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A REVIEW ON BUCOADHESIVE DRUG DELIVERY SYSTEM

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ABSTRACT

Buccal tablets were prepared using mucoadhesive polymers like Chitosan, HPMC K4M, Na CMC & amp; Sod. alginate by direct compression technique. Buccal tablets were characterized for number of parameters like Hardness, weight uniformity, thickness, % friability, swelling index, mucoadhesive strength, surface pH, drug–excipient interaction study, drug content uniformity and In vitro drug release study. The continuous secretion of saliva and its subsequent swallowing can lead to substantial drug depletion from the dosage form and hence low bioavailability. Therefore, other transmucosal routes such as nasal, rectal, vaginal,ocular and oral mucosae are being considered as alternatives to conventional oral dosage forms for drug delivery to avoid the above disadvantages associated with conventional oral delivery (i.e., tablets, capsules, syrups, etc.). Of these routes of delivery, the buccal oral mucosa has emerged as one of the target sites for administration of drugs in a wide variety of dosage forms, particularly for those drugs targeted for local delivery in the oral cavity and systemic absorption.

KEYWORDS: Buccal Tablets, Polymers, Mucoadhesion, Bioadhesion.

INTRODUCTION

The mucosa of the mouth is very different from the rest of the gastrointestinal tract and morphologically is more similar to skin. Although the permeability of skin is widely regarded as poor, it is not generally appreciated that the oral mucosa lacks the good permeability demonstrated by the intestine. These differences within the gastrointestinal tract can largely be attributed to the organization of the epithelia, which serve very different functions. A simple, single-layered epithelium lines the stomach, small intestine, and colon, which

provides for a minimal transport distance for absorbents. In contrast, a stratified or multilayered epithelium covers the oral cavity and esophagus and, in common with skin, is composed of layers with varying states of differentiation or maturation evident on progression from the basal cell layer to the surface. Drugs have been applied to the oral mucosa for topical applications for many years. However, recently there has been interestin exploiting the oral cavity as a portal for delivering drugs to the systemic circulation. Not withstanding the relatively poor permeability characteristics of the epithelium, a number of advantages are offered by this route of administration. Foremost among these are the avoidance of first-pass metabolism, ease of access to the delivery site, and the opportunity of sustained drug delivery predominantly via the buccal tissues.[1-4]

STRUCTURE AND FUNCTION OF ORAL MUCOSA

A stratified, squamous epithelium lines the oral cavity. Three different types of oral mucosa can be identified, i.e. masticatory, lining, and specialized mucosa, The masticatory mucosa covers the gingiva and hard palate. Itcomprises a keratinized epithelium strongly attached to underlying tissues by a collagenous connective tissue and as such is able to withstand the abrasion and shearing forces of the masticatory process. The lining mucosa covers all other areas except the dorsal surface of the tongue and is covered by a nonkeratinized and hence more permeable epithelium. This mucosa is capable of elastic deformation and hence stretches to accommodate speech and mastication requirements. The epithelium in humans varies in thickness according to the region, e.g., floor of the mouth, 190µm; hard palate, 310µm; buccal, 580 µm.[5]

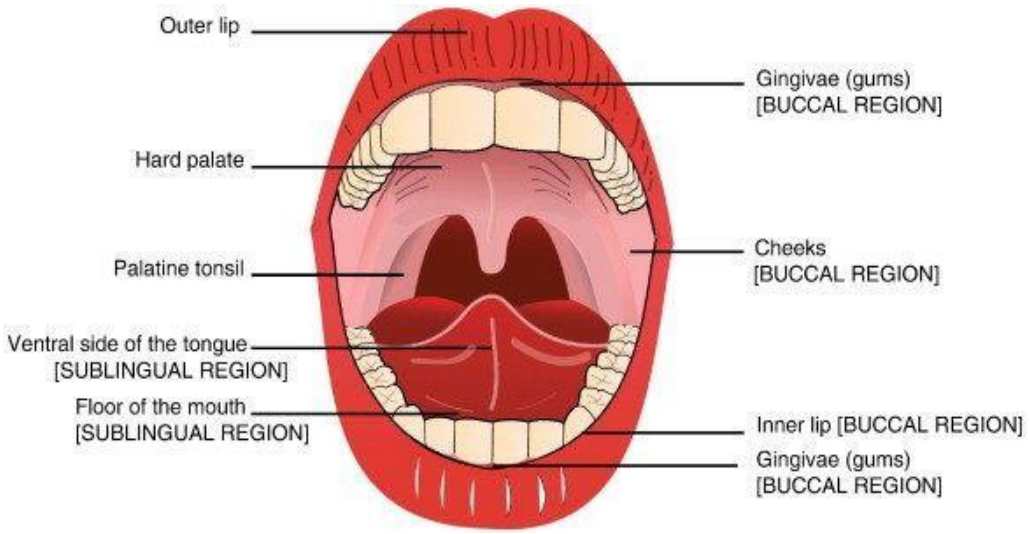

Figure 1: Different anatomical region of buccal cavity.[2]

The regional differences in morphology result in different permeability characteristics that have considerable influence on the design and siting of drug delivery systems. The differentiation process that gives rise to the regional differences occurs as the keratinocytes migrate from the buccal layers to the epithelial surface. Within the basal layer the keratinocytes are cuboidal or columnar with a surrounding plasma membrane and containing the usual intracellular organelles.

A constant population of epithelial cells is maintained by the division of the basal keratinocytes at a rate equating to the desquamation of surface cells. Aging and disease can result in a loss of this balance, which can lead to a thickening (hypertrophia) or thinning (atrophia) of the epithelium. The media turnover time is slower for keratinized tissue, e.g., hard palate 24 days and buccal mucosa 13 days. Also relevant to the development of drug delivery systems are the surface areas of the human mouth occupied by keratinized (50%) and nonkeratinized (30%) tissues. Percentages are expressed with reference to the total surface area of the mouth. Desmosomes are still present between cells in the surface cell layer where intercellular spaces are both wide and irregular. Membrane-coating granules appear as approximately 200-nm spheres in the prickle cell layers. Which subsequently fuse with cell membranes to discharge their contents in the superficial cell layer.[3,5,7]

NATURE OF THE LIPID BARRIERS

Phospholipids, cholesterol, and glycosylceramides predominate with the phospholipid fraction composed of sphingomyelin and phosphatidyl-choline, ethanolamine, serine, and inositol. Triglycerides and cholesterol esters are also present with traces of fatty acids and ceramide. This lipid cocktail may well give rise to fluid lamellae.[6,8,10]

SALIVA AND MUCUS

Saliva is essentially a protective fluid for the tissues of the oral cavity. The major component of the mucous secretions are the soluble mucins that can associate to form oligomericmucins. These structures provide both viscoelastic and lubricating properties. Salivary mucins have a number of host-defense functions including the establishment of a permeability barrier overlying the epithelia, lubrication of surface tissues, and modulation of the colonization of oral microorganisms. Approximately 750 mL of saliva is produced daily in an adult with 60% from the submandibular glands, 30% from the parotids, 5% from the sublingual glands, and around 6% from the minor salivary glands found beneath the epithelium in most regions of the oral mucosa. Saliva is a mixture of serous secretions, which are high in glycosylated

protein of low viscosity, and mucus secretions, which have a higher carbohydrate-to-protein ratio and little to no enzymatic activity. The parotids produce almost entirely serous secretions, the submandibular largely mucous secretions, while the sublingual glands produce a mixed serous/mucous secretion. Up to 70% of the total saliva mucin content arises from the minor salivary glands. Saliva contains a variety of esterases (mainly carboxylesterases) that may hydrolyze susceptible drug ester groups. The mode of administration of tablets for the oral transmucosal delivery of drugs and their disintegration rate were shown to influence saliva secretion and, because of the link between esterase activity and saliva flow rate, saliva esterase activity. The pH of saliva has been reported to vary between 6.5 and 7.5.with the principle buffering function ascribed to the bicarbonate system and to a lesser extent phosphate and protein buffers.[7-10]

Physiological aspects and functions of oral cavity

The oral cavity is accountable for the following primary functions:

- As a portal for intake of food material and water.
- To bring chewing, mastication and mixing of food stuff.
- Lubrication of food material and formation of bolus.
- Identification of ingested material by taste buds of tongue.
- Initiation of carbohydrate and fat metabolism. Absorption of catabolic
- Products thereafter metabolism.
- To aid in speech and breathing process.
- Slight antisepsis of ingested material and within oral cavity by saliva.

Functions of Mucus layer[11,12]

1. **Protective**: Resulting particularly from its hydrophobicity.
2. **Barrier**: The role of the mucus layer as a barrier in tissue absorption of drugs and other substrates is well known as it influences the bioavailability of drugs.
3. **Adhesion**: Mucus has strong cohensional properties and firmly binds to the epithelial cell surface as a continuous gel layer.
4. **Lubrication:** An important role of the mucus layer is to keep the mucosal membrane moist. Continuous secretion of mucus from the goblet cell is necessary to compensate for the removal of the mucus layer due to digestion, bacterial degradation and solubilization of mucin molecules.

MODES OF TRANSPORT ACROSS BUCCAL MUCOSA[12-14]

The physicochemical properties of a drug are important for its passive transport across the mucosa of the oral cavity. For drug absorption to take place through the buccal mucosa of the oral cavity, the dosage form must dissolve in saliva liberating the drug into a solution. Then the drug will partition into the mucus covering the buccal mucosa at which time it is available for permeation. There are two pathways by which passive drug transport across the buccal mucosa can take place for it to reach the local adjacent structures and systemic circulation: **transcellular** and **paracellular** routes that enable the drug to reach systemic circulation. Drugs can travel through these two routes simultaneously, but one route is preferred over the other depending upon the physicochemical properties of the molecules (i.e. molecular weight, polarity, etc.).

A. Transcellular Pathway

Drug permeation through the epithelial cells involves transport across the apical cell membrane, the intracellular space and the basolateral membrane as shown in **Figure 2.** Drug transport through the transcellular pathway, also known as the intracellular pathway, may be by passive transport (diffusion, pH partition) of small molecules or by active transport (facilitated and carrier-mediated diffusion) of ionic and polar compounds and endocytosis and transcytosis of macromolecules.

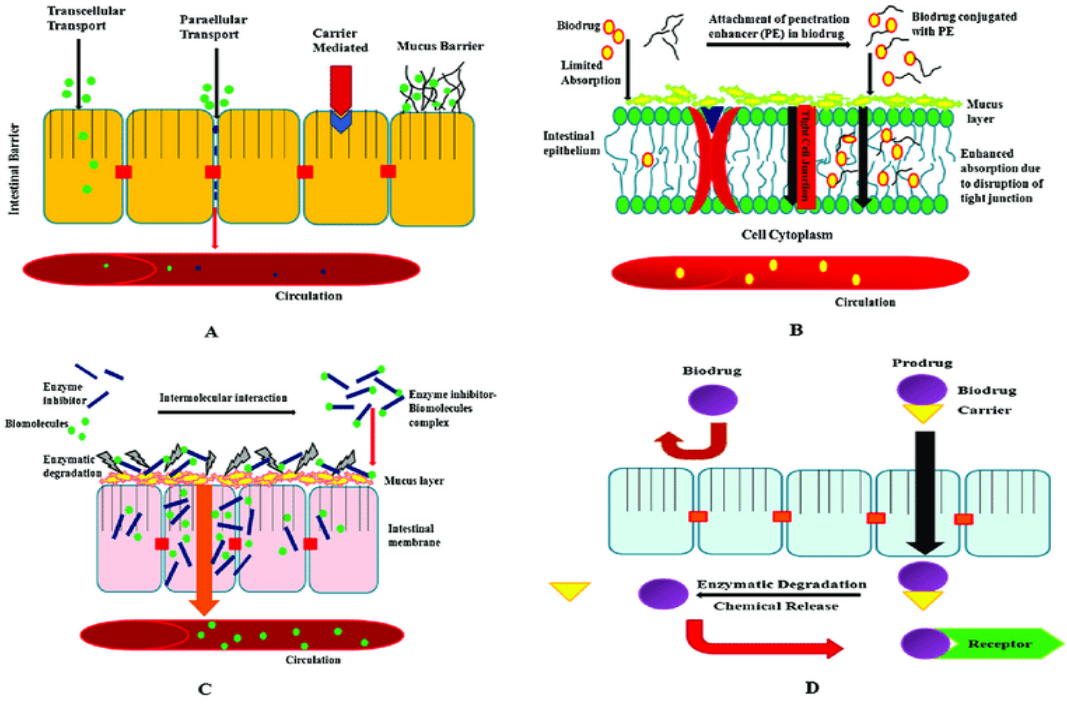

Figure 2: Transport pathways of molecules across buccal tissue.[14]

Drug transport through the transcellular pathway is a complex phenomenon that is dependent on various physicochemical parameters of the drug, including molecular weight, lipophilicity, hydrogen bond potential, charge and conformation. Lipophilic compounds and small hydrophobic molecules predominantly undergo transcellular transport. Transcellular diffusion is inversely proportional to the amount of membrane coating granules present in the intracellular spaces. Because the cell membrane is lipophilic in nature, hydrophilic drugs will have difficulty permeating the cell membrane due to a low partition coefficient. Passive transport of hydrophilic compounds, including macromolecules such as polypeptides and proteins, can be enhanced by theinteraction of the absorption enhancing excipients with both the phospholipid bilayer and the integrated proteins. Some small water-soluble molecules such as amino acids, ions and sugar scan be transported throughthe aqueous pores in the cell membrane.[12,14,15]

B. Paracellular Pathway

Drug permeation through the epithelial cells also involves transport through the lipids or in-between the epithelial cells as shown in **Figure 3.** The paracellular pathway (also known as the intercellular pathway) can be of two types: one is an essentially hydrophobic route, through the lipid bilayer and the other is a hydrophilic route associated with the narrow aqueous regions adjacent to the polar head groups of the lipid bilayers. For compounds transported through the paracellular route, tortuosity and intercellular space are the main hindrances to permeability. A substance with equal solubility in aqueous and lipid media can permeate by both para and transcellular pathways.[14,18]

Drug delivery via buccal route[15-20]

Buccal delivery refers to drug release which can occur when a dosage form is placed in the outer vestibule between the buccal mucosa and gingival. Various advantages and other aspects of this route are elucidated of the following.

Advantages of mucoadhesive buccal drug delivery[17,18]

Drug administration via the oral mucosa offers several advantages

1. Easy of administration and termination of therapy in emergency.
2. Permits localization of the drug for a prolonged period of time.
3. Can be administered to unconscious and trauma patients.
4. Offers an excellent route for the systemic delivery of drug which by passes first pass metabolism, there byoffering a greater bioavailability.

5. Significant reduction in dose can be achieved, there by reducing dose, dose dependent side effects, andeliminates peak-valley profile.
6. Drugs which are unstable in acidic environment of stomach or are destroyed by the enzymatic or alkalineenvironment of the intestine can be administered.
7. It offers a passive system for drug absorption.
8. It can be made unidirectional to insure only buccal absorption.
9. It allows for the local modification of tissue permeability, inhibition of protease activity or reduction in immunogenic response. Thus, selective uses of therapeutic agents like peptides, proteins and ionized species can be achieved.
10. Flexibility in physical state, shape, size and surface.
11. Maximized absorption rate due to intimate contact with the absorbing membrane and decreased diffusion barriers.

Disadvantages of mucoadhesive buccal drug delivery[15,16]

1. Drugs which are unstable at buccal pH cannot be administered.
2. Drugs which irritate the mucosa or have a bitter or unpleasant taste or an obnoxious odor cannot beadministered by this route.
1. Only drug with small dose requirement can be administered.
2. Only those drugs which are absorbed by passive diffusion can be administered by this route.
3. Eating and drinking may become restricted.
4. There is an ever present possibility of the patient swallowing the dosage form.
5. Over hydration may leads to slippery surface and structural integrity of the formulation may get disruptedby this swelling and hydration of the bioadhesive polymers.

FACTORS AFFECTING ORAL ABSORPTION[11,12,17]

a. Membrane factors

The permeability of the oral mucosa is not great compared to other mucosal membranes and represents a major obstacle in the successful development of the oral cavity as a site for systemic drug delivery. An understanding of the anatomy, physiology and composition of the different membranes that line the oral cavity is important. It may help in the identification and selection of the most appropriate site for delivery and consequently influence delivery system design. Regional variations exist within the oral cavity and both keratinized and nonkeratinised tissues of varying thickness and composition are found in the oral cavity.

Keratinized and nonkeratinised tissue occupy about 50% and 30% respectively of the total surface area of the mouth. The buccal (thickness: 500-600 ~tm, area: 50.2cm 3) and sublingual (thickness: 100-200 ~tm, area:26.5 cm 3) regions are nonkeratinised and contain a few neutral but mainly polar lipids, particularly cholesterol sulfate and glucosylceramides. Gingival (thickness: 200 ~tm) and palatal (thickness: 250 ~m, area: 20.1 cm) mucosa are keratinised and show a lipid pattern of mainly neutral lipids i.e. ceramides.

b. Environmental issues

1. Saliva

Saliva is the protective fluid for all the tissues of the oral cavity and its necessity for oral health generally onlybecomes significant when either the amount of saliva is reduced or its quality changes. These changes, particularly a reduction in the amount of saliva produced, occur in many systemic diseases, e.g. diabetes and as a consequence of the treatments of disease, e.g. radiation therapy or drugs. Saliva protects the soft tissues from abrasion by rough materials and from some chemicals. It allows the continuing mineralisation of the enamel of teeth after they erupt and aids remineralisation of the enamel in the early stages of dental caries. It also plays an important antibacterial role by either aiding or preventing the attachment of bacteria to the surfaces of the oral cavity. Such changes may also affect successful drug delivery via this route and thus it may be appropriate to consider what changes occur in saliva in disease conditions and as a consequence of the treatments.

2. Salivary glands

Saliva is produced in three pairs of major glands (parotid, submandibular and sublingual) each situated outside of the oral cavity and in minor salivary glands situated in the tissues lining most of the oral cavity.

(i) Major salivary glands: The parotid glands are situated anterior to the ear and in the retromolar fossa. The main excretory ducts (Stenson's Ducts) open into the mouth in the lining of the cheek or buccal mucosa adjacent to the upper first and second molar teeth. The saliva produced is very watery saliva – almost completely serous in composition. The submandibular glands lie mostly behind and below the free border of the mylohyoid muscle with a small extension above it. Wharton's Ducts open into the floor of the mouth on either side of the lingual fraenum. The sublingual glands lie between the mylohyoid muscle and the floor of the mouth. The saliva fromthese major glands reaches the mouth via Bartholin's Ducts which open with or adjacent to the submandibular ducts.

(ii) Minor salivary glands: In addition to the saliva produced in the major glands, saliva is also produced in the minor salivary glands (also called accessory and intrinsic glands). These are found beneath the epithelium throughout the mouth except for the anterior part of the hard palate and the alveolar ridges supporting the teeth. Most of the mucus present in the oral cavity is derived from the minor salivary glands, however minor glands do not all produce the same composition of saliva. The glands in the buccal mucosa are reported to produce mixed saliva and the labial glands of the lips mucous saliva.

c. Movement of oral tissues

A further aspect which has to be considered is the effect of swallowing, talking and eating on the movementof tissues in the oral cavity. If oral mucosal drug delivery systems are to remain in place for any period oftime some idea of the movement of the tissue at the site of attachment and on their movement over other tissues and of the movement of other tissues against the delivery system would be required. Least movement of any of the tissues in the oral cavity is during sleeping and this period may be the most appropriate for drug administration if dislodgment of delivery system proves to be a problem; however, swallowing and mouth movements do continue while sleeping. If delivery needs to be continued for prolonged periods, some investigation would need to be performed on the role of the tongue during oral mucosal drug delivery which,at various stages of mastication and swallowing, may compress against the palate, induce suction pressures and wipe across tissues and delivery systems. It may prove necessary to determine the exact movement of the tongue during mastication and talking and to measure what pressures is exerted on the various regions of the oral cavity during these activities.

Advances in Buccal Drug Delivery System[18,19,20]

Buccal mucoadhesive dosage forms can be categorized into three 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 into the oral cavity. Type-III is a unidirectional release device from which drug loss is minimal, since the drug is released only from the side adjacent to the buccal mucosa. This can be achieved by coating every face of the dosage form, except the one that is in contact with the buccal mucosa. Buccal dosage forms can also be classified as either reservoir or matrix

type. In the reservoir type, an excessive amount of the drug is present in there reservoir surrounded by a polymeric membrane which controls the drug's release rate. In the matrix type systems, the drug is uniformly dispersed in the polymer matrix and drug release is controlled by diffusion through the polymer network. In general, dosage forms designed for buccal drug delivery should be small and flexible enough to be acceptable for patients, and should not cause irritation. Other desired characteristics of a buccal mucoadhesive dosage form include high drug loading capacity, controlled drug release (preferably unidirectional release) good bioadhesive properties, smooth surface, tastelessness and convenient application. Erodible formulations can be beneficial because they do not require system retrieval at the end of desired dosing interval.

a) Buccal tablets

Tablets have been the most commonly investigated dosage form for buccal drug delivery to date. Buccal tablets are small, flat and oval with a diameter of approximately 5–8 mm. Unlike conventional tablets, buccal mucoadhesive tablets allow for drinking and speaking without major discomfort. They soften, adhere to the mucosa, and are retained in position until dissolution and/or release is complete. These tablets can be applied to different sites in the oral cavity, including the palate, the mucosa lining the cheek as well as between the lip and the gum. Successive tablets can be applied to alternate sides of the mouth. The major drawback of buccal bioadhesive tablets is their lack of physical flexibility, leading to poor patient compliance for long-term and repeate dose. Bioadhesive tablets are usually prepared by direct compression, but wet granulation techniques can also be used. Tablets intended for buccal administration by insertion into the buccal pouch may dissolve or erode slowly; therefore, they are formulated and compressed with sufficient pressure only to give a hard tablet. In order to achieve unidirectional release, every face of the tablet except the one that is in contact with the buccal mucosa can be coated with water impermeable materials such as ethylcellulose, hydrogenated castor oil, etc. using either compression or spray coating. Multilayered tablets may be prepared by sequentially adding and compressing the ingredients layer by layer.

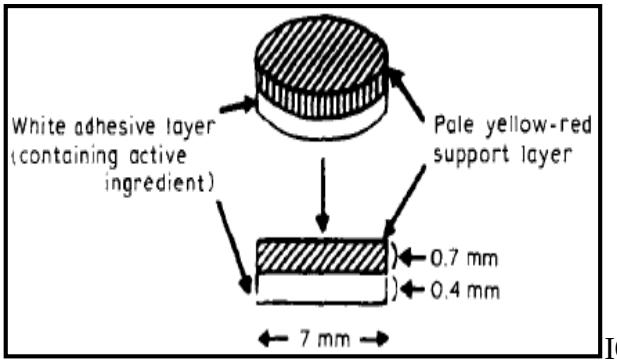

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Figure-3: Adhesive tablet.

b) Buccal patches

Patches are laminates consisting of an impermeable backing layer, a drug containing reservoir layer from which the drug is released in a controlled manner and a bioadhesive surface for mucosal attachment. Buccal patch systems are similar to those used in transdermal drug delivery. Two methods used to prepare adhesive patches include solvent casting and direct milling. In the solvent casting method, the intermediate sheet from which patches are punched is prepared by casting the solution of the drug and polymer(s) onto a backing layer sheet and subsequently allowing the solvent(s) to evaporate. In the direct milling method, formulation constituents are homogeneously mixed and compressed to the desired thickness and patches of predetermined size and shape are then cut or punched out. An impermeable backing layer may also be applied to control the direction of drug release, prevent drug loss and minimize deformation and disintegration of the device during the application period.

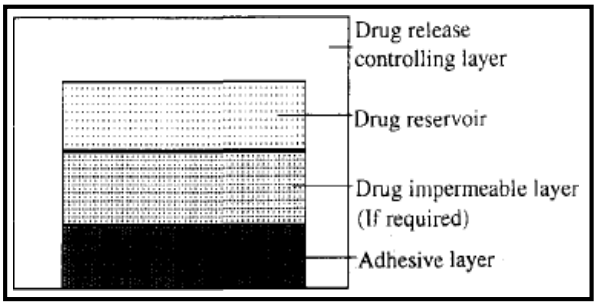

Figure 4: Bioadhesive sustained dosage form.

c) Buccal films

Films are the most recently developed dosage form for buccal administration. Buccal films may be preferred over adhesive tablets interms 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 the 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 or derto prevent discomfort. Bioadhesive films are similar to laminated patches in terms of their flexibility and manufacturing process. They are usually manufactured by a solvent casting method. The drug and polymer(s) are first dissolved in a casting solvent or solvent mixture. The solution is then cast into films, dried and finally laminated with a backing layer or a release liner. The backing layer helps retard the diffusion of saliva into the drug layer, thus enhancing the adhesion time and reducing drug loss into the oral cavity. The solvent casting method is simple, but suffers from some disadvantages, including long processing time, high cost and environmental concerns due to the solvents used.

These drawbacks can be overcome by the hot-melt extrusion method.

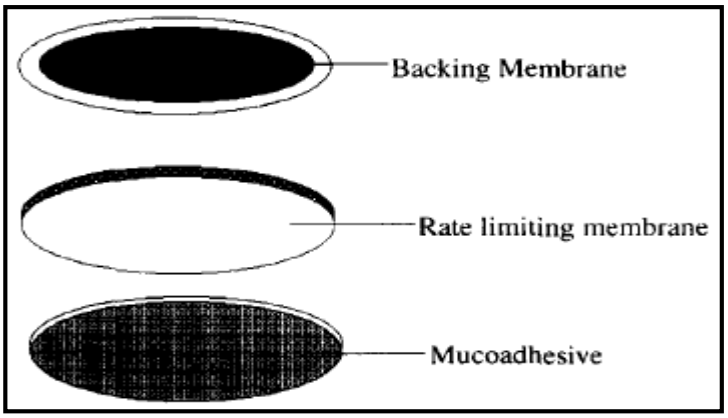

Figure-5: Prototype buccal mucoadhesive system.

d) Buccal gels and ointments

Semisolid dosage forms, such as gels and ointments, have the advantage of easy dispersion throughout theoral mucosa. However, drug dosing from semi solid 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 over come by using bioadhesive formulations. Certain bioadhesive polymers, e.g. poloxamer 407, sodium carboxymethyl cellulose, carbopol, hyaluronic acid and xanthan gum, undergo a phase change from a liquid to a semisolid. 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.

Hydrogels are also a promising dosage form for buccal drug delivery. They are formed from polymers that are hydrated in an aqueous environment and physically entrap drug molecules for subsequent slow release by diffusion or erosion. The application of bioadhesive gels provides an extended retention time in the oral cavity, adequate drug penetration, as well as high efficacy and patient acceptability. A major application of adhesive gels is the local delivery of medicinal agents for the treatment of periodontitis, which is an inflammatory and infectious disease that causes formation of pockets between the gum and the tooth, and can eventually cause loss of teeth.

Powders

Yamamoto 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 the beclomethasone was retained on the oral mucosa forover 4 hours. Although an increase in the penetration of beclomethasone into the oral mucosa was found, the potential clinical applications of this type of formulation would appear to be limited.

EVALUATION OF BUCCAL MUCOADHESIVE TABLETS[19-24]

Like any other formulation, the buccal muco-adhesive tablets must be subjected to various quality control tests to assure uniform standards and high safety margins. The various parameters which are used to standardize buccal tablets can be basically classified into following three types:

A) Physical Evaluations

a) Size and thickness

The thickness of tablets is measured using micrometer or screw gauge with least count of 0.01mm. The thickness can be measured by placing the tablets between two microscopic slides at five different points. The thickness of the film at different points was obtained by measuring the thickness of samples with assembly using a micrometer or screw gauge and subtracting the thickness of the two glass slides measured previously. The maximum probable size for buccal tablets is 15 mm but usual range of comfortable size is 1 to 3 cm2. The thickness of tablets must be limited to few millimeters. The best shapes comfortable to be used by patient are either ellipsoid or circular.

b) Weight variation

The average weight of 20 buccal tablets must be subtracted from individual weight of films.

If the differences are large then it is indicative of insufficiency of method adopted for preparation. Large weight variation causes variation in dose of drug and hence is therapeutically unacceptable.

c) Friability

Roche friabilator was used to determine the friability by following procedure. Pre weighed 10 tablets from each batch were taken in Roche friabilator (Pharma labs, Ahmedabad, India) apparatus that revolves at 100 rpm for 4 minutes dropping the tablets through a distance of 6 inches with each revolution. At the end of test, tablets were reweighed and the percentage loss was determined.

d) Hardness

The resistance of the tablet to chipping, abrasion or breakage under conditions of storage, transportation and handling before usage, depends on its hardness. The hardness of ten randomly selected buccal tablets from each batch was measured using Monsanto Hardness tester (Secor Scientific Eng Corporation India) and expressed in Kg/cm2. The mean and standard deviation values were calculated and reported.

B) Biological Evaluations

a) Mucoadhesion / Bioadhesion

Bioadhesion is an interfacial phenomenon in which two materials, at least one of which is biological, are held together by means of interfacial forces. The attachment could be between an artificial material and biological substrate, such as the adhesion between polymer or copolymer and a biological membrane. In the case of polymer attached to the mucin layer of mucosal tissue, the term “mucoadhesion” is employed.

b) Theories of Bioadhesion / Mucoadhesion

Mucoadhesion is proposed to occur in three stages. Initially, an intimate contact must form between the mucoadhesive and mucus (i.e., they must “wet” each other) then the mucus / mucoadhesive macromolecules interpenetrate and finally the molecules interact with each other by secondary non-covalent bonds. The bonding occurs chiefly through both physical and chemical interactions. Physical or mechanical bonds result from entanglement of the adhesive material and the extended mucus chains. Secondary chemical bonds may be due to electrostatic interactions, hydrophobic interactions, hydrogen bonding and dispersion forces. Covalent bonding such as occurs with cyanoacrylates is also possible for mucoadhesion but

is not yet common in pharmaceutical systems. Several theories of bioadhesion have been proposed to explain fundamental mechanism(s) of attachment. In a particular system one or more theories can equally well explain or contribute to the formation of bioadhesive bonds various theories propounded to explain mucoadhesion / bioadhesion are:

- Wetting theory
- Electronic theory
- Adsorption theory
- Diffusion theory
- Fracture theory

1. Wetting Theory

This theory best describes the adhesion of liquid or paste to a biological surface. The work of adhesion can beexpressed in terms of surface and interfacial tension (γ) being defined as the energy per cm^2 released when aninterface is formed.

According to Dupre's equation the work of adhesion is given by:

$$Wa = \gamma A+\gamma b-\gamma B \quad \ldots 1$$

Where the subscript A and B refer to the biological membrane and the bioadhesive formulation respectively.The work of cohesion is given by:

$$We = 2\ \gamma A=2\ \gamma\ B \quad \ldots 2$$

For a bioadhesive material B spreading on a biological substrate. A the spreading coefficient is given by:

$$SB/A = \gamma\ A – (\gamma\ B + \gamma\ AB) \quad \ldots 3$$

SB/A should be positive for a bioadhesive material to adhere to a biological membrane. For a bioadhesiveliquid B adhering to a biological membrane. A the contact angle is given by:

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

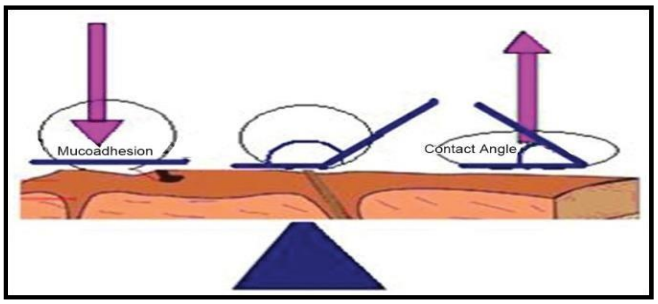

Figure 6: Influence of contact angle on mucoadhesion.

2. Diffusion Theory

Voyutski appears to be the first to discuss diffusion as a theory for adhesion. According to this theory the polymer chains and the mucus to a sufficient depth to create a semi-permanent adhesive bond. The polymer chains penetrate the mucus; the exact depth to which it penetrates to achieve sufficient mucoadhesion depends on diffusion coefficient, time of contact and other experimental variables. The diffusion coefficient depends on molecular weight and decreases rapidly as the cross-linking density increases. The molecular weight, chainflexibility, expanded nature of both the mucoadhesive and substrate as well as similarity in chemicalsstructure are required for good mucoadhesion.

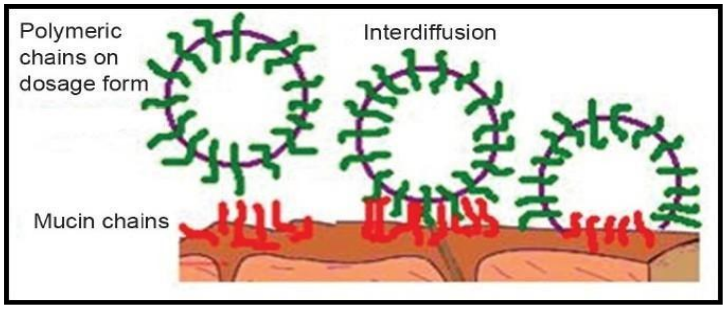

Figure 7: Secondary interaction between mucoadhesive device and mucus.

3. Electronic Theory

According to this theory electron transfer occurs on contact of adhesive polymer and the mucus glycoprotein network because of difference in their electronic structure. This results in the formation of electrical double layer at the interface. Adhesion occurs due to attractive forces across the double layer. The electronic theory of adhesion was suggested by Derjaguin and Smigla.

4. Fracture Theory

The fracture theory of adhesion is related to separation of two surfaces after adhesion. The fracture strength isequivalent to adhesive strength as given by:

$$\sqrt{\frac{E\varepsilon}{L}}$$

□ =

Where E is young's modulus of elasticity, □ is the fracture energy and L is the critical crack length when twosurfaces are separated. The work of fracture of an elastomer network Gc is given by:

$$Gc = K\,Mc$$

K is a constant dependent on the density of the polymer, effective mass, length and flexibility of a single mucin chain bond and bond dissociation energy. Gc of an elastomeric network increases with molecularweight Me of the network stands.

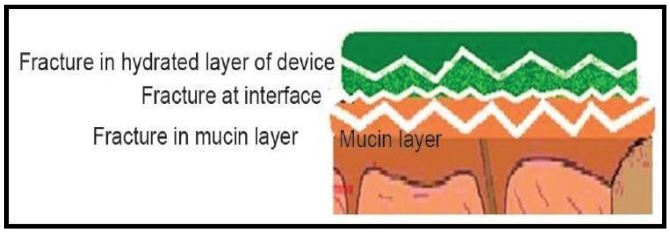

Figure-8: Fractures occurring for Mucoadhesion

5. Adsorption Theory

Adsorption theory has been described by Kembell and Hantsherger. According to this theory after an initial contact of two surfaces the material will adhere because of surface forces acting between the atoms in the two surfaces. Weak interaction of Vander Wall type plays an important role. However, if adsorption is due to chemical bonding i.e. chemisorption, then ionic, covalent and metallic bonds play an important role at the interface. From a drug delivery point of view the mechanism of mucoadhesion appears best explained by a combination of diffusion and electronic theory, although other mechanisms may simultaneously be operative at minor level. It may also be more appropriate to restrict the term "mucoadhesion" to describing the adhesionof hydrated dosage forms to those mucus membranes having a substantial mucus layer. The term "bioadhesion" or "mucosal adhesion" may be more suitable to describe adhesion to the mucosal of the oral cavity.

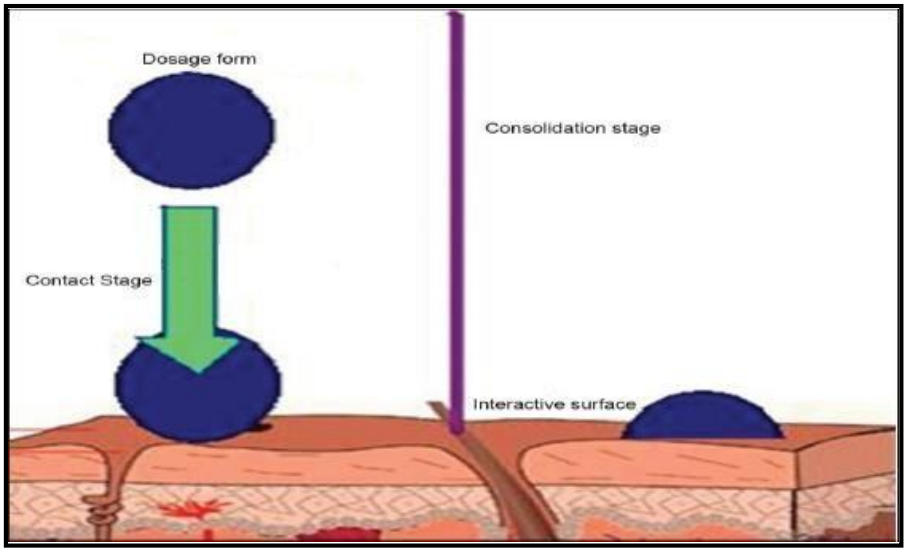

Figure-9: The process of consolidation.

3. MEASUREMENT OF BIOADHESION/MUCOADHESION

Several methods are proposed for bioadhesion measurements. The most prevalent are described here.

a) *IN VITRO* METHODS

1. Wilhelmy plate method

In this method the plates are coated with a polymer to be tested and immersed in a temperature controlled mucus solution. The force required to pull the plate out of the solution is determined under constant experimental condition.

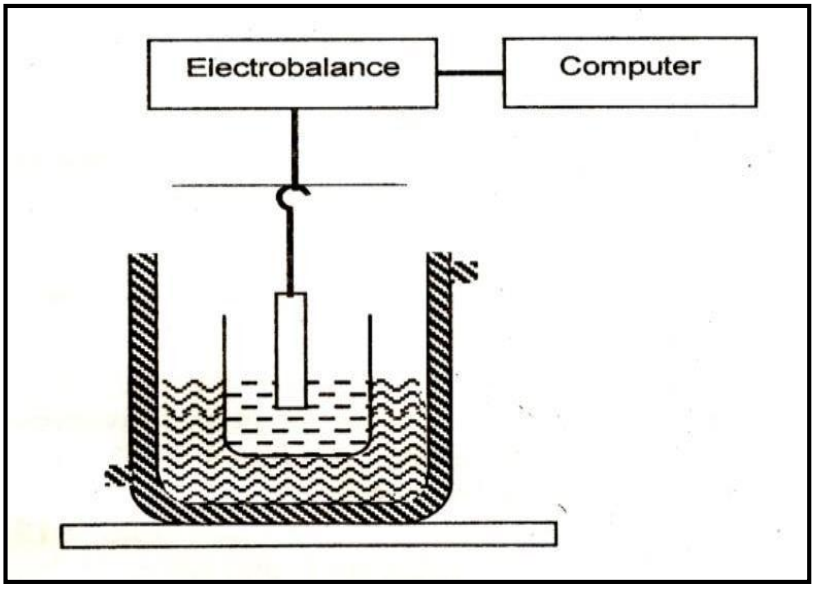

Figure-10: **Modified Wilhelmy Plate.**

2. Modified surface tensiometer

This method utilizes the forces required to separate a polymer from freshly excised rabbit stomach tissue as measure for bioadhesion. This method uses modified surface tensiometer. This method is particularly suitablefor studying insoluble polymers. In this method, a section of the tissue having the mucus side exposed is secured on a weighed glass vial placed in beaker containing USP simulated gastric fluid. Another section of the same tissue is placed over a rubber stopper again with mucus side exposed and secured with a vial cap anda small quantity of polymer is placed between the two mucosal tissues. The force required to detach the polymer from the tissue is then recorded.

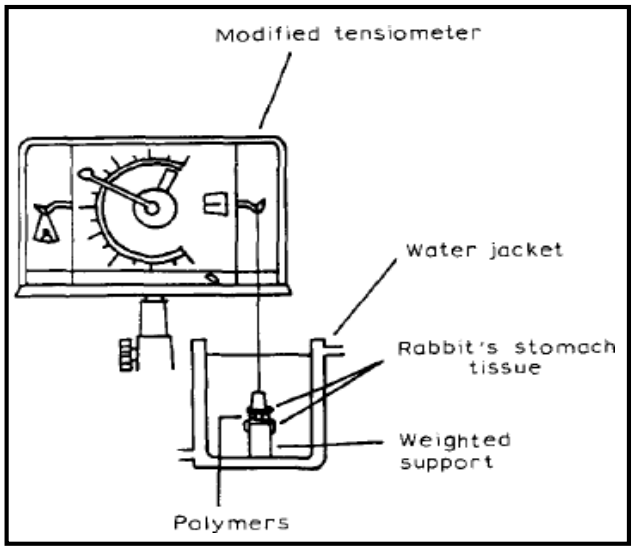

Figure-11: Modified Surface Tensiometer.

3. *In vitro* release rate profile

Various apparatus has been designed to study *in vitro* release rate profile of drug from bioadhesive drug delivery systems. To find out the mechanism of drug release from Losartan potassium buccal tablets, the *in vitro* release data was treated with different kinetic models, namely zero order, first order, Higuchi and Korsemeyer-Peppas. A criterion for selecting the most appropriate model was based on goodness of fit, high regression coefficient value.

b) *IN VIVO* METHODS

Chang et al studied *in vivo* gastric-transit using male Sprague-Dawley rats by administering capsules of test polymer. A capsule containing solid controller test material was surgically inserted into the stomach of anesthetized rats. The rates were permitted to awaken and at suitable times the animals were sacrificed. The small intestine well examined for polymer.

Irritancy Test

Both drug and excipients may act as irritants. There is the need for careful evaluation of the potential for mucosal irritation with new delivery systems and their components. Place et al applied aqueous formulations to the buccal mucosa of normal volunteers to asses for the irritancy potential of drugs. They found that the noninvasive system was capable of assessing the contact irritation of drugs under varying formulation conditions. It is important during preformulation studies that all additives should be critically evaluated for their irritancy, allergenic response and effect on the natural microbial flora.

c. CHEMICAL EVALUATIONS

The chemical standards of formulations, in to establish that drug is present in dose required to attain therapeutic level and the same level will be maintained during its storage life or shelf-life.

a) Assay for Drug Content

This involves extraction of drug in suitable solvent from buccal tablet and determination of drug content in extract. The drug content should be in close proximity to be labeled or desired dose of drug.

b) Drug-Excipient Interaction Studies

By use of various available spectrophotometric and chromatographic methods the incompatibility of drug with excipients or within different excipients can be detected. These interaction studies involves gross physical examination for organoleptic properties (discoloration, mal odour development, precipitation, polymorphism, development of bad taste), infrared spectra of drug versus formation IR spectra in same conditions and thin layer chromatography (TLC). Similarly, incompatibility in accelerated conditions or during storage must be thoroughly scrutinized.

c) Accelerated Stability Studies

This involves placing the formulation in accelerated conditions of temperature and humidity in presence of air and determining the drug content at suitable intervals of time. By the data so obtained two conclusions can be drawn. Firstly, the shelf-life of formulation can be established, secondly any incompatibility within formulation, if present can be detected.

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