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Review Article

A review on Mucoadhesive Buccal Patches

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ABSTRACT: The oral cavity is an attractive site for the delivery of drugs. Through this route it is possible to realize mucosal (local effect) and transmucosal (systemic effect) drug administration. In the first case, the aim is to achieve a site-specific release of the drug on the mucosa, whereas the second case involves drug absorption through the mucosal barrier to reach the systemic circulation.Absorption through the buccal mucosa overcomes premature drug degradation due to the enzyme activity and pH of gastro intestinal tract, avoids active drug loss due to presystemic metabolism, acid hydrolysis and therapeutic plasma concentration of the drug can be rapidly achieved. The adhesive properties of such drug delivery platforms can reduce the enzymatic degradation due to the increased intimacy between the delivery vehicle and the absorbing membrane. However, per oral administration of drugs has disadvantages such as hepatic first pass metabolism and enzymatic degradation within the GI tract, that prohibit oral administration of certain classes of drugs especially peptides and proteins. Consequently, other absorptive mucosa is considered as potential sites for drug administration. Transmucosal routes of drug delivery offer distinct advantages over per oral administration for systemic drug delivery.

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INTRODUCTION

Buccal delivery is a major alternative to the oral and buccal routes of systemic drug delivery[1]. The buccal mucosa provides readily accessible route for Transmucosal delivery[2].

Absorption through the buccal mucosa overcomes premature drug degradation due to the enzyme activity and pH of gastro intestinal tract, avoids active drug loss due to presystemic metabolism, acid hydrolysis and therapeutic plasma concentration of the drug can be rapidly achieved[3]. The adhesive properties of such drug delivery platforms can reduce the enzymatic degradation due to the increased intimacy between the delivery vehicle and the absorbing membrane[4]. It has also been used as pharmaceutical excipients in conventional dosage forms as well as in novel applications involving bioadhesion and transmucosal drug transport[5].Amongst the various routes of drug delivery, oral route is perhaps the most preferred to the patient and the clinician alike.

However, per oral administration of drugs has disadvantages such as hepatic first pass metabolism and enzymatic degradation within the GI tract, that prohibit oral administration of certain classes of drugs especially peptides and proteins. Consequently, other absorptive mucosa is considered as potential sites for drug administration. Transmucosal routes of drug delivery offer distinct advantages over per oral administration for systemic drug delivery[6]. These advantages include possible bypass of first pass effect, avoidance of presystemic elimination within the GI tract, and, depending on the drug, a better enzymatic flora for drug absorption. There are two permeation pathways for passive drug transport across the oral mucosa: paracellular and transcellular routes. Permeates can use these two routes simultaneously, but one route is usually preferred over the other depending on the physicochemical properties of the diffusion. Since the intercellular spaces and cytoplasm are hydrophilic in character, lipophilic compounds would have low solubility's in this environment[7].

The cell membrane, however, is rather lipophilic in nature and hydrophilic solutes will have difficulty permeating through the cell membrane due to a low partition coefficient. Therefore, the intercellular spaces pose as the major barrier to permeation of lipophilic compounds and the cell membrane acts as the major transport barrier for hydrophilic compounds. Since the oral epithelium is stratified, solute permeation may involve a combination of these two routes. The route that predominates, however, is generally the one that provides the least amount of hindrance to passage[8]. Oral Transmucosal Drug Delivery: Within the oral cavity delivery of drug is classified into several categories. Absorption of drug via mucous membranes of the oral cavity was noted as early as 1847 by Sobvero, the discovery of nitroglycerin, and systemic studies of oral cavity absorption was first reported by Walton in 1935. Due to its excellent accessibility and reasonable patient compliance oral mucosal cavity offers attractive route of drug administration. Within the oral mucosal cavity delivery of drug is classified into three categories:

Sublingual delivery: This is a systemic delivery of drug through the mucosal membrane lining the floor of the mouth[9]. Buccal delivery and Local delivery: for the treatment of conditions of the oral cavity. The oral cavity is foremost part of digestive system of human body. It is also referred to as "buccal cavity". It is accountable for various primary functions of body. Oral cavity can help in development of a suitable buccoadhesive drug delivery system. The buccal mucosa lines the inner cheek, and buccal formulations are placed in the mouth between the upper gums and cheek to treat local and systemic conditions. The buccal route provides one of the potential routes for typically large, hydrophilic and unstable proteins, oligonucleotides and polysaccharides, as well as conventional small drug molecules. The oral cavity has been used as a site for local and systemic drug delivery[10].

Anatomical Features: The outer surface of the oral cavity is a mucous membrane consisting of an epithelium, basement membrane and lamina propria overlying a submucousa containing blood vessels and nerves. The mucosa can be divided into three types: Masticator mucosa, found on the gingiva and hard palate. Lining mucosa, found on the lips, cheeks, floor of mouth, undersurface of the tongue and the soft palate. Specialized mucosa found on the upper surface of the tongue and parts of the lips. All consists of a squamous stratified epithelium, many cell layers (40-50 for buccal mucosa) overlying a connective tissue, layer, the lamina propria. The total surface area of oral cavity = 170 cm².

The careful examination of various features

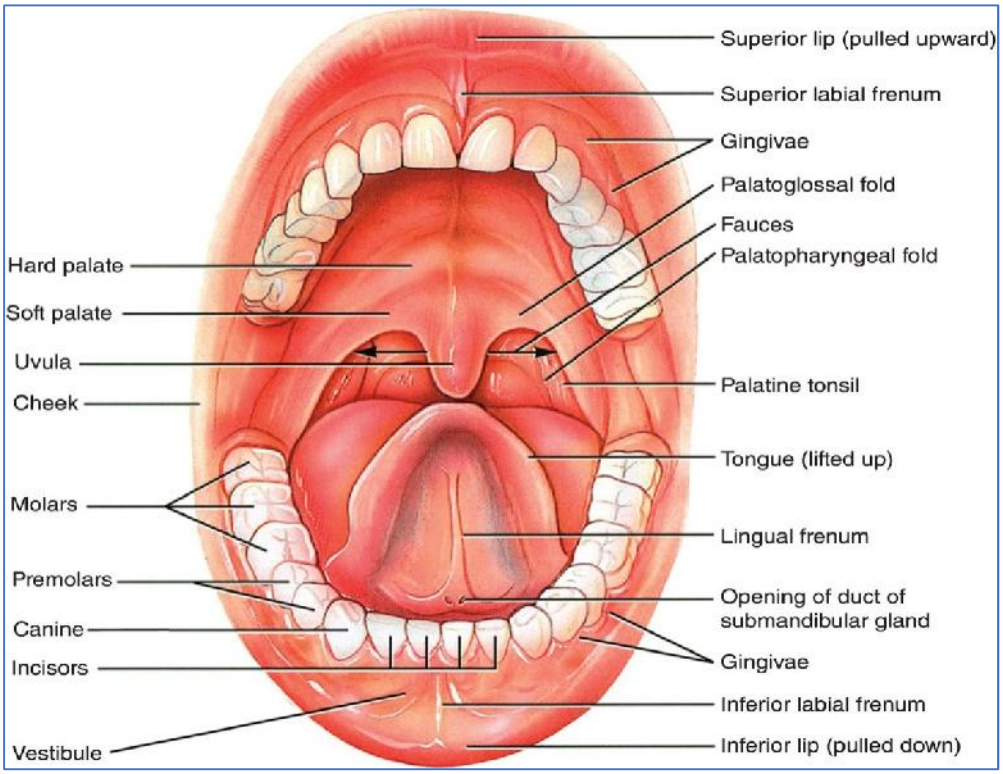

Table 1: Thickness and surface area of oral cavity membranes

Oral cavity membrane:Thickness (mm) Surface area (cm²) Buccal Mucosa 500-600 05.2 Sublingual Mucosa 100-200 26.5 Gingival Mucosa 200 -- Palatal 250 20.0. Drug Delivery via Buccal Rout: Buccal delivery refers to drug release which can occur when a dosage form is placed in the outer vestibule between the buccal mucosa and gingiva. Various advantages and other aspects of this route are elucidated in latter sections.

BUCCAL ABSORPTION

Buccal delivery refers to drug release which can occur when a dosage form is placed in the outer vestibule between the buccal mucosa and gingiva. Various advantages and other aspects of this route are elucidated in latter sections[11].

Factors Affecting Buccal Absorption: [13]

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. Some of these factors are:

Membrane factor

Environmental factor

- Saliva
- Salivary glands
- Movement of oral tissue

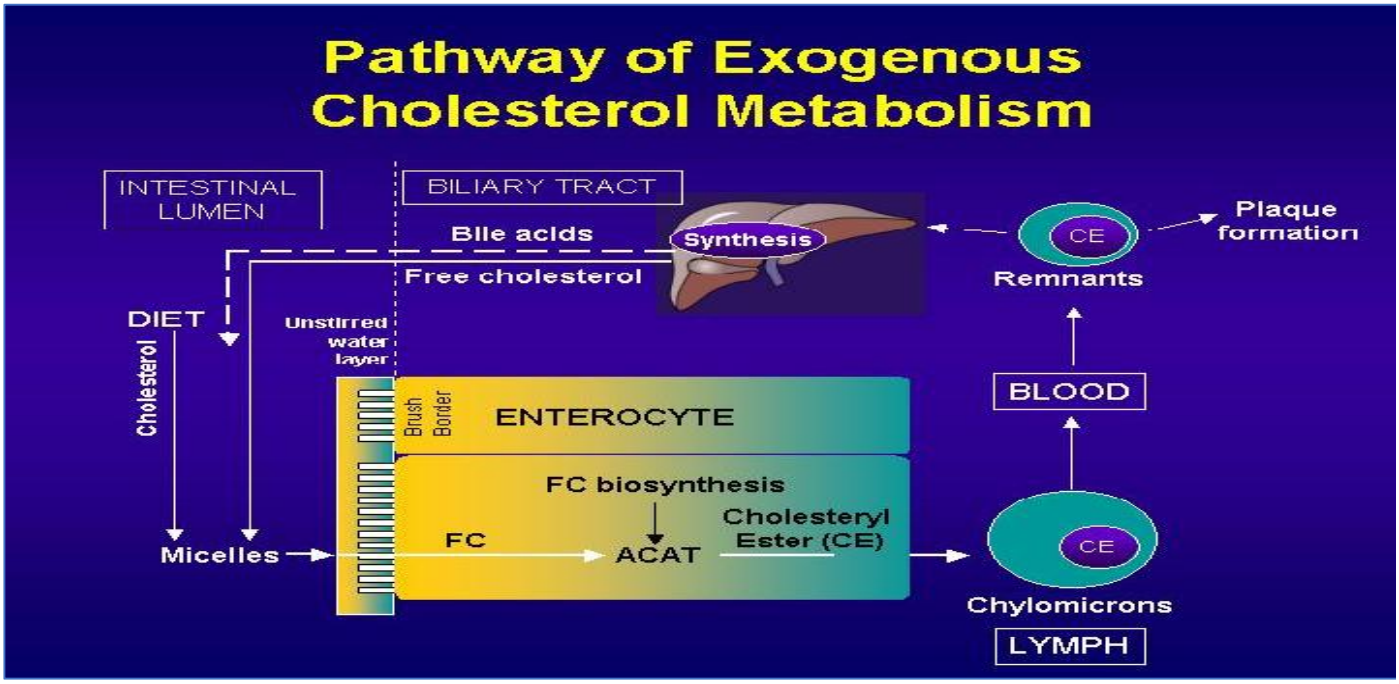

Fig.2: Buccal Routes of Drug Absorption

Mechanism: Oral mucosal drug absorption occurs by passive diffusion of the non-ionized species, a process governed primarily by a concentration gradient, through the intercellular spaces of the epithelium. The buccal mucosa has been said to behave predominately as a lipoidal barrier to the passage of drugs; as is the case with many other mucosa and (within limits) the more lipophilic (or less ionized) the drug molecule, the more readily it is absorbed. It has been concluded that the passive diffuses in accordance with the pH partition theory of drug absorption is the major route of drug absorption for most drugs. However, it has been reported that certain molecules e.g., some sugars and vitamins may be transported by a specialized transport system capable of saturation. It has been proposed that the intercellular route, rather than the transcellular route, is the predominant route for drug absorption. Large hydrophilic molecules are believed to be transported by the intercellular route and the presence of the contents of membrane-coating granules in the intercellular space may inhibit penetration in both keratinized and nonkeratinized mucosa[12].

Buccal patch is a non-dissolving thin matrix modified release dosage form 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

Buccal Patches: Buccal patch is a non-dissolving thin matrix modified release dosage form 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:

1. **Matrix type** (Bi-directionalThe 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.
2. **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.

Advantages of buccal drug delivery system: [14]

1. It is richly vascularized and more accessible for the administration and removal of a dosage form.
2. Buccal drug delivery has a high patient acceptability compared to other non-oral routes of drug administration.
3. Harsh environmental factors that exist in oral delivery of a drug are circumvented by buccal delivery.
4. Harsh environmental factors that exist in oral delivery of a drug are circumvented by buccal delivery.
5. Avoids acid hydrolysis in the gastrointestinal tract and by passing the first-pass effect.
6. Moreover, rapid cellular recovery and achievement of a localized site on the smooth surface of the buccal mucosa

Disadvantages of buccal drug delivery system:

1. Low permeability of the buccal membrane: specifically, when compared to the sublingual membrane.
2. Smaller surface area. The total surface area of the membranes of the oral cavity available for drug absorption is 170 cm^2 of which ~50 cm^2 represents non-keratinized tissues, including the buccal membrane [15].
3. The continuous secretion of saliva leads to subsequent dilution of the drug.
4. Swallowing of saliva can also potentially lead to the loss of dissolved or suspended drug and, ultimately, the involuntary removal of the dosage form. These are some of the problems that are associated with buccal.

Method(s) of Preparation:

Two methods used to prepare adhesive patches include:

Solvent Casting: In this, all patch excipients including the drug co dispersed in an organic solvent and coated onto a sheet of release liner. 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. The solvent casting method is simple, but suffers from some disadvantages, including long processing time, high cost, and environmental concerns due to the solvents used. These drawbacks can be overcome by the hot-melt extrusion method [16, 17].

Water soluble ingredients are dissolved in H2O and API and other agents are dissolved in:

Suitable solvent to form a clear viscous solution

↓

Both the solutions are mixed

↓

Resulting solution is cast as a film and allowed to dry

↓

Film is collected

Direct Milling;this, patches are manufactured without the use of solvents (solvent-free). 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. An impermeable backing membrane may also be applied to control the direction of drug release, prevent drug loss, and minimize deformation and disintegration of the device during application period [18].

API and excipients are blended by direct milling

↓

Blended mixture is rolled using rollers

↓

Backing material is laminated

↓

Film is collected

While there are only minor or even no differences in patch performance between patches fabricated with the two processes, the solvent-free process is preferred because there is no possibility of residual solvents and no associated solvent related health issue.

TYPES

1. **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.

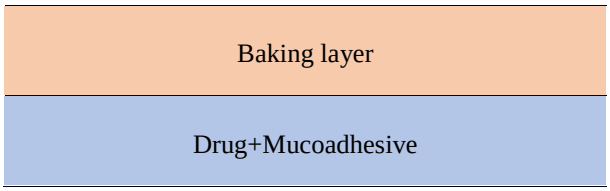

Fig. 1: Buccal Patch Bi-directional drug release

2. **Reservoir type (Uni-directional):** 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.

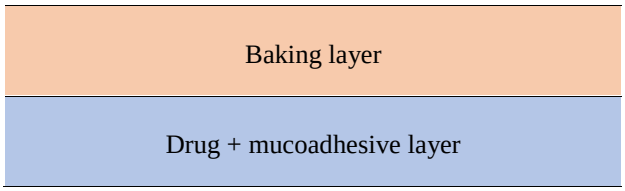

Fig. 2: Buccal patch designed for Uni-directional drug release

Pharmaceutical considerations

Great care needs to be exercised while developing a safe and effective buccal adhesive drug delivery device. Factors influencing drug release and penetration through buccal mucosa, organoleptic factors, and effects of additives used to improve drug release pattern and absorption, the effects of local drug irritation caused at the site of application are to be considered while designing a formulation.Polymers form the backbone of DS, which control the release of the drug from the device. Polymer matrix can be prepared by dispersion of drug in liquid or solid state synthetic polymer base. It should have biocompatibility and chemical compatibility with the drug and other components of the system. Additionally, they should provide consistent and effective delivery of a drug throughout the product's intended shelf life[19].

Penetration enhancers are chemical compounds that increase permeability of stratum corneum to attain higher therapeutic levels of the drug candidate.

It interacts with structural components of stratum corneum *i.e.*, proteins or lipids and subsequently alters the protein and lipid packaging of stratum corneum. It thus chemically modifies the barrier functions leading to increased permeability.

Pressure sensitive adhesive is a material that helps in maintaining an intimate contact between buccal system and the mucosal surface. It should have the following properties:

- Removable from the surface without leaving a residue
- Physio chemically and biologically compatible
- Aggressively and permanently tacky
- Exert a strong holding force
- Does not alter drug release

Backing layer must exhibit lowest modulus or high flexibility, it should provide good bond to the drug reservoir and prevent drug from leaving the dosage form through the top.

Release liner is a part of the primary packaging material rather than that of dosage form for delivering the drug. It is protective liner meant to cover the patch that is removed and discharged immediately before its application. As the liner is in intimate contact with the delivery system, it should comply with specific requirements regarding chemical inertness and penetration to the drug, penetration enhancer and water. It is composed of a base layer which may be non-occlusive (*e.g.* paper fabric) or occlusive (*e.g.* polyethylene, polyvinyl).

Solvents viz. water, acetone, chloroform, methanol, isopropanol and dichloromethane are used to prepare drug reservoir.

Plasticizers such as dibutylpthalate, triethylcitrate, polyethylene glycol and propylene glycol are added to provide plasticity to the Buccal patch.

Buccal adhesive polymersare a generic term used to describe a very long molecule consisting of structural units and repeating units connected by covalent chemical bonds. The term is derived from the Greek words: polys meaning many, and meros meaning parts.

The key feature that distinguishes polymers from other molecules is the repetition of many identical, similar, or complementary molecular subunits in these chains. These subunits, the monomers, are small molecules of low to moderate molecular weight, and are linked to each other during a chemical reaction called polymerization. Instead of being identical, similar monomers can have varying chemical substituents. The differences between monomers can affect properties such as solubility, flexibility, and strength. The term buccal adhesive polymer covers a large, diverse group of molecules, including substances from natural origin to biodegradable grafted copolymers and thiolated polymers. Bioadhesive formulations use polymers as the adhesive component. These formulations are often water soluble and when in a dry form attract water from the biological surface and this water transfer leads to a strong interaction. These polymers also form viscous liquids when hydrated with water that increases their retention time over mucosal surfaces and may lead to adhesive interactions.

Bioadhesive polymers should possess certain physicochemical features including hydrophilicity, numerous hydrogen bond-forming groups, flexibility for interpenetration with mucus and epithelial tissue, and viscoelastic properties.

Ideal characteristics: [20]

- Polymer and its degradation products should be non-toxic, non-irritant and free from leachable impurities.
- Should have good spreadability, wetting, swelling and solubility and biodegradability properties.
- pH should be biocompatible and should possess good viscoelastic properties.
- Should adhere quickly to buccal mucosa and should possess sufficient mechanical strength.
- Should possess peel, tensile and shear strengths at the bioadhesive range.
- Polymer must be easily available and its cost should not be high.
- Should show bioadhesive properties in both dry and liquid state.
- Should demonstrate local enzyme inhibition and penetration enhancement properties.
- Should demonstrate acceptable shelf life.
- Should have optimum molecular weight.
- Should possess adhesively active groups.
- Should have required spatial conformation.
- Should be sufficiently cross-linked but not to the degree of suppression of bond forming groups.
- Should not aid in development of secondary infections such as dental caries.

Evaluation

Evaluation of prepared mucoadhesive placebo buccal patches can be performed with following physical characteristics.

1. Patch Weight
2. Thickness
3. Folding Endurance
4. Surface pH
5. Drug Content
6. Swelling Index

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