IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

Review on Buccal Drug Delivery System

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ABSTRACT: The buccal drug delivery system is defined as the system which drug is administrated in the buccal mucosa and involves placing a drug between gumsand **cheek**, where it dissolves and is absorbed into your blood with systematic circulation. Both sublingual and **buccal** drugs, films, or sprays in the market. The review provides the knowledge about buccal delivery system its description, components and structure of buccal mucosa, anatomy & physiology of oral cavity, mucus layer of several parts, advantages and disadvantages and mechanism of mucoadhesion. The details about barriers, mucus and saliva, the several polymers used in mucoadhesive drug delivery system, theories of buccal drug delivery, adhesion and evaluation which takes places in these types of drug delivery and the several commercially available dosages forms in the market. All these details are described and demystified in this review article.

Keywords: GIT, Mucosal membrane, Mucoadhesive

1.INTRODUCTION:

Buccal drug delivery system is known as administration of particular drug through mucosal membrane. The ease of administration of drug and prevention of achieved drug degraded in the Gastro-intestinal tract (GIT) and by passing first pass metabolism, increases the bioavailability, hence buccal cavity is alluring site for drug delivery. It leads to bioadhesion in which materials binds with biological substrate (mucosal membrane).

There are four regions where the drug can be administrated mainly those are: palatal, sublingual, buccal, and gingival. The buccal delivery system leads to the delivery system in which drugs takes places within/through the mucosa to show local/systematic pharmacological action. This system is used for the treatment of diseases takes places in buccal cavity and also for the systematic diseases. There are several limitations i.e., small absorption area, residence time, and the barrier properties of buccal mucosa. This review article describes the buccal cavity anatomy and physiology, barriers, theories behind buccal system, formulation design of drug delivery system and evaluation of drug delivery by buccal cavity.

The buccal routes is less permeable than that of sublingual route and doesn't provides better bioavailability as seen in sublingual routes. The buccal routes are also having accessibility for administer of dosage because of presence of immobile mucosa and plain smooth muscle.

In 1980s, the concept of mucoadhesion was derived from the controlled delivery area. It is a natural/synthetic polymer which interacts with the mucus layer that overcomes the physiological barrier for longer period of time.

It is also defined by the American Society of Testing and Materials, by interfacial forces the two surfaces are held together which having valence forces and interlocking action, or both

actions. It becomes adhesive on hydration by utilizes the properties of bioadhesion with certain polymer. Hence, for extended period, it can be used for targeting a drug at particular region.

Fig 1: Structure of Buccal Mucosa

2. Anatomy & physiology of oral cavity

2.1 Mucus Layer:

The inner layer of mucoadhesive is known as mucus and the inner epithelial cell lining is covered with the fluid secreted by goblet cell. It having adhesive secretion which form thin, persist gel blanket which adhere to the epithelial surface and where mucus is translucent. It composed of water, mucin and the thickness are varying from 40µm-30µm and other components include proteins, lipids, mucopolysaccharides and electrolyte.

The mucus layers having several important roles and some of these are:

1.Protective Role: It is protected from the hydrophobicity and similarly, protects the mucosa from lumen diffusion of hydrochloric acid.

2.Barrier Role: The mucus layer creates a diffusion barrier for the molecules and especially against drug absorption. The nature of the mucus inference at the level of diffusion phenomena, notably by glycoprotein concentration and by cross-linking ratio and the average molecular weight between two junctions in the mucus networkas shown in equation:

$$\frac{D_{in}}{D_{iw}} KC_m^{-1/3} M_j \exp - \left[\frac{K^1 r_i^2}{\frac{1}{C_m - V}}\right]$$

Where,
Din = Diffusion Coefficient of the active ingredients through the mucus network
Diw = Diffusion coefficient in water
K & k1 are constant
Cm= Glycoprotein concentration in the mucus
Mj = average molecular weight between two junctions in the mucus
RI= molecular radius of the diffusing active ingredient; and V is the glycoproteinspecific volume.

Adhesion Role: Mucus shows the cohesive properties and epithelial cell which is continuousrigidly with it.

Lubrication Role: The mucosal membrane is moist from the mucus layer. The mucus is secreted by the goblet cells continuously and there is important to compensate from digestion for the removal of mucus, solubilized of mucin molecules and degradation it from bacteria.

3.Anatomy of Buccal mucosa

In mouth, the buccal region is bordered lateral and anterior from cheeks and lips, posteriorly and medially by the teeth or gums, above and below by the reflections of the mucosa from thelips and cheeks to the gums. The buccal gland is present between the mucous membrane and buccinators muscles. They are same as labial gland but smaller.

The molar glands are present between the masseter and distal extremity of parotid duct covered by muscles. They are extended mouth molar tooth opposite. The blood is supply through maxillary artery and the flow is faster (2.4ml/min/cm^2) than palatal region, sublingual and gingival. Buccal mucosa thickness is to be 500-800 µm. Hence it is suitable ofretentive delivery system.

They are 4- 4000 times greater permeable than the skin epidermis and are less permeable than intestinal mucosa. Buccal mucosa consist of several layers, the outermost layer refers to stratified squamous epithelium followed by basement membrane and below this, a lamina propria and submucosa. It also has many sensory receptors i.e., taste receptors of tongue. It also consists of lining (non-keratinized) mucosa, although masicatory (keratised) mucosa is found on the gingiva.

3.1 Epithelium:

The epithelium of buccal mucosa is same as the stratified squamous epithelium found in rest of the body. The thickness of epithelium cells is 40-50. The buccal mucosa basal layer is mitotically active and generate epithelial cell, which migrates through a several of intermediate layers. The epithelial cell is increasing the size and become flattened when it migrates to the surface and 5-6 days are considered as the period of the epithelium.

The one of the major biochemical features that has high molecular weight (40-70 KDa) protein called tonofilaments. The matrix of epithelium cells is rich in carbohydrate-protein complexes, which act as a lubricant. Epithelium specious layer is main barrier for drug diffusion.

3.2 Basement Membrane:

The basement membrane is bordered between epithelium elementary layer and connective tissue. They are trilaminar structure refers to lamina lucida (upper amorphous layer), lamina densa and a sublayer of fibrous material. The collagen is present in the lamina densa which give strength to the structure. They are having surface area larger as compared to epithelium. Hence it resists drugging permeation or transport by affecting the diffusional path length. Thealso having some important functions like adherences between the epithelium and underlying connective tissue and give mechanical strength to the epithelium and are bordered to the passage of cells and several macromolecules.

3.3 Connective tissue: It contains laminar propria and submucosa cells. It consists of several collagen, elastic fibres, and cellular components and which are rich in blood vessel that open into the jugular vein. So, this avoids the first-pass metabolism

4.Physiology of buccal route: Oral cavity is first part of digestive tract and it is responsible for the natural entry of foods and fluids inside the body. In two part they take places i.e., lips and cheeks. The oral cavity and outer oral vestibule are bounded with each other. It is formed by soft and hard palates. It is bordered with the mucous membrane which is moist and highly vascularized nature. Mucous membrane provides covering, protecting, secretary and absorptive functions. Under, this membrane total of arteries and capillaries takes places which are responsible for the penetration of the drug into the systemic circulation which leads to the fast drug absorption. The viscous fluid mucus present which is released by goblet cells which lubricates the mucosal membrane and acts as a protective barrier.

S.NO.	COMPOSITION	% AMOUNT
1.	WATER	95
2.	GLYCOPROTEINS & LIPIDS	0.5-5.0
3.	MINERAL SALTS	1
4.	FREE PROTEINS	0.5-1.0

5. Advantages:

Fig 2: Composition of mucous membrane

- Prolongation of residence of drug in gastrointestinal tract (GIT)
- Improved patient compliance
- Self-administrable
- The dosage forms are targeting and localized into a specific site
- The administration through buccal route is easy and painless.
- The buccal route by-pass the first-pass metabolism and also low enzymatic activity.
- The permeation through this route is much faster than other.
- The drug can be removed in case of toxicity

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6.Disadvantages:

- Unstable buccal pH drug that can't be administer from this route.
- Only small doses can be administrated
- The drugs have bitter taste and odour
- Eating and drinking are restricted.

7.Mucoadhesion/Bio adhesion: The term Bioadhesion describes the materials that bind or adhere to the biological substrates. The mucoadhesion is a term which describes the material that adheres to the mucosa at specific biological substrate.

7.1 Mechanism of Mucoadhesion: The interaction of Mucoadhesive material and mucus membrane is takes places in two steps:

Step 1: Contact stage: Because of mucus when it comes with contact of mucus membrane then close contact is formed between mucous membrane and mucoadhesive.

Step 2: Consolidation stage: The mucoadhesive material gets joined to the mucus membrane by different physiochemical forces of attraction. Thus, results a long lastingmucoadhesion.

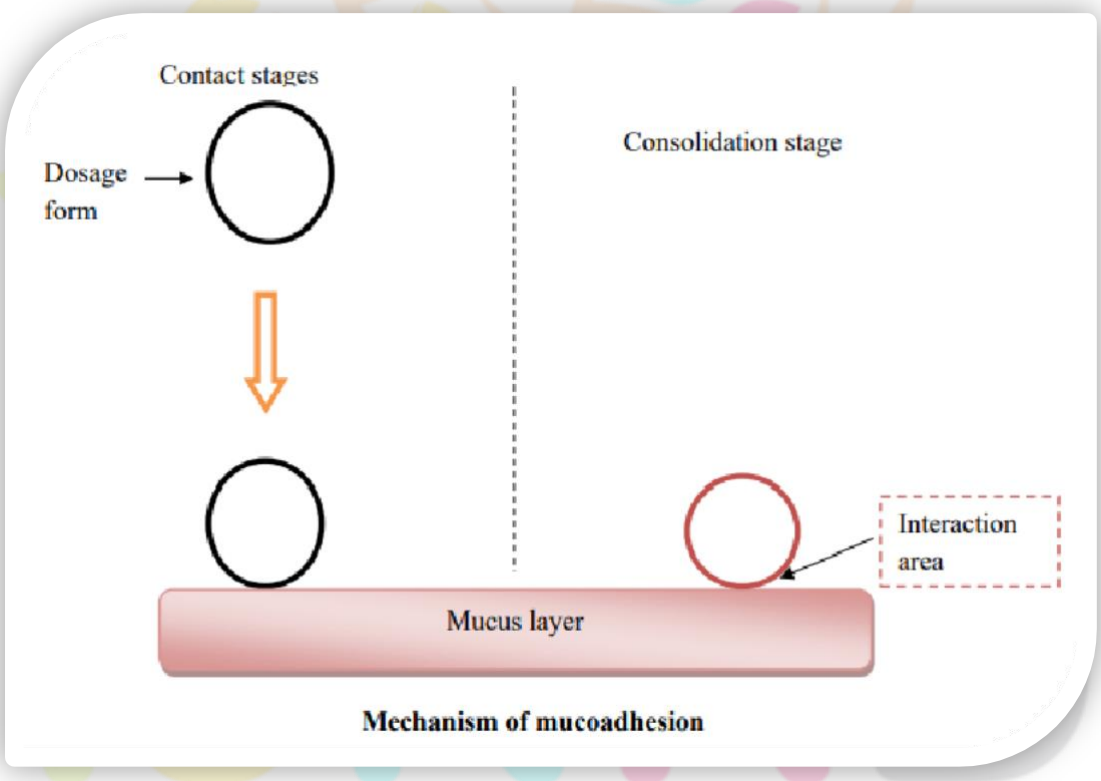

Fig 3: Mechanism of Mucoadhesion

7.2 Contact stage: when mucous membrane and mucoadhesive are coming to intimidate contact between them. These are the two surfaces which are brought together e.g., setting andholding a delivery system into the oral cavity, eye and vagina.

The GIT tract leads to an inaccessible site where mucoadhesive material cannot place directly onto the mucosal layer. Similarly, possible blockage of the GIT tract and adhesion may be catastrophic. Sometimes the peristaltic and the gastrointestinal movement is helping to the dosage form with larger particle has contacting with the mucosa. But do the smaller particle the adhesion with the gastrointestinal mucosa is mandatory. Other examples where the adhesion process is essential like administration of nanoparticle suspension to the procorneal region.

The DLVO theory used to define the adsorption process of the small particles. The movement of the particle within the body due to the Brownian motion, the peristalsis movement may help the movement of body fluids within the body cavity. When the particle approaches to the surface there has been an attractive and repulsive force. The repulsive force arises due to osmotic pressure, when the surface and particle shows same charges that result, double layer inter penetration, steric effects and also electrostatic interactions. Attractive force arises from Van der wall's forces interaction, if the surface and particle show opposite charges will give results the surface energy effect and electrostatic interactions. The attractive forces relative strength will differ it depend upon the particle natures, aqueous environment and particle and surface distance between them. e.g.: Smaller the particle size larger will be the surface area of the GIT tract and therefore greater will be the attractive forces.

7.3 Consolidation stage:

When the strong and prolonged adhesion then this stage is required. Mucoadhesive material adheres strongly to the dry surfaces as well as because of presences of moisture they get activated. The moisture act as plasticizer to become mucus layer from molecules of mucoadhesive Contact stages Consolidation stage Dosage form Interaction area freely, shape of the surface to be confirmed. The bond between them is very assorted so it will difficult to use spectroscopic techniques to finding the nature of bond and groups involved into this. The biopolymer & polymers in the solution tend to gather which produce a significant reduction in the surface energy. When the tensiometer studies are conduct with this system this is also observable, the high affinity of the material like carbomer for water almost appear which give "suction-like effect" and helping to hold the formulation onto the surface. Sometimes the mucus amount is very limited so that the dry mucoadhesive polymer is almost collapse the mucus layer through extract the water component of the gel and allows the freedom to the polymer molecules to interact with the epithelial surface through hydrogen bonding.

8.Factors affecting Mucoadhesion: There are various factors which affect to themucoadhesion that are:

- Polymer related factors
- Environment related factors
- Physiological factors

8.2 Polymer related factors:

Molecular weight: For mucoadhesion 100,000 molecular weight that is required e.g., polyethylene glycol (PEG) has molecular weight is 20,000, have low adhesion, whereas PEG with molecular weight is 200,000 and 400,000 have improved and better adhesive properties. It penetrates easily into mucus layer by polymer having low molecular weight and the higher

molecular weight polymers promote entangling. The higher molecular weight polymer will not expose groups easily for the interaction with the substrate but the lower molecular weight polymers will form loose gel and dissolve quickly.

Spatial conformation: In general, higher will be the molecular weight above 100,000 of the polymers higher will be the strength of the polymer. For example, Dextran has molecular weight 19,500,000 have higher strength and it is similar to the PEG with molecular weight 200,000.

Flexibility of the chain: For, the interpenetration and complications the chain flexibility is to be critical. The water-soluble polymers are forming cross linkage to the substrate; the mobility of the individual polymers is decreases so that the penetration of the polymers into the mucus is decreases and also reduces the mucoadhesion strength. Therefore, the polymer chain contains some degree of flexibilities to achieve the entanglement. In general, themobility and flexibility are related to their viscosity and diffusion coefficient.

Hydrogen bonding capacity: Hydrogen bonding is also another important factor for polymers mucoadhesion. The polymers contain the functional group (COOH, OH, etc.) which forms the hydrogen bonds. Polymers which have some degree of flexibility have potential to improve the hydrogen bonding. Examples are polyvinyl alcohol, poly methacrylic acid, and also their copolymers with better hydrogen bonding capacity.

Cross-linking density: There are mainly 3 beneficial and inter-related polymer network parameters are having average molecular weight, density and pore size of particular polymers. Lower cross-linking polymers by increase the density will be the diffusion of water into the polymer network diffusion of water which results the interpenetration between the polymer and mucin is also decreases and also causes the insufficient swelling rate.

Charge: The non-ionic polymers have smaller degree of adhesion as comparison to the anionic polymers. The cationic polymer has been demonstrating superior mucoadhesive properties especially in neutral or alkaline medium. For example, chitosan polymer has higher molecular weight which gives better adhesion properties. The strength of the mucoadhesion is better from the carboxyl group than the neutral groups.

Concentration: The optimum polymer concentration is required for the mucoadhesion. When the polymer concentration is beyond to the optimum concentration then the strength of the adhesion is drop due to coiled molecules in the polymer are become separated from the medium so that the chain availability for the interpenetration becomes limited. When the polymer concentration is less, than mucus is less the number of penetrating polymer chains per unit volume and small interaction between the polymers

Hydration (Swelling): Swelling is required for the proper macromolecular mesh and for expanding the polymer and induces the mobility into the polymer chain for enhancement of interpenetration with polymer and mucin. Swelling property depends upon the polymerconcentration, ionic strength and presence of water. However, a critical degree of swelling of mucoadhesive polymer shows where optimum swelling and bioadhesion occurs.

8.3 Environment related factors:-

Ph.: It influences the charge present on the mucous surface and on the ionizable mucoadhesive polymers. The mucous having different charge density which depends upon

the pH because of gap between the dissociation of carbohydrates functional groups & the amino acid of the polypeptide backbone.

When there are changes in pH, it leads in functional groups dissociation on the carbohydrate and backbone amino acid sequence of polypeptides leads in differences. Similarly, pH for the degree of hydration of the polymers is important. The pH is increases pH4 to pH7 it shows increases polymers degree of hydration. For example, polycarbophil doesn't show the mucoadhesion property above pH 5, because it is uncharged rather than ionized, mucin molecules react with the carboxyl groups. However, the chain is expelled due to electrostaticsrepulsion of the carboxylate ions by higher the pH

8.4 Mucin turnover: Mucin has large molecular masses ranging from 0.5to 20 MDa. There are mainly two reasons responsible for natural mucin turnover molecules from the mucous: -

➢ By the limit of mucin turnover, the residence time of mucoadhesive is expected. There is no matter how much the mucoadhesive strength. The mucoadhesive are detached from the surface because of mucin turnover. The presences of mucoadhesives the turnover rate is different.

➢ In mucin turnover the soluble mucin molecules is present in substantial amount. The molecules of mucin lead in interacting with mucoadhesive before interact with the mucous layer. It is depending upon the presences of food. On luminal surface, gastric mucosa secreted mucin in early stages. Mucin which is accumulated is released from ingested food passage or by freshly secreted acid.

8.5 Applied strength: The defined strength is necessary for the applying and placing the mucoadhesive system. With applied strength of polymer, the adhesion strength is increased (poly acrylic acid, Carbopol 934). When on mucoadhesive contact site, the pressure is gradually applied then the interpenetration depth can be affected. The polymer becomes mucoadhesive when applied pressure is high for sufficient period of time even, they don't have mucin attraction.

8.6 Initial Contact time: In between mucoadhesive and mucous layer there is presence of initial contact time which can determined the interpenetration of mucoadhesive chain and the extent of swelling. It will increase with increase mucoadhesive strength. It affects the performance of a system with the initial pressure.

8.7 Moistening: When there is spread of mucoadhesive polymer on the surface and form "Macromolecular network" mucin moistening molecules requires for sufficient interpenetration of polymer in sufficient sizes. The polymer chains mobility is increases with the moistening. For bioadhesion and best swelling there is critical level of hydration for Mucoadhesive polymer.

9. PYSIOLOGICAL FACTORS:

9.1 DISEASED STATE:

It is a simulated state of disease by particular organism which caused by overproduction/under of an explanatory biochemical and invasion of a living organism that produces materials which are destructive to the host. Similarly, leads to quick organism growth.

9.2 Tissue movement:

There are low active movements takes places in buccal region. So, several mucoadhesive polymers are incorporated to keeps dose at buccal region for longer period of time towithstand tissues movements during intake and if possible, during swallowing or eating.

9.3 Concomitant disease:

As, we known mouth has area larger for administer of drug and for accessibility. For,absorption of lipophilic drug readily occurs in mucous membrane in which GI motility, presence of other several substances and concomitant disease states.

9.4 Rate of renewal of mucosal cells:

The rate of renewal of mucosal cells is high. The regeneration, mucous gels and repair mechanism leads in protection of epithelia mucosal and there is high rate of rebuilding of mucosal cells.

9.5 Barriers: Through mucus, saliva, coating membrane granules (buccal mucosa) severalbarriers which delayed the rate & **expand of absorption of drug.**

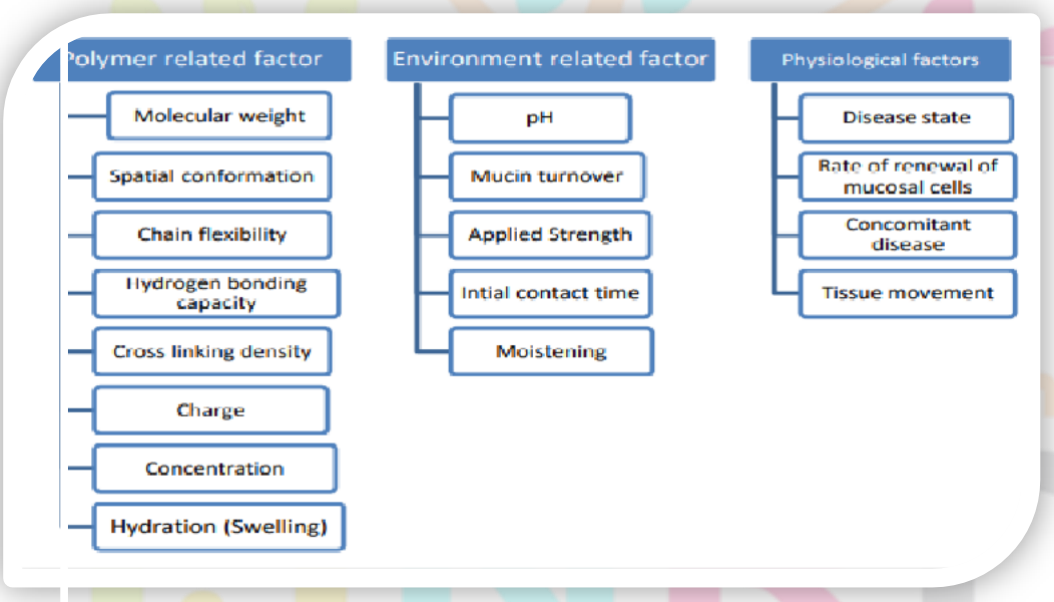

Fig 4: Several factors affecting the BDDS

9.6 Membrane coating granules

They are non-keratinizing epithelia around 0.2 µm diameter which are globular in shape and observed in humans including esophagus and cervix. Similarly, stratum corneum inter cell spaces, non-keratinizing epithelia apparent layer contains electron lucent materials, which leads in represent the non-lamellar lipids phases with lipid lamellae small stacks.

9.7 Basement membrane:

There is primary barrier for the entry of materials from the exterior which is indicated by apparent layer of oral epithelium which play virtual role by epithelial membrane in passing the material between the epithelium and connective tissue junction. They may decrease the rate of lipophilic components penetration due to charge on components of basal laminal which can easily cross the surface of epithelial barrier

9.8 Mucus

The buccal mucosa contains epithelial cells which are covered by intercellular materials called mucus with thickness that range between 40 µm and 300 µm. However, sublingual glands and only 10% of saliva is contributed by salivary gland and which are important in maintaining the mucus layer on the oral mucosa.

The mucus act as a lubricant which allow the migration of cells relatively with each other the cells to move relative to one another which play important role in mucoadhesive delivery systems adhesion.

At buccal pH, mucus forms a strongly gel adhesive assembly which bind with the epithelial cells surface as a gelatinous layer. There are several kinds of mucus are produced like G, L, S, P and F that forms the different gel networks. Another material like ions, protein chains and enzymes modified the interactions of molecules with their biochemical properties.

Mucus is mainly composed of inorganic salts and mucin readily suspended in water. They are large family, composed of glycosylated proteins fond of protein core. Mucins contain approx. 70-80 % carbohydrate, 12-25% protein & 5% of ester sulphate. The thick sugar coating of the mucus provides them with the ability to hold in water which made them resistance to proteolysis, which can be main in keep mucosal barrier maintained. Mucus is characterized not only by the large molecular mass, but also by the large molecular mass distribution, as seen by analytical ultra-centrifugation, and by powerful techniques of size exclusion chromatography to scatter multi-angle laser light. In solution, mucin can adopt as a random- coil conformation, which occupies average spherical domain in time which is defined by critical-point-drying electron microscopy & hydrodynamic.

9.9 Saliva

The mucosal surface has a saliva coating which is 70µm thick. High molecular weight mucin named MGI is present in saliva which binds to the oral mucosal surface to maintain hydration lubrication and attachment of micro-organisms is also limited by this mucin. Major salivary glands that secrete saliva which contain lobular ducts, the parotids through salivary ducts near the upper teeth the sub mandibular under the tongue and sublingual through many ducts inthe mouths surface.

In buccal mucosa lips lining of mouth & throat, there are around 600-1000 many tiny ducts are present known as minor salivary glands. The flow rate of total saliva is 1-2 ml/min through these ducts. Greater the output of the saliva has maintained and protect the harm of acid- prone tooth enamel by washing of the mouth. The secretion of saliva oxygen will be carried out and vasodilator material is produced, due to the glandular metabolism the glandular blood will be increases.

Saliva has contained 99.5% water additionally proteins, glycoproteins and other electrolytes such as potassium (7 x plasma), bicarbonate (3x plasma), calcium, phosphorus, chloride, thiocyanate, sodium (1 x plasma) and urea. The normal pH of the saliva is 5.6- 7.

The saliva has contained many enzymes namely- amylase, lysozymes which protect and digest bacterial cell walls and lingual lipase which breakdown the fats. Saliva performs many important functions like moisten the mouth, initiates digestion and protect the teeth decay. It also controls the microbial flora of the oral cavity. It plays a vital role in repairing new teeth and mineralization of erratic enamel lesions because saliva has contained calcium and phosphate in high quantity. It also protects the teeth by forming "protective pellicles".

The secretory IgA, lysozymes and salivary peroxidase plays important role in salivary antibacterial actions. Lysozyme increases the bacteria and activates autolysins and for the hosting tissue IgA interference with the adherence of microorganism. Peroxidase breaks down the salivary thiocyanate which oxidizes the enzyme which is involved in bacterial glycolysis. Saliva in the oral cavity produces difficulty to maintain the amount of drug for desired time period to facilitate absorption to the site of action.

In the development of dental caries role of saliva is the second important factor. In common intercellular spaces forms as major inhibitors for the transduction of lipophilic compound, and cell membranes those are lipophilic in nature serves as major transport barriers for the hydrophilic compound because of the low partition coefficient. This is difficult to allow through the cell membrane. The permeability varies gently between different areas of oral cavity due to different structure and functions.

Buccal cavity has 4-4000 times greater permeability than the skin. However, permeability is based on the thickness and level of keratinization of these tissues in order of sublingual>buccal>palatal

10. Polymers for mucoadhesive drug delivery system

Polymers used for mucoadhesive drug delivery system has been playing major role fordesigning such system for increasing the residence time of the active ingredient at theparticular site. It also determines the different parameters like mucoadhesive, thickness and in-vitro release of the active agent.

The polymer is selected on the basis of the origin of the polymer (natural, semisynthetic & synthetic), the kind of mucosa is applied to (buccal/ocular) and depending their chemical structure (cellulose/polyacrylates). Generally, high molecular weight polymer is used because they show effective release rate. The class of polymer is briefly described by their selection such as:

10.1 Hydrophilic polymer

The hydrophilic polymers are soluble in water. Therefore, when this polymer is put into the aqueous medium the matrix of polymer swelling up. The mucoadhesive nature of the polyelectrolytes is better than neutral polymers. The an ionic polyelectrolyte's have ability to shown the high hydrogen bonding with the mucin present in the mucosal layer e.g., ploy (acrylic acid) and carboxymethyl cellulose. The cationic polyelectrolyte's have better biocompatibility and biodegradable properties which is extensively used for the developing mucoadhesive polymer e.g., chitosan. The ionic polymer is used to develop ionic complex

with the drug molecules so the drug delivery matrix exhibits better mucoadhesive property. The hydrophilic polymer increases the viscosity when we dissolve into the water.

Hence, we use these polymers as a viscosity modifying/ enhancing agent in developing the liquid ocular delivery system to increases the bioavailability of active ingredient by reducing the drainage of the administered formulation. Methyl cellulose, chitosan, hyaluronic acid, hydroxyl propyl methyl cellulose, xanthum gum, gelan gum, guar gum and carrageenan are used in the ocular mucoadhesive delivery system. The cellulose and its derivative are used as a surface-active ingredient with its film forming capability. The cellulose derivative haslower surface-active agent are generally used in the ocular delivery system to prevent eye irritation. The cationic cellulose derivatives have been used in mixture with various ionic polymers for the development of sustained delivery systems

10.2 Non-covalent binding polymer:

The charge on the surface plays an important role in the mechanism of mucoadhesion. For anionic polymers, their carboxylic moiety (-COOH) is mainly assigned to mucoadhesion. Due to the -COOH group, the formation of hydrogen bonds is generated with the hydroxyl groups of oligosaccharides side chains of mucus proteins. The polyacrylates and carboxymethyl cellulose have shown a elevated buffer capacity and a high charge density. The anionic polymer is incompatible with some cations like Mg2+ and Ca2+.

These polymers once contact with the cations to form precipitate and reduce the adhesive property. The last group of the non-covalent binding polymer is amphillic in nature which reveal both cationic and anionic substructure. The mucoadhesion of the cationic polymer occurs due to interaction with negatively charged mucus structure and anionic polymer occurs due to hydrogen bonding. Covalent binding polymers. The new generation polymer is described in various literatures which are being able to form the covalent bond with themucus layer. Thiolate polymers are also called thiols, the thiolates polymer have bearing thiolgroup into the polymer backbone.

The thiol group which is present into the polymer backbone which form the disulphide bond with cysteine-rich sub-domain present into the mucin which is improve the mucoadhesive property e.g., chitosan and poly (acrylic acid). The various thiolates polymers include chitosan-iminothiolane, poly (acrylic acid)-cysteine, poly (acrylic acid)-homocysteine, chitosan-thioglycolic acid, chitosan thioethyl amidine, alginate- cysteine, poly (methacrylic acid)-cysteine and sodium carboxymethylcellulose-cysteine. Novel mucoadhesive polymers. In novel mucoadhesive polymer, the existing polymers vary but in others, the new polymer will be developed.

Lectins is a protein, occurs naturally which have fundamental in the phenomenon of biological recognition involving cells and proteins. It is belonging to structurally diverse group of proteins and glycoproteins that can bind inversely to specific residues of carbohydrate. After mucosal cell binding, lectins can either remain on the cell surface or internalized through endocytosis process, possibly for receptor mediated adhesion.

This phenomenon has been beneficial, the mucus layer provides an initial yet fully reversible binding site, after which lectin mediated delivery system is delivered to the cell layers

The lectins can be distinguished according to the molecular structure such as:

- Merolectins: having one carbohydrate recognizing domain
- Hololectins: having two or more carbohydrate recognizing domain
- Chimer lectins: having additional unrelated domain.

11. Theories of buccal:

1.ELECTRONIC THEORY- The mucus and adhesive polymer have different characteristics when they make contact with each other electric charges make a double layer is formed at the bio adhesive interface then due to the attractive forces from electron transfer adhesion develops

2.ADSORPTION THEORY- In this theory, bio adhesive polymers adhere to the tissue because of surface forces such as van-der Waals forces, hydrogen bonds etc. results in the formation of two types of chemical bonds that are primary covalent bonds and secondary chemical bonds. Hydrogen bonding is considered to be dominant force for a bio adhesive polymer with a carboxyl group.

Similarly, hydrophobic interactions explaining the fact that the binding of bioadhesive polymer with the hydrophobic substrate is tighter as compare to the hydrophilic substrate. This theory describes the adhesion of polymer to the biological surface. According to this theory quite wettable polymers have optimal adhesion to the cells resulting in decreased adhesion with very hydrophobic or hydrophilic polymers.

3.WETTING THEORY- This theory analyses the sticky and contact behavior for the ability of liquid to spread over a biological system and this theory is applicable for liquid bio adhesive systems.

In condition, of surface & interfacial tension(Y) expressed by work of adhesion being knownas released of energy per cm2 when interface is formed.

According to Dupers equation work of adhesion is given by: -

$$W_A=Y_A+Y_B-Y_{AB}$$

Where, A and B refers are biological membrane & bio adhesive respectively.The work of

cohesion is given by:

$$W_C=_{or}\ YB$$

For bioadhesive material, B flows on a biological substrate coefficient i.e.,

$$SB/A = YA-(YB+YAB)$$

SB/A for bioadhesive material it should be positive which adhere to a biological membrane.

4.DIFFUSION THEORY- This theory indicates that the mucus and polymer chains are mixed together to a sufficient limit which makes an adhesive semi-permanent bond and the mixing rate depends on time of contact &diffusion coefficient of both interacting polymers. Diffusion Coefficient depends on the molecular weight and cross-linking density. Diffusion Coefficient will decrease significantly as the cross-linking density decreases. To achieve bioadhesion, bioadhesive medium have good solubility in the mucus. Thus, the difference in

the solubility of glycoprotein and bioadhesive medium should be closed to zero and thebioadhesive medium has similar structure to glycoprotein.

5.FRACTURE THEORY- This theory is related to the strain in after adhesion in separationof two surfaces. The fracture strength is equal to the adhesive strength and is given by:

$$G = (Ee. L)\ 1/2$$

where,

E=Young's modulus of elasticity,e=Fracture

energy,

L= when separation of two surfaces of critical crack length

12. Buccal Drug Delivery Systems:

12.1 Solid adhesive dosage forms- These are the dry formulations and achieve bio adhesion via dehydrating the mucosal surface.

12.2 Buccal Tablets- These are most commonly used dosage form for the drug delivery through the oral route. They are designed in such a way that they can release the drug unidirectionally or multidirectional into the saliva. These are formulated for systemic delivery of drug by direct compression and the dosage form contain a backing layer to avoid the back flow of drug or to promote the unidirectional release of drug. Bio adhesive formulations contain bio adhesive polymer (e.g.-cellulose derivatives and polyacrylic acid) used in either combination or alone. These polymers take places into a matrix having excipients, active ingredient and impermeable layer known as provides backing layer for single directional release of drug.

12.3 Bio adhesive Nanoparticles- Nanoparticles do not make an intimate contact with the mucosal surface due to their physical properties but they have same advantages as tablets. These are more likely patient acceptable because these are incorporated in the ointments or are delivered by water suspension. The bioavailability of these nanoparticles is higher than the tablets. Nanoparticles do not cause irritation or any discomfort to the patients due to their small size.

13. Semi-solid dosage forms

13.1 Chewing gums- These are absorbed fastly and have more bioavailability as compare to capsules. They are having higher benefits as drug delivery devices for treatment of buccal cavity diseases and in nicotine replacement therapy. For example- (Nicorette and Nicotinell) smoking cessation these nicotine chewing gums are marketed.

13.2 Adhesive Gels- These formulations allow sustained release and used to deliver the drugs via buccal mucosa. It includes in the gel forming bio adhesive polymers that has been attached to surface of mucosa by cross linking polyacrylic acid and at the site of absorption provide controlled release. These have limited use for drugs having narrow therapeutic window due to their inability to deliver measured dose of drug at absorption.

13.3 Buccal patches- Patches deliver the measured amount of dose to absorption sites. These formulations contain the drug reservoir, backing membrane which is not permeable and a bio

adhesive surface which is attached to surface of mucosal. Flexible patches are prepared by hot melt extrusion and solvent evaporation technique and they release the drug in controlled manner.

14. Evaluation of Buccal Delivery System:

1) Weight Variation- From each formulation collects the 10 tablets which are having varying concentration of polymer. Calculate the average weight by calculating the single weight of tablet from the selected formulations and then comparing the individual weightwith the average weight.

2) Thickness- Collect randomly 3 tablets from each batch of formulation and measure the thickness by the help of vernier calliper. Calculate the average thickness.

3) Friability- From each batch weighed 6 tablets accurately (W1) and then placed in the friabilator known as Roche friabilator & rotated for 4 minutes at 25 rpm. After completion of rotations weigh the tablets again which is (W2). Determine the percentage.

4) Hardness- Hardness of 5 tablets is measured from each batch and then calculates average hardness. For, measured of hardness Monsanto hardness tester was used

5) In-vitro swelling studies- The amount of swelling of bio adhesive tablets are evaluated byusing 2%w/v agar gel plate. For, each formulation weigh 3 tablets and calculate the average weight (w1). Place the tablets on the gel surface in the petridish and then incubated at37+0.10 c. The tablets are then removed at 0.5,1,2,3,4,5 and 6 hours' time interval & the excess liquid on the surface is removed by using filter paper and then weigh the swollen tablet. Determine the average weight (w2) and then calculate the swelling index by using the formula.

% Swelling index= [(W2-W1)/W1] X 100

6) Determination of surface pH of tablets- To allows the tablets to swell for 2hrs on agar plate surface. Place the pH paper on the core surface of the swollen tablet and measure the surface ph.

15. Buccal Films:

1) Folding endurance- Determination of folding endurance is done by folding one film until it broke at the same place. This can be folded at same place many times without breaking i.e., It gave the folding endurance value up to 300

2) Measurement of film thickness- At 10 different spots thickness is measured from each batch by using the screw gauge micrometer.

3) Drug content uniformity- Dissolve the 5 weighed films using magnetic stirrer in 100 ml phosphate buffer having pH6.8. Filter the solution and then analyse the drug spectrometrically after dilution.

4) Film swelling- Take out the 3 films of one type of formulation then weigh the buccal films and place them on pre-weighed wire mesh. Swelling studies of film were done by using two media i.e., distilled water and simulated saliva fluid. A film sample was submerged into 15ml

medium. At defined time intervals increase in weight was determined until the continual weigh was observed.

5) In-vivo mucoadhesion studies- Healthy human volunteers are taken for the studies. At buccal mucosa the volunteers have to applied for 30s by pressing it. Human volunteers have to concluded problems like dryness of mouth, irritation of mucosa, taste etc. occurring when using the film and they are advised to perform their regular activities except eating food.

Chewing gum

Release of drug in saliva- In this case mechanical operation is required to drug released from medicated chewing gum. The release process is different from other dosage form, it may also affect by the person chewing activities.

16. Commercially available dosage forms:-

Table 1: Different dosage forms commercial avilable in the market:

Commercial name	Bioadhesive polymer	Company	Dosage form
Lauriad	Modified starch, CP-934	BioAlliance pharma	Buccal tablet
Buccastem	PVP, Xanthum gum, Locust bean gum	Rickitt Benckise	Buccal tablet
Suscard	HPMC	Forest laboratories	Buccal tablet
Corsodyl gel	HPMC	GlaxoSmithKline	Oromucosal gel
Corlan pellets	Acacia gum	Celltech Pharmaceuticals Inc.	Oromucosal pellets
Onsolis	Carboxymethylcellulose, Hydroxypropyl cellulose	Meda pharmaceuticals,Inc.	Buccal soluble film
Belbuca	Carboxymethylcellulose sodium	BioDelivery Sciences International Inc.	Buccal film
Bunavail	Carboxymethylcellulose sodium	BioDelivery Sciences International Inc	Buccal film
Oravig	Hypermellose	BioAlliance Pharma SA	Buccal film
Breakyl		Meda pharmaceuticals,Inc	Buccal film
Orabase	Pectin, Gelatin	ConvaTec	Oral paste
Striant® SR	Carbomer 934P, Hypermellose	Columbia Laboratories, Inc	Buccal tablet
Effentora		Teva Pharmaceuticals	Buccal tablet
Sitavig®	Starch, Lactose	BioAlliance pharma	Buccal tablet
Striant ® SR	Carbomer 934 P	Ardana Bioscience	Buccal tablet
Aftach ®	Hydroxypropyl cellulose, Polyacrylic acid	Teijin Ltd.	Buccal tablet
Dentipatch®		Noven pharmaceutical Inc.	Buccal patch
Travel-Gum		Meda pharmaceuticals,Inc	Chewing gum
Zilactin-B	Hydroxypropyl cellulose	Blairex Laboratories, Inc.	Gel

Nicorette	Acacia gum	GlaxoSmithKline	Chewing gum

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