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REVIEW ON BUCCAL MUCOADHESIVE DRUG DELIVERY SYSTEMS

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ABSTRACT

Oral cavity is an attractive target for systemic and local drug delivery. Buccal Drug Delivery means administration of drug through buccal mucosal linings. Buccal mucosa is relatively permeable, with rich blood supply, which makes it excellent site for absorption. It also bypasses first pass metabolism and enzymatic degradation. Objective of this article to review buccal adhesive drug delivery system by discussing anatomy and physiology, environment of oral cavity, Mucoadhesion, theories of Mucoadhesion, mucoadhesive polymers, permeation enhancers, different buccal adhesive dosage forms and their evaluation methods.

INTRODUCTION

Oral drug delivery has, for decades, been the most widely utilized route of administration for the systemic delivery of drugs. [1].The buccal region of the oral cavity is an attractive target for administration of the drug of choice. Buccal delivery involves the administration of the desired drug through the buccal mucosal membrane lining of the oral cavity[2].By avoiding hepatic first-pass metabolism and degradation in stomach and small intestine, the buccal route is an alternative choice to deliver drugs to the application site. In addition, this route shows high acceptance by patients. [3].Buccal mucosa is relatively permeable with rich blood supply and acts as anexcellent site for the absorption of drugs. The buccal cavity is easily accessible for self medication. [4].

Buccal delivery offers a safer mode of drug utilization, since drug absorption can be promptly terminated in cases of toxicity by removing the dosage form from the buccal cavity. A suitable buccal drug delivery system should possess good bioadhesive properties, so that it can be retained in the oral cavity for the desired duration. In addition, it should release the drug in a unidirectional way toward the mucosa, in a controlled and predictable manner, to elicit the required therapeutic response. [5].

ADVANTAGE OF BUCCAL DRUG DELIVERY[6]. **–**

1. Bypass of the gastrointestinal tract and hepatic portal system, increasing the bioavailability of orally administered drugs that otherwise undergo hepatic first metabolism.
2. Improved patient compliance due to the elimination of associated pain with injections; administration of drugs in unconscious or incapacitated patients.
3. Sustained drug delivery.
4. A relatively rapid onset of action can be achieved relative to the oral route, and the formulation can be removed if therapy is required to be discontinued.
5. Increased ease of drug administration.

LIMITATIONS OF BUCCAL DRUG DELIVERY[6]. **-**

Depending on whether local or systemic action is required the challenges faced while delivering drug via buccal drug delivery can be enumerated as follows,

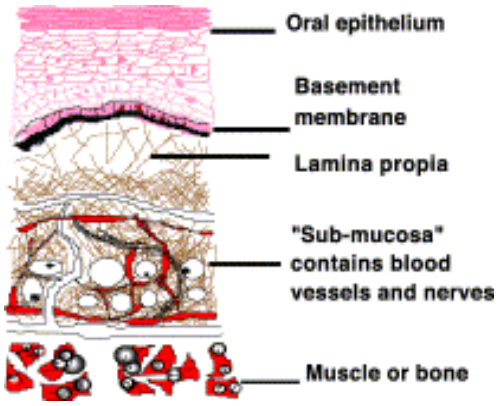
1. For local action the rapid elimination of drugs due to the flushing action of saliva or the ingestion of foods stuffs may lead to the requirement for frequent dosing.
2. The non-uniform distribution of drug within saliva on release from a solid or semisolid delivery system could mean that some areas of the oral cavity may not receive effective levels.

3. For both local and systemic action, patient acceptability in terms of taste, irritancy and 'mouth feel' is an issue. For systemic delivery the relative impermeability of oral cavity mucosa with regard to drug absorption, especially for large hydrophilic biopharmaceuticals, is a major concern.

ORAL CAVITY: ANATOMIC AND PHYSIOLOGIC FEATURES-

The oral mucosa presents a surface area of about 100 cm^2. Three different types of oral mucosa are recognized: the masticatory mucosa, the lining mucosa and the specialized mucosa. The masticatory mucosa, representing 25% of the total oral mucosa, is 100–200 μm in thickness and covers the gingiva and the hard palate. It is tightly attached to the underlying structures and is subjected to abrasion and shear stress during mastication. The lining mucosa (60% of the total oral mucosa) is 500–800 μm in thickness and covers the lips, cheeks, soft palate, lower surface of the tongue and the floor of the oral cavity. The specialized mucosa (15% of the total oral mucosa) is found on the dorsum of the tongue and is involved in taste. The term 'buccal', even if sometimes wrongly used to indicate the mucosa of the total oral cavity, refers to the lining of the cheek and the upper and lower lips, which represent one-third of the total oral mucosa surface. [7]. Buccal region is that part of the mouth bounded anteriorly and laterally by the lips and the cheeks, posteriorly and medially by the teeth and/or gums, and above and below by the reflections of the mucosa from the lips and cheeks to the gums. Numerous racemose, mucous, or serous glands are present in the submucous tissue of the cheeks. The buccal glands are placed between the mucous membrane and buccinator muscle: they are similar in structure to the labial glands, but smaller. [8].

The primary role of the buccal mucosa, like the skin, is to protect underlying structures from foreign agents. The surface of the buccal mucosa consists of a stratified squamous epithelium. [9]. The epithelium is attached to underlying structures by a connective tissue or lamina propia, separated by a basal lamina. These lining mucosa and the lamina propia regions provide mostly mechanical support and no major barrier for penetration of actives. The connective tissue also contains the blood vessels that drain into the lingual, facial, and retromandibular veins, which then open into the internal jugular vein . This is one of the main advantages of buccal over oral delivery: absorption through the buccal epithelium avoids the gastrointestinal tract conditions, such as gastric pH, enzyme content, and the first pass effect due to direct absorption into the portal vein. Once a given drug molecule reaches the connective tissue, it may be readily distributed, thus the permeation barrier is across the whole thickness of the stratified epithelium. [10].



THE ENVIRONMENT OF THE ORAL CAVITY-

The environment of the oral mucosa and its composition has been well studied . Its main characteristics are the continued secretion of saliva from major and minor salivary glands. Oral fluid can be considered the protective fluid for all tissues of the oral cavity. It acts as a buffer, maintaining a pH range from 5.75 to 7.05 and is mainly composed of water (99.5%), organic compounds (0.3%), inorganic and trace elements (0.2%) . For artificial items inside the mouth, for example, prosthetic or orthodontic devices, the environmental conditions inside a human's mouth are harsh: the humidity is mostly 100%. The temperature, though generally around 37 °C, can vary between +5 and +55 °C for short times at least, for example, when eating or drinking cold or hot meals or beverages. Mastication can generate forces of up to 500 N and abrasion can occur on the teeth and on any item that resembles a chewing surface. Despite its buffering properties, salivary pH can drop as low as 2 when consuming acidic drinks. Moreover, the healthy oral cavity is colonized by microorganisms like fungi, viruses and bacteria, of which more than 700 species or phylotypes have been detected in the oral cavity. Special attention must, therefore, be paid to the hygiene requirements of an artificial device inside the mouth. [11].

The cells of the oral epithelia are surrounded by an intercellular ground substance, mucus, the principle components of which are complexes made up of proteins and carbohydrates. These complexes may be free of association or some maybe attached to certain regions on the cell surfaces. This matrix may actually play a role in cell-cell adhesion, as well as acting as a lubricant, allowing cells to move relative to one another. Along the same lines, the mucus is also believed to play a role in bioadhesion of mucoadhesive drug delivery systems. In stratified squamous epithelia found elsewhere in the body, mucus is synthesized by specialized mucus secreting cells like the goblet cells, however in the oral mucosa, mucus is secreted by the major and minor salivary glands as part of saliva. Up to 70% of the total

mucin found in saliva is contributed by the minor salivary glands. At physiological pH the mucus network carries a negative charge (due to the sialic acid and sulfate residues) which may play a role in mucoadhesion. At this pH mucus can form a strongly cohesive gel structure that will bind to the epithelial cell surface as a gelatinous layer[12].

Role of Saliva [13].**:**

. Protective fluid for all tissues of the oral cavity.

. Continuous mineralization / demineralization of the tooth enamel.

. To hydrate oral mucosal dosage forms.

Role of Mucus [14].**:**

. Made up of proteins and carbohydrates.

. Made up of proteins and carbohydrates.

. Cell-cell adhesion

. Lubrication

PERMEABILITY

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. In general, the permeabilities of the oral mucosae decrease in the order of sublingual greater than buccal and buccal greater than palatal. This rank order is based on the relative thickness and degree of keratinization of these tissues, with the sublingual mucosa being relatively thin and non-keratinized, the buccal thicker and non-keratinized, and the palatal intermediate in thickness but keratinized. It is currently believed that the permeability barrier in the oral mucosa is a result of intercellular material derived from the so-called 'membrane coating granules' (MCG). When cells go through differentiation, MCGs start forming and at the apical cell surfaces they fuse with the plasma membrane and their contents are discharged into the intercellular spaces at the upper one third of the epithelium. This barrier exists in the outermost 200µm of the superficial layer[15].. Permeation studies have been performed using a number of very large molecular weight tracers, such as horseradish peroxidase and lanthum nitrate . When applied to the outer surface of the epithelium, these tracers penetrate only through the outermost layer or two of cells when applied to the submucosal surface they permeate upto, but not into the outer most cell layer of the epithelium. Accordingly to these results, it seems apparent that flattened surface cells present the main barrier to permeation, while the more isodiametric cell layers are relatively permeable to both keratinized and nonkeratinized epithelia, keratinization by

itself is not expected to play a significant role in the barrier function. The components of the MCG's in keratinized and non-keratinized epithelia are different, however the MCG's of keratinized epithelium are composed of lamellar lipid stacks, whereas the non-keratinised epithelia include sphingomyelin, glucosylceramides, ceramides and other nonpolar lipids however for non-keratinized epithelia, the major MCG's lipid component are glycophingolipids (Bodde, 1990). Aside from the present some resistance to permeation as well, however the outer epithelium still considered to be the rate limiting step to mucosal penetration. The structure of the basement membrane is not dense enough to exclude relatively large molecules[16].

ROUTES OF PERMEATION:

There are two possible routes of drug absorption through the squamous stratified epithelium of the oral mucosa:

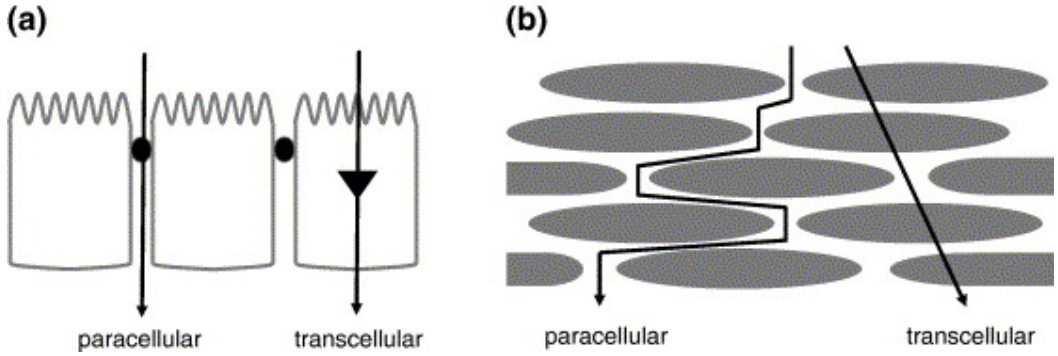
. Transcellular (intracellular, passing through the cell)

. Paracellular (intercellular, passing around the cell)

The transcellular route may involve permeation across the apical cell membrane, the intracellular space and the basolateral membrane either by passive transport (diffusion, pH partition) or by active transport (facilitated and carrier-mediated diffusion, endocytosis). The transcellular permeability of a peptide is a complex function of various physicochemical properties including size, lipophilicity, hydrogen bond potential, charge and conformation. There are a few reports in the literature suggesting that small polar drugs penetrate buccal epithelium via the intracellular route. One should also consider that transport via aqueous pores in the cell membranes of the epithelium is also possible for substances of low molar volume (80 cm^3/mol) [17].

Permeation across the buccal mucosa has been reported to be mainly by the paracellular route through the intercellular lipids produced by membrane-coating granules. Although passive diffusion is the main mechanism of drug absorption, specialized transport mechanisms have been reported to exist in other oral mucosa (that of the tongue) for a few drugs and nutrients; glucose and cefadroxil were shown to be absorbed in this way. The buccal mucosa is a potential site for the controlled delivery of hydrophilic macromolecular therapeutic agents (biopharmaceuticals) such as peptides, oligonucleotides and polysaccharides. However, these high molecular weight drugs usually have low permeability leading to a low bioavailability, and absorption enhancers may be required to overcome this. The buccal mucosa also contains proteases that may degrade peptide-based drugs. In addition, the salivary enzymes may also

reduce stability. Disease states where the mucosa is damaged would also be expected to increase permeability. This would be particularly true in conditions that result in erosion of the mucosa such as lichen planus, pemphigus, viral infections and allergic reactions. Biopharmaceutics of Buccal and Sublingual Absorption [18].



MUCOADHESION

The concept of mucoadhesion has been pioneered in the 1980s. [19]. mucoadhesive controlled-release dosage forms has gained considerable interest[20]. Mucoadhesive drug delivery systems offer some benefits over other delivery methods including extended residence time of the drug at the site of application, a relatively large permeability of the mucus membranes that allows rapid uptake of a drug into the systemic circulation, and enhanced bioavailability of therapeutic agents resulting from the avoidance of some of the body's natural defense mechanisms[21].Mucoadhesion is provided by the formation of non-covalent bonds such as hydrogen bonds and ionic interactions or physical entanglements between the mucus gel layer and polymers. Mediated by mucoadhesive polymers[22]. Mucoadhesion or bioadhesion can be defined as the state in which two materials, at least one of which is biological in nature, are held together for a prolonged time period by means of interfacial forces[23].

Over the last two decades Mucoadhesion has become of interest for its potential to optimise localised drug delivery , by retaining a dosage form at the site of action or systemic delivery by retaining a formulation in intimate contact with the absorption site[24].

MECHANISMS INVOLVED IN MUCOADHESION

the process involved in the mucoadhesion phenomenon can be described in three steps: first of all, the wetting and swelling of the polymer should allow an intimate contact with the tissue, secondly interpenetration of the polymer chains and entanglement between the polymer and the mucin chains should be attained and finally, the formation of weak chemical bonds should be possible[25]. The mechanism of mucoadhesion is generally divided into two steps: the contact stage and the consolidation stage. The first stage is characterized by the

contact between the mucoadhesive and the mucus membrane, with spreading and swelling of the formulation, initiating its deep contact with the mucus layer. In the consolidation step, the mucoadhesive materials are activated by the presence of moisture. Moisture plasticizes the system, allowing the mucoadhesive molecules to break free and to link up by weak vander Waals and hydrogen bonds[26].

Physical interaction [27]

1. Van der waals force:

i)London dispersion forces,

ii) Dipole–dipole interactions,

iii) Debye type force.

2. Hydrogen bonds.

3. Hydrophobic bonds.

Chemical Interaction [27]-

1. Ionic bonds.

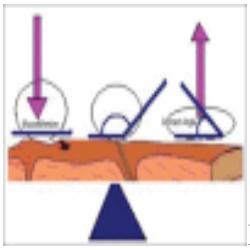
2. Covalent bonds

THEORIES OF MUCOADHESION

Mucoadhesion is a complex process and numerous theories have been proposed to explain the mechanisms involved. These theories include mechanical interlocking, electrostatic, diffusion interpenetration, adsorption and fracture processes[28].

1. Wetting theory

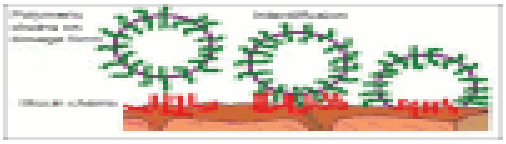
The wetting theory applies to liquid systems which present affinity to the surface in order to spread over it. This affinity can be found by using measuring techniques such as the contact angle. The general rule states that the lower the contact angle, the greater is the affinity. The contact angle should be equal or close to zero to provide adequate spreadability. The spreadability coefficient,$\boldsymbol{S_{AB}}$, can be calculated from the difference between the surface energies $\gamma\boldsymbol{B}$ and $\gamma\boldsymbol{A}$ and the interfacial energy $\gamma\boldsymbol{AB}$, as indicated in the equation given below. This theory explains the importance of contact angle and reduction of surface and interfacial energies to achieve good amount of mucoadhesion[28]



Influence of contact angle on Mucoadhesion, $\boldsymbol{S_{AB}} = \gamma\boldsymbol{B} - \gamma\boldsymbol{A} - \gamma\boldsymbol{AB}$

2.Diffusion theory

Diffusion theory describes the interpenetration of both polymer and mucin chains to a sufficient depth to create a semi-permanent adhesive bond. It is believed that the adhesion force increases with the degree of penetration of the polymer chains. This penetration rate depends on the diffusion coefficient, flexibility and nature of the mucoadhesive chains, mobility and contact time. According to the literature, the depth of interpenetration required to produce an efficient bioadhesive bond lies in the range 0.2–0.5 μm. This interpenetration depth of polymer and mucin chains can be estimated by the following equation:



Secondary interaction between mucoadhesive device and of mucus, $l = (tD_b)^{1/2}$

Where t is the contact time and D_b is the diffusion coefficient of the mucoadhesive material in the mucus. The adhesion strength for a polymer is reached when the depth of penetration is approximately equivalent to the polymer chain size. In order for diffusion to occur, it is important that the components involved have good mutual solubility, that is, both the bioadhesive and the mucus have similar chemical structures. The greater the structural similarity, the better is the mucoadhesive bond[28].

3. Fracture theory *:*

According to this theory, the adhesive bond between systems is related to the force required to separate both surfaces from one another. This ‘‘fracture theory” relates the force for polymer detachment from the mucus to the strength of their adhesive bond.The work fracture has been found to be greater when the polymernetwork strands are longer or if the degree of cross-linking withinsuch as system is reduced. This theory allows the determination offracture strength (r) following the separation of two surfaces via its relationship to Young’s modulus of elasticity (E), the fracture energy(e) and the critical crack length (L) through the following equation [29].

$r = (E \times e / L)^{1/2}$  Fractures occurring for Mucoadhesion

4. The electronic theory

According to electronic theory, attractive electrostatic forces between glycoprotein mucin network and bioadhesive material. Because of different electronic properties of

mucoadhesive polymer and the mucus glycoprotein, electron transfer between these two surfaces occurs. Electron transfer between these two forming double layer of electric charges at the interface. This theory describes adhesion occurring by means of electron transfer between mucus and mucoadhesive system arising through differences in their electron structure. Thus it results in the formation of electronic charges at the mucus and mucoadhesive interface with subsequent adhesion due to attractive forces [30].

5. Adsorption Theory

According to the adsorption theory, after an initial contact between two surfaces, the materials adhere because of surface forces acting between the chemical structures at the two surfaces. When polar molecules or groups are present, they reorientate at the interface. Chemisorption can occur when adhesion is particularly strong. The theory maintains that adherence to tissue is due to the net result of one or more secondary forces (van der Waal's forces, hydrogen bonding, and hydrophobic bonding). [31]

3.3.FACTORS AFFECTING MUCOADHESION

1.Polymer related factors: The adhesive bond between a bioadhesive system and mucin gel can be investigated in term of contribution of the following factors: [32].

a. Molecular Weight: The optimum molecular weight for maximum mucoadhesion depends upon the type of mucoadhesive polymer and tissue. Numerous studies have identified that there is a certain molecular weight at which bioadhesive is at a maximum. The interpenetration of polymer molecules is favorable for low molecular weight polymers whereas entanglements are favors for high molecular weight polymers. The optimum molecular weight for the maximum bioadhesion depends on the type of polymer. According to Gurny et al., (1984) it seems that the bioadhesive forces increases with the molecular weight of bioadhesive polymer up to 100,000 and that beyond this level there is not much effect.

b. Flexibility of polymer chains: Flexibility is important for interpenetration and entanglement. As water-soluble polymer becomes cross-linked, the mobility of the individual polymer chain decreases. As the cross linking density increases the effective length of the chain, which can penetrate into mucus layer, decreases even further and mucoadhesive strength is decreased.

c. Spatial conformation: Despite a high molecular weight of 19,500,000 for dextrans, spatial conformation of a molecule is also important. They have adhesive strength similar to that of polyethyleneglycol, which has a molecular weight of 200,000. The helical conformation of

electrons may shield many adhesively active groups, primarily responsible for adhesion unlike PEG polymers that have a linear conformation. Also the effect of polymer concentration is dependable on the physical state (solid / liquid) of the bioadhesive drug delivery systems; more is the polymer concentration results the higher bioadhesive strength in Solid BDDS while an optimum concentration is required for best bioadhesion in liquids.

2. Environment Related Factors [33].

a. Applied strength: To place a solid bioadhesive system, it is required to concern a defined strength. Whatever the polymer, poly(acrylic acid / vinyl benzene poly (HEMA) or carbopol 934, the adhesion strength increases with the applied strength or with the period of its application, upto an optimum. the pressure initially applied to the mucoadhesive tissue contact site can influence the depth of interpenetration. If high pressure is applied for a sufficiently long period of time, polymers become mucoadhesive even though they do not have attractive interaction with mucin.

b. pH: It can manipulate the formal charge on the surface of mucus as well as certain ionis capable bioadhesive polymers. Mucus will have a different charge density depending on pH due to difference in dissociation of efficient groups on the carbohydrate moiety and the amino acids of the polypeptide backbone. pH of the medium is important for the degree of hydration of crosslinked polyacrylic acid, showing consistently increased hydration from pH 4 to 7 and then a reduce as alkalinity and ionic strength increases.

c. Initial Contact Time: Contact time between the bioadhesive and mucus layer determines the extent of swelling and interpenetration of the bioadhesive polymer chains. Bioadhesive strength increases as the initial contact time increases.

d. Swelling: It depends on the polymer concentration, ionic concentration, as well as the presence of water. Over hydration results in formation of a mucilage without adhesion.

3. Membrane Factors[34].

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.

POLYMERS FOR MUCOADHESIVE SYSTEMS:

Mucoadhesive polymers are water-soluble and water insoluble polymers, which are swellable networks, jointed by cross-linking agents. These polymers possess optimal polarity

to make sure that they permit sufficient wetting by the mucus and optimal fluidity that permits the mutual adsorption and interpenetration of polymer and mucus to take place [35].

CHARACTERISTICS OF AN IDEAL MUCOADHESIVE POLYMER [35]

1. The polymer and its degradation products should be nontoxic and should be nonabsorbable from the gastrointestinal tract.
2. It should be non-irritant to the mucous membrane.
3. It should preferably form a strong non-covalent bond with the mucin-epithelial cell surfaces.
4. It should adhere quickly to most tissue and should possess some site-specificity.
5. It should allow incorporation to the daily dose of the drug and offer no hindrance to its release.
6. The polymer must not decompose on storage or during the shelf life of the dosage form.
7. The cost of polymer should not be high so that the prepared dosage form remains competitive.

CLASSIFICATION OF POLYMERS: [36]

Mucoadhesive polymer are classified as follows:

1.First generation polymer:

a.Anionic polymer: poly(-acrylic acid), carbopol, polycarbophil,

b.Cationic polymer: Chitosan

2.Second generation polymer: Lecitins, bacterial adhesion ,Thiomers

1.First generation polymers:

The first generation polymers are divided into three major groups according to their surface charges which include anionic, cationic and non-ionic polymers. The anionic and cationic polymers exhibit stronger Mucoadhesion. Anionic polymers are the most widely employed mucoadhesive polymers within pharmaceutical formulations due to their high mucoadhesive functionality and low toxicity. Such polymers are characterized by the presence of carboxyl and sulfate functional groups that give rise to a net overall negative charge at pH values exceeding the pKa of the polymer. Typical examples include polyacrylic acid (PAA) and its weakly cross-linked derivatives and sodium carboxymethyl cellulose (Na CMC). PAA and Na CMC possess excellent mucoadhesive characteristics due to the formation of strong hydrogen bonding interactions with mucin . Among the cationic polymer systems, undoubtedly chitosan is the most extensively investigated within the current scientific literature . Chitosan is a cationic polysaccharide, produced by the deacetylation of chitin, the

most abundant polysaccharide in the world, next to cellulose. Chitosan is a popular polymer to use due to its biocompatibility, biodegradability and favorable toxicological properties. Chitosan has been reported to bind via ionic interactions between primary amino functional groups and the sialic acid and sulphonic acid substructures of mucus. The major benefit of using chitosan within pharmaceutical applications has been the ease with which various chemical groups may be added, in particular to the C-2 position allowing for the formation of novel polymers with added functionality[37].

2. Newer second generation polymers

They have the following advantages [38].

i. More site specific hence called cytoadhesives.

ii. Are least effected by mucus turnover rates.

iii. Site specific drug delivery is possible.

I) Lectins

Lectins are naturally occurring proteins that are useful in biological recognition involving cells and proteins. Lectins are a class of structurally diverse proteins and glycoprotein that bind reversibly to specific carbohydrate residues. After binding to the cell the lectins may either remain on the cell surface or may be taken inside the cell via endocytosis, they hence allow a method for site specific and controlled drug delivery. The lectins have many advantages but they also have the disadvantage of being immunogenic[38].

II) Thiolated polymers

Thiolated polymers (thiomers) are a type of second-generation mucoadhesive derived from hydrophilic polymers such as polyacrylates, chitosan or deacetylated gellan gum. The presence of thiol groups allows the formation of covalent bonds with cysteine-rich sub domains of the mucus gel layer, leading to increased residence time and improved bioavailability. In this respect thiomers mimic the natural mechanism of secreted mucus glycoproteins that are also covalently anchored in the mucus layer by the formation of disulphide bonds. Whilst first-generation mucoadhesive platforms are facilitated via non-covalent secondary interactions, the covalent bonding mechanisms involved in second-generation systems lead to interactions that are less susceptible to changes in ionic strength and/or the pH. Moreover the presence of disulphide bonds may significantly alter the mechanism of drug release from the delivery system due to increased rigidity and cross-linking. In such platforms a diffusion-controlled drug release mechanism is more typical, whereas in first-generation polymers anomalous transport of API into bulk solution is more common [39].

III) Polyox WSRA:

Class of high molecular weight polyethylene molecular weight polyethylene oxide. Homopolymers having the following properties,

. Water soluble

. Hydrophilic nature

. High molecular weight

. Functional group for hydrogen bonding

. Biocompatible and non toxic

. Can be formulated into tablets, films, gels, microcapsules, syrups [40].

IV) Bacterial Adhesion:

The adhesive properties of bacterial cells, as a more complicated adhesion system, have recently been investigated. The ability of bacteria to adhere to a specific target is rooted from particular cell-surface components or appendages, known as fimbriae that facilitate adhesion to other cells or inanimate surfaces. These are extracellular, long thread like protein polymers of bacteria that play a major role in many diseases. Bacterial fimbriae adhere to the binding moiety of specific receptors. A significant correlation has been found between the presence of fimbriae on the surface of bacteria and their pathogenicity. The attractiveness of this approach lies in the potential increase in the residence time of the drug on the mucus and its receptor-specific interaction, similar to those of the plant lectins. [40].

METHODS TO INCREASE DRUG DELIVERY VIA BUCCAL ROUTE

1.Permeation enhancers: [41].

Permeation enhancers are substances added to pharmaceutical formulation in order to increases the membrane permeation rate or absorption rate of a co-administered drug. They are used to improve bioavailability of drugs with normally poor membrane permeation properties without damaging the membrane and causing toxicity. Enhancer efficacy depends on the physiochemical properties of the drug, administration site, nature of the vehicle and whether enhancer is used alone or in combination.

#Categories and examples of membrane permeation enhancers

A. Bile salts and other steroidal detergents: Sodium glycocholate, Sodium taurocholate, Saponins, Sodium tauro dihydro fusidate and Sodium glycol dihydro fusidate.

B. Surfactants:

1. Non- ionic: Laureth-a, Polysorbate-9, Sucrose esters and do-decyl maltoside

2. Cationic: Cetyl trimethylammonium bromide

3. Anionic: sodium lauryl sulfate

C. Fatty acids: oleic acid, lauric acid, caproic acid

D. Other enhancers:

1. Azones

2. Salicylates

3. Chelating agents

4. Sulfoxides e. g. Dimethyl Sulfoxide (DMSO)

MECHANISM OF PERMEATION ENHANCER:

The mechanism by which enhancers act are been poorly understood. Surfactants such as sodium lauryl sulphate interact at either the polar head groups or the hydrophilic tail regions of the molecules comprising the lipid bilayer disrupting the packing of the lipid molecules, increasing the fluidity of the bilayer and facilitating drug diffusion. Interaction of enhancers with the polar head groups may also cause or permit the hydrophilic regions of adjacent bilayers to take up more water and more apart, thus opening the Para cellular pathway. Non ionic surfactants and long chain acids and alcohols also increase membrane components, thereby increasing the permeability. Agents such as DMSO, polyethylene glycol, and ethanol can, if present insufficient high concentrations in the delivery vehicle enter the aqueous phase of the stratum corneum and alter its solublizing properties, thereby enhancing the partitioning of drugs from the vehicle into the skin.

• Mechanisms by which permeation enhancers are thought to improve mucosal absorption include the following:

.Changing mucus rheology
. Increasing fluidity of lipid bilayer membrane
. Affecting the components involved in the formation of intracellular junctions
. Overcoming the enzymatic barrier
. Increasing the thermodynamic activity of drugs.

2. Prodrugs

Hussain et al delivered opioid agonists and antagonists in bitterless prodrug forms and found that the drug exhibited low bioavailability as prodrug. Nalbuphine and naloxone bitter drugs when administered to dogs via the buccal mucosa, the caused excess salivation and swallowing. As a result, the drug exhibited low bioavailability. Administration of nalbuphine and naloxone in prodrug form caused no adverse effects, with bioavailability ranging from 35 to 50% showing marked improvement over the oral bioavailability of these compounds, which is generally 5% or less [42].

3. pH

Shojaei et al evaluated permeability of acyclovir at pH ranges of 3.3 to 8.8, and in the presence of the absorption enhancer, sodium glycocholate. The in vitro permeability of acyclovir was found to be pH dependent with an increase in flux and permeability coefficient at both pH extremes (pH 3.3 and 8.8), as compared to the mid-range values (pH 4.1, 5.8, and 7.0) [43].

4. Patch design

Several in vitro studies have been conducted regarding on the type and amount of backing materials and the drug release profile and it showed that both are interrelated. Also, the drug release pattern was different between single-layered and multi-layered patches [44].

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 1-3cm2 and a daily dose of 25mg or less are preferable. The maximal duration of buccal delivery is approximately 4-6h. The excipients used in the formulation should be GRAS-listed (Generally Recognized as Safe) [45].

BUCCAL MUCOADHESIVE DOSAGE FORMS:

Buccal mucoadhesive dosage forms can be categorized into three types based on their geometry.

Type I: It is a single layer device with multidirectional drug release. This type of dosage form suffers from significant drug loss due to swallowing.

Type II: It is a device in which 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 into the oral cavity.

Type III: It is a unidirectional drug release device, from whichdrug 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 [46].

a) Adhesive tablets

Adhesive tablets are held between the gum and cheek. These are generally flat, elliptical or capsule-shaped. The parotid duct empties into the mouth at a point opposite the crown of the second upper molar, near the spot where buccal tablets are usually placed. This location provides the medium to dissolve the tablets and to provide for release of the medication.

Buccal tablets are prepared either by the procedures used for granulation or by direct compression. Formulation contains no disintegrants, so the tablet will dissolve slowly. Flavouring agents and sweeteners are sometimes added to make the tablets more palatable, but this may result in increased flow rate of saliva, which is not desirable. It is also importantto minimize the swallowing of saliva during the time that the buccal tablet is held in place. Since buccal tablets are to be held in the mouth for relatively long periods of time, particular care should be taken to see that all the ingredients are finely divided so that the tablets are not gritty or irritating. Buccoadhesive tablet may be monolithic or bilaminated system. The main disadvantages of the monolayer tablet is the multidirectional release of the drug, hence some of the fraction of drug may swallowed. In order to avoid multidirectional release of the drug a bilaminated system was used. The Bilayered tablet made up of two layers, drug containing core layer and backing layer. The backing layer may be of water insoluble material like Ethyl cellulose or hydrogenated caster oil or may be polymeric coating layer which functioning as a adhesive and backing layer. A mucoadhesive delivery system with a backing layer on one side can be used for local as well as systemic transmucosal drug delivery. Such a backing layer avoids sticking of the tablet to the finger during application in the oral cavity [47].

b) **Patches**

Flexible adhesive patches have been developed in an effort to overcome some of the drawbacks of other dosage forms. Transmucosal delivery patches have unique characteristics, including relatively rapid onset of drug delivery, sustained drug release and rapid decline in the serum drug concentration when the patch is removed. Also, a buccal patch is confined to the buccal area over which it is attached and therefore the absorption profile may have less inter- and intra-individual variability. In general, oral mucosal patches can be classified into three categories: patches with a dissolvable matrix, patches with a non-dissolvable backing, and patches with a dissolvable backing. Patches with a dissolvable matrix are designed to release drug into the oral cavity. They work similarly to, and share many of the limitations of, the solid dos e form. The mucoadhesive layer, either in the drug matrix or attached to drug matrix as an additional layer, prolongs the duration of drug matrix in the oral cavity. Therefore, compared with other open dosage forms, these types of patches are longer acting and can potentially deliver more drug. They also use the entire oral cavity mucosa as compared with other closed systems that typically use smaller areas. These types of patches are also suitable for treating local diseases such as candidiasis or mucositis. Patches with non-

dissolvable backing are usually designed for systemic delivery. Since they are closed systems and the formulations are protected from saliva, the drug concentrations are controlled and drug is continuously delivered for 10 to 15 h. The disadvantages of these systems are that they use only a small mucosal area and the backings have to be removed by the patient after drug administration. Patches with dissolvable backing share many characteristics of patches with non-dissolvable backing, but they have the advantage of the entire patch dissolving in the oral cavity. Patches with dissolvable backings are shorter acting than patches with non-dissolvable backing. Oral mucosal dosage forms are convenient, easy to use, and have the potential to offer a low-cost and painless alternative to more invasive routes of administration. Each delivery form offers very distinct delivery characteristics that can be used in a broad range of therapies. The majority of patches provide a longer period over which to deliver the formulated as either solvent-cast mucoadhesive polymer discs or drug to and through the buccal mucosa [48].

c) Wafers:

Wafers is a novel periodontal drug delivery system. This is used for the treatment of microbial infection [49].

d) Lozenges:

Lozenges are used as topically within mouth including antimicrobials, corticosteroids, local anaesthetics, 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 subtherapeutic levels[49].

e) Buccal films

Films are the most recently developed dosage form for buccal administration. Buccal films may be preferred over adhesive tablets in terms of flexibility and comfort. In addition, they can circumvent the relatively short residence time of oral gels on the mucosa, which are easily washed away and removed by saliva. Moreover, in case of local delivery for oral diseases, the films also help protect the wound surface, thus helping to reduce pain and treat the disease more effectively. An ideal film should be flexible, elastic, and soft, yet adequately strong to withstand breakage due to stress from mouth movements. It must also possess good bioadhesive strength in order to be retained in the mouth for the desired duration of action. Swelling of film, if it occurs, should not be too extensive in order to prevent discomfort[50].

f) Buccal gels and ointments Semisolid dosage forms, such as gels and ointments, have the advantage of easy dispersion throughout the oral mucosa. However, drug dosing from

semisolid dosage forms may not be as accurate as from tablets, patches, or films. Poor retention of the gels at the site of application has been overcome by using bioadhesive formulations .Certain bioadhesive polymers, e.g. poloxamer 407, sodium carboxy methylcellulose, carbopol, hyaluronic acid, and xanthan gum, undergo a phase change from a liquid to a semisolid 16. This change enhances the viscosity, which results in sustained and controlled release of drugs. However, these polymers have been investigated for this purpose primarily in ocular drug delivery[50].

g) Biobadhesive Spray:

Buccoadhesive sprays are gaining important over other dosage forms because of flexibility, comfort, high surface area and availability of drug in solution form.The first FDA-approved (1996) formulation was developed by fentanyl Oralet ™ to take advantage of oral transmucosal absorption for the painless administration of an opioid in a formulation acceptable to children. In 2002, the FDA approved Subutex (buprenorphine) for initiating treatment of opioid dependence (addiction to opioid drugs, including heroin and opioid analgesics) and Suboxone (buprenorphine and naloxone) for continuing treatment of addicts. In 2005, Oral-lyn buccal spray was approved for commercial marketing and sales in Ecuador[51].

h) Buccal chewing gums:

Although medicated chewing gums pose difficulties in regulating the dose administered, they still have some advantages as drug delivery devices, particularly in the treatment of diseases in the oral cavity and in nicotine replacement therapy. Some commercial products are available in the market34. Caffeine chewing gum, Stay Alert®, was developed recently for alleviation of sleepiness. It is absorbed at a significantly faster rate and its bioavailability was comparable to that in capsule formulation. Nicotine chewing gums (e.g., Nicorette® and Nicotinell®) have been marketed for smoking cessation. The permeability of nicotine across the buccal mucosa is faster than across the skin. However, chewing gum slowly generates a steady plasma level of nicotine rather than a sharp peak as experienced when smoking. Possible swallowing of considerable amount of nicotine during chewing may lead to decreased effectiveness of the chewing gum due to first-pass metabolism and gastrointestinal discomfort[52].

i) Powders:

Yama moto et al., have described a hydroxypropyl cellulose and beclomethasone-diproprionate containing powder that was sprayed onto the oral mucosa of rats. A significant

increase in the residence time relative to an oral solution was seen, and 2.5% of beclomethasone was retained on buccal mucosa for over 4 hours[53].

j) Liquid dosage forms:

They are solutions or suspensions of drugs in suitable aqueous vehicles. Such types of dosage forms are usually employed to exert local action into the oral cavity and several antibacterial mouthwashes and mouth-freshener are commercially available for this purpose. The limitation associated with these liquid dosage forms are that they are not readily retained or targeted to buccal mucosa and can deliver relatively uncontrolled amounts of drug throughout oral cavity. From the wide range of polymer solutions, chitosan represents the greatest binding, followed by methylcellulose, gelatin, carbopol and polycarbophil. Viscous liquids may be used to coat buccal surface either as protectants or as drug delivery vehicles to the mucosal surface. Dry mouth is treated with artificial saliva solutions that are retained on mucosal surfaces to provide lubrication. These solutions contain sodium CMC as bioadhesive polymer. [54]

METHODS OF EVALUATION

Testing methods are important during design and development of bioadhesive controlled release system as they ensure compatibility, physical and mechanical stability, surface analysis and bioadhesive bonding strength. [55]

Buccal adhesive drug delivery devices are subjected to the routine evaluation tests such as weight variation, thickness variation, friability, hardness, content uniformity, in vitro dissolution for tablets; tensile strength, film endurance, hygroscopicity etc. for films and patches; viscosity, effect of aging etc. for gels and ointments. They should also to be evaluated specifically for their bioadhesive strengths and permeabilities. [56]

1. Moisture absorption studies for buccal patches[56]

The moisture absorption studies for the buccal patches give an indication about the relative moisture absorption capacities of polymers and an idea whether the buccal patches maintain their integrity after absorption of moisture. Moisture absorption studies have been performed in 5 % w/v agar in distilled water, which while hot was transferred to petri plates and allowed to solidify (112). Then six buccal patches from each formulation were selected and weighed. Buccal patches were placed in desiccator overnight prior to the study to remove moisture if any and laminated on one side with water impermeable backing membrane. Placed on the surface of the agar plate and incubated at 37° C for 2 hrs in incubator. The patches were weighed again and the percentage of the absorbed moisture was calculated using the formula:

% Moisture absorbed = Final weight – Initial weight×100Initial weight

2 .Swelling and erosion studies for buccal tablets[56]

Swelling and erosion studies for buccal tablets were determined gravimetrically in phosphate buffer, of pH 6.6 (56, 111). The tablets were attached to pre-weighed glass supports using a cyanoacrylate adhesive sealant. The supports with tablets were immersed into the phosphate buffer at 37 .C. At pre-determined time intervals, the devices were removed from the media, blotted with tissue paperto remove excess water, and weighed. After determination of the wet weight, the tablets were dried at 40°C until constant mass. Swelling index (S.I) and erosion were determined gravimetrically according to the following equations.

Swelling index (%)=ws-wd/wd

Erosion (% mass loss)=Original weight – remaining dry weight×100Original weight

Where Wd and Ws are the weights of dry and swollen devices, respectively

3. Determination of tensile strength[57]

Tensile stress is also termed Maximum Stress or Ultimate Tensile Stress. The resistance of a material to a force tending to tear it apart, measured as the maximum tension the material can withstand without tearing. Tensile strength can be defined as the strength of material expressed as the greatest longitudinal stress it can bear without tearing apart. As it is the maximum load applied in breaking a tensile test piece divided by the original cross-sectional area of the test piece, it is measured as Newtons/sq.m. Specifically, the tensile strength of a material is the maximum amount of tensile stress that it can be subjected to before failure. The definition of failure can vary according to material type and design methodology.

There are three typical definitions of tensile strength:

▪Yield Strength — The stress a material can withstand without permanent deformation.

▪Ultimate Strength — The maximum stress a material can withstand.

▪Breaking Strength — The stress coordinate on the stress–strain curve at the point of rupture.

Methods using the tensile strength usually measure the force required to break the adhesive bond between a model membrane and the test polymers.

4. Colloidal gold staining method [57].

Park proposed the colloidal gold staining technique for the study of bioadhesion. The technique employs red colloidal gold particles, which were adsorbed on mucin molecules to form mucin–gold conjugates, which upon interaction with bioadhesive hydrogels develops a red color on the surface. This can be quantified by measuring at 525 nm either the intensity on the hydrogel surface or the conjugates.

5. Direct staining method[57].

It is a novel technique to evaluate polymer adhesion to human buccal cells following exposure to aqueous polymer dispersion, both ***in vitro*** and ***in vivo***. Adhering polymer was visualized by staining with 0.1% w/v of either Alcian blue or Eosin solution; and the uncomplexed dye was removed by washing with 0.25 M sucrose. The extent of polymer adhesion was quantified by measuring the relative staining intensity of control and polymer treated cells by image analysis. Carbopol 974 P, polycarbophil and chitosan were found to adhere to human buccal cells from 0.10% w/w aqueous dispersions of these polymers. Following ***in vivo*** administration as a mouthwash, these polymers persisted upon the human buccal mucosa for at least one hour. This method is only suitable for assessing the liquid dosage forms, which are widely employed to enhance oral hygiene and to treat local disease conditions of the mouth such as oral candidacies and dental caries.

6. Shear stress method: [58].

The measurement of the shear stress gives an direct correlation to the adhesion strength. In a simple shear stress measurement based method two smooth, polished plexi glass boxes were selected one block was fixed with adhesive araiditeon a glass plate, which was fixed on leveled table. The level was adjusted with the spirit level. To the upper block, a thread was tied and the thread was passed down through a pulley, the length of the thread from the pulley to the pan was 12cms. At the end of the thread a pan of weight 17gms was attached into which the weights can be added.36,37 A recent method involves the measurement of mucoadhesion by use of a stainless steel rotating cylinder which was coated with freshly excised porcine intestinal mucosa to which polymer discs were attached. The cylinder was placed in a dissolution apparatus and rotated at 125rpm. It was analysed every 30 mins for the attachement of the polymers discs.

7. Detachment force measurements: [58].

The Wilhelmy plate method is one of the traditional methods for the measurement of the force of adhesion of various bioadhesive dosage forms. The method involves the measurement of the dynamic contact angles and utilizes a microtensiometer and a microbalance.39 The CAHN dynamic contact angle analyzer is used for this purpose. Wilhelmy plate method measures the bioadhesive force between the mucosal tissue and the polymer/dosage form attached to a metal wire and suspended into the microtensiometer. The mucosal tissue(usually rat jejunum) is used which is placed in the tissue chamber, this chamber is raised so as to make contact between the tissue and the test material. After a

certain period(7 mins for microspheres) the stage is lowered and the force of adhesion is measured. This apparatus measures the following parameters:

i. Fracture strength: force per unit area required to break the adhesive bond.

ii. Deformation to failure: it is the distance required to move the stage before complete separation occurs.

8. Surface pH study: The surface pH study for buccal tablets has to be done to investigate the possibility of any side-effect in vivo. An acidic or alkaline pH may irritate the buccal mucosa, so the surface pH of tablet should be almost neutral. The tablets are allowed to swell by placing them in an agar plate for 2hr. The surface pH was measured by using a pH digital meter placed on the core surface of the swollen tablet. Bottenberg et.al used a combined glass electrode for the study. In this method the tablet was allowed to swell by placing it in contact with 1mL of distilled water (pH 6.5±0.05) for 2hrs at room temperature. The pH was determined by bringing the electrode into contact with the tablet surface and allowing the surface to equilibrate for 1minute[59].

9. *In-vitro* drug permeation study: Can be performed using Keshary-chien type glass diffusion cell at 37±0.2 °C. The fresh pig buccal mucosa (buccal membrane closely resembles the human buccal membrane in terms of structure and permeability) is to be mounted between donor and receptor compartments, the buccal tablet is placed with the core facing the mucosa and the compartments are clamped together. The donor compartment is to be filled with 1mL of phosphate buffer pH6.8 and receptor compartment with phosphate buffer pH7.4, hydrodynamics between compartments is maintained with a magnetic bead at a uniform slow speed. The samples at pre-determined intervals of time are analyzed with the help of a U.V Spectrophotometer[59].

10. *In vitro* drug release studies:

In-vitro release studies can be performed according to USP XXII type2 dissolution apparatus at suitable pH conditions. The temperature should be maintained at 37±0.5°C and the rotation speed of 100 rpm. Then 5 ml of sample should be withdrawn at varioustime intervals and replenished with an equal volume of fresh dissolution media. The drug content in the sample can be analyzed spectrophotometrically at specific wavelength (nm) [60].

10. *In vivo* tests:

There is scant information available on the in vivo behavior of mucoadhesive formulations, especially in humans. Säkkinen et al. (2006) applied gamma scintigraphy to analyze mucoadhesion in vivo of chitosan within the gastrointestinal tract. Gamma scintigraphy

allows the immediate visualization of all the formulation transit, with low exposure of the subjects to radiation. The study emphasized the importance of in vivo studies, because although chitosan exhibits an outstanding mucoadhesion capacity in vitro, the retention time at the absorption site in the human gastrointestinal tract was relatively short and not sufficiently reproducible. The gastrointestinal transit time in animals can also be evaluated in a non-invasive way, in which the release systems can be formulated with opaque radioisotopes and signals can be followed by X-rays, without affecting normal gastrointestinal motility.

The number of methodologies applied to analyze mucoadhesion is constantly growing, although the use of different methods may sometimes lead to incoherence among results due to the heterogeneity of parameters and conditions used. Ahuja et al. examined various studies that used the tension resistance method and each had employed different models of mucous membrane and equipment. Despite the large body of evidence obtained to date, further investigations aimed at standardizing the methodologies are warranted [61].

CONCLUSION

Buccal drug delivery provides a convenient administration of drug locally and is an promising site for systemic delivery for orally inefficient drugs. Buccal adhesive drug delivery systeme offers various advantages like accessibility, ease of administration and withdrawal, patient compliance and also by-passes first pass metabolism. Mucoadhesive polymers may provides an important tool to improve the bioavailability of active ingredient by improving the resident time at the site of delivery. The in vitro and ex vivo techniques which are employed for evaluation of the performance of the materials and dosage forms. Efforts should be made to develop standard in vitro and ex vivo biological models that allow one to characterize and compare different material and formulation in terms of their capability to promote drug absorption via the buccal route.

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