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BUCCAL MUCOADHESIVE BASED DRUG DELIVERY DEVICES

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ABSTRACT

Among the various routes of drug delivery, oral route is the most suitable, convenient and most widely accepted. However, after oral drug administration many drugs are subjected to presystemic clearance in liver, which often leads to a lack of correlation between membrane permeability, absorption and bioavailability. Here the oral cavity is an attractive site for drug delivery due to ease of administration and avoids possible drug degradation in the gastrointestinal tract as well as first pass hepatic metabolism. This is due to direct access of the drug into the systemic circulation through the internal jugular vein bypasses drugs from the hepatic first pass metabolism leading to higher bioavailability. This paper gives a concise review of buccal dosage forms and their formulation accepts in this type of drug delivery technology.

Keywords: Bio-adhesion, Penetration enhancer, Buccal devices, Mucoadhesive polymers.

INTRODUCTION

Bioadhesion may be defined as the state in which two materials, at least one of which is of biological nature, are held together for extended periods of time by interfacial forces and the American Society of Testing and Materials has defined it as the state in which interfacial forces, which may consist of valence forces, interlocking action, or both, hold two surfaces together.[1] For drug delivery systems, the term *bioadhesion* implies attachment of a drug carrier system to a specific biological location. The biological surface can be epithelial tissue, or the mucous coat on the surface of a tissue. If adhesive attachment is to mucous coat, the phenomenon is referred to as mucoadhesion.[2,3] Adhesion is a process, simply defined as the ‘‘fixing” of two surfaces to one another or can be defined as the bond produced by contact

between a pressure-sensitive adhesive and a surface. The bond formed between two biological surfaces or between a biological and synthetic surface is referred to as the bioadhesion. Generally in bioadhesive drug delivery, the adhesion between the synthetic or natural polymers and the gastrointestinal mucosa or any other soft tissues like buccal tissue is used to describe the term bioadhesion or synonymously used with the terms mucoadhesion and buccoadhesion.[4,5] In the recent years the interest is growing to develop a drug delivery system with the use of a mucoadhesive polymer that will attach to related tissue or to the surface coating of the tissue for targeting various absorptive mucosa such as ocular, nasal, pulmonary, buccal, vaginal, etc. Thus mucoadhesion may be defined as drug delivery systems that utilize property of bioadhesion of certain water-soluble polymers that become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for extended periods of time. This system of drug delivery is called mucoadhesive drug delivery system.[5] The buccal region of oral cavity is an attractive target for administration of drug of choice. Buccal drug delivery involves the administration of desired drug through the buccal mucosal lining of the oral cavity.[6,7] According to the potential site of application mucoadhesive drug delivery can be classified as follows.

1. Buccal drug delivery system
2. Vaginal drug delivery system
3. Rectal drug delivery system
4. Nasal drug delivery system
5. Ocular drug delivery system
6. Sublingual drug delivery system
7. Gastrointestinal drug delivery system

One strategy that has been reasonably successful to overcome such problems is to administer drugs systemically through an alternate route of administration such as intranasal (IN), buccal/sublingual, pulmonary or transdermal (TD).[7] Transmucosal routes of drug delivery which comprise of the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity offer excellent opportunities and potential advantages over peroral administration for systemic drug delivery. These advantages include possible bypass of first pass effect, avoidance of presystemic elimination within the GI tract and depending on the particular drug, a better enzymatic flora for drug absorption.[8]

The sites of drug administration in the oral cavity include the floor of the mouth (sublingual), the inside of the cheeks (buccal) and the gums (gingival).[9] Hydrophilic high molecular weight

therapeutic agents such as proteins and peptides are readily available for therapeutic use. Though it was administered by the oral route, these agents suffer from problems such as degradation and poor absorption. To overcome these obstacles and for successful delivery of proteins and peptides, the buccal route of drug delivery has acquired significant attention.[10] To accomplish site-specific drug delivery, a lot of interest has been turned on to the concept of mucoadhesion, which encompasses a pharmaceutical formulation incorporating mucoadhesive hydrophilic polymers along with the active pharmaceutical ingredient (API). The rationale being that the formulation will be 'held' on a biological surface for localized drug delivery and the release of drug will be close to the site of action leading to enhanced bioavailability.[11] This paper gives a concise review of buccal dosage forms and their formulation accepts in this type of drug delivery technology.

Mucoadhesion is known to increase the intimacy and duration of contact between drug-containing polymer and a mucous surface. It is believed that the mucoadhesive nature of the device can increase the residence time of the drug in the body. The bioavailability of the drug is improved because of the combined effects of the direct drug absorption and the decrease in excretion rate. Increased residence time and adhesion may lead to lower drug concentrations and decreases the frequency of administration to achieve the desired therapeutic outcome.[12]

Characteristics of an Ideal Buccoadhesive System[13-16]

The ideal characteristics of a bucco-adhesive system are as follows:

1. Should adhere to the buccal mucosa quickly and have optimum mechanical strength.
2. Drug should release in a controlled manner.
3. Facilitates the rate and extent of drug absorption.
4. Should have patient compliance.
5. Should not obstruct normal functions such as talking, eating and drinking.
6. Should achieve the unidirectional release of drug towards the mucosa.
7. Should not aid in development of secondary infections such as dental caries.
8. Possess a wide margin of safety both locally and systemically.
9. Should have good resistance to the flushing action of saliva.

Advantages of Buccal Drug Delivery Devices[11, 17-25]

1. Excellent accessibility and presence of smooth muscle and relatively immobile mucosa, makes it suitable for administration of retentive dosage forms.

2. The two designs of sublingual mucosal dosage forms are, rapidly disintegrating tablets and soft gelatin capsules, which create a very high drug concentration in the sublingual region before they are systemically absorbed in the buccal mucosa.
3. The buccal mucosa is the preferred site for delivery of controlled- and sustained- drug devices. It has an expanse of smooth and relatively immobile mucosa whereas sublingual mucosa lacks it. The placement of drug device is difficult on sublingual mucosa because it is constantly washed by a considerable amount of saliva.
4. The nasal cavity as a route for systemic drug delivery is less attractive route due to its potential irritation and irreversible damage to the ciliary action from chronic application of nasal dosage forms.
5. The large inter-subject and intra-subject variations in the mucus secretion of nasal cavity largely affect the drug absorption from this site.
6. Peptides and proteins are highly susceptible to the acidic environment of stomach and cannot be delivered through gastric mucosa.
7. Proteins are characterized with high molecular size and hydrophilic nature. Hence they cannot permeate the intestinal mucosa as easily as they can the buccal tissues.
8. The ocular, rectal and vaginal mucosae have specific advantages, but poor patient acceptability limits these sites for local drug delivery, rather than systemic administration of drugs.
9. As a result of adhesion and intimate contact, the formulation stays longer at the delivery site improving API bioavailability using lower API concentrations for disease treatment.
10. Harsh environmental factors that exist in oral delivery of a drug are circumvented by buccal drug delivery.
11. It offers a passive system of drug absorption and does not require any activation.
12. The presence of saliva ensures relatively large amount of water for drug dissolution unlike in case of rectal or transdermal routes.

Disadvantages of Buccal Drug Delivery Devices[10, 26]

1. Limited absorption area
2. Barrier properties of the mucosa
3. The continuous secretion of the saliva (0.5-1.5L/day) leads to subsequent dilution of the drug
4. The hazard of choking by involuntarily swallowing the delivery system is a concern

5. Swallowing of saliva can also potentially lead to the loss of dissolved or suspended drug and ultimately the involuntary removal of the dosage form.

Structure and function of the oral mucosa

The oral mucosa is composed of an outermost layer called stratified squamous epithelium and below a basement membrane; a lamina propria followed by the sub-mucosa as the inner most layer. It also contains many sensory receptors including the taste receptors of the tongue. The blood epithelium is classified as non-keratinized tissues.[26] Light microscopy reveals several distinct patterns of maturation in the epithelium of the human oral mucosa based on various regions of the oral cavity. Three distinctive layers of the oral mucosa are the epithelium, basement membrane, and connective tissues as shown in figure 1. The oral cavity is lined with the epithelium, below which lies the supporting basement membrane. The basement membrane is in turn, supported by connective tissues.[27]

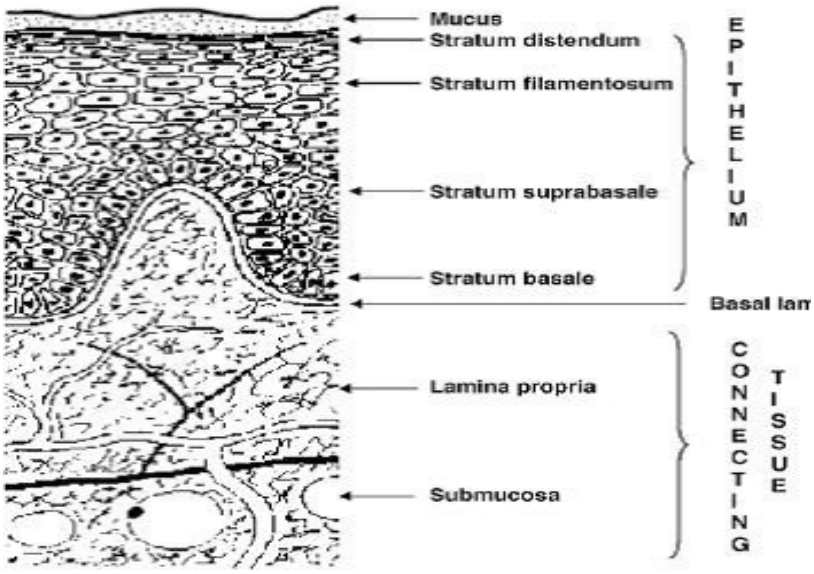

Fig.1. Section of Buccal Mucosal Layer

- The oral mucosa is highly perfused with blood vessels with a high blood flow rate of 20- 30mL/min for each 100gm of the tissue[28]. The blood vessels are close to the surface and the lymphatic drainage is also well developed. Hence therapeutic concentrations of the drug can be achieved rapidly.[29] The oral mucosa in general is somewhat leaky epithelia intermediate between that of the epidermis and intestinal mucosa. It is estimated that the permeability of the buccal mucosa is 4-4000 times greater than that of the skin.[30] The permeability coefficients for most compounds are

consistently higher for the buccal and oral mucosa than for normal and hydrated skin. There are two permeation pathways for passive drug transport across the oral mucosa, Para cellular and Trans cellular routes. The Para cellular route (intercellular, passing around the cell) drug transport occurs between the cells, where as transcellular route (intracellular, passing through the cell) of drug transport occurs across the cell membranes into the cells[31] as shown in figure 2. The intercellular spaces are less lipophilic in character than the cell membrane hence hydrophilic compounds have higher solubilities in this environment. The cell membrane, however, is highly lipophilic in nature, and hydrophilic solutes have great difficulty permeating the cell membrane because of a low partition coefficient[8]. Depending on the physico-chemical properties of the diffusant. The solutes traverse from one route more than the other.[28] Therefore, the intercellular spaces pose the major barrier to passive permeation of lipophilic compounds, and the cell membrane acts as the major transport barrier for hydrophilic compounds.[28,32]

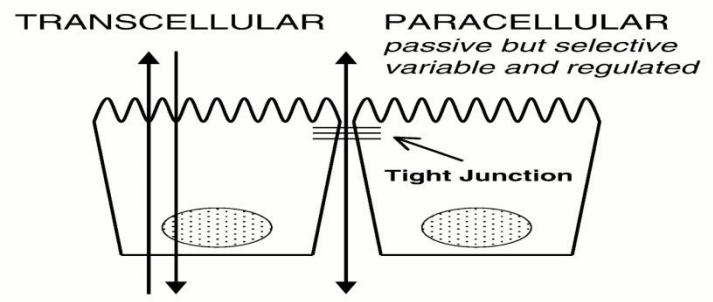

Fig. 2: The Mechanism of Paracellular and Transcellular routes of transport.

Barriers to penetration across buccal mucosa

The barriers such as saliva, mucus, membrane coating granules, basement membrane etc., retard the rate and extent of drug absorption through the buccal mucosa. The main penetration barrier exists in the outermost quarter to one third of the epithelium.

Membrane Coating Granules or Cored Granules

In non keratinized epithelia, the accumulation of lipids and cytokeratins in the keratinocytes is less evident and the change in morphology is far less marked than in keratinized epithelia. The mature cells in the outer portion of non-keratinized epithelia become large and flat retain nuclei and other organelles and the cytokeratins do not aggregate to form bundles of filaments as seen in keratinizing epithelia. As cells reach the upper third to quarter of the epithelium, membrane-coating granules become evident at the superficial aspect of the cells

and appear to fuse with the plasma membrane, to extrude their contents into the intercellular space. The membrane-coating granules found in non-keratinizing epithelia are spherical in shape, membrane-bounded and measure about 0.2µm in diameter. Such granules have been observed in a variety of other human non keratinized epithelia, including uterine cervix and esophagus. [13]

Basement Membrane: Although the superficial layers of the oral epithelium represent the primary barrier to the entry of substances from the exterior, it is evident that the basement membrane also plays a role in limiting the passage of materials across the junction between epithelium and connective tissue. A similar mechanism appears to operate in the opposite direction. The charge on the constituents of the basal lamina may limit the rate of penetration of lipophilic compounds that can traverse the superficial epithelial barrier relatively easily.[33]

Mucus: The epithelial cells of buccal mucosa are surrounded by the intercellular ground substance called mucus with the thickness varies from 40µm to 300µm. Though the sublingual glands and minor salivary glands contribute only about 10% of all saliva, together they produce the majority of mucus and are critical in maintaining the mucin layer over the oral mucosa. It serves as an effective delivery vehicle by acting as a lubricant allowing cells to move relative to one another and is believed to play a major role in adhesion of mucoadhesive drug delivery systems, as shown in figure 3. A thorough understanding of the glycoprotein mucin component is very important with regard to understanding the properties of mucus. Mucin glycoproteins may be described as consisting of a basic unit made from a single-chain polypeptide backbone with two distinct regions.[33]

Function of the mucus

1. Made up of proteins and carbohydrates.
2. Cell-cell adhesion.
3. Lubrication.
4. Bioadhesion of mucoadhesive drug delivery systems.
5. 1. A heavy glycosylated central protein core to which many large carbohydrate side chains are attached, predominantly via O-glycosidic linkages.
6. 2. One or two terminal peptide regions where there is little glycosylation. These regions are often referred to as ‘naked protein regions’.
7. Mucins are secreted as massive aggregates by prostaglandins with molecular masses of roughly 1 to 10 million Da. Within these aggregates, monomers are linked to one

another mostly by non-covalent interactions, although intermolecular disulphide bonds also play a role in this process. Oligosaccharide side chains contain an average of about 8–10 monosaccharide residues of five different types namely L-fucose, D-galactose, N-acetyl-D-glucosamine, N-acetyl-D-galactosamine and sialic acid. Amino acids present are serine, threonine and proline. Because of the presence of sialic acids and ester sulfates, mucus is negatively charged at physiological salivary pH of 5.8–7.4. The mucosal surface has a salivary coating estimated to be 70µm thick, which act as unstirred layer. Within the saliva there is a high molecular weight mucin named MG1 that can bind to the surface of the oral mucosa in order to maintain hydration, provide lubrication, concentrate protective molecules such as secretory immunoglobulins, and limit the attachment of microorganisms. Several independent lines of evidence suggest that saliva and salivary mucin contribute to the barrier properties of oral mucosa.

8. Saliva is composed of 99.5% water in addition to proteins, glycoproteins and electrolytes. It is high in potassium (7×plasma), bicarbonate (3×plasma), calcium, phosphorous, chloride, thiocyanate and urea and low in Na (1/10×plasma). The normal pH of saliva is 5.6–7. Saliva contains enzymes namely α-amylase (breaks 1–4 glycosidic bonds), lysozyme (protective, digests bacterial cell walls) and lingual lipase (break down the fats).

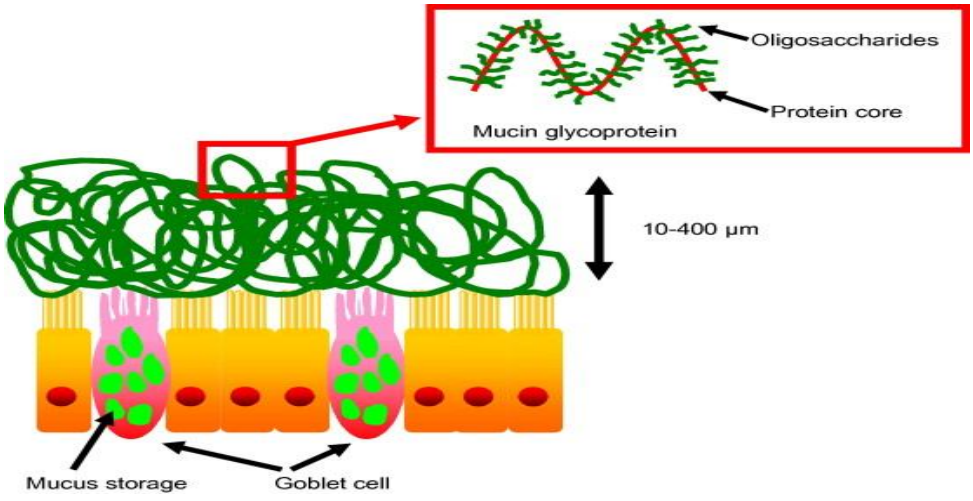

Fig.3: The composition and interaction of glycoprotein chains within mucus

Function of the Saliva[31]

1. Protective fluid for all tissues of the oral cavity.
2. Continuous mineralization / demineralization of the tooth enamel.

3. To hydrate oral mucosal dosage forms
4. It moistens the mouth, initiates digestion and protects the teeth from decay.
5. It also controls bacterial flora of the oral cavity.
6. Because saliva is high in calcium and phosphate, it plays a role in mineralization of new teeth repair and precarious enamel lesions.
7. It protects the teeth by forming "protective pellicle". This signifies a saliva protein coat on the teeth, which contains antibacterial compounds.

Formulation Considerations

For buccal drug delivery, it is cardinal to prolong and augment the contact between drug and mucosa to obtain the desired therapeutic effect. Buccal adhesive drug delivery systems with the size 1-3cm^2 and a daily dose of 25mg or less are preferable. The maximal duration of buccal delivery is approximately 4-6h.[34] The excipients used in the formulation should be GRAS-listed (Generally Recognized as Safe).

Mucoadhesive polymers

Polymer is 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 more meaning parts.[35] 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. The concept of mucoadhesives has alerted many investigators to the possibility that these polymers can be used to overcome physiological barriers in long-term drug delivery.[36] The development of Orahesive® followed, leading to trials of Orabase® in 1959. Orabase® was formulated from natural gums and represented the first purposely developed mucoadhesive. Orabase® product (Adcortyl in Orabase®) provides local relief of mouth ulcers via a twofold mechanism: barrier function and an anti-inflammatory function (due to triamcinolone acetonide).

MECHANISM OF MUCOADHESION

Mucoadhesion is the attachment of the drug along with a suitable carrier to the mucous membrane. It is a complex phenomenon which involves wetting, adsorption and interpenetration of polymer chains.

Mucoadhesion has the following mechanism

1. Intimate contact between a bioadhesive and a membrane (wetting or swelling phenomenon also called as contact stage).

2. Penetration of the bioadhesive into the tissue or into the surface of the mucous membrane (interpenetration or consolidation stage).

Residence time for most mucosal routes is less than an hour and typically in minutes, it can be increased by the addition of an adhesive agent in the delivery system which is useful to localize the delivery system and increases the contact time at the site of absorption. The exact mechanism of mucoadhesion is not known but an accepted theory states that a close contact between the mucoadhesive polymer and mucin occurs which is followed by the interpenetration of polymer and Mucin is shown in figure 4. The adhesion is prolonged due to the formation of vandervaals forces, hydrogen bonds and electrostatic bonds.[3]

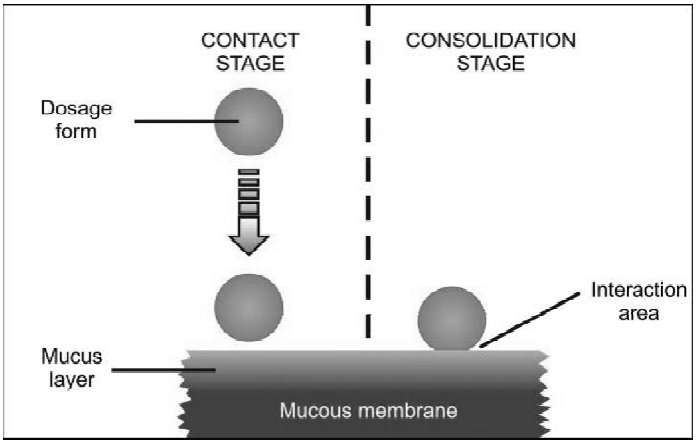

Fig. 4: The two steps of the process of mucoadhesion

THEORIES OF MUCOADHESION

Bioadhesion may be defined as the state in which two materials, at least one of which is biological in nature, are held together for extended periods of time by interfacial forces. In the pharmaceutical sciences, when the adhesive attachment is to mucus or a mucous membrane, the phenomenon is referred to as mucoadhesion. Various theories have been developed in the formation of bioadhesive bonds[23] and are based on the formation of mechanical bonds, while others focus on chemical interactions is shown below.

The following are the theories for the mechanism of mucoadhesion

Theory	**Mechanism**
Electronic theory	In this both Mucoadhesive and biological materials possess opposing electrical

	charge, which form double layer at the interface, attractive forces within this electronic double layer determines the mucoadhesive strength
Wetting Theory	This applies to liquid systems which present affinity to the surface in order to spread over it.
Adsorption theory	In this Mucoadhesive device adheres to the mucus by secondary chemical interactions, such as in vander Waals and hydrogen bonds, electrostatic attraction or hydrophobic interactions
Diffusion Theory	Formation of network between the polymer chains and mucin strands.
Mechanical Thoery	The diffusion of the liquid adhesives into the micro-cracks and irregularities present on the substrate surface thereby forming an interlocked structure which gives rise to adhesion.
Fraction Theory	Fracture theory is concerned only with the force required to separate the parts, it does not take into account the interpenetration or diffusion of polymer chains.

Factors affecting mucoadhesion

The mucoadhesion of a drug carrier system to the mucous membrane depends on the below mentioned factors**.**

1. Polymer based factors:
    - Molecular weight of the polymer
    - Concentration of polymer used
    - Flexibility of polymer chains
    - Swelling factor
    - Stereochemistry of polymer

2. Physical factors:
    - pH at polymer substrate interface
    - Applied strength
    - Contact time
3. Physiological factors:
    - Mucin turnover rate
    - Diseased state

The adhesive polymers can be classified as synthetic vs. natural, water-soluble vs. water insoluble, and charged vs. uncharged polymers. Table 1 summarizes the mucoadhesive polymers used in buccal drug delivery.[26]

Table No.1: Mucoadhesive Polymers used in Buccal Drug Delivery

Criteria	Categories	Examples
Source	**Semi-natural/natural**	Agarose, chitosan,gelatin, Hyalorunic acid, Various gums(guar, hakea, xanthan, gellan, Carrageenan, pectin and sodium alginate
	Synthetic	**Cellulose Derivatives** CMC, thiolated CMC, sodium CMC, HEC, HPC, HPMC, MC, methylhydroxyethylcellulose
		Poly(acrylic acid)-based polymers CP, PC, PAA, polyacrylates, poly(methylvinylether-co-methacrylic acid), poly(2-hydroxyethyl methacrylate), poly(acrylic acidco- ethylhexylacrylate), poly(methacrylate),poly(alkylcyanoacrylate),poly(isohexylcyanoacrylate),poly(isobutylcyanoacrylate), copolymer of acrylic acid and PEG
		Others polyoxyethylene, PVA, PVP, thiolated polymers
Aqueous Solubiltiy	**Water -soluble**	CP, HEC, HPC, HPMC (cold water), PAA, sodium CMC, sodium alginate
	Water-insoluble	Chitosan (soluble in dilute aqueous acids), EC, PC

Charge	**Cationic**	Aminodextran, chitosan, (DEAE)-dextran, TMC
	Anionic	Chitosan-EDTA, CP, CMC, pectin, PAA, PC, sodium alginate,sodium CMC, xanthan gum
	Non-ionic	Hydroxyethyl starch, HPC, poly(ethylene oxide), PVA, PVP, scleroglucan
Potential Bioadhesive forces	**Covalent**	Cyanoacrylate
	Hydrogen bond	Acrylates [hydroxylated methacrylate, poly(methacrylic acid)], CP, PC, PVA
	Electrostatic interaction	Chitosan

New generation of mucoadhesive polymers (with the exception of thiolated polymers) can adhere directly to the cell surface, rather than to the mucus. They interact with the cell surface by means of specific receptors or covalent bonding instead of non-specific mechanisms. Incorporation of L-cysteine into thiolated polymers and the target-specific, lectin-mediated adhesive polymers. These classes of polymers hold promise for the delivery of a wide variety of new drug molecules, particularly macromolecules, and create new possibilities for more specific drug-receptor interactions and improved targeted drug delivery.[37-43,26] Thiolated polymers or designated thiomers are mucoadhesive basis polymers, which display thiol bearing side chains. These polymers are obtained by addition of conjugated sulfidryl groups.[44] Thiolated polymers are a type of second-generation mucoadhesive polymer derived from hydrophilic polymers such as polyacrylates, chitosan or deacetylated gellan gum.[45]

PENETRATION ENHANCERS

Penetration enhancers are the substances, which increase the buccal mucosal membrane permeation rate. Although most penetration enhancers were originally designed for purposes other than absorption enhancement, a systemic search for safe and effective penetration enhancers must be a priority in drug delivery.[45] With the rapid development of biotechnology, more and more protein, peptide, and nucleotide drugs are becoming available, most of which have low membrane-absorption characteristics including:

- A large size with high molecular weight.
- Domains of different hydrophobicity.
- Irregular shapes.

- Delicate structures easily inactivated.

These drugs are unable to cross membrane barriers in therapeutic amounts and thus reaches into the penetration enhancers becomes ever more important.[45] Table 2 shows the formulations of buccal tablets along with their drug and permeation enhancers and polymer used. A new absorption promoter for buccal delivery named lysalbinic[47] acid has been studied using hamster cheek mucosa as a simple animal model for the initial evaluation of absorption promoters. It was shown that co-administration of lysalbinic acid with relatively small proteins (6-16kDa), such as α-inteferon and insulin, can significantly increase their absorption via the buccal epithelium. Thus lysalbinic acid has been shown to increase significantly permeability of the hamster oral mucosa for peptide compounds of low-to middle-molecular weight.[47] Table 3, provides the proposed mechanisms of action of penetration enhancers for the delivery of the drug through the buccal route.

Table No.2: Formulation of buccal tablet with different Bioadhesive polymers along with permeation enhancers

S.No	Drug	Bioadhesive Polymers	Permeation Enhancers	References
1	Diltiazem HCL	Carbopol, HPMC, SCMC, Sodium alginate	PEG-6000, D-Mannitol	48
2	Propranolol HCL	Carbopol,PVP,Sodium alginate	PEG-4000, D-Mannitol	49
3	Pravastatin sodium	Carageenangum, PVP, Pluronic	----------	50
4	Flurbiprofen	Carbopol, HEC, HPMC, Carbomer 940	----------	51
5	Terbutaline sulphate	Carbopol, HPMC, SCMC	----------	52
6	Ondansetron hydrochloride	Carbopol, Sodium alginate, gelatin	----------	53
7	Metoprolol tartarate	Carbopol, Methocel		54
8	Nicotine	Carbopol, HPMC, Sodium alginate, Chitosan	Citric acid, PEG4000	55
9	Hydralazine	Carbopol, CMC, Hydroxy propyl	D-Mannitol	56

	hydrochloride	cellulose		
10	Meconazole nitrate	Carbopol, HPMC, PVP	D-Mannitol	57

Table No.3: Mechanism of Buccal Permaeation Enhancers

Classification	Examples	Mechanism
Surfactants	**Anionic**: sodium lauryl sulfate, Sodium laurate **Cationic**: cetylpyridiniumchloride **Nonionic**: poloxamer, Brij, Span, Myrj, Tween **Bile salts**: sodium glycodeoxy cholate, sodium glycocholate, sodiumtaurodeoxycholate, sodium taurocholate, Azone	Perturbation of intercellular lipids, protein domain integrity
Fatty acids	Oleic acid, caprylic acid	Increase fluidity of phospholipids domains.
Cyclodextrins	α-, β, γ-cyclodextrin, methylated β-cyclodextrins	Inclusion of membrane compounds
Chelators	EDTA, sodium citrate Polyacrylates	Interfere with Ca^{2+}
Positively charged polymers, cationic compounds	Chitosan, trimethyl chitosan, Poly-L-arginine, L-lysine	Ionic interaction with negative charge on the mucosal surface

Mechanisms involved in drug absorption across the oral mucosa

The main mechanism involved in drug transfer across the oral mucosa, common with all regions of the gastrointestinal tract, is passive diffusion, although facilitated diffusion has also been shown to take place, primarily with nutrients[96]. . The mechanism are represented in Figure 5. Passive diffusion involves the movement of a solute from a region of high concentration in the mouth to a region of low concentration within the buccal tissues.

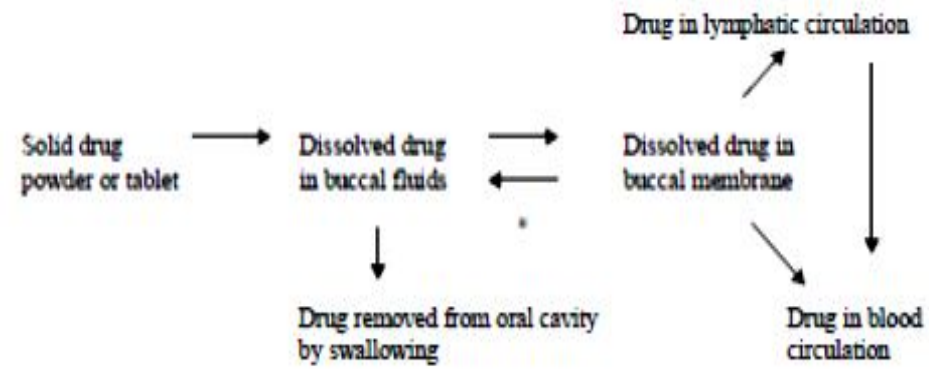

Fig.5: Schematic representation of the absorption kinetics of buccally presented drugs

Buccal Dosage Forms Design

Buccal mucoadhesive dosage forms can be categorized into three types depending upon the release of the medicament is shown in figure 6a.

Type I (Multidirectional): This device has a single layer with drug release multiple directions. The disadvantage of this type of dosage form is that it suffers from significant drug loss due to swallowing.

Type II(Bi-layered): In this type, an impermeable backing layer is superimposed on top of the drug loaded bioadhesive layer, creating a double-layered device and preventing drug loss from the top surface of the dosage form into the oral cavity.

Type III (Unidirectional): This is a uni-directional release device, from which drug loss is minimal, since the drug is released only from the side adjacent to the buccal mucosa. This can be achieved by coating every face of the dosage form, except the one that is in contact with the buccal mucosa.

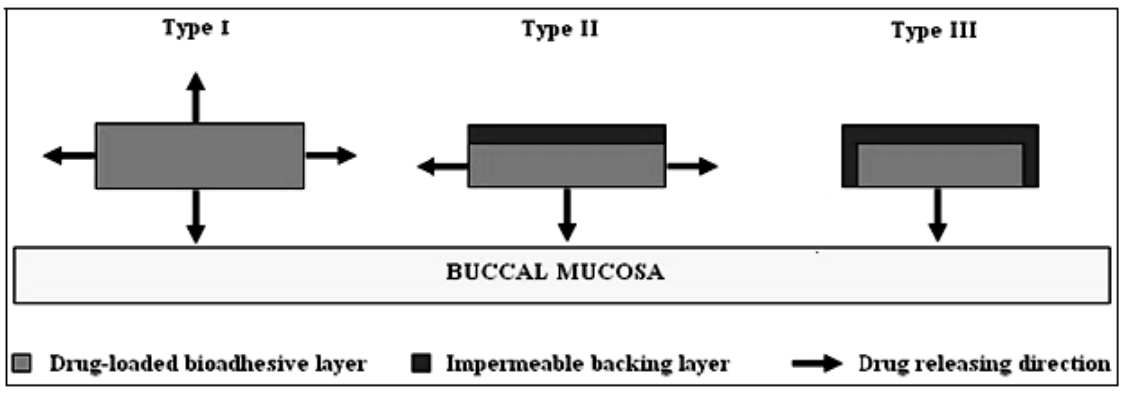

Fig.6(a): Buccal mucoadhesive dosage forms

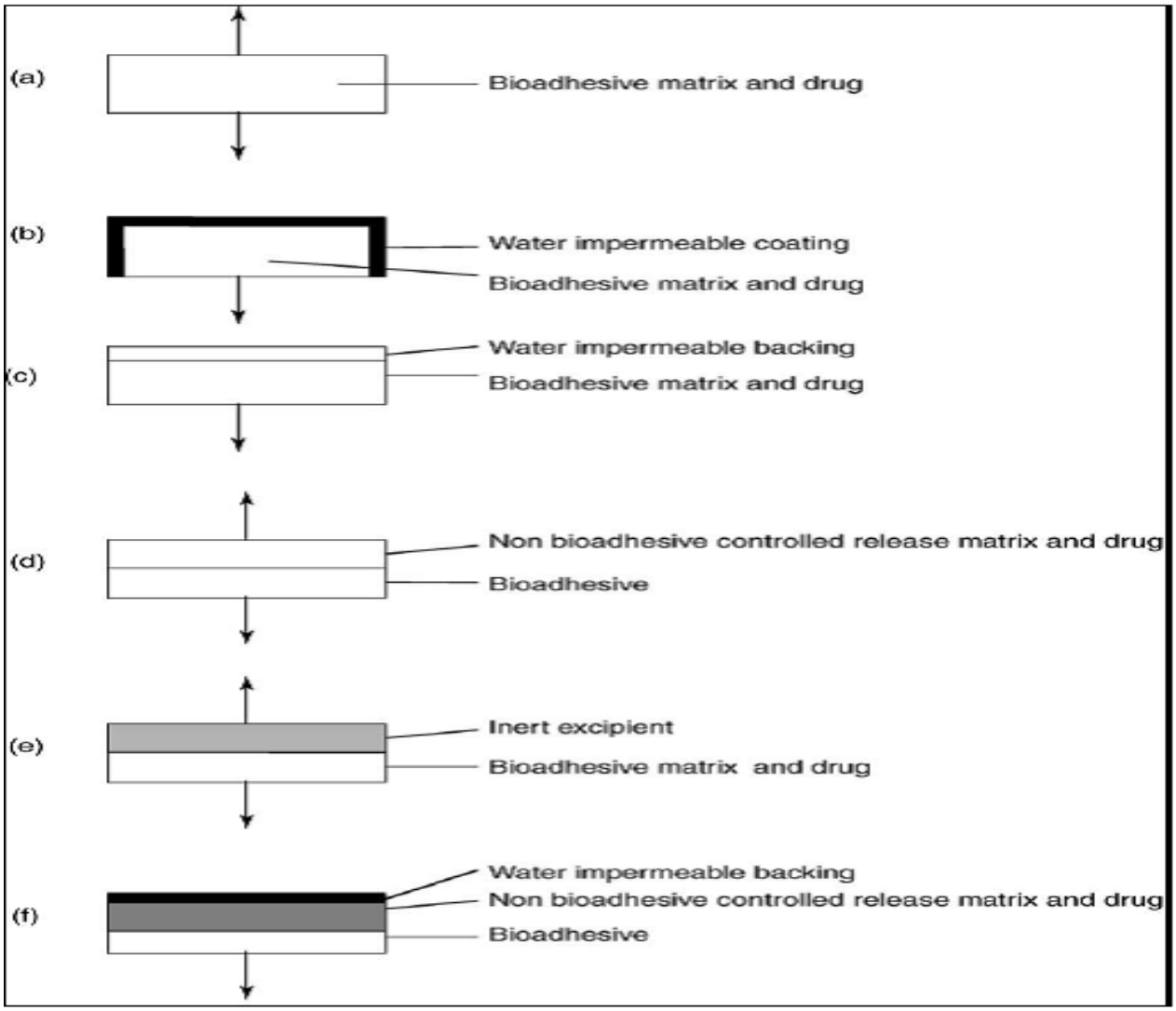

Fig.6(b): Matrix Type Buccal dosage forms

Buccal dosage forms can also be classified as either a “reservoir” or “matrix” type. In the reservoir type, a large amount of the drug is present in the reservoir covered by a polymeric membrane, which controls the drug’s release rate. In the matrix type systems, as shown in figure 6b, the drug is uniformly distributed in the matrix of polymer, and drug release is controlled by diffusion through the polymer network.[58]

A number of related buccal mucoadhesive dosage forms have been developed for a variety of drugs. Several peptides like thyrotropin-releasing hormone (TRH), insulin, protirelin, buserelin and oxytocin, have been administered via the buccal route, although with relatively low bioavailability (0.1–5%) pertaining to their hydrophilicity and large molecular weight, as well as the inherent permeation and enzymatic barriers of the buccal mucosa.

Classification of Buccal devices

Buccal dosage forms can be classified into

1. Tablets 2. Semisolids 3. Patches 4. Films 5. Powders

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 in order to achieve some desirable properties e.g. enhanced activity and prolonged drug release.[59]

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 muosa. Certain bioadhesive polymers for example, sodium carboxymethylcellulose[60] undergo a phase change from a liquid to a semisolid. This change enhances or improves 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.[21]

3. Buccal Patches

Buccal patches are described as laminates which comprise of an impermeable backing layer, a drug-containing reservoir layer which releases the drug in a controlled manner, and a bioadhesive surface for mucosal attachment. Two commonly known methods are used to prepare adhesive patches

1. Solvent casting method and
2. Direct milling

In the first method, the intermediate sheet from which patches are punched is prepared by casting the solution of the drug and polymer onto a backing layer sheet, and subsequently allowing the solvent to evaporate.

4. Buccal films

In recent years, numerous bioadhesive dosage forms for delivery of drug via the buccal route have been developed such as films, tablet, patches, discs, gels and ointments.[62-63, 64-71] Buccal films are preferable over mucoadhesive discs and tablets in terms of patient comfort and flexibility and they ensure more accurate drug dosing and longer residence time compared to gels and ointments and thereby sustaining drug action. Buccal films also reduce pain by protecting the wound surface and hence increase the treatment effectiveness.[72]

Ideal properties of buccal film should be that it should possess flexibility, elasticity, and softness and also strong enough to withstand breakage due to stress from activities in the mouth. Moreover, it should also possess good mucoadhesive strength so that it is retained in the mouth for the duration which is dsired.[73]

5. Buccal Powders

Buccal bioadhesive powders are a mixture of Bioadhesive polymers and the drug and are sprayed onto the buccal mucosa the reduction in diastolic B.P after the administration of buccal tablet and buccal film of nifedipine.

Buccal Mucoadhesive Marketed Products

Table 4 shows the commercially available list buccal dosage forms, the commercially administered steroid are methyl testosterone propionate and testosterone propionate. Cyclodextrins are used as additives to enhance the absorption of these steroidal hormones Prochlorperazine and oxytocin are also found to be effective when administered in the form buccal devices.

Table No.4: Commercially Available Buccal Devices

S.No	Drugs available as buccal devices	Manufacturers (trade name)
1.	Nitro-glycerine	Glenmark (nitrogard)
2.	Miconazole	BioAlliancePharmaSA (loramyc)

3.	Methyl testosterone	Bayer Schering Pharma (Oreton methyl)
4.	Hydrocortisone	Auden Mckenzie (corlan pellets)
5.	Fentanyl	Cephalon (fentora CII)
6.	Insulin buccal delivery	Shreyalife sciences (Oral Recosulin)
7.	Prochlorperazine	ReckittBenckiser(Buccastem)
8.	Testosterone	Actient pharmaceuticals (Striant)
9.	Clotrimazole	Lotrimin, Mycelex
10.	Desmopressin	Ferring pharmaceuticals (DDAVP)
11.	Omeprazole	Astrazeneca (Prilosec)
12.	Vitamin-C	Zhongnuo (CSPC)

Table No.5: Investigated Buccal Tablets and Polymers Used

Active ingredient	Polymers	References
Baclofen	NaMC, Sodium alginate and Methocel K15M	73
Carvedilol	HPMC K4M and CP 934P	74
Carvedilol	HPMC K4M, HPMC K15M and CP 934	75
Chlorhexidine diacetate	Chitosan and Na alginate	61
Chlorpheniramine maleate	Hakea gum from *Hakea gibbosa*	76
Diltiazem HCL	NaCMC, HPMC, Na alginate and guar gum.	77
Flurbiprofen	HPMC K15M, HEC, CP971 and Carbomer 940	78
Itraconazole	Eudragit 100M, HPMC K4M and CP 934P	79
Morphine sulfate	HPMC K100M, CP 910 and Eudragit RSPM	80
Nicotine	CP 934 and HPC	81
Nifedipine	CMC, CP 934P, HPMC, PVP	82

	K30 and PVA	
Omeprazole	Na alginate, HPMC	83
Ondansetron	HPMC 15 cps, CP 934, Na alginate and Na CMC.	84
Oxytocin	Mucilage of *Diospyros peregrina* fruit	85
Piroxicam	HPMC K4M and CP934	86
Pravastatin Na	PVP K-30 and Pluronic F127and EC	87
Prednisolone	HPMC, CP 934 and Na CMC	88
Propranolol HCL	Na alginate, CP 971P and PVP K30	89
Propranolol HCL	HPMC K4M, Xanthan gum, EC and acrypol 934P	90
Salbutamol sulphate	HPMC K4M and EC	91
Tizanidine HCL	CP 934, HPMC K4M, HPMC K15M and Na CMC and EC	92
Verapamil HCL	CP934 P, HPMC K4M, HEC and NaCMC	93

Forthcoming Challenges and possibilities

Interest today is to develop variant innovative drug transport systems with the help of conventional polymer networks. Buccal adhesive drug delivery is more important, which is focusing on the preparation and use of responsive polymeric system. The use of many hydrophilic macromolecular drugs as potential therapeutic agents is their inadequate and unsteady oral absorption. The future challenge of pharmaceutical scientists will not only be polypeptide cloning and synthesis, but also to develop effective non-parenteral delivery of intact proteins and peptides to the systemic circulation.[94] Buccal permeation can be improved by using various classes of transmucosal and transdermal penetration enhancers such as bile salts, surfactants, fatty acids and derivatives, chelators and cyclodextrins Successfully developing these novel formulations requires gathering of a great deal of emerging information about the chemical nature and physical structure of these new materials.

CONCLUSION

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. The safety and efficacy of current treatments may be improved if their delivery rates, biodegradation, and site specific targeting can be predicted, monitored and controlled. The buccal mucosa is a promising delivery route for drugs that need to avoid the gastrointestinal tract due to degradation by the gastric pH, intestinal enzymes, or due to a substantial hepatic first pass effect. However, the manufacture of patient safe and friendly dosage forms, while improving technologies will keep challenging the pharmaceutical scientist.

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