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BUCCAL TABLETS A COMPREHENSIVE REVIEW

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ABSTRACT

Buccal route is excellent for the systemic delivery, there by rendering great bioavailability. Owing to the ease of the administration, the oral cavity is an attractive site for the delivery of drugs. Through this route it is possible to realize mucosal (local effect) and transmucosal (systemic effect) drug administration. In the first case, the aim is to achieve a site-specific release of the drug on the mucosa, whereas the second case involves drug absorption through the mucosal barrier to reach the systemic circulation. The present study involved is buccal tablets of irbesartan an anti-hypertensive drug which has low solubility, so, by using different mucoadhesive polymers such as Carbopol 934, Sodium alginate and HPMC K4M in combination The effective physiological removal mechanisms of the oral cavity that take the formulation away from the absorption site are the other obstacles that have to be considered. The formulations were developed with different concentration of mucoadhesive polymers in each formulation. The formulated buccal tablets were tested for surface pH, in vitro drug release and moisture absorption

KEYWORDS: Buccal Tablets, Irbesartan, Formulation design, Mucoadhesive polymers.

INTRODUCTION

Buccal delivery of drugs provides an attractive alternative to the oral route of drug administration, particularly in overcoming deficiencies associated with the latter mode of dosing .Problems such as first pass metabolism and drug degradation in the GIT environment can be circumvented by administering the drug via buccal route. Moreover, the oral cavity is easily accessible for self medication and be promptly terminated in case of toxicity by removing the dosage form from buccal cavity. It is also possible to administer drugs to patients who cannot be dosed orally via this route Successful buccal drug delivery using buccal adhesive system requires at least three of the following
(a) A bioadhesive to retain the system in the oral cavity and maximize the intimacy of contact with mucosa
(b) A vehicle the release the drug at an appropriate rate under the conditions prevailing in the mouth and
(c) Strategies for overcoming the low permeability of the oral mucosa. Buccal adhesive drug delivery stem promote the residence time and act as controlled release dosage forms

The use of many hydrophilic macromolecular drugs as potential therapeutic agents is their in adequate and erratic oral absorption. However, therapeutic potential of these compounds lies in our ability to design and achieve effective and stable delivery systems. Based on our current understanding, it can be said that many drugs can not be delivered effectively through the conventional oral route.

The main reasons for the poor bio-availability of many drugs through conventional oral route are:
☐ Pre-systemic clearance of drugs.
☐ The sensitivity of drugs to the gastric acidic environment which leads to gastric irritation.
☐ Limitations associated with gastro intestinal tract like variable absorption characteristics.

Buccal mucosa composed of several layers of different cells. The Epithelium is similar to stratified squamous epithelia found in rest of the at least one of which is biological nature are held together by means of interfacial forces.[1]

Buccal drug delivery is a type of bioadhesive drug delivery especially it is a mucoadhesive drug delivery system is adhered to buccal mucosa.

Mucoadhesive drug delivery systems

These may be defined as drug delivery systems which utilize the property of bioadhesion of certain water soluble polymers which 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. These drug delivery systems are adhered to the mucous layer that covers a mucosal tissue.

☐ The term bioadhesion is commonly defined as an adhesion between two materials where at least one of the materials is of biological origin. In the case of bioadhesive drug delivery systems, bioadhesion often refers to the adhesion between the excipients of the formulation (i.e. the inactive media) and the biological tissue.

☐ The term mucoadhesion can be considered to refer to a sub group of bioadhesion and, more specifically, to the case when the formulation interacts with the mucous layer that covers a mucosal tissue.

The mucosal layer lines a number of regions of the body including gastrointestinal tract, urogenital tract, airway, ear, nose and eye. Hence mucoadhesive drug delivery system includes the following.
1. Buccal delivery system
2. oral delivery system
3. Ocular delivery system
4. Vaginal delivery system
5. Rectal delivery system
6. Nasal delivery system

Buccal mucoadhesive drug delivery system
These are the drug delivery system in which drug is delivered via the buccal mucosa which is present in oral cavity. Drug delivery via the membranes of the oral cavity can be subdivided as follows.
• Sublingual delivery, which is administration of the drug via the sublingual mucosa to the systemic circulation.
• Buccal delivery, which is administration of the drug via buccal mucosa (the linking of the cheek) to the systemic circulation.
• Local deliver for the treatment of conditions of the oral cavity, principally aphthous ulcers, fungal infections.

Types of buccal mucoadhesive dosage forms[2]
Buccal mucoadhesive dosage forms can be categorized in to 3 types based on their geometry.
☐ Type I is a single layer device with multidirectional drug release. This type of dosage form suffers from significant drug loss, due to swallowing.
☐ In type II devices, 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 in to the oral cavity.

☐ Type III is a unidirectional release device, from which drug loss in 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.

Mainly the following types of buccal dosage forms are available in the market.
i. Buccal tablets
ii. Buccal patches
iii. Buccal films
iv. Buccal gels
v. Buccal ointments

Advantages of drug delivery through buccal mucosa[3-5]
☐ The buccal mucosa is easily accessible, so dosage forms can be easily administered and even removed form the site of application
☐ It is a passive system and does not require activation.
☐ Enzymatic activity is very low as compared to stomach.
☐ It bypasses hepatic first-pass metabolism, prevents gastric acid liability, thus increases bioavailability of drugs showing poor and low absorption in stomach.
☐ Buccal mucosa is highly perfused with blood vessels and offers greater permeability than skin.
☐ It can be easily removed in case of emergency.
☐ Therapeutic serum concentration can be achieved rapidly.
☐ The drug delivery system can be mace unidirectional to ensure only buccal absorption.
☐ Permits localization of drugs to the oral cavity for a prolonged period of time.
☐ A significant reduction in dose can be achieved, there by reducing dose dependent side effects.
☐ The buccal mucosa lacks prominent mucus secreting goblet cells and therefore there is no problem of diffusion limited mucus buildup beneath the applied dosage form.
☐ The presence of saliva ensures relatively large amount of water for drug dissolution unlike in the case of rectal and transdermal routes.

Rathbone et al., (1996) suggested that as a site for drug delivery, the oral cavity offers several advantages over the gastro intestinal route and other alternative routes.

Table 1: Comparison of gastro intestinal route and buccal mucosal route and nasal route for drug delivery (Rathbone et al., 1996)

Parameter	Gastro intestinal	Buccal mucosal	Nasal
Accessibility	Poor	Good	Good
Permeability	Excellent	Good	Excellent
Reactivity	Good	Excellent	Poor
Surface area	Excellent	Excellent	Good
Surface environment	Poor	Excellent	Good
Vascular drainage	Excellent	Good	Excellent
First pass clearance	Poor	Excellent	Excellent
Patient acceptability	Good	Excellent	Good

Limitations[6-7]

☐ Drugs, which irritate the mucosa or have a bitter or unpleasant taste or an abnoxious odour can not be administered by this route.

☐ Drugs that are impermeable to the buccal mucosa can not be used.

☐ Surface area available for absorption is low.

☐ The buccal mucosa is relatively less permeable than small intestine, rectal etc.

☐ Only drugs with small dose requirements can be administered.

☐ Drugs which are unstable at buccal pH, can not be administered by this route.

Oral cavity as a site for drug delivery

a) Physical description of oral cavity: The oral cavity can be divided into two regions; the outer oral vestibule which is bounded by lips and cheeks and the oral cavity it self. The borders being formed by the hard and soft palates, the floor of the mouth and the pillars of the fauces and tonsils.

b) Regional variations in the composition of oral mucosa pertinent to systemic drug delivery: Several membranes line the oral cavity and each offers different problems for its utilization as a portal for drug entry into the systemic circulation. The membranes that line the oral cavity as a total area of approximately 200cm2 and show differences in structure, thickness and blood flow depending on their location. Both keratinized and non-keratinized tissues of varying thickness and composition are found in the oral cavity. In general, non-keratinized tissue, is considerably thicker than keratinized tissue, but the non-keratinized floor of the mouth is very thin (approximately 100µm). The keratinized layers of the oral mucosal epithelia from a protective surface, which is mechanically tough and resistant to physical insult and penetration by any foreign substance.

C) Blood supply to the oral mucosa: The blood supply to the oral cavity tissue is deliver via the external carotid artery, which branches into the maxillary, lingual and facial arteries. Blood from the capillary beds is collected by three main veins that finally flows in to the internal jugular vein.

"Squire et al.,(1976)" have documented values for blood flow through the oral mucosa of Rhesus monkey as given in table 2.

Table 2: Blood flow through buccal mucosa of Rhesus monkey

| Site	Blood flow (ml/min/cm^2)
Buccal	2.40
Sublingual	0.97
Gingival	1.47
Palatal	0.89

Although blood flow through oral mucosa of humans has not been reported, but it is generally considered that the blood flows through oral mucosa, even during disease is sufficiently fast as not to be rate limiting factor in the absorption of drugs via the oral mucosa.

d) Saliva[8]

There are three major glands supplying saliva to the oral cavity. They are parotid, sublingual and submaxillary. Saliva is composed of 99% water and is a complex fluid containing organic and inorganic materials. The pH of saliva ranges from 6.0-7.5. It has a low buffering capacity and principle buffer of saliva being bicarbonate. Saliva is low in enzyme content and its other components such as potassium, calcium and proteins do not appear to adversely affect drug delivery.

7) Overview of the buccal mucosa[9-10]

a) Buccal mucosa structure and its suitability

Buccal mucosa present as a lining of the buccal region which is a part of the mouth bounded anteriorly and laterally by lips and the cheeks, posteriorly and medially by the teeth and gums, and above and below by the reflections of the mucosa from the lips and cheeks to the gums.
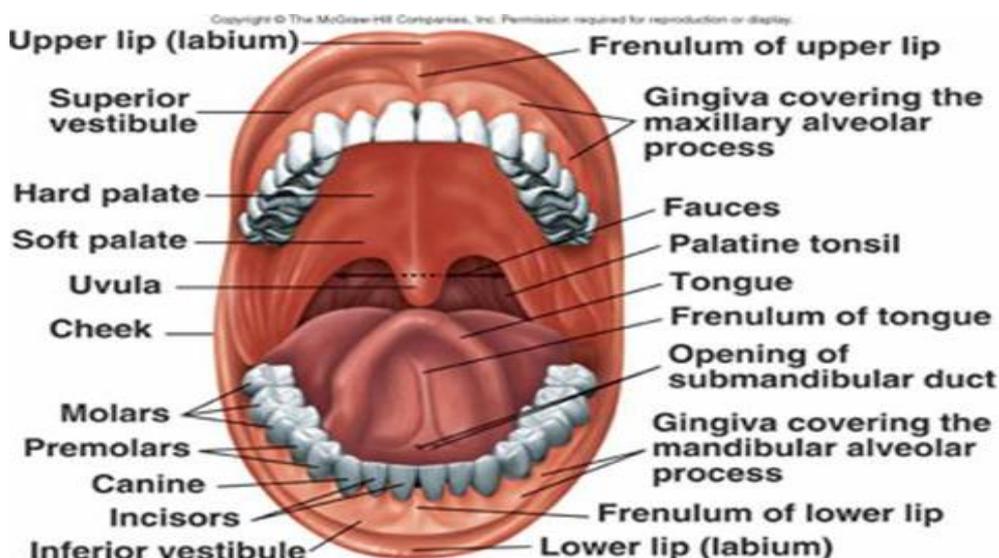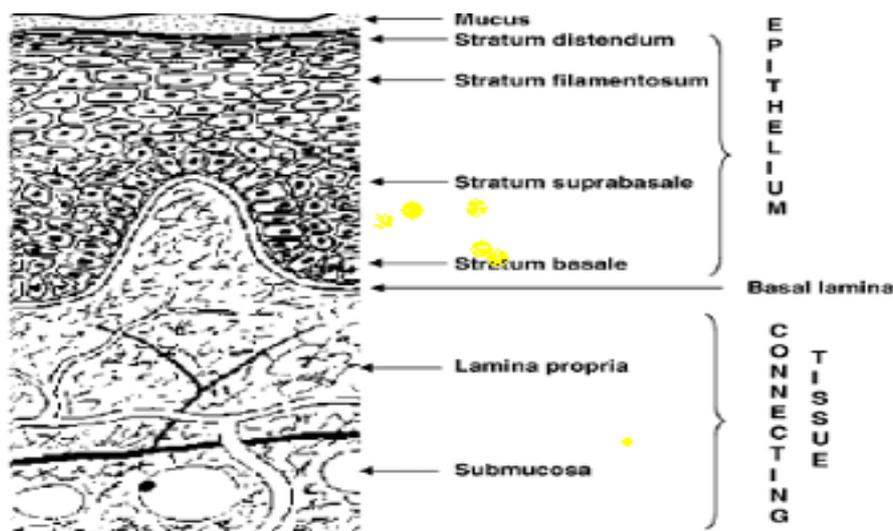
Fig 1: buccal cavity and Cross section of buccal mucosa

Buccal mucosa composed of several layers of different cells. In cross-section of mucosa mainly we can observe three layers like epithelium, basal lamina and connecting tissue which contains lamina propria and submucosa.

The primary function of buccal epithelium is protection of the underlying tissues. In non-keratinized regions, lipid based permeability barriers in the outer epithelial layers protect the underlying tissues against fluid loss and entry of potentially harmful environmental agents such as antigens, carcinogens, microbial toxins and enzymes from foods and beverages.

☐ Basal lamina also called basement membrane separates the epithelium and connective tissue.

☐ Connecting tissue which is present below the basal lamina consists of lamina propria and submucosa. Lamina propria is rich with blood vessels and capillaries that open to the internal jugular vein.

8) Factors effecting buccal mucosal drug delivery system designs[11]
Many factors affect the successful delivery of a drug molecule into the systemic circulation via buccal mucosa. In general, the approach taken in the development of oral mucosal drug delivery systems is to identify suitable drug candidate based on both their physicochemical properties and ability to penetrate the buccal mucosa and to optimize their delivery through rational drug delivery system design the factors affecting the buccal mucosal drug delivery system are given below:

1. Drug factors
- Taste
- Discoloration of teeth
- Solubility
- Partition coefficient
- pka
- Biological half life
- Rate of absorption

- Irritation potential
- Allergenicity
- Diffusion coefficient in the epithelium
- Drug stability

2. Biological factors
- Area
- Thickness (effective diffusional path length)
- Composition of buccal mucosa
- Structure of buccal mucosa
- pH of environment
- Saliva flow rates
- Composition of saliva

3. Delivery system factors
- Feel of delivery system
- Taste, odour, staining, etc of excipients
- Visibility
- Release characteristics
- Retentive properties
- Protection from saliva
- Mobility of backing layer of delivery system
- Size, shape and texture
- Irritation potential and allergen city

9) Factors to be considered in buccal formulation design
a. Drug characteristics[12]
The penetration of drugs or other chemicals into or through the buccal mucosa depends on a number of factors. These include the physicochemical properties of the drug and the condition of buccal mucosa, the composition and thickness of the buccal mucosa, the presence of other chemicals (E.g.: penetration enhancers) and external conditions impelled by the oral fluids such as pH amongst others. The physicochemical properties of the drug influence the rates of diffusion and partitioning

with in the delivery system and buccal mucosa by affecting the:

- Drug's physical state in the dosage form. Eg: Dissolved or Suspended
- Release rate of the drug from the delivery system
- Concentration of released drug in the saliva film
- Percentage of absorbable non-ionized species at the site of absorption
- Drug's ability to partition into the superficial layers of epithelium
- Concentration of drug in the superficial layers of epithelium
- Diffusion rate through the membrane

b. Drug release from the formulation
When designing a buccal mucosal drug delivery systems there are two options available for the formulation scientist. Firstly, the design of delivery system is slower than the rate of transport though the buccal mucosa. In such a case the drug plasma profiles would be controlled by the release characteristics of the delivery systems. Second, the design of delivery system whose rate of release from the formulation into the salivary film is faster than drug transport across the epithelial layer. In such a case the drug plasma profiles would be controlled by the penetration rate of drug through the buccal mucosa. In either case the rate of release from a formulation would be dependent upon the drug (its physicochemical properties) and the delivery system (its ingredient and formulation).

c. Drug dissolution in the salivary film
The driving force for transport across bucal mucosa is the chemical potential gradient. To create this gradient with in the buccal mucosa, released drug becomes dissolved in saliva and establishes a certain concentration of drug in the outer surface of the buccal epithelium. This occurs because the drug has an affinity for both the saliva and the buccal epithelium. Thus, if the delivery system is designed such that release of drug does not control blood levels, i.e. passage of drug through the membrane is the determinant of drug plasma profiles, to ensure maximal absorption rates the drug should exist in the salivary film at its solubility limit.

d. Partitioning in to the superficial layers of the epithelium
The partition coefficient is usually assumed to be concentration independent, and can be determined from knowledge of the concentrations of the drug at equilibrium in each phase. Clearly, such a value is difficult to determine experimentally and often the partition coefficient of the drug between a suitable buffered aqueous solution (which mimics the saliva) and an organic solvents such as octonol (which mimics the lipid properties of the epithelium) is used.

e. Ionization
An inherent assumption of partition coefficient is that the same drug species exist in both the aqueous and organic phases. In other words the drug must exist in the non-ionized form in both phases. The degree of ionization of a drug is a function of both its pka and pH of the aqueous phase. Changes in pH can significantly alter the apparent partition coefficient of the drug and its rate of absorption. It has been shown using the buccal absorption test technique that for most of the weak acids and bases studied to date, only the non-ionized form of the compound is absorbed across human buccal mucosa, Becket et al.,1968. Absorption is observed to be highest when pH values dictate that the drug is present predominantly in the non-ionized form, and as the degree of ionization increases with a change in solution pH, the absorption decreases in a characteristics sigmoidal fashion.

These observations are explained by considering that the non-ionized form of the drug possesses a high degree of lipid solubility and therefore an affinity for the oral cavity membrane. In contrast the ionized drug species are poorly lipid soluble and remain confine to the aqueous environment of the saliva in the oral cavity.

f. Diffusion across the epithelial layer[13]
Once the drug has partitioned into the outer epithelial layer lipids, it will setup a concentration gradient and diffuse along that gradient according to Fick's Law of diffusion. Due to the barrier properties of the epithelium it is assumed that passage across the epithelium is the slowest, and therefore rate controlling step in the process of drug absorption across buccal mucosa. In this case, the rate of transport from the saliva into and across the buccal mucosa can be described by the following approximation of Fick's First Law of diffusion:

$$J = D KP \Delta Ce / h$$

Where
J is the flux of drug across the epithelium $(gm/cm^2/sec.)$,
D is diffusivity of the drug in the epithelial layer $(cm^2/sec.)$,
ΔCe is the difference in drug concentration between one side of the epithelium and the other (gm/cm^3),
KP is the membrane: saliva partition coefficient and
h is the effective diffusional path length of the epithelium (cm).

In above equation both the diffusivity and the concentration difference are closely tied to properties of the drug and components of the epithelium.

F. Dependence of diffusivity on molecular size and weight
Molecular size and weight influence the diffusivity of the drug through the epithelial layer. Diffusivity can be viewed as a rough measure of the ease with which a molecule can move above with in a medium (in this case, the epithelial layer). As a general rule, the larger the molecule the more difficult it is to move about and the lower the diffusivity. For large molecules in non-homogenous media (such as the epithelium), the

dependence of diffusivity on molecular weight would be evident because of physical hindrance of movement as the molecular size of the drug approaches the dimensions of the pathways available for diffusion. It is likely that for hydrophilic drugs, the rate of absorption would be related to its molecular size. Indeed, small molecules (<75-100 Daltons) appeared to cross buccal mucosa rapidly, however permeability falls off rapidly as molecular size increases.

g. Partitioning into and transport away by the blood

The partitioning into and transport away by the blood is considered to the rapid and does not contribute any barrier to the whole permeation process. Thus far we have considered the physicochemical properties of the drug that effect its selection as a drug candidate to penetrate the buccal mucosa.

Other factors include organoleptic properties of the drug and excipients, texture of delivery system, irritation or allergenic properties, discoloration or erosion of the teeth, the potential to alter the natural micro flora. Any of these properties may limit the drug candidate list for this route.

h. Organoleptic properties

The organoleptic properties of a drug or the delivery system may result in poor patient compliance or acceptance of the product. The detection of a bad taste would be detrimental to the success of the delivery system. This can be overcome through the formulation of a unidirectional delivery system which will prevent the release of the drug in to the oral cavity. The texture of the delivery system may also affect patient compliance or acceptability.

i. Daily dose size

The buccal epithelium being an efficient barrier to drug penetration allows only small quantities of drug for penetration even over a period of a day. This means that an upper limit exists on daily delivery of drug. For example, realistically an unidirectional buccal drug delivery system would not cover an area of buccal mucosa larger than 2cm^2 and would be unlikely to be retained on the buccal mucosa for longer than 24 hours. The total amount of drug that could be systematically delivered across buccal mucosa from a 2cm^2 system in one day has been estimated to be 20-50 mg (Robinson et al., 1987). Therefore, buccal drug delivery is suitable only for drugs whose daily dose is on the order of few mg. clearly the resultant plasma concentration of the drug will depend upon the clearance. It should be also noted that the physical size of the delivery system itself will also defined the amount of drug that can be incorporated into such a system.

j. Toxicity to buccal mucosa

If a pharmacologically active material is to be presented to the mucosa over an extended period, there is the potential for an irritant or allergic response to the drug. It should be noted that the sensitization should not only be limited to the drug but also to the components of the delivery system which are also in intimate contact with the buccal mucosa. Again the toxic effects of excipients e.g.: penetration enhancers would be enhanced by the occlusive nature of the system and by extended contact times of the system in contact with the mucosa.

10) Possible routes for drug transport across the buccal mucosa

The cellular structure of the buccal mucosa suggests that there are two permeability barriers. The intercellular space and cytoplasm are essentially hydrophilic in character and become a transport barrier for lipophilic compounds mainly because the solubility of a lipophilic compound in this environment is low. In contrast, the cell membrane is lipophilic and the penetration of a hydrophilic compound into the cell membrane is low due to a low partition coefficient.

The co-existence of the hydrophilic and lipophilic regions in the buccal mucosa suggests that there are two routes for drug transport, i.e. the paracellular and the trans- cellular routs as shown in **figure 2.**

The paracellular route is the primary route for hydrophilic compounds, because it is difficult for a hydrophilic compound to penetrate into the lipophilic cell membrane and thus, the intercellular space is the preferred route for drug transport. In this case, the limited surface area of the inter cellular space and the tortuous pathway with in the area are the main limitations for this route.

For lipophilic compounds, the partition coefficient is high because the surface area for the trans cellular route is large and the path length for trans cellular movement is relatively short, permeability of lipophilic compounds across the epithelial cell membrane is typically high.
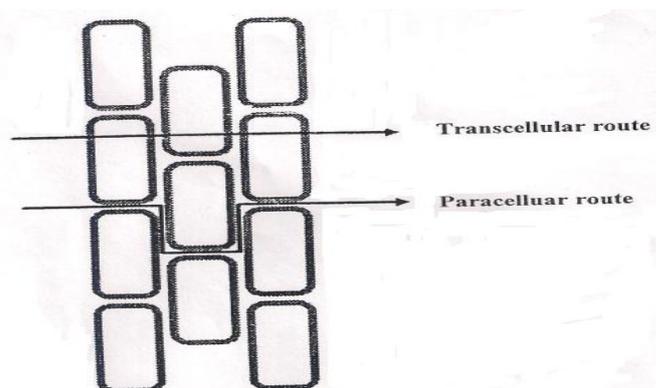

Fig 2: Two possible routes of drug transport across the buccal membrane

The flux of drug movement through the paracelluar route can be written as:

$$JH = DH \, \varepsilon \, CD / hH$$

Where

ε   =   The fraction of surface area of the paracellular route

DH   =   The diffusion coefficient in the intercellular spaces

hH   =   The path length of the para cellular route

CD   =   The donar site drug concentration

The flux of drug in the transcellular route can be expressed as:

$$J_L = (1- ε) \, DL \, KP \, CD / hL$$

Where,

KP   = The partition coefficient between lipophilic region (cell membrane) and hydrophilic region (delivery solution)

hL   =   The path length of trans cellular route

DL   =   The diffusion coefficient

CD   =   The donor side drug concentration

Thus as per equations if the drug is transported via para cellular route the permeability of the drug is independent on its partition coefficient, conversely if the drug is transported via the trans cellular route, the permeability of drug is partition coefficient dependent.

11) Buccal mucoadhesive polymers[14]

Polymer is a generic term used to describe a very long molecule consisting of structural units and repeating units connected by covalent chemical bonds. Bioadhesive formulations use polymers as the adhesive component. These formulations are often water soluble and when in a drug form attract water from the biological surface and this water transfer leads to a strong interaction. These polymers also form viscous liquids when hydrated with water that increases their retention time over mucosal surfaces and may lead to adhesive interactions. Bioadhesive polymers should posses certain physicochemical features including hydrophilicity, numerous hydrogen bond forming groups, flexibility for interpenetration with mucus and epithelial tissue and visco-elastic properties.

a. Ideal characteristics

➢ Polymer and its degradation products should be non-toxic, non-irritant and free leachable impurities.

➢ Should have good spreadability, wetting, swelling and solubility and biodegradability properties.

➢ pH should be biocompatible and should possess good visco-elastic properties.

➢ Should adhere quickly to buccal mucosa and should possess sufficient mechanical strength.

➢ Should possess peel, tensile and shear strengths at the bioadhesive range.

➢ Polymer must be easily available and its cost should not be high.

➢ Should demonstrate local enzyme inhibition and penetration enhancement properties.

➢ Should have optimum molecular shelf life

➢ Should have optimum molecular weight.

➢ Should possess adhesively active groups.

➢ Should have required spatial conformation.

b. Classification

Mucoadhesive polymers in buccal delivery can be classified as follows.

Table 3: Classification of polymers

Criteria	Categories	Example
Source	Seminatural or natural synthetic	Agarose, Chitosan gelatin, Sodium alginate Cellulose derivatives like CMC, Sodium CMC, HEC, HPMC.; Poly (acrylic acid) based polymers like CP,PC etc.
Aqueous solubility	Water soluble Water insoluble	CP, HEC, HPS, HPMC, Sodium CMC, Sodium alginate etc. Chitosan, Ethyl cellulose, CP etc.
Charge	• Cationic • Anionic • Non-ionic	Aminodextran,Chitosan trimethylated chitosan etc. Chitosan-EDTA, CP, CMC, PC, Sodium alginate, Sodium CMC etc. Hydroxy ethyl starch, HPC, HPMC etc.
Potential bioadhesive forces	• Covalent • Hydrogen bond • Electrostatic interaction	Cyanoacrylate CP,PC etc

12) New generation of mucoadhesive polymers

The older generation of mucoadhesive polymers lack specificity and targeting capability. They adhere to the mucus non-specifically and suffer short retention times due to the turn over rate of the mucus.

The new generation of mucoadhesive polymers (with the exception of thiolated polymers) can adhere directly to the cell surface, rather than to mucus. They interact with the cell surface by means of specific receptors or covalent bonding instead of non-specific mechanisms, which are characteristic of the previous polymers. These classes of polymers hold promise for the delivery of a wide variety of a new drug molecules, particularly macromolecules and create new possibilities for more specific drug-receptor interactions and improved targeted drug delivery.

There are three classes of new generation polymers. They are:
1. Thiolated mucoadhesive polymers
2. Target-specific, lectin mediated bioadhesive polymers
3. Bacterial protein polymers

1. Thiolated mucoadhesive polymers
Through a covalent attachment between a cysteine (cys) residue and a polymer of choice, such as polycabophic, polyacylic acid and chitosan, a new generation of mucoadhesive polymers have been created. The mediated thiol bond, exhibit interaction, improved tensile strength, high cohesive properties, rapid swelling and water uptake behaviour. As one example to illustrate the improved bioadhesive properties of thiolated polymers, Berkop-Schnurch et al, have reported a positive correlation between the adhesive properties and increasing amounts of polymer in drug compacts polycarbophil covalently bound to L-cysteine.

2. Target-specific, lectin mediated bioadhesive polymers
Specific proteins or glycoproteins, such as lectins, which are able to bind certain sugars on the cell membrane, can increase bioadhesion and potentially improve drug delivery via specific binding and increase the residence time of the dosage forms. In this class lectins are incorporated in the delivery system so that they will mediate the interaction of polymers with cell surface. This type of bioadhesion should be more appropriately termed as cytoadhesion. A site specific interaction with the receptor could potentially trigger intra cellular signaling for internalization of the drug or the carrier system (endocytosis through cytoadhesion) in to the lysosomes or into other cellular compartments, such as the nucleus.
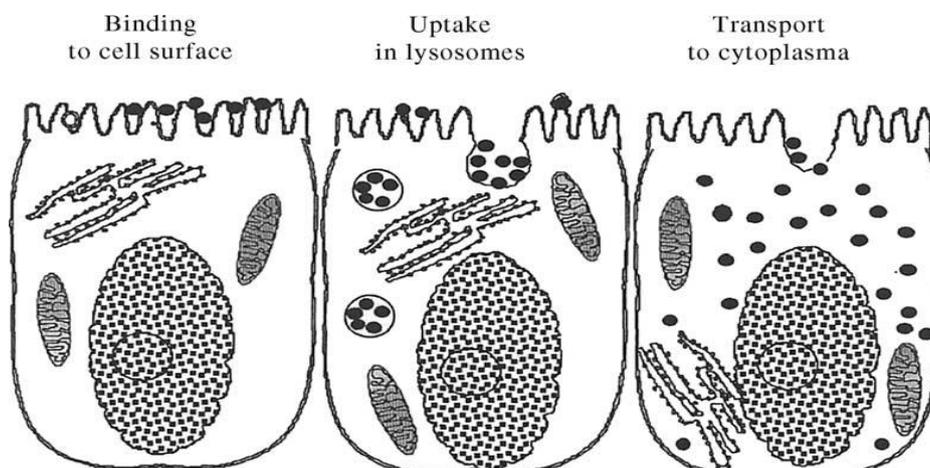

Fig 3: Different fates of lectin-mediated cytoadhesive ligands or drug carrier systems upon specific binding to surface receptors on the epithelial cells

Although lectins are also found in bacteria, those from the plant kingdom still remain the largest group of this class lectin isolated from tomato fruit (Lycopersicum esculentum) has been reported to specifically and safely bind N-Acetyglucosamine (GluMAc) on this surface of several cell monolayers.

Technological advances in biomaterials andtechniques have resulted in novel designsmeeting the challenges of physicochemicalproperties of the drug and thus contributing tothe therapeutic efficacy of Buccal drug delivery.

3. Bacterial protein polymers
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, which facilitate adhesion to other cells or inanimate surfaces. These are extra cellular, long thread like protein polymers of bacteria that play a major role in many diseases. The bacterial protein polymers are covalently attached to bioadhesive polymers. The attractiveness of this approach lines in the potential increasing the residence tome of the drug on the mucus and its receptor specific interaction similar to those of the plant lectins.

As an example Escherichia coli has been reported to specifically adhere to the lymphoid follicle epithelium of the ileal Peyer's patch in rabbits.Bernkop-Schnurch et al., covalently attached a fimbrial protein (antigen k99 form E.coli) to poly (acrylic acid) polymer and substantially improved the adhesion of the drug delivery system to the GI epithelium.
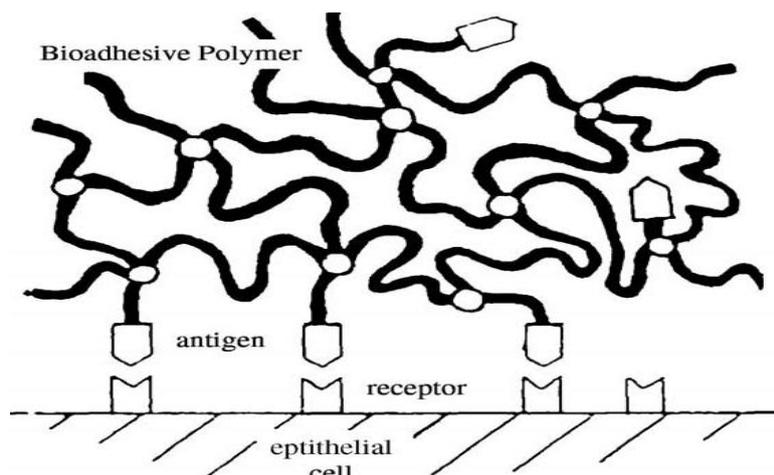
Fig 4: A diagram of covalently attached fimbrial protein (K99 from E.coli) to poly acrylic acidas a carrier system

Mucoadhesion

Bioadhesion is the phenomenon between two materials which are held together for extended periods of time by interfacial forces. It is generally referred as bioadhesion when interaction occurs between polymer and epithelial surface; mucoadhesion when occurs with the mucus layer covering a tissue.

A) Theories of Mucoadhesion[15-16]

Many theories have been proposed to explain the forces that underpin mucoadhesion.

1. Electronic theory

This theory suggests that electron transfer occurs upon contact of adhering surfaces due to differences in their electronic structure. This proposed to result in the formation of an electrical double layer at the interface, with subsequent adhesion due to attractive forces.

2. Wetting theory

This theory is primarily applied to liquid systems and considers surface and interfacial energies. It involves the ability of a liquid to spread spontaneously on to a surface as a prerequisite for the development of adhesion.

3. Adsorption theory

It describes the attachment of adhesives on the basis of hydrogen bonding and Vanderwaal's forces. It has been proposed that these forces are the main contributors to the adhesion interaction. A subsection of this, the chemisorption theory, assumes an interaction across the filter phase occurs as a result of strong covalent bonding.

4. Diffusion theory

It describes inter diffusion of polymers change across an adhesive interface. This process is driven by concentration gradients and is affected by the available molecular change lengths and their mobilities. The depth of inter penetration depends on the diffusion coefficient and the time of contact. Sufficient depth of the penetration creates semi-permanent adhesive bond.

5. Mechanical theory This theory assumes that adhesion arises from an interlocking of a liquid adhesive in to irregularities on a rough surface. However, rough surfaces also provide an increased surface area available for interaction along with an enhanced viscoelastic and plastic dissipation of energy during joint failure, which are thought to be more important in the adhesion process than a mechanical effect.

6. Fracture theory

It differs a little form the other five in that it relates the adhesive strength to the forces required for the detachment of the two involved surfaces after adhesion. These assume that the failure of the adhesion bond occurs at the interface.

B) Mechanism of mucoadhesion[17]

The mechanism of mucoadhesion can be explained by two steps:

Step I – contact stage: An intimate contact (wetting) occurs between the mucoadhesive and mucus membrane. In this stage two processes takes place for contact formation:

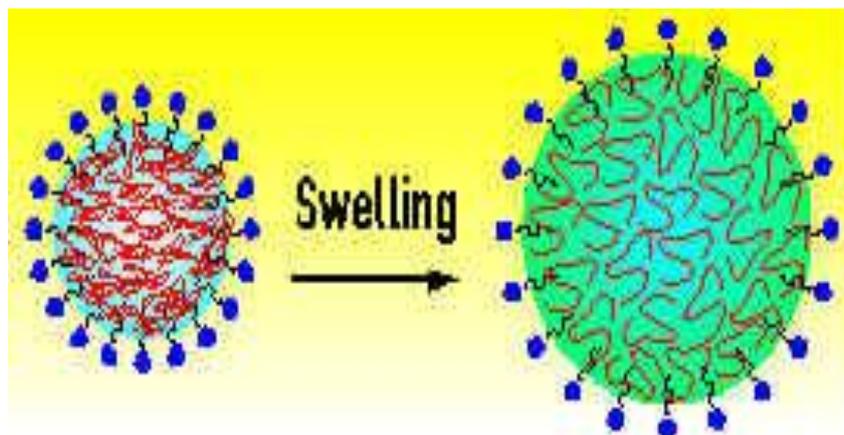1   Wetting and swelling of the polymer molecule on hydration.

Fig 5: A diagram showing the swelling of polymer on hydration

2   Interpenetration of polymer chains and mucin glycoprotein chains across the interface.
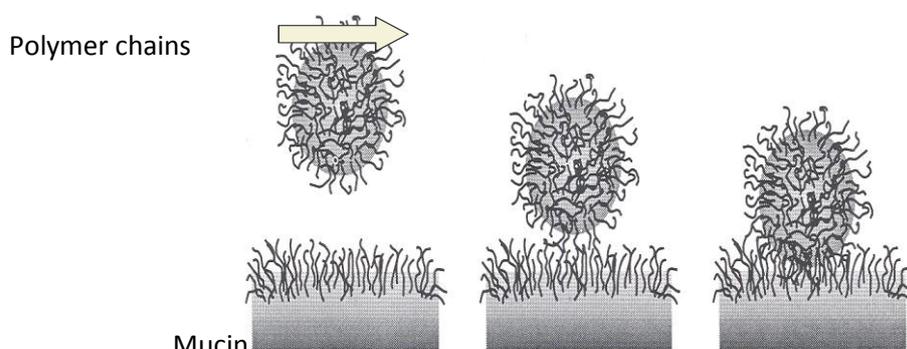

Polymer chains

Mucin
Fig 6: A diagram showing interpenetration of polymer and mucin

Step II – consolidation stage
After inter penetration and contact formation between mucoadhesive and mucosal surface, various physicochemical interactions occur to consolidate and strengthen the adhesive joint, leading to prolonged adhesion. In this stage mainly bond formation will takes place between two surfaces.

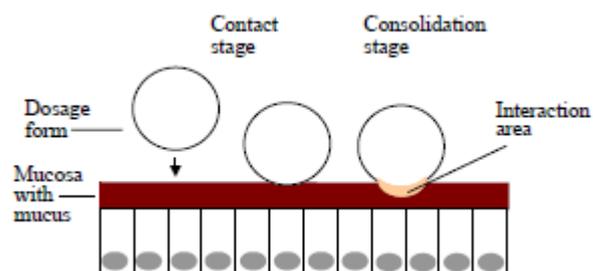The overall mechanism of mucoadhesion can be represented as follows:

Figure 7: The two stages in mucoadhesion

C) Factors affecting mucoadhesion in the oral cavity:
Mucoadhesive characteristics are a factor of both the bioadhesive polymer and the medium in which the polymer will reside. A variety of factors affect the mucoadhesive properties of polymers:
a. Polymer related factor
1. Molecular weight
2. Flexibility.
3. Hydrogen bonding capacity
4. Cross-linking density with in polymer network
5. Charge
6. Concentration
7. Hydration

b. Environmental factors
The mucoadhesion of a polymer not only depends on its molecular properties, but also on the environmental factors adjacent to the polymer.

1. Saliva
2. Mucin turnover time

CONCLUSION

Mucoadhesive drug delivery system utilize the property of bioadhesion of certain water soluble polymer which become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for an extended period of time. The main objective of using bioadhesive systems orally would be achieved by obtaining a substantial increase in residence time of the drug for local drug effect and to permit once daily dosing. The buccal mucosa offers several advantages over controlled drug delivery for extended periods of time. The mucosa is well supplied with both vascular and lymphatic drainage and first-pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract are avoided. The area is well suited for a retentive device and appears to be acceptable to the patient. With the right dosage form design and formulation, the permeability and the local environment of the mucosa can be controlled and manipulated in order to accommodate drug permeation.

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