which temporarily decrease the barrier resistance of a biological membrane, such as the skin or mucous membranes, so a drug can pass through it. Usually, the structure of cell membrane lipid and proteins changes, often creating reversible perforations of the barrier. There are several types: alcohols, fatty acids, surfactants, terpenes. Alcohols, such as ethanol, enhance drug solubility and are also thought to enhance penetration through the lipid bilayer; fatty acids such as oleic acid interact with membrane lipids and enhance permeability. The mechanism of surfactants, such as sodium lauryl sulphate, is based on the principle of surface tension reduction and promotes the passage of drug molecules. Terpenes are carbon-hydrogen compounds that have been isolated from essential oils such as menthol and limonene; they act synergistically with lipid components to

open transient pathways for drugs and provide enhanced absorption without permanent tissue damage[104,105].

Physical Enhancers

Physical enhancement techniques utilize external forces or technologies to facilitate greater drug absorption by causing temporary channels or pores in the barrier. Iontophoresis uses a low-level electric current to propel charged drugs through tissues, thus showing extensive application in the transdermal and ocular drug delivery systems. Electroporation uses short pulses of high voltages that cause a momentary disruption in the cell membrane resulting in the formation of pores of size in the order of micro's where larger drug molecules can pass through the diseased tissue. Microneedles: A microneedle is just like a tiny, pain-free needle that penetrates the outer skin to form microscopic channels for the delivery of drugs to the deeper tissues more effectively. Ultrasound, or sonophoresis, is the utilization of low frequency sound waves to create microscopic bubbles, thus disturbing the lipid bilayer of cell membranes, hence improving drug permeation, specially in skin and buccal delivery systems. These techniques ensure delivery depth and dose; therefore they are apt for extremely challenging or high-molecular weight drugs[106-108].

Biochemical Enhancers

Biochemical enhancers; these can be made of peptides and enzymes by affecting cell structures to enhance the transport of drugs. Cell-penetrating peptides (CPPs) are short sequences that can introduce drugs into cells without affecting the cell structure, which favors large or sensitive drugs such as proteins and gene therapies. Enzymes; these can be in the form of proteases and lipases, break parts of the tissue like the extracellular matrix proteins. This breaks the junctions between the cells temporarily, allowing increased permeability. They find particular application in targeting mucosal and cellular barriers where the need is to achieve precision and biocompatibility to make drug delivery effective[109,110].

Mechanism of Action

Chemical permeation enhancers either react with or change the lipid bilayer and protein elements of the cell membranes in a temporarily reversible manner to enhance permeability. Alcohols increase the solubility of drugs and fluidize the lipid layer in ways that facilitate drug passage across membranes. Fatty acids, including oleic acid, insert into the lipid bilayer, somehow creating temporary "holes" by relaxing the pack of the tightly held lipids, which then becomes permeable to larger drug molecules. Surfactants, such as sodium lauryl sulphate, reduce the surface tension and break intercellular lipids, reducing the barrier resistance of the membrane. Terpenes, a class of compounds in the essential oils, insert themselves between the lipid molecules, altering lipid packing and thereby making the cell membrane more permeable. It must be reversible and accurately regulated so that there is minimal major impact on the tissue[111,112].

Physical permeation enhancers take advantage of external forces to temporarily change the barrier properties, thus the diffusion of drugs can be improved without compromising the integrity of the membrane permanently. An example of an iontophoresis makes use of a low-level electrical current that drives charged drugs across tissues through pushing them forward through the aqueous pathways and enhancing electrorepulsion, which assists the drug movement through pores or ion channels. Electroporation applies short, high-voltage pulses that create temporary pores in cell membranes. These pores are permeable and allow large or hydrophilic drugs to permeate through them and close once the electric pulses cease. Microneedles penetrate the stratum corneum, creating micro-channels, which permit direct delivery into the dermis or mucosa. Ultrasound (sonophoresis) creates microbubbles that oscillate in cavitation disrupting lipid bilayers and create a temporary passage for drug molecules into the tissue. These physical methods exhibit very good control over dosage and depth so that they are quite suitable for localized delivery of drugs[113,114].

Biochemical enhancers, on a cellular level, break down biological structures so that drugs can penetrate tissues by changing barriers at the cellular or intercellular level. The CPPs work from an interaction with cell membranes and creating transient pores or through endocytosis, allowing the drug attached to cross into cells. They work through entry mechanisms that often involve association with membrane lipids that lead to a transitory breakdown in the integrity of the membrane. Enzyme-based enhancers, like proteases and lipases, hydrolyse particularly proteins or lipids in the barrier, the extracellular matrix or junctions between the cells, thus loosen it and get passage for larger molecules through. This is effective for drug delivery across tissues with dense cellular junctions; it's one case that gets such a mechanism workable, in such complex tissues like the buccal mucosa, where enzymes give selective permeability on the broad spectrum without disruption[115,116].

Safety and Toxicity Considerations

Compatibility with Polymer Matrix

The permeation enhancer should be compatible with the polymer without causing unwanted chemical interactions or degradation. Incompatible interactions could weaken the polymer structure, affecting drug stability and release.

Concentration of Permeation Enhancer

Selecting an optimal concentration is crucial, as higher concentrations can lead to tissue irritation or cytotoxicity, while insufficient concentrations may not achieve the desired permeation effect. Fine-tuning dosage within the polymer matrix minimizes toxicity risks.

Controlled Release of the Enhancer

Incorporating a controlled release mechanism within the polymer can prevent sudden, high doses of the enhancer, reducing irritation and providing a sustained, safe enhancement of drug permeability.

Effect on Polymer Mechanical Properties

The permeation enhancer should not significantly alter the mechanical properties of the polymer, such as elasticity, flexibility, or adhesion. This ensures that the polymer maintains its intended function, particularly in mucoadhesive systems.

Enhancer Stability within Polymer Matrix

The enhancer’s stability within the polymer matrix is essential for long-term efficacy and safety. Any instability

could lead to early degradation, releasing unintended byproducts that might cause toxicity or reduce permeation efficiency.

Minimizing Enhancer Diffusion to Surrounding Tissues

Ensure that the enhancer remains within the target area to avoid diffusion into surrounding tissues, which could lead to systemic toxicity. Encapsulation within the polymer matrix helps localize the enhancer's effect.

Biodegradability and Safe Metabolite Profile

When using biodegradable polymers, the degradation products of both the polymer and enhancer should be non-toxic. Metabolite safety should be verified to ensure that breakdown products do not cause adverse effects.

pH and Environmental Sensitivity

Some permeation enhancers may exhibit pH sensitivity, affecting their interaction with the polymer and surrounding tissue. Ensuring compatibility with the intended application environment prevents unwanted reactivity and tissue irritation.

Long-term Biocompatibility

For applications requiring prolonged use, the biocompatibility of the enhancer-polymer combination must be evaluated over time. Chronic exposure studies can reveal any delayed or cumulative toxic effects.

Absence of Irritation or Sensitization

Testing for irritation or sensitization is critical, particularly for polymer-based systems used on sensitive tissues (e.g., buccal, transdermal). The polymer-enhancer formulation should pass rigorous testing to ensure it doesn't induce local irritation or allergic reactions[117-121].

Novel Permeation Enhancement Strategies

Nanocarrier Systems

Nanocarrier systems, including liposomes, solid lipid nanoparticles, and polymeric micelles, encapsulate drugs and permeation enhancers in nanoscale carriers. These enhance the drug solubility, stability, and absorption due to greater contact with the biological barrier. They also provide controlled release, which minimizes irritation potential by optimizing permeation at the target tissue by localizing the effect of the enhancer[122].

Peptide-based Enhancers

Among the permeation enhancers, peptide-based ones - especially CPPs - have received a great deal of interest because they can open membrane pathways without damaging the structure. The direct translocation of drugs into cells and translocation of large or hydrophilic drugs that may pose difficulties to penetrate barriers might be facilitated by CPPs. These peptides are promising for targeted application due to precision in the form of cell type and/or membrane region targeting[123].

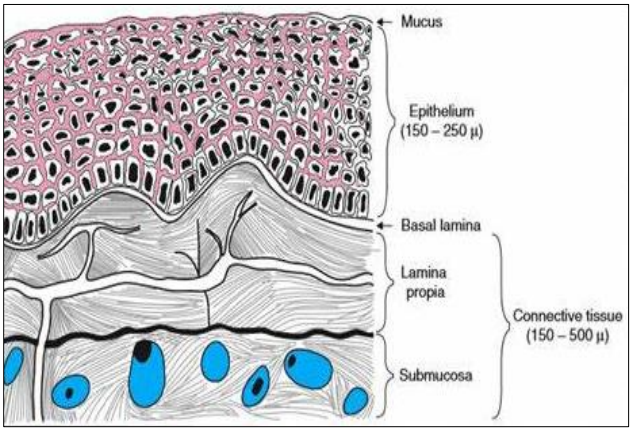

Figure 1: Structure of Buccal Mucosa[16]

Iontophoresis and Electroporation

Iontophoresis and electroporation are non-invasive, electrically driven methods that promote penetration by making temporary pores in a cell membrane. Iontophoresis uses low-intensity electrical currents to drive charged drug particles across biological barriers, whereas electroporation employs brief pulses of high voltage that temporarily open channels in the cell membrane. The former techniques are most efficient at delivering charged or large molecules and lead to controlled release with minimal tissue disruption[124,125].

Microneedle Arrays

Microneedles are designed as structures that create microscopic channels in the skin or mucosa, thus bypassing the outer barrier layer and hence drugs can enter. They can be made from biocompatible or dissolvable material in order to enable the wide application, ranging from transdermal drug delivery to vaccine administration. They enhance the passage of small and large molecules alike by reducing the need for chemical enhancers that can cause irritation[126].

Sonophoresis (Ultrasound-assisted Delivery)

Sonophoresis is a method of altering the permeation of the drug through disruption of cell membranes due to ultrasound waves, thereby enhancing tissue fluid dynamics. Low-frequency ultrasound induces microbubbles, which oscillate and disrupt the lipid bilayer, opening up temporary pathways for drug molecules to enter. This technique is mainly useful in transdermal and mucosal applications, with controlled depth and dosage, and minimized reliance on chemical permeation enhancers[127].

Stimuli-responsive Polymers

Drug delivery systems comprising of intelligent polymers that are responsive to specific stimuli, such as pH and temperature or enzymes, along with permeation enhancers are designed to control dynamic drug release. Smart polymers only send drugs in response to certain environmental cues that minimize off-target effects, improving targeted delivery. For example, if the polymer is pH-sensitive, it can release drugs upon encountering a particular acidic or basic environment. In the same way, an enzyme-responsive polymer will only release its load if some specific enzymes are present for the conditions to be met during drug delivery[128].

Hydrogel-based Carriers

Hydrogels are cross-linked polymer networks that swell in the presence of moisture, permitting them to carry drugs and release those drugs over a period. Hydrogels may be modified with addition of permeation agents to assist drug absorption through mucosal and dermal barriers and thus find applications in sustained and controlled release formulation requirements. Hydrogel formulations are particularly useful in the delivery of proteins, peptides, and hydrophilic drugs, since they provide for maintenance of a moist environment which Favors effective permeation[129].

Formulation Aspects of Dual-functional Films

Design Considerations

The design of dual-functional films for buccal delivery requires careful planning to optimize mucoadhesion, drug release kinetics, and overall user experience. Key factors include:

Film Thickness and Flexibility

For buccal films to be comfortable and minimally invasive, they must be thin yet flexible. This helps ensure that the film conforms to the contours of the buccal mucosa, improving both adhesion and patient comfort. Thickness directly impacts the drug release profile and the film's residence time in the mouth; thus, it must be optimized to balance rapid onset and prolonged release.

Mechanical Strength

Dual-functional films must have adequate mechanical strength to resist disintegration or tearing during handling, application, and drug release. Mechanical strength is typically achieved by optimizing the polymer blend and ensuring appropriate cross-linking within the film matrix. Insufficient strength can result in premature detachment, reducing efficacy.

Homogeneity and Drug Distribution

A key objective is uniform drug distribution within the polymer matrix to prevent variability in dosage across the film. Homogeneity is especially important in dual-functional films where uneven drug dispersion may impact release rates and therapeutic effectiveness.

Integration of Permeation Enhancers and Smart Polymers

Achieving a dual-functional outcome requires incorporating both permeation enhancers (to increase drug permeability) and responsive polymers (to regulate drug release based on environmental triggers like pH or temperature). The challenge lies in selecting materials that function synergistically without compromising the stability or biocompatibility of the film[130-132].

APPROACH FOR MATERIAL SELECTION

Selecting materials for dual-functional films requires a balanced approach to meet both functional and regulatory standards:

Mucoadhesive Polymers

Chitosan, hydroxypropyl methylcellulose (HPMC), and carbopol are highly used as they can bond on to the moist buccal mucosa and thereby create a stable interface, making the drug susceptible for a longer duration. Chitosan is very mucoadhesive because of its positive charge that sticks to the negatively charged mucosal surface, whereas HPMC is flexible and compatible with a broad range of drugs.

Smart Polymers

Polymers that respond to a particular stimulus, such as pH, temperature, enzymes, or light, are highly suitable for controlled release.

For example, Ph responsive polymers can initiate selective release depending on the environment inside the oral cavity. Eudragit-like is a polymer that responds to pH changes. When exposed to a certain pH, it initiates the release of the drug, hence being more specific in its approach to drug delivery.

Plasticizers

Plasticizers, either glycerol or PEG, are essential plasticizers for improving the workability and flexibility of films. These compounds reduce the brittleness and make the film allow adherence to the buccal tissue, enhancing patient comfort and adhesion. The rate of drug release can be affected by the choice of plasticizer, as PEG can enhance drug permeability and release.

Active Pharmaceutical Ingredient (API)

For example, physicochemical properties of drug (solubility, stability, molecular weight), etc- decide the material choice. Surfactants or specific polymers have to be used with hydrophobic drugs for better dispersion. The drugs are sensitive to oxidation, so they have to be protected with antioxidants. Another aspect is that the interaction of API with mucoadhesive and permeation-enhancing agents has to be studied and evaluated in the interest of avoiding adverse reactions or degradation[133-135].

Manufacturing Techniques

Solvent Casting

The main method of film production in buccal delivery is solvent casting. In this technique, the drug, polymer, and other additives are dissolved in an appropriate solvent to give a homogeneous solution. It is spread on a plane surface and left to dry.

This forms a thin sheet. The virtue is that it is quite simple, thus offering films of controlled thickness. However, a major problem lies with the removal of residual solvents and uniform drug distribution. A solvent is considered a good choice if it is compatible with the drug and polymer and at least safe for residual traces[136].

Hot-melt Extrusion

Hot-melt extrusion is the process in which polymer and drug are melted together to produce a homogenous mixture, which further can be pressed into a thin film. This technique has some advantages, like no usage of solvents and presumably better solubility for drug molecules that are highly insoluble in water, but the technique is sensitive to heat-stable drugs and polymers that can only be used for the substances that are unable to degrade when heated at high temperatures. Hot-melt extrusion also provides the possibility of finer control over drug release through polymer modification either in terms of crystallinity or film density[137].

Electrospinning

Electrospinning employs an electrostatic field for extraction of extremely fine fibers from a polymer solution to yield a non-woven, fibrous matrix with great surface area. Such a process has the advantage that films of high porosity and rapid drug release are feasible, truly needed for immediate therapeutic action. Equipment for electrospinning is somewhat complex and as such the method may yield high variability in fiber diameter and uniformity. These porous electrospun films are very useful in drug delivery, especially drugs that require rapid buccal absorption[138].

Critical Quality Attributes

Critical quality attributes (CQAs) ensure the film's safety, effectiveness, and reliability:

Mucoadhesive Strength: This determines the film's ability to adhere to the mucosa for extended periods, facilitating sustained drug exposure. High mucoadhesive strength helps

prevent premature detachment, which is tested using mucoadhesion testers under simulated buccal conditions.

Drug Content Uniformity: Uniform drug distribution within the film is vital for dose consistency. Testing is conducted by sampling multiple points across the film and analysing drug content to ensure minimal variance.

Mechanical Strength: Mechanical strength is essential for ensuring that the film withstands handling and application. Parameters such as tensile strength and elongation at break are measured to verify the film's robustness and flexibility.

Release Profile: A controlled release profile ensures that the drug is released at the desired rate over time. Release testing in simulated saliva provides insight into how the drug will perform in vivo.

Film Thickness and Surface pH: Film thickness affects drug load and release, while surface pH must align with buccal pH to prevent irritation. Thickness is measured with micrometres, and surface pH is tested to ensure patient comfort[139-141].

Characterization Methods

Characterization is crucial to confirm that films meet desired specifications:

Mechanical Testing: Instruments like texture analysers measure tensile strength, flexibility, and elasticity, providing data on the film's resilience and ability to endure the application.

Mucoadhesion Testing: To simulate the buccal environment, tests are often conducted with ex vivo tissue or synthetic substrates, measuring the force needed to detach the film from the surface, indicating adhesive strength.

Drug Release Studies: In vitro release studies, typically performed in simulated saliva, measure the release rate and extent of the drug over time, essential for predicting therapeutic performance.

Surface Morphology Analysis: Scanning electron microscopy (SEM) provides detailed images of the film's surface and internal structure, verifying uniformity and smoothness, especially important for electrospun films.

Thickness Measurement: Consistent thickness is essential for dosage uniformity and patient comfort. Micrometers or thickness gauges ensure that each batch meets specified dimensions.

Moisture Content Analysis: Moisture content impacts mechanical properties and stability. Techniques like thermogravimetric analysis (TGA) assess water content, which is especially critical for films sensitive to humidity.

Thermal Analysis: Differential scanning calorimetry (DSC) is used to assess the thermal behavior of the film, such as melting point and glass transition temperature, which are critical for evaluating heat stability, especially for hot-melt extruded films[142-149].

Recent Technological Advances

Nanocomposite Films

Nanocomposite films are advanced versions of a buccal film in which nanoparticles are dispersed in a polymer matrix to improve the stability, bioavailability, and controlled release of drugs. These nanoparticles could be composed of silica, silver, gold, or even polymers that have special properties, acting as tiny drug carriers within the film. Their high surface area-to-volume ratio enhances the efficiency of drug loading and offers sustained drug release due to controlled diffusion or gradual degradation of the nanoparticles. Adding nanoparticles increases the permeability of the film: therefore, easy passage of the drug across the buccal barriers with a reduced dose frequency. Compositions of nanocomposite films can then be seen, particularly for drugs that are poorly soluble, or those that are susceptible to degradation, in that the nanostructure offers the dual advantage of both shielding and slow, time-controlled release. This increases the therapeutic effect over time[150-152].

Multilayer Systems

A multilayer buccal film is carefully designed with various layers to have several functional layers. Each functional layer addresses a specific drug delivery issue, like adhesion, drug release, or stability. The adhesive layer in a traditional multilayer system ensures firm adherence to the buccal mucosa and long-term contact that promotes better absorption of drugs. The drug-loaded layer controls the release profile, and additional layers may act as barriers protecting the drugs from saliva or environmental degradation. In this way, functions can be separated by delivering optimized drug stability and a tailored release rate, even to fine-tune for specific therapeutic requirements. Multilayer systems are particularly advantageous to drugs that have to be released differently or in precise amounts, since they ensure that the film remains in place while releasing the drug at an optimal rate for patient compliance and therapeutic coherence[153,154].

In Situ Forming Films

The advantages of in situ forming films include the fact that they are patient-friendly, flexible, start as liquid or semi-solid in state but form a solid film when brought into contact with buccal mucosa, usually because of some environmental trigger such as temperature, pH, or ionic content of saliva that triggers the formulation to form an intimate film that sticks tautly on the mucosal surface. In-situ films are advantageously applied since their flexibility permits easy application since the patients can apply the formulation in a comfortable spreadable form which rapidly hardens and thus ensures an even and strong adhesion. Hence, the in-situ forming films afford rapid drug release and the drug is released at a sufficiently fast rate to rapidly attain therapeutic concentrations while comfortably avoiding the rigidity of a preformed film[155].

3D Printed Buccal Films

Advanced films produced by 3D printing, with great precision and their ability to be tailored to enhance drug delivery tailored to individualized patient needs. The layer-by-layer approach used in fabrication can enable control over every shape, thickness, and drug distribution within a film to allow for specific porosities or unique tailored release patterns. This precision also enables the encapsulation of multiple drugs within one film with individual release rates. This means that 3D printed films are ideal for tailored treatment regimens. Additionally, 3D printing enables customized dosage forms in that clinicians can tailor the most targeted films for certain conditions where dosages need to be very precise or controlled; for

instance, chronic or complex diseases, and therefore also yielding scopes for bespoke therapy according to the needs of individual patients[156,157].

Integration of Biosensors

Buccal films where biosensors have been integrated, constitute a frontier in drug delivery as it couples therapeutic action with the monitoring capability in real-time. Biosensors in such films can detect particular physiological markers, like glucose levels or pH, and can trigger immediate drug release or send data to monitoring devices.

The dynamic approach would ensure that drug release to the patient is in accord with the real-time needs of the patient's physiology. These types of responsive systems are valuable for the tracking of diseases and fine titration needs, such as diabetes, where treatment can be handled in a more specific, data-driven fashion. The integration of biosensors with buccal films enhances the precision of therapy and adherence to treatment by means of slow, controlled release of therapeutic agents, providing a potent approach to the management of chronic disease and dynamic adjustment of therapy commensurate with changes in biomarkers[158].

CONCLUSION

Systemic drug administration via the buccal route is promising and non-invasive because it directly enters systemic circulation with minimal interaction with first-pass metabolism. Dual-functionality mucoadhesive films with enhanced releases through permeation enhancers and smart polymers overcome critical challenges that involve limited retention time and mucosal permeability, thereby guaranteeing controlled and sustained drug release. Moderate permeability and distinct barriers at anatomy of the buccal mucosa require formulation strategies as mucoadhesive as well as innovative responsive polymers tailored to the environmental stimuli of pH and temperature. Recent technological innovations include nanocomposite and multilayer films, in situ forming films, 3D printing, and biosensor integration; all have broadened the possibilities of buccal films toward personalized targeted drug delivery systems with increased precision and patient compliance. Collectively, these inventions confirm the position of buccal delivery in the development of efficient patient-centered drug delivery systems that promise greater therapeutic effectiveness for a large number of medical applications.

ABBREVIATIONS

GIT: Gastrointestinal tract; 3D: Three Dimensional; DSC: Differential scanning calorimetry; TGA: Thermogravimetric analysis; SEM: Scanning electron microscopy; CQAs: Critical quality attributes; API: Active Pharmaceutical Ingredient; HPMC: hydroxypropyl methylcellulose; PEG: Polyethylene glycol; CPPs: Cell-penetrating peptides; LCST:lower critical solution temperature; PNIPAAm: Poly (N-isopropylacrylamide); CAP: Cellulose acetate phthalate; PVA: Polyvinyl alcohol; PAA: Poly(acrylic acid); PMAA: Poly(methacrylic acid); PLGA: Poly(lactic-co-glycolic acid);

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