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A ROLE OF NATURAL POLYMERS IN MUCOADHESIVE BUCCAL TABLETS

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ABSTRACT

The oral administration of pharmaceutical compound has been several troubles such as irregular and variable absorption, GI intolerance, decreased bioavailability; pre-systemic exclusion has provoked the consideration of other possible route for administration. For example, it is complicated to continue the medicament at the preferred site so that it can be absorbed, distributed and metabolized effortlessly. Buccal route is well vascularised connected to the heart directly via the internal jugular vein. So, it has been mainly examined as a possible site for controlled drug delivery in a variety of chronic systemic therapies. Based on existing considerate of physiological and biochemical features of absorption and metabolism of various biotechnologically formed drugs. The two major mechanisms concerned for the penetration of different substances include passive transmission intra cellular or Trans cellular (crossing through the cell membranes with a lipid domain and a polar) whereas the passive diffusion intercellular or para cellular (passing around between the cells) carrier intervened transport and pinocytosis. Bioadhesive polymers plays key role in buccal drug delivery systems of drugs. Bioadhesive Polymers are also used in matrix devices in which the drug is surrounded in the polymer matrix, which manages the level of discharge of drugs. The Bioadhesive was resulting from the need to limit drugs at a definite site in the body. Significantly at the absorption site, enhance the degree of drug absorption is restricted by the residence time of the drug. The buccal tablet designed in a reservoir type system comprises a cavity for the additives and drug separate from the adhesive. Mucoadhesive polymers are the significant constituent in the improvement of sustained release or controlled mucoadhesive buccal delivery systems.

Keywords: Ivabradine Hydrochloride, Buccal tablet, Mucoadhesive, Natural Polymers.

1. INTRODUCTION:

The oral administration of pharmaceutical compound has been several troubles such as irregular and variable absorption, GI intolerance, decreased bioavailability; pre-systemic exclusion has provoked the consideration of other possible route for administration. For example, it is complicated to continue the medicament at the preferred site so that it can be absorbed, distributed and metabolized effortlessly. This restriction leads to the enhancement of other routes of administration[1]. Furthermore, the modern enlargement of a large amount of drugs has strengthened the examination of mucoadhesive buccal drug delivery system. Mucoadhesion is a feature of bioadhesion that was resultant from the necessitate to limit drugs at an assured mucosal site in the body. The most significant purpose in mucoadhesion consist of increasing of residence time, drug

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targeting, sustained or controlled releasing, decreasing of adverse effects, long-term drug delivery and minimizing of the first pass effect[2]. The oral cavity can be categorized into sublingual, buccal, and gingival regions have effective drug delivery can be attained. Absorption of therapeutic agents from the oral cavity offers a straight entry of such agents into the general circulation, thus evades the gastrointestinal degradation and first-pass hepatic metabolism.[3-5]

1.1 Necessitate of Mucoadhesive DDS:

The buccal mucosa is very helpful route for the healing of either systemic or local therapies prevails over the problem of conservative administration routes. Buccal route is well vascularised connected to the heart directly via the internal jugular vein. So, it has been mainly examined as a possible site for controlled drug delivery in a variety of chronic systemic therapies. Bioadhesive polymers have delayed contact time with the tissues and can particularly develop the act of several drugs[6]. Within the oral mucosal cavity, delivery of drugs is classified into three categories:

- Sublingual drug delivery, which is general administration of drugs during the mucosal membranes lining the floor of the mouth.
- Buccal drug delivery, which is drug delivery through the mucosal membranes lining the cheeks (buccal mucosa).
- Local drug delivery, which is drug administration into the oral cavity.

Adhesion is well termed as the ‘‘fixing” of two surfaces to one another. ‘Bioadhesion’ as a process is simply described as the binding of a synthetic or natural polymer at least one biological tissue, are held together for an unlimited phase of time by interfacial forces[7, 8].

1.2 Mucoadhesive Buccal Drug Delivery System

In the foremost case, involves drug absorption through the mucosal barrier, to attain the systemic circulation whereas the second cases to attain a site-specific release of the drug on the mucosa[9]. Buccal region is that part of the mouth surrounded anteriorly and diagonally by the cheeks and the lips, medially and posteriorly by the gums and teeth, and over and under by the signs of the mucosa from the cheeks and lips to the gums.

Based on existing considerate of physiological and biochemical features of absorption and metabolism of various biotechnologically formed drugs; they cannot be delivered efficiently through the conservative oral route. Since, after oral administration numerous drugs are subjected to pre-systemic clearance wide in liver which repeatedly leads to a lack of considerable relationship between absorption, bioavailability and membrane permeability. The permeable part buccal mucosa and sublingual mucosa is thinner part and which there is elevated surface area and blood flow; it is a reasonable site when a fast onset of action is required.

Mucoadhesive agents are utilized to sustain and long-lasting contact of the formulation with the absorption site while infiltration enhancers progress the drug permeation crosswise mucosa (trans-mucosal delivery) or into innermost layers of the epithelium (mucosal delivery). The enzyme inhibitors preferably guard the drug from the deprivation through mucosal enzymes[10-12].

It should acquire definite physicochemical characteristics together with abundant hydrogen bond-forming groups, hydrophilicity, epithelial tissue, flexibility for interpenetration with visco-elastic properties and mucus**.** Buccal drug delivery system is well acknowledged since it is enclosing some advantages.[13]

1.3 Anatomic and Physiologic Features of Oral cavity

The buccal mucosal region provides an smart route of drug administration for systemic drug delivery. The mucosa has been an affluent blood supply and it is moderately permeable.

The oral mucosal cavity presents a surface area of about 100 cm^2

The thickness of buccal mucosa is considered to be 500-800 µm

Three dissimilar types of oral cavity are known

- Lining mucosa
- Masticatory mucosa
- Specialized mucosa

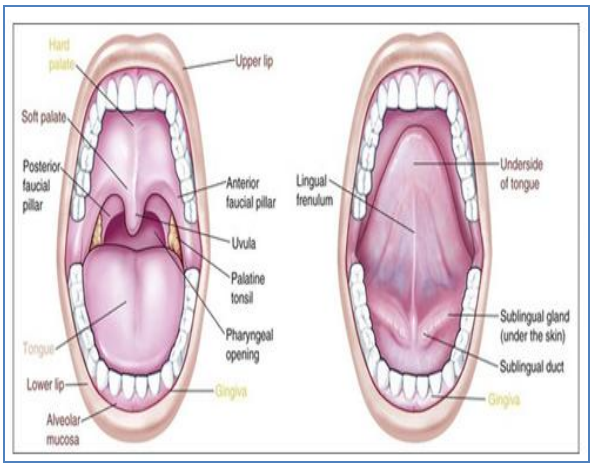

Figure 1: Schematic diagrams of oral mucosa

1.4 Structure of mucosa

The oral mucosa consists of three distinctive layers and it's consists of an outer most layer of stratified squamous epithelium. They are epithelium, connective tissues and basement membrane. Buccal cavity is lined with epithelium; supported by basement membrane which intern supported by connective tissues.

The epithelium acts as a defensive layer for the primary tissues and it is divided into[].

- Surface which is Non-keratinized lining of the soft palate, surface, tongue, lips vestibule and cheeks.
- Hard plate and further non flexible regions Keratinized epithelium which is found in oral cavity.

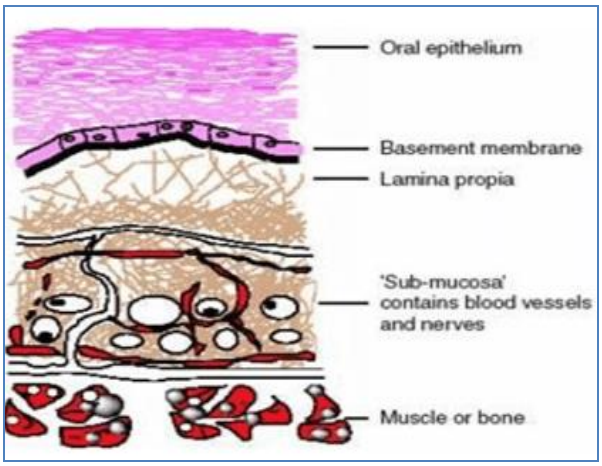

Figure 2: Cross-section of buccal mucosa

The basement membrane also plays a part in channel of materials across the intersection between connective tissues and epithelium forms a distinctive layer and mechanical support. The primary connective tissues offer a lot of the involuntary properties of oral mucosa. The plane which is non keratinized tissue is a fraction of buccal epithelium which is penetrated by connective tissues that are conical in form and tall. These tissues, which are also referred to as consists of smooth muscles, blood vessels, the lamina propria, collagen fibers and a supporting layer of connective tissues. Lamina propria is followed by the sub mucosa (Fig.1.2).

The peripheral carotid artery supplies to the oral mucosa. The foremost resources of blood supply to the lining of the cheek in the buccal cavity are resulting from the buccal artery, a few terminal branches of the infra orbital artery, the posterior alveolar artery, and the facial artery.[18-21]

1.4.1 Permeability

The buccal mucosal epithelium is generally fairly intermediate and leaky between that of the intestinal and epidermis mucosa. The permeability of oral buccal mucosa is 4to 4000 times larger than that of the skinIn common, the permeability of the oral mucosa decreases in the order of sublingual greater than buccal and buccal greater than palatal.[22]

1.4.2Environment

The intercellular ground substance surrounded by the oral epithelium called mucus which covers the whole oral cavity[23]. Mucus primarily contain approximately 0.5–5% of water insoluble glycoproteins, 95–99% water and several other components in small quantities, such as nucleic acids, free proteins (1%), electrolytes, and enzymes[24]. Mucus composition can differ based on the origin of the mucus secretion in the body[25]. The volume of salivary secretion per day is between 0.5 to 2 liters and plays a key role to hydrate oral mucosal dosage forms[26].

1.5 Barriers to penetration across buccal mucosa

About quarter to one third of the epithelium consists of barrier which is primarily helpful for penetration. The barriers which hinder the extent and rate of drug absorption through the buccal mucosa are,

- Membrane coating granules
- Basement membrane
- Mucus
- Saliva

1.5.1 Membrane coating granules or cored granules

Membrane-coating granulesare which extrudes into the intercellular area of both non-keratinized and keratinized oral epithelium and are liable for avoiding the transmucosal penetration. The keratinized epithelium includes membrane coating granules of lamellar lipid stacks, while the non-keratinized epithelium composed of membrane coating granules that are of non lamellar. The membrane coating granule lipids of keratinized epithelia include ceramides, glucosylceramides, other non polar lipids and sphingomyelin, yet for non-keratinized epithelia, the main membrane coating granule lipid components are glycosphingolipids, cholesterol and cholesterol esters.[27]

1.5.2 Basement membrane

Although a permanent layer of extracellular materials and plays a role in limiting the passage of materials between the connective tissue, basal layer of epithelium of the lamina propria and sub mucosa. The exterior layer of the oral epithelium signifies barrier to some larger molecules across the oral mucosal[28].

1.5.3 Mucus

1. Mucus is a bulky fluid composed mostly of inorganic salts and mucins that are suspended in water mucins are of huge family primarily comprises glycosylated proteins composed of oligosaccharide chains[29] having approximately 12–25% protein, 70–80% carbohydrate, 5% ester sulphate]. [30, 31] The thick sugar coating offers substantial water holding capacity for mucins and also makes them divergent to proteolysis, which may be vital in maintaining mucosal barrier.

Table.1 The composition of oral mucosa

Mucosa	Structure	Epithelial cell Thickness(µm)	Residence Time	Blood flow rate (ml/min/cm^2)
Buccal mucosa	Non-keratinized Epithelium	500-600	+	2.40
Sublingual mucosa	Non-keratinized Epithelium	100-200	--	0.97
Gingival mucosa	Keratinized Epithelium	200	+	1.47
Palatal mucosa	Keratinized Epithelium	250	--	0.89

1.5.4 Saliva

Saliva is complex fluid containing inorganic and organic materials. Saliva consists of high molecular weight mucin named MG1 which offers lubrication, retains hydration, contemplate protective molecules such as limit the attachment of microorganisms and secretary immunoglobulin's by connecting to the surface of oral cavity. Secretion is caused by three pairs of major glands, sub-maxillary, parotid, and the sublingual glands which are located in outer surface of the oral cavity in insignificant salivary glands located in tissues lining nearly all of the oral cavity. The surface of

oral cavity is continually bathed with a flow of saliva roughly 1litre/day by salivary glands. The pH of saliva varies from 6.5 to 7.5. It has a low buffering capacity and principal buffer of saliva being bicarbonate. [32, 33]

1.6 Routes of Drug Transport across the buccal mucosa

The two major mechanisms concerned for the penetration of different substances include passive transmission intra cellular or Trans cellular (crossing through the cell membranes with a lipid domain and a polar) whereas the passive diffusion intercellular or para cellular (passing around between the cells) carrier intervened transport and pinocytosis[34]. The convey of drugs permeation across the buccal mucosa has been principally involved in passive diffusion carrier intervened transport plays a little role up to various extent.

- Passive diffusion
- Carrier mediated transport
- Endocytosis

The drug transport crosswise the buccal epithelium may follow dissimilar pathways but their choice depends upon the character of the permeant, i.e. the lipophilicity, general charge and molecular geometry. The majority of the drug compounds disperse through the buccal membrane by simple Fickian diffusion or passive diffusion.

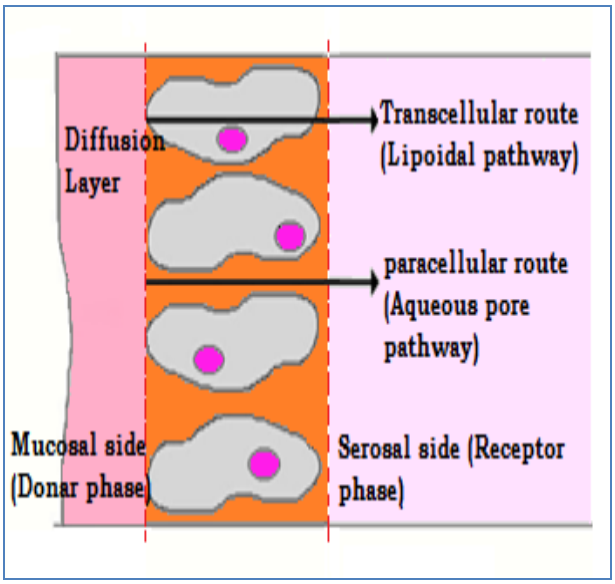

Figure 3: Drug absorption pathway across buccal mucosa

1.7 Improvement of membrane Permeation

The buccal mucosal membrane shows inadequate permeability depending on site of administration, physicochemical properties of the drug, nature of the vehicle, and symbolizes a key limitation in the improvement of a buccal adhesive drug delivery system[39]. Furthermore, the short exposure time and the limited absorptive area due to the cleaning effect of saliva can reduce absorption competence even more. 'Permeation enhancers' are used to permeate the drugs across buccal epithelial barriers. Though, proper penetration enhancers are used to develop the drug permeability[36].

1.7.1 Mechanisms of action for permeation enhancers

- Changing mucus rheology
- Rising the fluidity of lipid bilayer membrane
- Acting on the constituents at rigid junctions
- By surmounting the enzymatic barrier
- Increasing the thermodynamic activity of drugs[28]

1.8 Theories of Muco/Bioadhesion via polymer attachment

Theories of adhesion are a intricated process and it has been offered to clarify the forces that underpin bioadhesion implicated[45].

1.8.1 The electronic theory

This theory relies on the hypothesis that the two materials approach together, electron transfer takes place in an effort to balance Fermi charge levels. This electron transport between the mucus results in the formation of attractive forces within this an electronic binary layer of charges at the mucus line, with sub of the two resources.

1.8.2 The adsorption theory

According to this model, the mucoadhesive bond between the mucus substrate and adhesive polymer is due to hydrophobic interactions, Vander Waals interactions and hydrogen bonding. These forces are fragile, but

the huge numbers of connections generate the mucoadhesive bond.

1.8.3 The wetting theory

This theory is primarily valid to low viscosity or liquid bioadhesive systems reasonably spreadability and wettability of polymers have been revealed to show best linkage to human endothelial cells.

1.8.4 The diffusion theory

This theory explains inter diffusion of mucoadhesive polymer chains into the glycoprotein chain of the mucus layer. This method is motivated by concentration gradients and is influenced by the existing chain lengths and their mobilities. The intensity of interpenetration depends on the time of contact and the dispersion coefficient. Adequate depth of penetration generates a partially stable adhesive bond.

1.8.5 The fracture theory

It relates the force for the polymer essential for the disconnection of two involved surfaces from the mucus to the potency of their after adhesion. This presumes that the breakdown of the adhesive bond occurs at the interface. It has been found that work rupture is larger when the system filaments are longer or the level of cross-linking is reduced.

1.9 Basic components of bioadhesive buccal drug delivery system

- ❖ Drug components
- ❖ Bioadhesive polymers
- ❖ Backing layer membrane
- ❖ Adhesive substances

2. BIOADHESIVE POLYMERS:

Bioadhesive polymers plays key role in buccal drug delivery systems of drugs. Bioadhesive Polymers are also used in matrix devices in which the drug is surrounded in the polymer matrix, which manages the level of discharge of drugs.

2.1 Criteria should be followed in polymer selection

- It should form a tough non covalent bond with the epithelial surface/mucin.
- It should have a narrow distribution and high molecular weight.
- It should be well-matched with the biological mucus membrane

2.2 Backing layer membrane

It is also one of the substances which offer unidirectional drug release flow to buccal mucosa. It averts the drug to be suspended in saliva and hence swallowed evading the contact between saliva and drug. The substance employed for backing membrane must be impermeable to drugs, inert and penetration enhancers. Eg: magnesium stearate, ethyl cellulose, Cellophane-325, Polyglassine paper.

2.3 Adhesive substances

Bioadhesive are the materials that are competent of interrelating with the biological matters and being holding them or maintained on them collectively for unlimited phase of time. The frequently used bioadhesive substances are gelatin, HPMC, Carbomers, HPC, polycarbophil, sodium alginate, etc.

3. FACTORS AFFECTING BIOADHESIVE BUCCAL DRUG DELIVERY SYSTEM:

Bioadhesive features are a part of both the mucoadhesive polymer and the medium in which then polymer will exist in.

3.1 Polymer related factors

- Molecular weight
- Concentration of active polymer
- Elasticity of polymer chains
- inflammation

3.2 Environment related factors

- pH of polymer - substrate interface
- Applied strength
- Initial contact time

3.3 Physiological variables factors

- Mucin turns over
- Disease state

3.4 Polymer related factors

- **Molecular weight**

It required for successful bioadhesion is at least 100 000 dalton molecular weight[32].

- **Concentration of active polymer**

In more concentrated polymer system, away from the finest level, though, the bioadhesive potency drops considerably since the coiled molecules turned into divided from the medium so that the sequences obtainable for interpenetration becomes restricted.

- **Flexibility of polymer chains**

Chain flexibility is critical for entanglement and interpenetration with the mucus. In common, flexibility and mobility of polymers can be linked to their diffusion coefficients and viscosities, where the maximum elasticity of a bioadhesive polymer causes elevated diffusion to the mucus membrane. [32]

- **Swelling/Hydration**

Hydration characteristics are linked to the mucoadhesive itself and its surroundings. Swelling depends on the polymer concentration, the presence of water and ionic strength. Throughout the energetic procedure of mucoadhesion, advanced mucoadhesion *in-vitro* occurs with optimum water content. Over hydration effects in the creation of a wet greasy mucilage without adhesion. [51]

4. MUCOADHESIVE DRUG DELIVERY SYSTEM:

Bioadhesive in drug delivery have newly achieved attention among pharmaceutical scientists of supporting dosage form residence time as well as increasing relationship of contact with different absorptive membranes of the biological system [35]. The mucoadhesive drug delivery system may comprise of the following[56]

- Bucoadhesive Delivery system
- Vaginal Delivery system
- Sublingual Delivery system
- Rectal Delivery system
- Nasal Delivery system
- Gastro Intestinal Delivery system
- Ocular Delivery system

4.1 Use of Buccal Adhesive Preparations

The Bioadhesive was resulting from the need to limit drugs at a definite site in the body. Significantly at the absorption site, enhance the degree of drug absorption is restricted by the residence time of the drug. The mucus layer, which covers the epithelial surface, has various roles.

- Protective role
- Barrier role
- Adhesion role
- Lubrication Role

5. FORMULATION DESIGN -GENERAL CONSIDERATION:

Buccoadhesive drug delivery systems with the size 1–3 cm^2 and a day by day dose of 25 mg or lessare suitable. The common deliberation in buccal dosage form design incorporates:

- Physiological aspects
- Pathological aspects
- Pharmacological aspects
- Pharmaceutical aspects[36]

5.1 Physiological aspects

Earlier to the scheming of buccoadhesive dosage form physiological factors such as surface of buccal mucosa, consequence of saliva, breadth of the mucus layer, its turn over time, and other ecological factors are to be measured. Saliva has certain enzymes (carbohydrases, phosphatases, esterases) that may degrade a few drugs. Though saliva secretion assists automatic swallowing of saliva, the dissolution of drug also affects its bioavailability. These disadvantages can be evaded by mounting unidirectional release systems with backing layer. This perception may also results in enhanced drug bioavailability[39].

5.2 Pathological aspects

Several diseases can affect the width of the epithelium, resulting in the modification of the barrier property of the mucosa. Mucus properties are inclined with a few diseases or treatments may also influence the discharge of the saliva as well as mucus. If any alterations at the mucosal surface due to the pathological conditions, which cause difficulties to the

bioadhesive device be retention at site of application. Therefore, accepting the nature of the mucosa under significant disease condition is required for developing an efficient buccal drug delivery system[40].

5.3 Pharmacological aspects

In case of systemic circulation buccal dosage form is planned and in local therapy of oral mucosa. The dosage form can be exaggerated mostly due to the drug distinctiveness, at the treated site and target site of action (periodontal pocket, gingival, teeth, buccal mucosa or systemic). For the healing of oral diseases, the residence time and the local concentration of the drug in the mucosa are vital consideration. For systemic effect, the highest amount of drug transported across the buccal mucosa into the circulatory system is a determinant of dosage forms. [38]

5.4 Pharmaceutical aspects

The liberation of core from the dosage form can be delayed by its solubility in saliva. The absorption of feebly water-soluble drugs can be improved by solubilizing the drug in cyclodextrin and administered via buccal route. The morphological characters, physicochemical characteristics of the drug all influence the absorption and desirable drug release[62]. In case of dosage forms, for increasing the acceptability and effectiveness, various excipients may be included. A variety of permeation enhancers raise permeability of the buccal mucosa. Enzyme inhibitors may be incorporated in the buccal dosage forms to avoid enzyme degradation and pH modifiers may be integrated in order to momentarily alter the microenvironment at the application site for improved drug absorption.

6. DESIGN OF MUCOADHESIVE BUCCAL DOSAGE FORM:

- **Matrix type buccal system**

The buccal tablet designed in a matrix formation includes drug, additives and adhesive substance mixed collectively.

- **Reservoir type buccal system**

The buccal tablet designed in a reservoir type system comprises a cavity for the additives and drug separate from the adhesive. A resistant backing layer membrane is applied to manage the path of drug delivery; to decrease tablet disintegration and deformation while in the mouth; and to avoid drug loss. Moreover, the buccal tablet formulation can be constructed to endure least degradation in the mouth, or can be considered to suspend instantly.

6.1 Mucoadhesive buccal dosage forms

- **Single layer device**

A single layer release device with multidirectional drug release, this type of buccal dosage form experience from important drug loss due to swallowing.

- **Double-layered device**

Double-layered release device in which a resistant backing layer is overlay on top of the drug-loaded bioadhesive layer, avoiding drug loss from the top surface of the dosage form and creating a double-layered device into the oral cavity.

- **Unidirectional device**

It is a unidirectional release device, because the drug is discharged only from the side next to the buccal mucosa from which drug loss is least. This can be accomplished by coating every face of the buccal dosage form, apart from the one that is in contact with the mucosa.

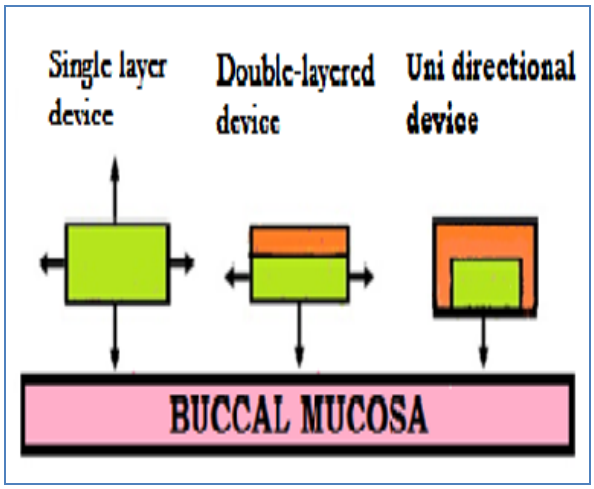

Figure 5: Design of mucoadhesive buccal dosage forms

7. MUCOADHESIVE POLYMERS:

Mucoadhesive polymers are the significant constituent in the improvement of sustained release or controlled mucoadhesive buccal delivery systems. Bioadhesive polymers which remains on to the epithelial/mucin surface are efficient facilitates retention of dosage form and lead to considerable improvement of oral drug delivery. Bioadhesive formulations are frequently water soluble and when in a dry form which in turn leads to a tough interface by attracting water from the biological surface[40].

7.1 Ideal characteristics:

- The polymers should have non-irritant, non-toxic to the mucous membrane and non-absorbable from the GI tract.
- Should possess good visco-elastic properties and biocompatible pH.
- Should possess sufficient mechanical strength and adhere quickly to buccal mucosa.
- Should possess bioadhesive ranges of tensile, shear and peel strengths.
- Should prove bioadhesive properties in both hydrous and anhydrous state.

7.2 Classification mucoadhesive polymers

- **Based on source**

○ **Natural:** e.g. Gelatin, Chitosan, Agarose, Hyaluronic acid, various gums like xanthan, guar, hakea, carragenan, Pectin, gellan, and sodium alginate.

○ **Synthetic:** e.g. Cellulose derivatives like HEC, CMC, HPC, HPMC, Thiolated CMC, MC, and SCMC.

- **Based on aqueous solubility**

○ **Water soluble:** e.g. HPC, HPMC, CP, SCMC, HEC sodium alginate.

○ **Water insoluble:** e.g. EC, Chitosan.

- **Based on charge**

○ **Cationic:** e.g. Dextran, Chitosan, Dimethylaminoethyl (DEAE).

○ **Anionic:** e.g. CMC, xanthan gum, CP, pectin, sodium alginate, SCMC.

○ **Non-ionic:** e.g. Poly (ethylene oxide), PVA, HPC.

- **Based on potential bioadhesive forces**

○ **Covalent bond:** e.g. Cyanoacrylate.

○ **Hydrogen bond:** e.g. CP, PVA, Acrylates.

○ **Electro-static interaction:** e.g. Chitosan[9]

7.3 Natural polysaccharide

The natural polymersprovide certain precise advantages over artificial polymers such as biodegrability, non-toxic, biocompatibility, easy availability, pollution-free processing and multiple functions in a dosage form. Several innate polysaccharide materials have been effectively used in sustained-release or controlled release of drugs, such as gum and mucilage. Mucilage and Gums are two important classes of polysaccharides. Mucilages and gums hold an intricate polymeric structure for the preparation of mucoadhesive formulations. [37]

8. MARKETED PRODUCTS OF MUCOADHESIVE BUCCAL DOSAGE FORMS:

Table 2: Mucoadhesive buccal dosage forms (Market available)

Drug Name	Manufacturers Name/Brand name
Nitro-glycerine	Glenmark (nitrogard)
Miconazole	BioAlliancePharmaSA (loramyc)
Methyl testosterone	Bayer Schering Pharma (Oreton methyl)
Hydrocortisone	Auden Mckenzie (corlan pellets)
Fentanyl	Cephalon (fentora CII)
Insulin buccal delivery	Shreyalife sciences (Oral Recosulin)
Omeprazole	Astrazeneca (Prilosec)
Vitamin-C	Zhongnuo (CSPC)
Clotrimazole	Lotrimin, Mycelex
Testosterone	Actient pharmaceuticals (Striant)

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