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Review Article

A Comprehensive Review on Buccal Drug Delivery System

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ABSTRACT: Buccal delivery involves the administration of the desired drug through the buccal mucosal membrane lining of the oral cavity. The objective of this article is to review buccal drug delivery by discussing the structure and environment of the oral mucosa and highlighting the mechanisms of drug permeation and methodology in evaluating buccal formulations. This review also highlights a brief description of advantages, limitations of buccal drug delivery and theories involved in mucoadhesion along with method of preparation mucoadhesive system, mucoadhesive polymer, and classification of buccal system.

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INTRODUCTION

Amongst the various routes of administration tried so far in the novel drug delivery systems, localized drug delivery to tissues of the oral cavity has been investigated for the treatment of periodontal disease, bacterial and fungal infection. Over the decades mucoadhesion has become popular for its potential to optimize localized drug delivery, by retaining a dosage form at the site of action (e.g. within the gastrointestinal tract) or systemic delivery by retaining the formulation in intimate contact with the absorption site (e.g. buccal cavity) [1].

Well defined bio adhesion is the ability of a material (synthetic or biological) to adhere to a biological tissue for an extended period. The biological surface can be epithelial tissue or it can be the mucus coat on the surface of a tissue. If adhesion is to a mucous coat, the phenomenon is referred to as mucoadhesion.

The use of mucoadhesive polymers in buccal drug delivery has a greater application. Various mucoadhesive devices, including tablets, films, patches, disks, strips, ointments and gels, have recently been developed. However, buccal patch offer greater flexibility and comfort than the other devices. In addition, a patch can circumvent the problem of residences time of oral gels on mucosa, since the gels are easily washed away by saliva. [2].

An ideal buccal patch should be flexible, elastic and soft yet adequately strong to withstand breakage due to stress from mouth activities. Moreover, it must also exhibit good muco adhesive strength so that it can be retained in the mouth for a desired duration. As such, the mechanical, mucoadhesive, and swelling properties of buccal patches are critical and essential to be evaluated. The buccal route has high acceptance due to avoidance of 1st pass metabolism and possibility of being accessible for controlled drug release [3-5].

The pharmaceutical industry has made itself of significant importance by making a major contribution in the healthcare industry. The improvement and developments made by pharmaceutical industry have significantly donated in relationships of treatment of disease, thereby improving the quality of life [6]. Among the delivery routes, oral route is most preferred route by medical practitioner and manufacturer due to highest acceptability of patients, ease of ingestion, pain avoidance and versatility [7].

The concept of mucosal adhesion or mucoadhesive was introduced into controlled drug delivery area in the early 1980's, which is become a major part of novel drug delivery system in the recent era. Some of the potential sites for attachment of any mucoadhesive system are include buccal cavity, nasal cavity, eyes, vagina, rectal area, sublingual route and gastrointestinal area. Amongst the various routes of administration tried so far for novel drug delivery systems localized delivery to tissue of the oral cavity has been investigated for several applications including the treatment of toothaches, periodontal disease, bacterial and fungal infections, apathos and dental stomatitis and facilitating tooth movement with prostaglandins [8]. Oral Trans mucosal drug delivery may be of 3 types like sublingual, gingival, and buccal [9].

Buccal route of drug delivery provides the direct access to the systemic circulation through the jugular vein bypassing the first pass hepatic metabolism leading to high bioavailability. Other advantages such as excellent accessibility, low enzymatic activity, suitability for drugs or excipients that mildly and reversibly damage or irritate the mucosa, painless administration, easy withdrawal, facility to include permeation enhancer/ enzyme inhibitor or pH modifier in the formulation, versatility in designing as multidirectional or unidirectional release system for local or systemic action [2].

Pharmaceutical aspects of mucoadhesion have been the subject of great interest during recent years because it provides the possibility of avoiding either destruction by gastrointestinal contents or hepatic first-pass inactivation of drug. The mucoadhesive drug delivery system includes the following:

1. Buccal drug delivery systems
2. Sublingual drug delivery systems
3. Rectal drug delivery systems
4. Vaginal drug delivery systems
5. Ocular drug delivery systems
6. Nasal drug delivery systems [10]

Ideal characteristics [11, 12]:

- Polymer and its degradation products should be non-poisonous, non-irritant and free from leachable impurities.
- Should have good spreadability, wetting, swelling and solubility and biodegradability properties.
- Should adhere quickly to buccal mucosa and should have sufficient mechanical strength.
- It must possess peel, tensile and shear strengths at the bio-adhesive range.
- Polymer must be simply available and inexpensive.
- In dry and liquid state, it should possess bio-adhesion properties.
- It should exhibit local enzyme inhibition and penetration enhancement properties.
- It should show suitable shelf life.
- It should have adhesively active groups.
- It should be adequately cross-linked but not to the degree of suppression of bond forming groups. (Justify the sentence)
- It should not support in development of secondary infections such as dental caries.

Advantages of buccal drug delivery system [13-15]:

Buccal drug delivery system has following advantages over conventional drug delivery systems.

- Persists the residence time of the dosage form at the absorption site, hence rises the bioavailability.
- Outstanding availability, rapid onset of action possible.
- Fast absorption because of huge blood supply and good perfusion rates.
- An alternative to oral route, whereby the drug is secure from degradation in the acidic environment of the GIT.
- Preferable patient acquiescence.
- Likewise, rapid cellular recuperating and healing of the local site.
- In this, there is reduced dosing frequency.
- Extreme utilization of drug facilitating reduction in total amount of drug administered.

Limitations of buccal drug delivery system [13-15]:

- By this route, the drugs which irritate the oral mucosa, have a bitter or unpleasant taste and odor, cannot be administered.
- Only drugs, which are absorbed by passive diffusion, can be administered by this route.
- By this route, drugs which are unstable at buccal pH, cannot be administered
- Only drugs with lesser dose requirements can be administered.
- Drugs may be swallowed along with the saliva and fail the benefits of buccal route.
- Eating and drinking may become restricted.
- It may get displaced.
- Over hydration may lead to the formation of slippery surface and structural integrity of the formulation may get disrupted by the swelling and hydration of the bio-adhesive polymers.

Various mucoadhesive polymers can broadly be categorized as follow [16]:

Synthetic polymers

1. Cellulose derivatives (Methylcellulose (MC), Ethyl cellulose (EC), Hydroxy ethyl cellulose (HEC), Hydroxyl propyl cellulose (HPC), Hydroxy propyl methylcellulose (HPMC), Sodium carboxy methylcellulose (NaCMC)

2. Poly (Acrylic acid) polymers (Carbomers, Polycarbophil)
3. Poly hydroxyl ethyl methylacrylate
4. Poly ethylene oxide
5. Poly vinyl pyrrolidone
6. Poly vinyl alcohol

Natural polymers:

1. Tragacanth
2. Sodium alginate
3. Guar gum
4. Xanthan gum
5. Soluble starch
6. Gelatin
7. Chitosan

Table 1: Mucoadhesive Polymers used in the Oral Cavity [17]

S. No.	Criteria	Categories	Examples
1	Source	Semi natural/Natural	Agarose, chitosan, gelatin, Hyaluronic acid, Various gums (guar gum, xanthan, gellan, carragenan, pectin and sodium alginate).
		Synthetic	Cellulose derivatives: [CMC, thiolated CMC, NaCMC, HEC, HPC, HPMC, MC
			Poly(acrylic acid)-based polymers:[CP, PC, PAA, polyacrylates, poly(methyl vinyl ether-co-methacrylic acid), poly(2- hydroxy ethyl methacrylate),poly(acrylic acid co-ethylhexyl acrylate), poly (methacrylate), poly(isobutylcyanoacrylate), copolymer of acrylic acid and PEG].
			Others: polyoxyethylene, PVA, PVP, thiolated Polymers
2	Aqueous Solubility	Water-soluble	CP, HEC, HPC, HPMC (cold water), PAA, NaCMC, sodium alginate
		Waters-insoluble	Chitosan (soluble in dilute aqueous acids), EC, PC.
3	Charge	Cationic	Aminodextran, Chitosan, (DEAE)- dextran, TMC
		Anionic	Chitosan-EDTA, CP, CMC, pectin, PAA, PC, sodium alginate, NaCMC, xanthan gum
		Non-ionic	Hydroxy ethyl starch, HPC, poly(ethylene oxide), PVA,
	Potential	Covalent	PVP, scleroglucan
		Hydrogen bond	Cyanoacrylate
5	Bioadhesive Forces	Electrostatic interaction	Acrylates [hydroxylated methacrylate, poly(methacrylic acid)], CP, PC, PVA, Chitosan

Composition of buccal drug delivery system [18]:

A. Active ingredient.
B. Polymers (adhesive layer): HEC, HPC, poly vinyl pyrrolidone (PVP), polyvinyl alcohol (PVA), carbopol and other mucoadhesive polymers.
C. Diluents: Lactose DC is selected as diluents for its high aqueous solubility, which make it suitable for direct compression. Another example: microcrystalline starch and starch.
D. Sweetening agents: Sucralose, aspartame, Mannitol, etc.
E. Flavoring agents: Menthol, vanillin
F. Backing layer: Ethylcellulose etc.
G. Penetration enhancer: Cyanoacrylate, etc.
H. Plasticizers: PEG-100, 400, propylene glycol, etc

Tragacanth

Tragacanth is a natural gum obtained from the dried juice of several species of the genus Astragalus, including *A. adscendens*, *A. gummifer*, *A. brachycalyx* and *A. tragacanthus*. Tragacanth gum is a viscous, odourless, tasteless and water-soluble mixture of polysaccharides [19, 20].

Sodium alginate

Alginic acid or alginate is an anionic polysaccharide, also called as algin and obtained in the cell walls of brown algae. It has ability of binding with water and forming a viscous gum. Alginic acid is capable of absorbing 200-300 times its own weight in water when water extracted from alginate. Alginate is mainly extracted from seaweed. Alginic acid is mainly produced by two bacterial genera such as *Pseudomonas* and *Azotobacter*. These play an important role in the preparation of its biosynthesis pathway [21].

Guar gum

Guar gum is naturally occurring form of galactomannan and called guaran [22]. It is primarily ground endosperm of guar beans. Guar gum contains about 80% galactomannan, 12% water, 5% protein, 2% acid soluble ash, and 0.7% fat. The molecular weight of guar gum is approximately 1 million that give high viscosity in solution. The high viscosity of guar gum is due to its long chain structure and high molecular weight. Guar gum is a polysaccharide composed of the sugars galactose and mannose [23, 24].

Chitosan

Chitosan a derivative form of chitin is a naturally occurring biopolymer. Chitosan is a linear polysaccharide composed of randomly distributed β- (1-4)-linked D-glucosamine (deacetylated unit) and N acetyl-D-glucosamine (acetylated unit). Commercial chitosan is derived from the shells of shrimp and other sea crustaceans, including *Pandalus borealis* [25].

Oral mucosal sites

Within the oral mucosal cavity, delivery of drugs is classified in to three categories-

1. Sublingual delivery: is the administration of the drug via the sublingual mucosa (the membrane of the ventral surface of the tongue and the floor of the mouth) to the systemic circulation.
2. Buccal delivery: is the administration of drug via the buccal mucosa (the lining of the cheek) to the systemic circulation.
3. Local delivery: for the treatment of conditions of the oral cavity, principally ulcers, fungal conditions and periodontal disease. These oral mucosal sites differ greatly from one another in terms of anatomy, permeability to an applied drug and their ability to retain a delivery system for a desired length of time [26, 27].

Overview of oral mucosa

The anatomical and physiological properties of oral mucosa had been extensively reviewed by several authors [28-30]. The oral cavity comprises the lips, cheek, tongue, hard palate, soft palate and floor of the mouth. The lining of the oral cavity is referred to as the oral mucosa, and includes the buccal, sublingual, gingival, palatal and labial mucosa. The buccal, sublingual and the mucosal tissues at the ventral surface of the tongue accounts for about 60% of the oral mucosal surface area. The top quarter to one-third of the oral mucosa is made up of closely compacted epithelial cells. The primary function of the oral epithelium is to protect the underlying tissue against potential harmful agents in the oral environment and from fluid loss [31]. Beneath the epithelium are the basement membrane, lamina propia and submucosa. The oral mucosa also contains many sensory receptors including the taste receptors of the tongue. Three types of oral mucosa can be found in the oral cavity; the lining mucosa is found in the outer oral vestibule (the buccal mucosa) and the sublingual region (floor of the mouth).

The specialised mucosa is found on the dorsal surface of tongue, while the masticatory mucosa is found on the hard palate (the upper surface of the mouth) and the gingiva (gums) [32]. The lining mucosa comprises approximately 60%, the masticatory mucosa approximately 25%, and the specialized mucosa approximately 15% of the total surface area of the oral mucosal lining in an adult human. The masticatory mucosa is in the regions particularly susceptible to the stress and strains resulting from masticatory activity. The superficial cells of the masticatory mucosa are keratinized, and a thick lamina propia tightly binds the mucosa to underlying periosteum. Lining mucosa on the other hand is not nearly as subject to masticatory loads and consequently, has a non-keratinized epithelium, which sits on a thin and elastic lamina propia and a submucosa. The mucosa of the dorsum of the tongue is specialized gustatory mucosa, which has a well papillated surface; which are both keratinized and some non-keratinized [33].

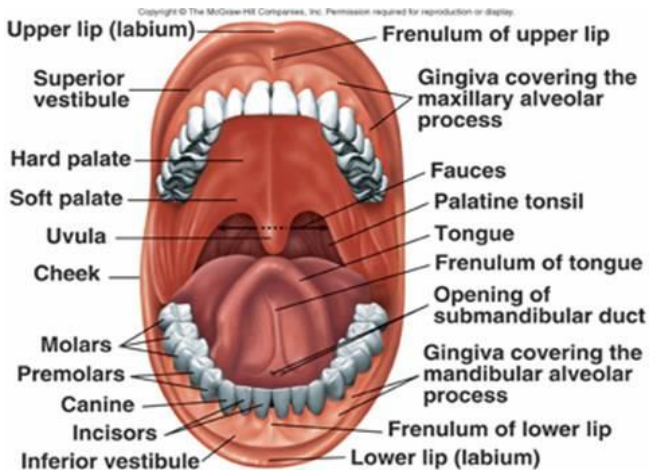

Fig. 1: Structure of Oral mucosa

Physiological aspects and functions of oral cavity [34]:

- As a portal for intake of food material and water
- Helps in chewing, mastication and mixing of food stuff.
- Helps to lubricate the food material and bolus
- To identify the ingested material by taste buds of tongue.
- To initiate the carbohydrate and fat metabolism
- To aid in speech and breathing process

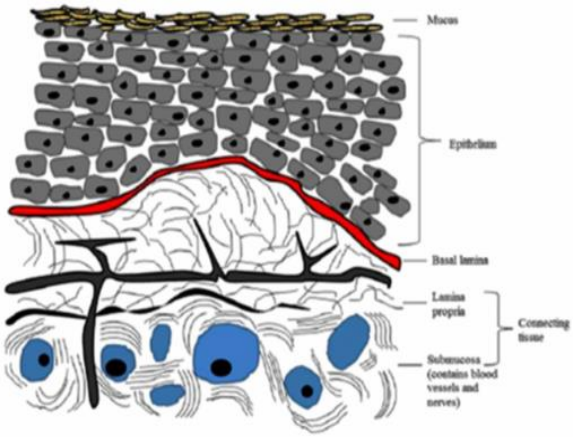

Fig. 2: Structure of Buccal mucosa

Classification of buccal drug delivery systems [35]:

Recent buccal mucoadhesive formulations prove to be an alternative to the conventional oral medications as they can be readily attached to the buccal cavity retained for a longer period and removed at any time. Mucoadhesive drug delivery systems using tablets, films, layered systems, discs, micro particles, ointments, wafers, lozenges and hydrogel systems has been studied by various research groups.

1. **Buccal tablets:** Bioadhesive tablets may be prepared using different methods such as direct compression or wet granulation technique. For delivery of drug via buccal route, the tablets which are inserted into the buccal pouch may dissolve or erode; therefore, they must be formulated and compressed with sufficient pressure only to give a hard tablet. To enable or to achieve unidirectional release of drug, water impermeable materials, like ethyl cellulose, hydrogenated castor oil, etc. may be used either by compression or by spray coating to coat every face of the tablet except the one that is in contact with the buccal mucosa. Bilayered and multilayered tablets are already formulated using bioadhesive polymers and excipients. If necessary, the drug may be formulated in certain physical states, such as microspheres, prior to direct compression to attain some desired properties e.g. enhanced activity and prolonged drug release.
2. **Buccal semisolid dosage forms:** These are semisolid dosage forms having the advantage of easy dispersion throughout the oral mucosa over the other type of dosage forms. Bioadhesive formulations have been used to overcome the poor retention of gels on the buccal mucosa. Certain bioadhesive polymers for example, sodium carboxy methylcellulose undergo a phase alteration from a liquid to a semisolid. This alteration improves or enhances the viscosity, resulting in sustained or controlled release of drugs. Buccal bioadhesive semisolid dosage forms consists of finely powdered natural or synthetic polymer dispersed in a polyethylene or in aqueous solution like Arabase.
3. **Buccal films:** In recent years, numerous bio adhesive dosage forms for delivery of drug via the buccal route have been developed such as films, tablet, patches, discs, gels and ointments. Buccal films are preferable over muco adhesive discs and tablets in terms of patient comfort and flexibility and they ensure more precise drug dosing and longer residence time compared to gels and ointments and thereby sustaining drug action. Buccal films also reduce pain by protecting wound surface and increasing drug effectiveness.
4. **Buccal powders:** Buccal bio adhesive powders are a mixture of drug and Bio adhesive polymers which are sprayed onto the buccal mucosa, the reduction in diastolic B.P. after the administration of buccal tablet and buccal film of nifedipine.
5. **Micro particle:** Micro particles have more advantages than tablet. The physical properties of microspheres enable to make them closely contact with a large mucosal surface. They can also be delivered to less accessible sites like GI track and nasal cavity and they cause less local irritation at the site of adhesion but the success of these microspheres is limited due to their short residence time at site of absorption.
6. **Wafer:** Wafer is a novel periodontal drug delivery system. This is used for the treatment of microbial infection.
7. **Lozenges:** Lozenges are used topically within mouth as antimicrobials, corticosteroids, local anesthetics, antibiotics and antifungals. In lozenges, multiple daily dosing is required because the release of drug in oral cavity is initially high and then rapidly decline to the sub-therapeutic levels.

Structure and Design of Buccal Dosage Form [27]:

1. Matrix type: The buccal patch designed in a matrix configuration contains drug, adhesive, and additives mixed together.
2. Reservoir type: 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.

Buccal absorption [36-38]:

Buccal absorption leads systemic or local action via buccal mucosa.

Mechanism of buccal absorption

Buccal drug absorption occurs by passive diffusion of the non-ionizeda 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 [36-37]. 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 Tomlison (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 follow:

$$- dm/dt = Kc/ViVt_1$$

Where, M - Mass of drug in mouth at time t_1, K - Proportionality constant, C - Concentration of drug in mouth at time, Vi - The volume of solution put into mouth cavity and Vt - 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 [38].

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. Physiological 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 muco adhesive dosage forms, it is potential barrier to drug penetration.
   c. **Movement of buccal tissues**: Buccal region of oral cavity shows less active movements. The muco adhesive 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 [39].

Bio adhesion [29, 40-42]:

'Bio adhesive' is defined as a substance that can interact with biological material and being retained on them or holding them together for persistent period.

Bio adhesive are classified into three categories:

1) Bio adhesion among biological layers without involvement of artificial materials. e.g. Cell diffusion and cell aggregation
2) Bio adhesion can be showed by cell adhesion into culture dishes or adhesion to a variety of substances including metals, woods and other synthetic materials.
3) Adhesion of artificial substances to biological substrate such as adhesion of polymer to soft tissue or skin.

Mechanism of bioadhesion [40, 42-45]:

For bio-adhesion to occur, three steps take place:

1. A close contact among a bio adhesive and a membrane either from a good wetting of the bio adhesive and a membrane or from the swelling of bio adhesive.
2. Penetration of the bio-adhesive into the tissue takes place.
3. Inter penetration of the chains of the bio adhesive with mucous takes place. Low chemical bonds can then settle.

The bonding between the mucus and the biological substance occurs mainly through both physical and chemical interactions results from expansion of the adhesive material and chemical bonds due to electrostatic interaction, hydrophobic interactions, hydrogen bonding and dispersion forces.

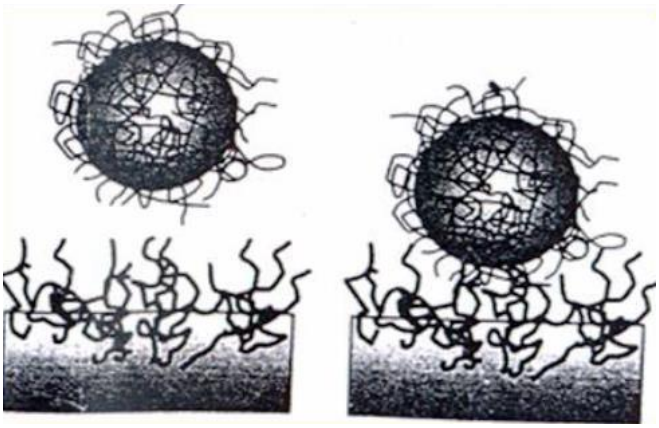

Fig. 3: Inter penetration of bio adhesive and mucus polymer chain

Factors affecting bio adhesion [6]:

Structural and physicochemical properties of a potential bio adhesion material influence bio adhesion.

A. **Polymer related factors**:
   i. Molecular weight:
      - The bio adhesive force rises with molecular weight of polymer upto 10,000 and beyond this level there is no much effect.
      - To allow chain interpenetration, the polymer molecule must have an adequate length.
   ii. Concentration of active polymers
      - There is an ideal concentration of polymer resultant to the best bio adhesion.
      - In extremely concentrated systems, the adhesive strength drops considerably.
      - In concentrated solutions, the coiled molecules become solvent poor and the chains presented for interpenetration are not abundant.
   iii. Flexibility of polymer chain:
      - Flexibility is necessary part for interpenetration and enlargement.
      - When water soluble polymers become cross linked, the mobility of individual polymer chain declines.
      - As the cross-linking density increases, the effective length of the chain which can penetrate into the mucus layer drops further and mucoadhesive strength is reduced.
   iv. Spatial conformation:
      - Beside molecular weight or chain length, spatial conformation of a molecule is also important.
      - Despite a high molecular weight of 19,500,000 for dextrans, they have same adhesive strength to that of polyethylene glycol with a molecular weight of 200,000.
      - The helical conformation of dextran may shield many adhesively active groups, primarily responsible for adhesion, different PEG polymers which have a linear conformation.

B. **Physiological factors**:

C. pH: The pH influences the charge on the surface of both mucus and the polymers. Mucus will have a different charge density depending on pH because of change in dissociation of functional groups on the Carbohydrate moiety and amino acids of the polypeptide back bone.

a. Strength: To place a solid bio adhesive system, it is necessary to apply a defined strength.

b. Initial contact time: As soon as the muco adhesive strength increases, the initial contact time is also increases.

c. Selection of the model substrate surface: The viability of biological substrate should be confirmed by examining properties such as permeability, Electrophysiology of histology.

d. Swelling: Swelling depends on both polymers concentration and on presence of water. When swelling is too great a decrease in bio adhesion occurs.

Theories of Bio adhesion or Muco-adhesion [29, 44, 46, 47]:

a) **Wetting Theory**: Wetting theory is predominantly applicable to liquid bio adhesive systems and analyzes adhesive and contact behavior in terms of a liquid or a paste to spread over a biological system. The work of adhesion [expressed in terms of surface and interfacial tension (γ) being defined as energy per cm^2 released when an interface is formed.

According to Dupres equation, work of adhesion is given by:

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

Where, A and B refers to the biological membrane and the bio adhesive formulation respectively. The work of cohesion is given by

$$Wc = 2\ \gamma_A \text{ or } \gamma_B$$

For a bio adhesive material B spreading on a biological substrate, the spreading coefficient is given by:

$$S_{B/A} = \gamma_A - (\gamma_B + \gamma_{AB})$$

$S_{B/A}$ should be positive for a bio adhesive material to adhere to a biological membrane. For a bioadhesive liquid B adhering to a biological membrane A, the contact angle is given by:

$$\text{Cos } \phi - (\phi A - \phi AB / \phi B).$$

b) **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 cross-linking density decreases.

c) **Electronic Theory**: According to this theory, electronic transfer occurs upon contact of an adhesive polymer and the mucus glycoprotein network because of differences in their electronic structure. This result in the formulation of an electronic double layer at the interface adhesion occurs due to attractive forces across the double layer.

d) **Fracture Theory**: According to Fracture theory of adhesion 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= Young's module of elasticity, ε = Fracture energy, L= Critical crack length when two surfaces are separated.

e) **Adsorption Theory**: According to this theory, after an initial contact between two surfaces, the materials adhere because of surface forces acting between the atoms in the two surfaces. Two types of chemical bonds such as primary covalent (permanent) and secondary chemical bonds (including electrostatic forces, Vander Waals forces and hydrogen and hydrophobic bonds) are involved in the adsorption process.

f) **Mechanical theory**: 48 Mechanical theory proposes that the adhesion is due to the filling of the irregularities on a rough surface by a mucoadhesive liquid. The roughness enhances the interfacial area available to interactions thereby aiding dissipation of energy.

Basic Components of Buccal Drug Delivery System:

1. Drug substance
2. Bio adhesive polymers
3. Backing membrane
4. Permeation enhancers

1. **Drug substance**: Before formulating mucoadhesive drug delivery systems, one has to decide whether the intended, action is for rapid release/prolonged release and for local/systemic effect. The selection of suitable drug for the design of buccal adhesive drug delivery systems should be based on pharmacokinetic properties.

The drug should have following characteristics [37]:

- The conventional single dose of the drug should be small.
- The drugs having biological half-life between 2-8 hrs are good candidates for controlled drug delivery.
- T_{max} of the drug shows wider-fluctuations or higher values when given orally.
- The drug absorption should be passive when given orally.

Table 1: Theories and mechanisms of bioadhesion [49]

S. No.	Theory	Mechanism of bio adhesion	Comments
1.	Wetting theory	Ability of bio adhesive polymer to spread and develop intimate contact with the mucous membrane.	Spreading coefficient of polymers must be positive. Contact angle between polymer and cells must be near to zero.
2.	Diffusion theory	Physical entanglement of mucin strands and flexible polymer chains.	For maximum diffusion and best adhesive strength, solubility parameters of the bio adhesive polymer and the mucus glycoproteins must be similar
3.	Electronic theory	Attractive electrostatic forces between glycoprotein mucin network and the bio adhesive material.	Electrons transfer occurs between the two forming a double layer of electric charge at the surface
4.	Fracture theory	Analyses the maximum tensile stress developed during attachment of the trans mucosal DDS from the mucosal surface	Does not require physical entanglement of bio adhesive polymer chains and mucous strands, hence it is appropriate to study the bio adhesion of hard polymers which lack flexible chains
5.	Adsorption theory	Surface force resulting in chemical bonding.	Strong primary force: covalent bonds. Weak secondary forces: hydrogen bonds and van der Waal's forces
6.	Mechanical theory	Adhesion arises from an interlocking of liquid adhesive into irregularities on the rough surface.	Rough surfaces provide an increased surface area available for interaction along with an enhanced viscoelastic and plastic dissipation of energy during joint failure, which are more important in the adhesion process than a mechanical effect.

2. **Bio adhesive polymer**: The first step in the development of buccal adhesive dosage forms is the selection and Characterization of appropriate bio adhesive polymers in the formulation. Bio adhesive polymers play a major role in buccoadhesive drug delivery systems of drugs. Polymers are also used in matrix devices in which the drug is embedded in the polymer matrix, which control the duration of release of drugs.38 Bio adhesive polymers are from the most diverse class and they have considerable benefits upon patient health care and treatment [50]. The drug is released into the mucous membrane by means of rate controlling layer or core layer. Bio adhesive polymers which adhere to the mucin/epithelial surface are effective and lead to significant improvement in the oral drug delivery [51].

An ideal polymer for buccal adhesive drug delivery systems should have following characteristics [52-53]:

- It should be inert and compatible
- The polymer and its degradation products should be non-toxic absorbable from the mucous layer.
- It should adhere quickly to moist tissue surface and should possess some site specificity.
- 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.
- It should allow easy incorporation of drug in to the formulation.

Criteria followed in polymer selection:

- It should form a strong non-covalent bond with the mucine/epithelial surface.
- It must have high molecular weight and narrow distribution.
- It should be compatible with the biological membrane.

3. **Backing membrane**: Backing membrane plays a major role in the attachment of bio adhesive devices to the mucus membrane. The materials used as backing membrane should be inert, and impermeable to the drug and penetration enhancer. Such impermeable membrane on buccal bio adhesive patches prevents the drug loss and offers better patient compliance. The commonly used materials in backing membrane include carbopol, magnesium stearate, HPMC, HPC, CMC, poly carbopol etc. [54].
4. **Permeation enhancers**: Substances that facilitate the permeation through buccal mucosa are referred as permeation enhancers. Selection of enhancer and its efficacy depends on the physicochemical properties of the drug, site of administration, nature of the vehicle and other Excipients.

Mechanisms of action of permeation:

1) Changing mucus rheology:
   a. By reducing the viscosity of the mucus and saliva overcomes this barrier.
2) Increasing the fluidity of lipid bilayer membrane
   a. Disturb the intracellular lipid packing by interaction with either lipid packing by interaction with either lipid or protein components.
3) **Acting on the components at tight junctions**:
   a. 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.
4) **Increasing the thermodynamic activity of drugs**:
   a. Some enhancers increase the solubility of drug there by alters the partition coefficient [55].

Table 3: Examples of Permeation Enhancers with mechanism

S. No.	Category	Examples	Mechanism(s)
1.	Surfactants and Bile Salts	Surfactants and Bile Salts Sodium dodecyl sulphate Sodium lauryl sulphate Polysorbate 80	Acting on the components at tight junctions Increasing the fluidity of lipid bilayer membrane
2.	Fatty Acids	Oleic acid, Cod liver oil, Capric acid, Lauric acid	Increasing the fluidity of lipid bilayer membrane
3.	Polymers and Polymer Derivatives	Chitosan Trimethyl chitosan Chitosan-4 thiobutylamide	Increasing the fluidity of lipid bilayer membrane; increased retention of drug at mucosal surface
4.	Others	Ethanol, Azone, Octisalate, Padimate, Menthol	Acting on the components at tight junctions; Increasing the fluidity of lipid bilayer membrane

Methods of preparation:

1. **Solvent casting:** In this method, 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 [39].
2. **Direct milling:**-Drug and excipients are mixed by kneading, usually without the presence of any liquids. After the mixing process, material is rolled on a release liner until the desired thickness is achieved. The backing material is then laminated as previously described [57]. While there are only minor or even no differences in patch performance between patches fabricated by the two processes, the solvent-free process is preferred because there is no possibility of residual solvents and no associated solvent-related health issues [58].
3. **Hot melt extrusion of films:** In hot melt extrusion blend of pharmaceutical ingredients is molten and then forced through an orifice to yield a more homogeneous material in different shapes such as granules, tablets, or films. Hot melt extrusion has been used for the manufacture of controlled release matrix tablets, pellets and granules, as well as oral disintegrating films. However, only hand full articles have reported the use of hot melt extrusion for manufacturing mucoadhesive buccal films [59].

Evaluations of buccal patch [56]:

1. **Drug-excipients interaction studies:** Assessment of possible incompatibilities between an active drug substance and different excipients plays an important part of the formulation stage during the development of solid dosage form. Fourier Transform Infra-Red Spectrum (FTIR), Differential scanning calorimeter (DSC), thin layer chromatography and X Ray Diffraction (XRD) can be used to assess possible drug excipient interaction. DSC allows the fast evaluation of possible incompatibilities, because it shows changes in appearance, shift of melting endotherms and exotherms, and variation in the corresponding enthalpies of the reaction [60].
2. **Physical evaluation:** It includes Weight uniformity, Content uniformity, and Thickness uniformity. Weigh variation was tested by comparing the averages weighed of 10 different randomly selected patches from each batch with individual patch. The thickness of the film sample should be measured at five locations (centre and four corners), and the mean thickness is calculated. Samples with air bubbles, nicks or tears and having mean thickness variation of greater than 5% are excluded from analysis. Three patches (each of 20mm diameter) of each formulation were taken in separate 100 ml volumetric flasks, 100 ml of pH 6.8 phosphate buffer was added and continuously stirred for 24 hrs. The solutions were filtered, diluted suitably and analyse by using UV spectrophotometer. The average of three patches was taken as final reading [61].
3. **Surface pH:** The surface pH of the buccal patch is determined in order to investigate the possibility of any side effects *in vivo*. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was determined to keep the surface pH as close to neutral as possible [62]. A combined glass electrode was used for this purpose. The patches were allowed to swell by keeping it in contact with 1 ml of distilled water (pH 6.5 ± 0.05) for 2 hours at room temperature, and pH was noted down by bringing the electrode in contact with the surface of the patch and allowing it to equilibrate for 1 minute [63].

4. **Swelling studies:** Weight increase due to swelling: A drug-loaded patch of 1x1 cm^2 was weighed on a pre-weighed cover slip. It was kept in a petri dish and 50 ml of phosphate buffer, pH 6.6 was added. After every five minutes, the cover slip was removed and weighed upto 30 minutes. The difference in the weights gives the weight increase due to absorption of water and swelling of patch [64]. Area increase due to swelling: A drug loaded patch size of 1x1cm^2 was cut and placed in a petridish. A graph paper was placed beneath the petridish, to measure the increase in the area. Fifty ml of phosphate buffer, pH 6.6, was poured into the petridish. An increase in the length and breadth of the patch was noted at five min intervals for 60 min and the area was calculated. The percent swelling (%S) was calculated using the following equation:

$$\% = \frac{Xt - Xo}{Xo} \times 100$$

Where, Xt is the weight or area of the swollen patch; after time t; Xo is the original patch weight or area at zero time [65].

5. **Palatability test:** Palatability study is conducted based on taste, after bitterness and physical appearance. All the batches are rated A, B and C grades as per the criteria. When the formulation scores at least one A grade, formulation is considered as average. When the formulation scores two A grade then it would be considered as good and the one with all three A grade would be the very good formulation [66].

Grades: A = very good, B = good, C = poor

6. ***Ex vivo* mucoadhesive strength:** A modified balance method used for determining the *ex vivo* mucoadhesive strength. Fresh buccal mucosa (sheep and rabbit) obtained, used within 2 hours of slaughter. The mucosal membrane separated by removing underlying fat and loose tissues. The membrane washed with distilled water and then with phosphate buffer pH 6.8 at 37°C. The buccal mucosa cut into pieces and washed with phosphate buffer pH 6.8. A piece of buccal mucosa was tied to the glass vial, which was filled with phosphate buffer. The two sides of the balance made equal before the study, by keeping a 5g weight on the right-hand pan. A weight of 5g was removed from the right-hand pan, which lowered the pan along with the tablet over the mucosa. The balance was kept in this position for 5 minutes' contact time. The water (equivalent to weight) was added slowly with an infusion set (100 drops/min) to the right-hand pan until the tablet detached from the mucosal surface. This detachment force gave the mucoadhesive strength of the buccal tablet in grams. The glass vial was tightly fitted into a glass beaker (filled with phosphate buffer pH 6.8, at 37°C ±1°C) so that it just touched the mucosal surface. The buccal tablet was stuck to the lower side of a rubber stopper with cyanoacrylate adhesive [29].
7. ***Ex vivo* mucoadhesive time:** The *ex vivo* mucoadhesion time performed after application of the buccal patch on freshly cut buccal mucosa (sheep and rabbit). The fresh buccal mucosa was tied on the glass slide, and a mucoadhesive core side of each tablet was wetted with 1 drop of phosphate buffer pH 6.8 and pasted to the sheep buccal mucosa by applying a light force with a fingertip for 30 seconds. The glass slide was then put in the beaker, which was filled with 200 ml of the phosphate buffer pH 6.8, and kept at 37°C ± 1°C. After 2 minutes, a 50 rpm stirring rate was applied to simulate the buccal cavity environment, and tablet adhesion was monitored for 12 hours. The time for the tablet to detach from the buccal mucosa was recorded as the muco adhesion time [67].
8. ***In vitro* drug release:** The United States Pharmacopoeia (USP) XXIII rotating paddle method used to study the drug release from the bilayered and multilayered tablets. The dissolution medium consists of phosphate buffer pH 6.8. The release was performed at 370 C± 0.50 C, with a rotation speed of 50 rpm. The backing layer of buccal tablet attached to the glass disk with instant adhesive (cyanoacrylate adhesive). The disk was allocated to the bottom of the dissolution vessel. Samples (5 ml) were withdrawn at predetermined time intervals and replaced with fresh medium. The samples filtered through Whatman filter paper and analyzed after appropriate dilution by UV spectrophotometry at suitable nm [68].
9. ***In vitro* drug permeation:** The in vitro buccal drug permeation study of Drugs through the buccal mucosa (sheep and rabbit) performed using Keshary-Chien/Franz type glass diffusion cell at 37±0.2°C. Fresh buccal mucosa mounted between the donor and receptor compartments. The buccal tablet was placed with the core facing the mucosa and the compartments clamped together. The donor compartment filled with 1 ml of phosphate buffer pH 6.8. The receptor compartment was filled with phosphate buffer pH 7.4, and the hydrodynamics in the receptor compartment maintained by stirring with a magnetic bead at 50 rpm. A one ml sample can be withdrawn at predetermined time intervals and analyzed for drug content at suitable nm using a UV spectrophotometer [69].
10. **Stability study in Human saliva:** Stability study of fast dissolving films is carried out for all the batches according to ICH guidelines. After predetermined time intervals, the films are evaluated for the drug content, disintegration time and physical appearance [70]. The stability study of optimized mucoadhesive patch formulation was performed at 37±0.5°C & 75±5% RH for three months. The value of all parameter after three months remains same as their values and minor changes occur in value of volume entrapment efficiency, % elongation & % drug release after 8 hour which was considerable [71].
11. **Measurement of mechanical properties:** Mechanical properties of the patches were evaluated using a microprocessor based advanced force gauze equipped with a motorized test stand (Ultra Test, Mecmesin, West Sussex, UK), equipped with a 25kg load cell. Film strip with the dimensions 60 x 10 mm and without any visual defects were cut and positioned between two clamps separated by 3cm. Clamps were designed secure the patch without crushing it during the test, the lower clamp was held stationary and the strips were pulled apart by the upper clamp moving at a rate of 2mm/sec until the strip broke.

The force and elongation of the film at the point when the strip broke was recorded. The tensile strength and elongation at break values was calculated using the formula [72];

Tensile strength (kg. mm^{-2}) =

$$\frac{\text{Force at break (kg)}}{\text{Initial cross sectional area of the sample } (mm^2)} \times 100$$

Elongation at break (%.mm^{-2}) =

$$\frac{\text{Increase in length (mm)}}{\text{Original length Cross sectional area } (mm^2)} \times 100$$

12. **Folding endurance:** Folding endurance of the patches was determined by repeatedly folding one patch at the same place till it broke or folded up to 300 times manually, which was considered satisfactory to reveal good patch properties. The number of times the patch could be folded at the same place without breaking gives the value of the folding endurance. This test is done on five patches [73].
13. **Viscosity:** Aqueous solutions containing both polymer and plasticizer prepared in the same concentration as that of the patches. A model LVDV-II Brookfield viscometer attached to a helipath spindle number 4 used. The viscosity measured at 20 rpm at room temperature. The recorded values the mean of three determinations [74].
14. **Ageing:** Patches subjected to accelerated stability testing. Patches packed in glass Petri dishes lined with aluminum foil and kept in an incubator maintained at 37±0.5°C and 75±5%RH for 6 months. Changes in the appearance, residence time, release behaviour and drug content of the stored Bioadhesive patches investigated after 1, 2, 3, 4, 5 and 6 months. The data presented the mean of three determinations. Fresh and aged medicated patches, after 6 months' storage, investigated using scanning electron microscope [66].

CONCLUSION

Buccal adhesive systems offering numerable advantages in terms of accessibility, administration and withdrawal, retentivity, low enzymatic activity, economy and high patient compliance. This overview about the mucoadhesive buccal patches might be useful tool for the efficient design and characterization of mucoadhesive buccal patches. Mucoadhesive buccal patches have applications from different angles includes avoiding first-pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract. The area is well suited for a retentive device and appears to be acceptable to the patient. With the right dosage form design and formulation, the permeability in the local environment of the mucosa can be controlled and manipulated in order to accommodate drug permeation. Buccal drug delivery is a promising area for continued research with the aim of systemic delivery of orally inefficient drugs as well as a feasible and attractive alternative for non-invasive delivery of potent peptide and protein drug molecules.

However, the need for safe and effective buccal permeation absorption enhancers is a crucial component for a prospective future in the area of buccal drug delivery. With the great influx of new molecules stemming from drug research, mucoadhesive systems may play an increasing role in the development of new pharmaceuticals.

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