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REVIEW ARTICLE

A REVIEW ON STUDY OF BUCCAL PATCHES: CURRENT STATUS OF FORMULATION AND EVALUATION METHODS

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*corresponding Author's E-mail: navpreetkaur5453@gmail.com**ABSTRACT**

The main barrier for the oral delivery of most of the drugs as potential therapeutic agents is their extensive presystemic metabolism, instability in acidic environment resulting into inadequate and erratic oral absorption. Parenteral route of administration is the only established route that overcomes all these drawbacks. But, these formulations are costly, have least patient compliance, require repeated administration. Buccal administration of drug provides a convenient route of administration for both systemic and local drug actions. Direct access to the systemic circulation through the internal jugular vein bypasses drug from the hepatic first pass metabolism leading to high bioavailability. In buccal drug delivery systems mucoadhesion is the key element so various mucoadhesive polymers have been utilized in different dosages form. The objective of writing this review on buccal drug delivery system was to compile the recent literature with special focus on buccal patches by discussing buccal mucosa and pathways of drug absorption, theories and mechanism of mucoadhesion. This review also summarizes the methodology in evaluating buccal patches.

Key Words: Buccal drug delivery system, buccal mucosa, buccal absorption mucoadhesion, buccal patches.

INTRODUCTION

Amongst the various routes of drug delivery, oral route is perhaps the most preferred to the patient and the clinicians. Based on our present understandings of biochemical and physiological aspects of absorption and metabolism, many drugs cannot be delivered successfully through the conventional oral route, because after administration the drugs are subjected to extensive pre-systemic clearance, which often leads to a lack of significant correlation between membrane permeability, absorption and bioavailability.¹

On the contrary of per oral route, mucosal layer (nasal, rectal, vaginal, ocular and oral cavity) are often considered as potential sites for drug administration and having distinct advantages for systemic drug delivery. These advantages include possible liver bypass effect, avoidance of presystemic elimination within the GI tract with improved absorption and hence better bioavailability.²

The nasal cavity has been investigated as a site for systemic drug delivery but the potential irritation and the irreversible damage to the ciliary action of the nasal cavity from chronic application of nasal dosage, as well as the large intra- and inter-subject variability in mucus secretion in the nasal mucosa, could significantly affect drug absorption from this site. Even though the rectal, vaginal, and ocular mucosae all offer certain advantages, but the poor patient acceptability associated with these sites renders them reserved for local applications rather than systemic drug administration.^{3, 4, 5} The buccal route has the capability to maintain a delivery system at a

particular position for an extended period of time therefore it has a great appeal for both local as well as systemic drug bioavailability. The buccal mucosa is relatively permeable with a rich blood supply and absorption occurring from this place is efficient, and additionally the route also provides rapid drug transport to the systemic circulation and avoids degradation by gastro-intestinal enzymes and first pass hepatic metabolism.⁶

MUCOADHESIVE DRUG DELIVERY SYSTEM IN ORAL CAVITY:

Drug delivery via the membranes of the oral cavity can be subdivided as follows:

- **Sublingual delivery:** is systemic delivery of drug through the mucosal membranes lining the floor of the mouth.
- **Buccal delivery:** is drug administration through the mucosal membranes lining the cheeks.
- **Local delivery:** is drug delivery into the oral cavity.⁷

ADVANTAGES OF BUCCAL DRUG DELIVERY SYSTEM^{8, 9, 10, 11}

Bypass of the gastrointestinal tract and hepatic portal system, increasing the bioavailability of orally administered drugs that otherwise undergo hepatic first-pass metabolism. In addition the drug is protected from degradation due to pH and digestive enzymes of the middle gastrointestinal tract.

1. Improved patient compliance due to the elimination of associated pain with injections.
2. A relatively rapid onset of action can be achieved relative to the oral route.
3. The formulation can be removed if therapy is required to be discontinued.
4. Improve the performance of many drugs, as they are having prolonged contact time with the mucosa.
5. The residence time of dosage form at the site of absorption is prolong, hence increases the bioavailability.
6. High blood supply and good blood flow rate cause rapid absorption.
7. It offers a passive system of drug absorption and does not require any activation.
8. Significant cost reductions may be achieved and dose-related side effects may be reduced due to API localization at the disease site.

DISADVANTAGES OF BUCCAL DRUG DELIVERY^{12, 13, 14, 15}

As compared to the sublingual membrane the buccal membrane has low permeability.

1. Limited surface area is available for absorption.
2. This route cannot administer drugs which irritate the mucosa or have a bitter or unpleasant taste or an obnoxious odour.
3. This route is unacceptable for those drugs which are unstable at pH of buccal environment.
4. The continuous secretion of the saliva (0.5-2 l/day) leads to subsequent dilution of the drug.
5. Drugs with large dose are difficult to be administered.

STRUCTURAL FEATURES OF ORAL CAVITY^{16, 17, 18, 19}

The oral cavity consists of two regions:

- Outer oral vestibule, which is bounded by cheeks, lips, teeth and gingival (gums).
- Oral cavity proper, which extends from teeth and gums back to the fauces (which lead to pharynx) with the roof comprising the hard and soft palate.

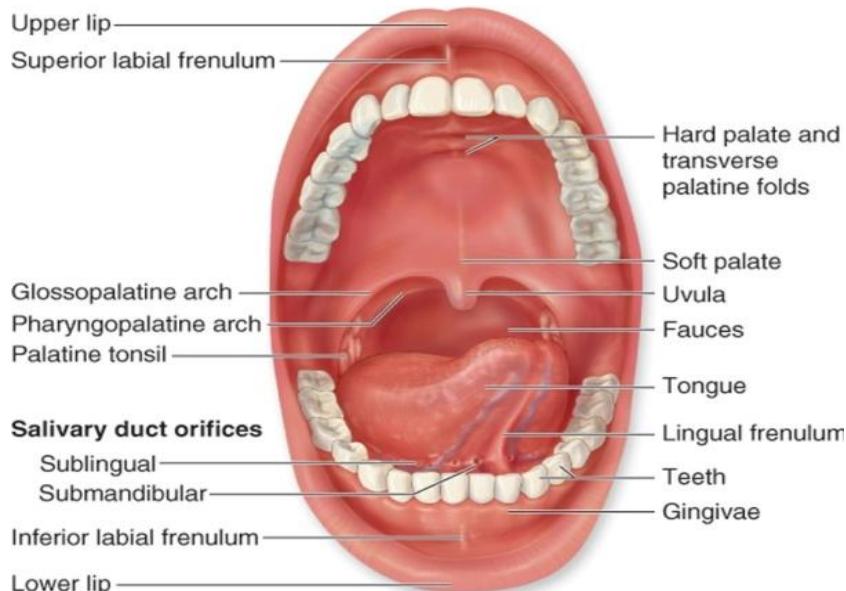


Figure 1: Anatomical structure of Oral Cavity

OVERVIEW OF BUCCAL MUCOSA

Oral mucosa is divided into two parts:

A. Epithelium: The epithelium, as a protective layer for the tissues beneath, is divided into:

(a) non-keratinized surface in the mucosal lining of the soft palate, the ventral surface of the tongue, the floor of the mouth, alveolar mucosa, vestibule, lips, and cheeks.

(b) Keratinized epithelium which is found in the hard palate and non-flexible regions of the oral cavity.

B. Basement membrane and connective tissue: Basement membrane is a boundary between the basal layer of epithelium and connective tissue. It consists of extracellular materials. The organisation which determines the mechanical stability, resistance to deformation, extendibility of tissue is made up of bulk of connective tissue.

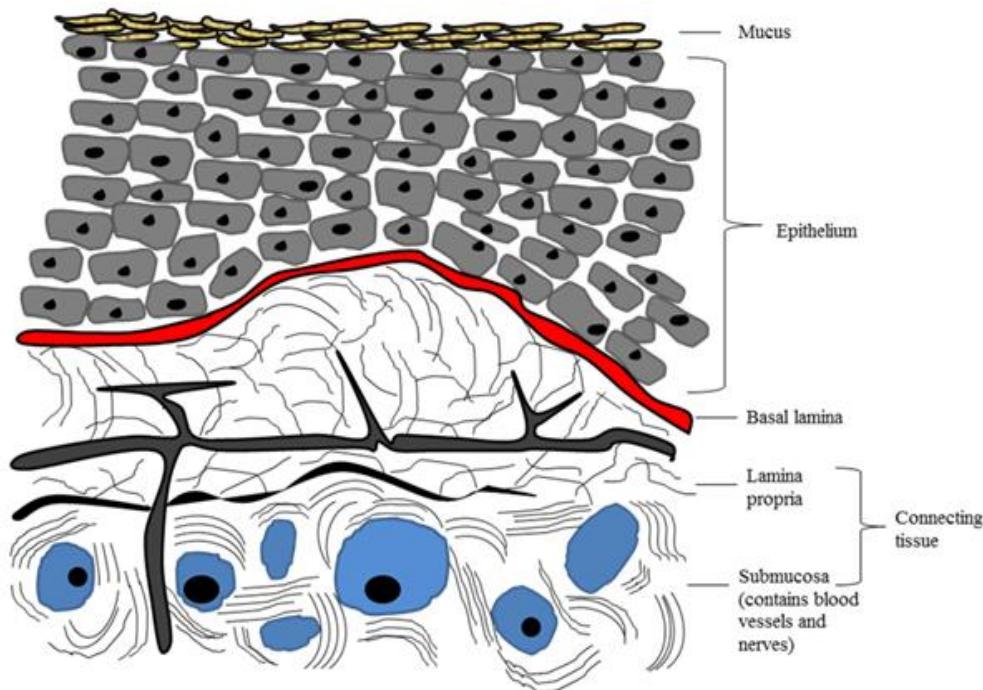


Figure 2: Structure of Buccal Mucosa

The Mucus Layer:¹⁴ Mucus is a translucent and viscous secretion which forms a thin, continuous gel blanket adherent to the mucosal epithelial surface. The mean thickness of this layer varies from about 50 to 450 μm in humans. It is secreted by the goblet cells lining the epithelia or by special exocrine glands with mucus cells acini. The exact composition of the mucus layer varies substantially depending on the species, the anatomical location and the pathophysiological state. However, it has the following general composition:

1. Water - 95%
2. Glycoproteins and Lipids - 0.5 to 5%
3. Mineral salts - 0.5 to 1%
4. Free Proteins - 0.5 to 1%

Functions of mucus layer:²⁰

- Mucus layer is protective in nature because of its hydrophobicity.
- Mucus layer acts as a barrier in tissue absorption of drugs and other substrates.
- Mucus has strong adhesion properties and firmly binds to the epithelial cell surface as a continuous gel layer.
- An important role of mucus layer is to lubricate the mucosal membrane and keep it moist.

Permeability:

It is estimated that the permeability of the buccal mucosa is 4-4000 times greater than the skin.²¹ There are considerable differences in permeability between different regions of the oral cavity because of diverse structures and functions of the different oral mucosae. In general, the permeabilities of the oral mucosae decrease in the order of sublingual greater than buccal and buccal greater than palatal.¹ This rank order is based on the relative thickness and degree of keratinization of these

tissues, with the sublingual mucosa being relatively thin and non-keratinized, the buccal thicker and non-keratinized, and the palatal intermediate in thickness but keratinized.

The permeability barrier property of the oral mucosa is predominantly due to intracellular materials derived from the so called – “membrane coating granules” (MCGS).²²

Passive diffusion is the primary mechanism for the transport of drugs across the buccal mucosa, carrier mediated transport has been reported to have a small role. In buccal mucosa two routes of passive transport are found:

Paracellular: involves the transport of compounds through the intercellular space between the cells.

Transcellular: involves passage into and across the cells.^{4,23}

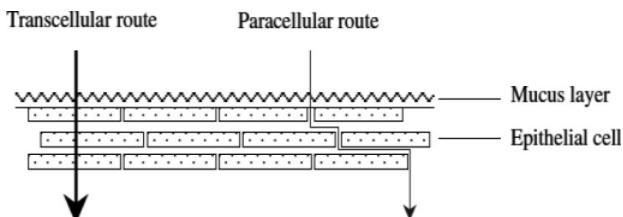


Figure 3: Mechanism of Drug Transport

Environment:⁷

The oral cavity is marked by the presence of saliva produced by the salivary glands and mucus which is secreted by the major and minor salivary glands as part of saliva. Saliva is the protective fluid for all tissues of the oral cavity. It protects the soft tissues from abrasion by rough materials and from chemicals. The daily salivary volume is between 0.5 to 2 liters and it is this amount of fluid that is available to hydrate oral mucosal dosage forms. The main reason behind the selection of

hydrophilic polymeric matrices as vehicles for oral transmucosal drug delivery systems is this water rich environment of the oral cavity.

Role of Saliva:²⁴

- Protective fluid for all tissues of the oral cavity.
- Continuous mineralization / demineralization of the tooth enamel.
- To hydrate oral mucosal dosage forms.

Mucoadhesivity:²⁵

For the development of Buccal drug delivery systems, mucoadhesion of the device is a key element. For proper and good mucoadhesion, mucoadhesive polymer have been utilized in many different dosages forms such as tablets, patches, tapes, films, semisolids and powders. Addition of various polymers to drug delivery systems such as gums, increased the duration of attachment of the formulations to the mucous surface and also increased the efficacy. To serve as mucoadhesive polymers, the polymers should possess some general physiochemical features such as:

- Predominantly anionic hydrophilicity with numerous hydrogen bond-forming groups.
- Polymer and its degradation products should be non-toxic, non-irritant and free from leachable impurities.
- Good spreadability, wetting, swelling and solubility and biodegradability properties.
- pH should be biocompatible and should possess good viscoelastic properties.
- Should possess peel, tensile and shear strengths at the bioadhesive range.

NOVEL BUCCAL DOSAGE FORMS^{26,27}

The novel type buccal dosage forms include buccal adhesive tablets, patches, films, semisolids (ointments and gels) and powders.

A. Buccal mucoadhesive tablets: Buccal mucoadhesive tablets are dry dosage forms that have to be moistened prior to placing in contact with buccal mucosa. They can deliver drug multidirectionally into the oral cavity or to the mucosal surface.

B. Patches and Films: Buccal patches consists of two laminates or multilayered thin film that are round or oval in shape, consisting basically of adhesive polymeric layer and impermeable backing layer to provide unidirectional flow of drug across buccal mucosa.

C. Semisolid Preparations (Ointments and Gels): Bioadhesive gels or ointments have less patient acceptability than solid bioadhesive dosage forms, and most of the dosage forms are used only for localized drug therapy within the oral cavity.

D. Powders: Buccal bioadhesive powder dosage forms are a mixture of bioadhesive polymers and the drug and are sprayed onto the buccal mucosa

BUCCAL ABSORPTION

Buccal absorption leads systemic or local action via buccal mucosa.

Mechanism of buccal absorption: Buccal drug absorption occurs by passive diffusion of the nonionized species. Passive diffusion is a process governed primarily by a concentration gradient, through the intercellular spaces of the epithelium. The passive transport of non-ionic species across the lipid membrane of the buccal cavity is the primary transport mechanism. The buccal mucosa has been said to be a lipoidal barrier to the passage of drugs, as is the case with many other mucosal membrane and the more lipophilic the drug molecule, the more readily it is absorbed.²⁸ The dynamics of buccal absorption of drugs could be adequately described by first order rate process. Several potential barriers to buccal drug absorption have been identified. Dearden and Tomlinson (1971) pointed out that salivary secretion alters the buccal absorption kinetics from drug solution by changing the concentration of drug in the mouth. The linear relationship between salivary secretion and time is given as follows:

$$- \frac{dm}{dt} = Kc/ViVt$$

Where, M - Mass of drug in mouth at time t K - Proportionality constant C - Concentration of drug in mouth at time V_i - The volume of solution put into mouth cavity and V_t - Salivary secretion rate

Factors affecting buccal absorption: The oral cavity is a complex environment for drug delivery as there are many interdependent and independent factors which reduce the absorbable concentration at the site of absorption.^{29,30}

1. Membrane Factors: This involves degree of keratinization, surface area available for absorption, mucus layer of salivary pellicle, intercellular lipids of epithelium, basement membrane and lamina propria. In addition, the absorptive membrane thickness, blood supply/ lymph drainage, cell renewal and enzyme content will all contribute to reducing the rate and amount of drug entering the systemic circulation.

2. Environmental Factors:

A. Saliva: The thin film of saliva coats throughout the lining of buccal mucosa and is called salivary pellicle or film. The thickness of salivary film is 0.07 to 0.10 mm. The thickness, composition and movement of this film affect the rate of buccal absorption.

B. Salivary glands: The minor salivary glands are located in epithelial or deep epithelial region of buccal mucosa. They constantly secrete mucus on surface of buccal mucosa. Although, mucus helps to retain mucoadhesive dosage forms, it is potential barrier to drug penetration.

C. Movement of buccal tissues: Buccal region of oral cavity shows less active movements. The mucoadhesive polymers are to be incorporated to keep dosage form at buccal region for long periods to withstand tissue movements during talking and if possible during eating food or swallowing.

BIOADHESION AND MUCOADHESION^{24,31,32}

The term bioadhesion refers to any bond formed between two biological surfaces or a bond between a biological

and a synthetic surface. In the case of bioadhesive drug delivery systems, it is a bond formed between polymers and soft tissues. If the bond is formed between mucus and polymer, it is described as mucoadhesion. Although the target of many bioadhesive delivery systems may be a soft tissue cell layer (i.e. epithelial cells), the actual adhesive bond may form with either the cell layer, a mucous layer or a combination of the two. In instances in which bonds form between mucus and polymer, the term mucoadhesion is used synonymously with bioadhesion. In general, bioadhesion is an all-inclusive term used to describe adhesive interactions with any biological or biologically derived substance, and mucoadhesion is used only when describing a bond involving mucus or a mucosal surface.

Mechanism of Mucosal Adhesion^{33, 34, 35, 36}

Several theories proposed the mechanism of mucoadhesion by the interaction of polymer and mucus. The mechanism of mucoadhesion is divided into two steps, first is contact step and second is consolidation step. In the first step the mucus layer come in contact with mucoadhesive and mucous membrane and the formulation swell and spread over mucus membrane. In the second consolidation step the moisture activates the mucoadhesive material, this plasticizes the system, this allow to mucoadhesive molecules to break free and link up by weak Vander walls and hydrogen bonds. The diffusion and dehydration theory explain the consolidation step.

The diffusion theory is the mutually interacting of mucoadhesive molecules and glycoprotein of mucus and building of secondary bonds by interpenetration of their chains.

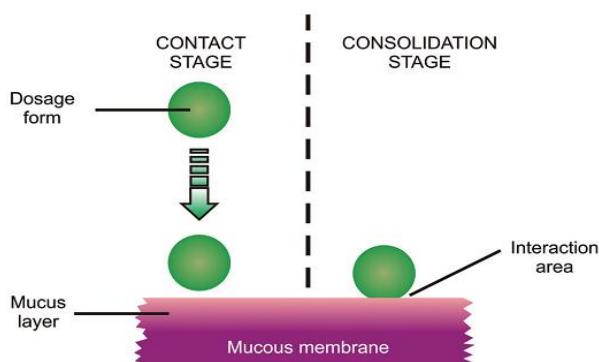


Figure 4: Two steps of Mucoadhesion Process

According to the dehydration theory the material get gelify when it come in contact with the mucus in the aqueous environment. The drawing of water into the formulation due to concentration gradient until the osmotic balance is reached. This process increases the contact time of mucous membrane with the mixture of formulation and mucus. So it is not the interpenetration of macromolecules chains, it is the water motion that lead to the consolidation of the adhesive bond. The dehydration theory is not applicable for highly hydrated forms or solid formulations.

THEORIES OF MUCOADHESION

i) The Electronic Theory: According to this theory, electron transfer occurs upon contact of an adhesive polymer with a mucus glycoprotein network because of differences in their electronic structures. This results in the formation of an electrical double layer at the interface. Adhesion occurs due to attractive forces across the double layer.

ii) The Adsorption Theory: According to this theory, after an initial contact between two surfaces, the material adheres because of surface forces acting between the atoms in the two surfaces. Two types of chemical bonds resulting from these forces are:

- Primary chemical bonds of covalent nature.
- Secondary chemical bonds having many different forces of attraction including electrostatic forces, Vander Waals forces, and hydrogen and hydrophobic bonds.^{14, 37}

iii) The Wetting Theory^{24, 33, 35}: This theory applies to those liquid systems which present affinity to the surface in order to spread over it. The contact angle is a measuring technique used to find the affinity. It is a general rule that greater be the affinity lower the contact angle. For the adequate spredability the contact angle must be equal or close to zero. The spreadability coefficient (SAB) is calculated by the equation:

$$SAB = \gamma_B - \gamma_A - \gamma_{AB}$$

Where: γ_B is Surface energy and γ_A is Interfacial energy

If greater the interfacial energy in relating to the individual surface energy, greater the adhesion work W_A , i.e., greater the energy needed to separate the two phases.

$$W_A = \gamma_A + \gamma_B - \gamma_{AB}$$

iv) The Diffusion Theory: According to this theory the polymer chains and the mucus mix to a sufficient depth to create a semi permanent adhesive bond. The exact depth to which the polymer chains penetrate the mucus depends on the diffusion coefficient and the time of contact. This diffusion coefficient, in turn, depends on the value of molecular weight between cross-links and decreases significantly as the linking density increases.

v) The Fracture Theory: For measurement of the mucoadhesion mechanism this is most studied theory. This theory is related to separation of two surfaces after adhesion. The fracture strength is equivalent to adhesive strength as given by

$$G = (E\varepsilon / L)^{1/2}$$

Where: E is Young's modules of elasticity, ε is Fracture energy and L is Critical crack length when two surfaces are separated^{24, 33, 35}.

BUCCAL PATCHES^{38, 39}

Buccal patch is a non dissolving thin matrix modified-release dosage form. The patch is composed of one or more polymer films or layers containing the drug and/or other excipients. The patch may contain a mucoadhesive

polymer layer which bonds to the oral mucosa, gingiva, or teeth for controlled release of the drug into the oral mucosa (unidirectional release), oral cavity (unidirectional release), or both (bidirectional release). The patch is removed from the mouth and disposed of after a specified time.

TYPES OF BCCCAL PATCHES^{20, 35, 39}

- a) **Matrix type (Bi-directional):** The buccal patch designed in a matrix configuration contains drug, adhesive, and additives mixed together. Bi-directional patches release drug in both the mucosa and the mouth.
- b) **Reservoir type (Unidirectional):** The buccal patch designed in a reservoir system contains a cavity for the drug and additives separate from the adhesive. An impermeable backing is applied to control the direction of drug delivery; to reduce patch deformation and disintegration while in the mouth; and to prevent drug loss. Basically unidirectional types of buccal patches are used for drug delivery in the buccal cavity for local as well as systemic effect.

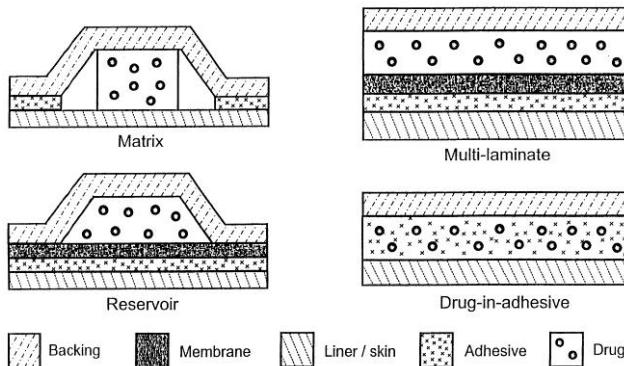


Figure 5: Matrix and Reservoir type Buccal Patches

Characteristics of an Ideal Buccal Patch^{6, 40}

An ideal buccal adhesive system should possess the following characteristics:

- 1) Quick adherence to the buccal mucosa and adequate mechanical strength.
- 2) Should release the drug in a controlled fashion.
- 3) Should facilitate the rate and extent of drug absorption.
- 4) Should possess good patient compliance.
- 5) Should not hinder normal functions such as talking, eating and drinking.
- 6) Should accomplish unidirectional release of drug towards the mucosa.
- 7) Should not aid in development of secondary infections such as dental caries.
- 8) Should possess a wide margin of safety both locally and systemically.
- 9) Should have good resistance to the flushing action of saliva.

COMPOSITION OF BUCCAL PATCHES:

The basic components of buccal bioadhesive drug delivery system are:

1. Active Pharmaceutical Ingredient
2. Mucoadhesive polymers
3. Backing membrane
4. Penetration enhancers
5. Plasticizers

1. ACTIVE PHARMACEUTICAL INGREDIENT (API): For buccal drug delivery, it is important to prolong and increase the contact between API and mucosa to obtain the desired therapeutic effect. The important drug properties that affect its diffusion through the patch as well as the buccal mucosa include molecular weight, chemical functionality and melting point.⁴⁰

The selection of a suitable drug for design of buccal mucoadhesive drug delivery system should be based on following characteristics⁴¹:

- The conventional single dose of the drug should be low.
- The drugs having biological half-life between 2-8 hours are good candidates for controlled drug delivery.
- The drug absorption should be passive when given orally.
- Drug should not have bad taste and be free from irritancy, allergenicity and discoloration or erosion of teeth.

2. MUCOADHESIVE POLYMERS: Mucoadhesives are synthetic or natural polymers that interact with the mucus layer covering the mucosal epithelial surface and main molecules constituting a major part of mucus.⁴⁰

The first step in the development of mucoadhesive dosage forms is the selection and characterization of appropriate mucoadhesive polymers in the formulation. Polymers are also used in matrix devices in which the drug is embedded in the polymer matrix, which controls the duration of release of drugs.

Characteristics of Ideal Mucoadhesive Polymers^{42, 43}:

An ideal polymer for mucoadhesive drug delivery system should have the following characteristics:-

- The polymer and its degradation products should be non-toxic and non-absorbable from the GIT.
- It should be non-irritant to the mucus membrane.
- It should preferably form a strong non-covalent bond with the mucin epithelial cell surfaces.
- It should adhere quickly to moist tissue surface and should possess some site specificity.
- It should allow easy incorporation of the drug and offer no hindrance to its release.
- The polymer must not decompose on storage or during the shelf life of the dosage form.
- The polymer should be easily available in the market and economical.

Table 1: Mucoadhesive Polymers for Buccal Patches^{18, 40, 44}

CRITERIA	CATEGORY	EXAMPLES
Source	Semi-Natural/Natural	Agarose, Chitosan, Gelatine, Hyaluronic acid, Various gums (guar, hakea, xanthan, gellan, carragenan, pectin and sodium alginate)
	Synthetic	Cellulose derivatives CMC, Thiolated CMC, Sodium CMC, HEC, HPC, HPMC, MC, Methyl hydroxyl ethyl cellulose. Poly(acrylic acid)-based polymers CP, PC, PAA, Polyacrylates, Poly(methylvinylether-co-methacrylic acid), Poly (2-hydroxyethylmethacrylate), Poly (acrylicacid-co-ethylhexylacrylate), Poly (methacrylate), Poly(alkylcyanoacrylate), Poly(isohexylcyanoacrylate), Poly(isobutylcyanoacrylate), Copolymer of acrylic acid and PEG Others Poly (N- 2- hydroxypropylmethacrylamide), Polyxyethylene, PVA, PVP, Thiolated polymers.
Aqueous Solubility	Water soluble	CP, HEC, HPC (water < 38°C), HPMC (cold water), PAA, sodium CMC, Sodium alginate, Chitosan (soluble in dilute aqueous acids), EC, PC
Charge	Cationic	Aminodextran, chitosan, dimethylaminoethyl-dextran, trimethylated chitosan
	Anioic	Chitosan-EDTA, CP, CMC, pectin, PAA, PC, sodium alginate, sodium CMC, xanthan gum
	Nonionic	Hydroxyethyl starch, HPC, poly(ethylene oxide), PVA, PVP, scleroglucan
Potential Bioadhesive Forces	Covalent	Cyanoacrylate
	Hydrogen Bonding	Acrylates [hydroxylated methacrylate, Poly (methacrylic acid)], CP, PC, PVA
	Electrostatic interaction	Chitosan

3. BACKING MEMBRANE: Backing membrane plays a major role in the attachment of bioadhesive devices to the mucus membrane. The materials used as backing membrane should be inert, and impermeable to the drug and penetration enhancer. The commonly used materials in backing membrane include carbopol, magnesium separate, HPMC, HPC, CMC, polycarbophil etc.²⁶

4. PENETRATION ENHancers: Substances that facilitate the permeation through buccal mucosa are referred as permeation enhancers. One of the major disadvantages associated with buccal drug delivery is the low flux of drugs across the mucosal epithelium, which results in low drug bioavailability. Various compounds have been investigated for their use as buccal penetration and absorption enhancers to increase the flux of drugs through the mucosa.²⁰

Mechanisms of Action of Permeation Enhancers^{4, 45}:

Mechanisms by which penetration enhancers are thought to improve mucosal absorption are as follows:

a. **Changing mucus rheology:** Mucus forms viscoelastic layer of varying thickness that affects drug absorption. Further, saliva covering the mucus layers also hinders the absorption. Some permeation

enhancers' act by reducing the viscosity of the mucus and saliva overcomes this barrier.

- b. **Increasing the fluidity of lipid bilayer membrane:** The most accepted mechanism of drug absorption through buccal mucosa is intracellular route. Some enhancers disturb the intracellular lipid packing by interaction with either lipid packing by interaction with either lipid or protein components.
- c. **Acting on the components at tight junctions:** Some enhancers act on desmosomes, a major component at the tight junctions thereby increases drug absorption.
- d. **By overcoming the enzymatic barrier:** These act by inhibiting the various peptidases and proteases present within buccal mucosa, thereby overcoming the enzymatic barrier. In addition, changes in membrane fluidity also alter the enzymatic activity indirectly.
- e. **Increasing the thermodynamic activity of drugs:** Some enhancers increase the solubility of drug thereby alters the partition coefficient. This leads to increased thermodynamic activity resulting better absorption.

Table 2: Example of Permeation Enhancers^{27, 40}:

CATEGORY	EXAMPLES
Surfactants	Ionic Sodium lauryl sulfate, Sodium laurate, Polyoxyethylene-20-cetyl ether, Laureth-9, Sodium dodecyl sulfate(SDS), Dioctyl Sodium sulfosuccinate Non-ionic Polyoxyethylene-9-lauryl ether, Tween 80, Nonylphenoxyethoxyethylene, Polysorbates, Sodium glycolate.
Bile Salts and Derivatives	Sodium deoxycholate, Sodium taurocholate, Sodium taurodihydrofusidate, Sodium glycocidihydrofusidate, Sodium glycocholate, Sodium deoxycholate.
Fatty acids and derivatives	Oleic acid, Caprylic acid, Mono(di)glycerides, Lauric acid, Linoleic acid, Acylcholines, Acylcarnitine, Sodium caprate.
Chelating Agents	EDTA, Citric acid, Salicylates.
Sulfoxides	Dimethyl sulfoxide(DMSO), Decylmethyl sulfoxide
Polyols	Propylene glycol, Polyethylene glycol, Glycerol, Propanediol.
Monohydric Alcohols	Ethanol, Isopropanol.
Others	Urea and derivative, Unsaturated cyclic urea, Azone (1- dodecylazacycloheptan-2-one), Cyclodextrin, Enamine derivatives, Terpenes, Liposomes, Acyl carnitines and cholines.

6. Plasticizers: These are the materials used to achieve softness and flexibility of thin films of polymer or blend of polymers. Examples of common plasticizers used are glycerol, propylene glycol, PEG 200, PEG 400, castor oil etc. The plasticizers help in release of the drug substance from the polymer base as well as act as penetration enhancers. The choice of the plasticizer depends upon the ability of plasticizer material to solvate the polymer and alters the polymer- polymer interactions. When used in correct proportion to the polymer, these materials impart flexibility by relieving the molecular rigidity.²⁶

PREPARATION OF MUCOADHESIVE PATCHES

Mucoadhesive buccal patches can be prepared by the following methods:

1. Solvent casting: In this method, all ingredients are weighed accurately and mixed in pestle and mortar. Then the mixture is added gradually to magnetically stir solvent system, which contains the plasticizer. The stirring is continued until a clear solution is obtained. The solution is then transferred quantitatively to petri-dish. The petri-dish is covered with inverted funnels to allow evaporation of the solvents^{46, 47}. These are kept at 20-25°C temperature for 24 to 48 hours depending upon the solvent system used. After solvent evaporation a thin layer of the protective backing material is laminated onto the sheet of coated release liner to form a laminate that is die-cut to form patches of the desired size and geometry.⁴⁸

2. Direct milling: In this, patches are manufactured without the use of solvents. Drug and excipients are mechanically mixed by direct milling or by kneading, usually without the presence of any liquids. After the mixing process, the resultant material is rolled on a

release liner until the desired thickness is achieved. The backing material is then laminated onto the sheet of coated release liner to form a laminate that is die-cut to form patches of the desired size and geometry.⁴⁹

EVALUATION OF BUCCAL PATCHES

The following tests are used to evaluate the Buccal Patches:

- Weight uniformity:** Five different randomly selected patches from each batch are weighed and the weight variation is calculated.
- Thickness uniformity:** The thickness of each patch is measured by using digital vernier callipers at five different positions of the patch and the average is calculated.
- Folding Endurance:** The folding endurance of each patch is determined by repeatedly folding the patch at the same place till it is broken or folded up to 300 times, which is considered satisfactory to reveal good film properties.⁵⁰
- Surface pH:** The prepared buccal patches are left to swell for 2 hrs on the surface of an agar plate, prepared by dissolving 2% (w/v) agar in warm phosphate buffer of pH 6.8 under stirring and then pouring the solution into a Petri dish till gelling at room temperature.⁵¹ The surface pH is determined by placing pH paper on the surface of the swollen patch. The mean of three readings is recorded.⁵²
- Drug content uniformity:** For drug content uniformity, a 3 cm patch (without backing membrane) is separately dissolved in 100 ml of ethanol and simulated saliva solution (pH 6.2) mixture (20:80) for 12 h under occasional shaking. The resultant solution is filtered and the drug content of is estimated spectrophotometrically. The averages of three determinations are taken.⁵³

6. Swelling Index: Buccal patches are weighed individually (w_1) and placed separately in petri dishes containing phosphate buffer pH 6.8. The patches are removed from the petri dishes and excess surface water is removed using filter paper. The patches are reweighed (w_2) and swelling index (SI) is calculated as follows:^{54,55}

$$SI = (W_2 - W_1)/W_1$$

7. Moisture Content and moisture absorption⁵⁶: The buccal patches are weighed accurately and kept in dessicator containing anhydrous calcium chloride. After 3 days, the patches are taken out and weighed.¹² The moisture content (%) is determined by calculating moisture loss (%) using the formula:

$$\text{Moisture content (\%)} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

The buccal patches are weighed accurately and placed in a dessicator containing 100 ml of saturated solution of aluminium chloride, which maintains 76% and 86% humidity (RH). After 3 days, films are taken out and weighed. The moisture absorption is calculated using the formula:

$$\text{Moisture absorption (\%)} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

8. In-vitro drug release: The United States Pharmacopeia (USP) XXIII-B rotating paddle method is used to study the drug release from the bilayered and multilayered patches. The dissolution medium consisted of phosphate buffer pH 6.8. The release is performed at $37^\circ\text{C} \pm 0.5^\circ\text{C}$, with a rotation speed of 50 rpm. The backing layer of buccal patch is attached to the glass disk with instant adhesive material. The disk is allocated to the bottom of the dissolution vessel. Samples (5 ml) are withdrawn at predetermined time intervals and replaced with fresh medium. The samples are then filtered through wattman filter paper and analyzed for drug content after appropriate dilution.⁵⁷

9. Ex-vivo mucoadhesion time: The *ex-vivo* mucoadhesion (residence) time is determined by locally modified USP disintegration apparatus using 800 mL of simulated saliva (pH 6.2) and the temperature is maintained at $(37 \pm 1)^\circ\text{C}$. A porcine buccal mucosa obtained from local slaughter house within 2 h of slaughter is used to mimic the human buccal mucosa in the *in-vivo* conditions. The mucosal membrane is carefully separated by removing the underlying connective tissues using surgical scissors. The separated mucosal membrane is washed with deionized water and then with simulated saliva (pH 6.2).⁵⁸ Porcine buccal mucosa (3 cm diameter) is glued on the surface of a glass slab. One side of the buccal patch is hydrated with one drop of simulated saliva (pH 6.2) and brought into contact with porcine buccal mucosa by gentle pressing with a fingertip for few seconds. The glass slab is vertically fixed to the shaft of the disintegration apparatus and allowed to move up and down (25 cycles per min). The patch is completely

immersed in simulated saliva at the lowest point and is out of the solution at the highest point. The time of complete erosion or detachment of the patch from the mucosal surface is recorded as *ex-vivo* mucoadhesion time.⁵⁹

10. Ex-vivo mucoadhesive strength: The force required to detach the attachment of mucoadhesive film from the mucosal surface was applied as a measure of the mucoadhesive strength. This study was carried out on a specially fabricated physical balance assembly. Porcine buccal mucosa was glued on a dry petri dish surface by placing the mucosal surface outward and it was moistened with few drops of simulated saliva (pH 6.2). The right side pan of the balance was replaced by a glass disc glued with a buccal patch of 3 cm diameter. The balance was adjusted for equal oscillation by keeping sufficient weight on the left pan. A weight of 5 g (w_1) was removed from the left pan, which lowered the pan and buccal patch was brought in contact with pre moistened mucosa for 5 min. Then weights were increased gently on the left pan until the attachment breaks (w_2). The difference in weight ($w_2 - w_1$) was taken as mucoadhesive strength.⁵⁹ The mucoadhesive force was calculated from the following equation:

$$\text{Mucoadhesive force (kg/m/s)} =$$

$$\frac{\text{Mucoadhesive strength (g)} \times \text{acceleration due to gravity}}{1000}$$

Here, acceleration due to gravity 9.8 m/s^{-1}

11. Ex-vivo permeation study: The *ex-vivo* buccal permeation through the porcine buccal mucosa is performed using a modified Franz glass diffusion cell. Porcine buccal mucosa is obtained from a local slaughterhouse and used within 2 h of slaughter. Freshly obtained porcine buccal mucosa is mounted between the donor and receptor compartments. The patch is placed on the smooth surface of mucosa by gentle pressing and the compartments are clamped together. The donor compartment is moistened with 1 ml of simulated saliva (pH 6.2) and the receptor compartment is filled to touch the membrane with a mixture of 100 ml of ethanol and isotonic phosphate buffer (20:80).^{60, 61} The fluid motion in the receptor compartment is maintained by stirring with a magnetic bead at 50 rpm. The temperature is maintained at $(37 \pm 0.2)^\circ\text{C}$ by water jacket surrounding the chamber. At predetermined time intervals, a 2 ml sample is withdrawn (replaced with fresh medium) and analyzed spectrophotometrically. The permeation study is performed in triplicate.

12. Stability Studies in Human Saliva⁶²: The stability study of buccal patches is performed in natural human saliva. The human saliva is collected from humans (age 18-50 years). Buccal patches are placed in separate Petri dishes containing 5 ml of human saliva and placed in a temperature-controlled oven at $37^\circ\text{C} \pm 0.2^\circ\text{C}$ for 6 hours. At regular time intervals (0, 1, 2, 3, and 6 hours), the patches are examined for change in colour, shape and drug content.

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