A REVIEW: MUCOSAL DRUG DELIVER

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ABSTRACT:

Drug actions can be improved with a new drug delivery system, such as an Mucoadhesive Drug Delivery System. The system remains very close to the absorption tissues, the mucous membranes, releasing the drug into the action area resulting in an improvement in both local and system effects. There are many routes of the mucoadhesive drug delivery system, the oral route is very old and is preferred by the patient for easy taking. However the per oral line has errors such as hepatic first pass metabolism and enzymatic deterioration in GIT which is a barrier to the absorption of many proteins and groups of drug peptides. The mucosa of the oral cavity presents a formidable barrier to drug entry, and one way to increase drug delivery is to use adhesive-form forms and the mucosa is rich in blood and enters. The buccal mucosa is best suited for a bioadhesion system due to its smooth and stable surface and accessibility. Mucoadhesion can be obtained using mucoadhesive polymers. There are various types of mucoadhesive polymers available. Liquids are designed to achieve continuous drug release.

KEY WORDS: Mucoadhesive, Oral Mucosa, Bioadhesive.

INTRODUCTION:

Oral mucosal drug delivery system is categorized into two routes, i.e. buccal and sublingual. Buccal cavity is commanly apply for drug administration through orally and in sublingual route, it is an widely useful for quickest onset of action as in case of chest pain. The buccal mucosa composes the inner cheek, and this preparations are placed in the mouth in between the upper gums and cheek to treat local and systemic cases. The buccal route provides one of the powerful routes for large, hydrophilic and unstable proteins, different carbohydrates, as well as small drug molecules. The oral cavity has been used as a site for local and systemic drug delivery.

HISTORICAL BACKGROUND

from the recent 40 years, the concept of mucoadhesion has giving the application in prolonging the places time, as well as controlled release effect of different bioadhesive dosage forms through various mucosal routes of administration. The preparations depends on the mucoadhesive drug delivery system that have shown the increased bioavailability of different drugs. The use of different mucoadhesive polymers have reached the

notable interest in preparing the sustained release dosage form, extended release dosage formas and also prolonged release dosage

forms. The mucoadhesive drug delivery giving considerable absorption and increased bioavailability of dosage forms due to the greater surface area and greater blood flow in the mouth cavities. The delivery over the mucus membrane giving different advantages over other types of drug delivery routes i.e., avoid the hepatic first pass metabolism ,destroyed of drugs by different gastrointestinal enzymes and also intestinal flora . For the intended mucoadhesive potential of the mucoadhesive dosage forms, there are different mucoadhesive polymers that can are to be incorporated .These polymers are naturally or synthetically prepared macromolecules which are able of attaching to the mucosal inner surfaces. From last recent three decades, the use of different mucoadhesive polymers has reached a considerable interest in the field of pharmaceutical technology. Nowadays, the use of mucoadhesive polymers has been received as an important plan to prolong the residence time and to progress the restrict effects of drug delivery systems on different mucus membranes of a biological system .

Limitations

• The drugs having astringent taste shall not be preapared.

• The drugs having inflammation in oral mucosa, produces sensitive reactions and defects of teeth cannot be preapared.

• If preparation contains antimicrobial agents, effects the natural microbes in the mucous cavity.

• The patient senses tenderness in eating, drinking and speaking.

• Only the drugs which are absorbed by passive diffusion

• can be administered by mucosal route.

• Drugs that are unstable at mucous pH shall not be administered by

• oral route.

• Sometimes, the destruction of moisture sensitive drugs may take

• site by saliva [16].

Advantages:

Drugs administration through oral route giving several edges

- Simple route of administration.
- Stoppage of treatment is simple.
- Allow localization of drug to the mucosal cavity for a extended period of time.
- Can be administered to insensible patients.
- Offers an outstanding route, for the systemic delivery of drugs with great first pass metabolism, hence giving a greater bioavailability of drugs.

- A remarkable decrease in dose can be reaches hence, decreasing dose related adverse effects.
- Drugs which are unreliable in the acidic conditions are degradation by enzymatic or alkaline conditions of intestine can be administered by this route.
- Drugs that are low bioavailability *through* the oral route can be administered smoothly.
- It gives a passive system of drug absorption and does not need any activation.
- The existence of saliva secure relatively high amount of water for drug dissolution and different in case of rectal and transdermal routes.
- Systemic absorption is quick.

Disadvantages

• little crossable of the mucosal layer as compared to the sublingual layer.

• The total surface area of buccal cavity available for drug absorption is 170 cm2, out of which ~50 cm represents non-keratinized tissues, consisting the buccal cavity.

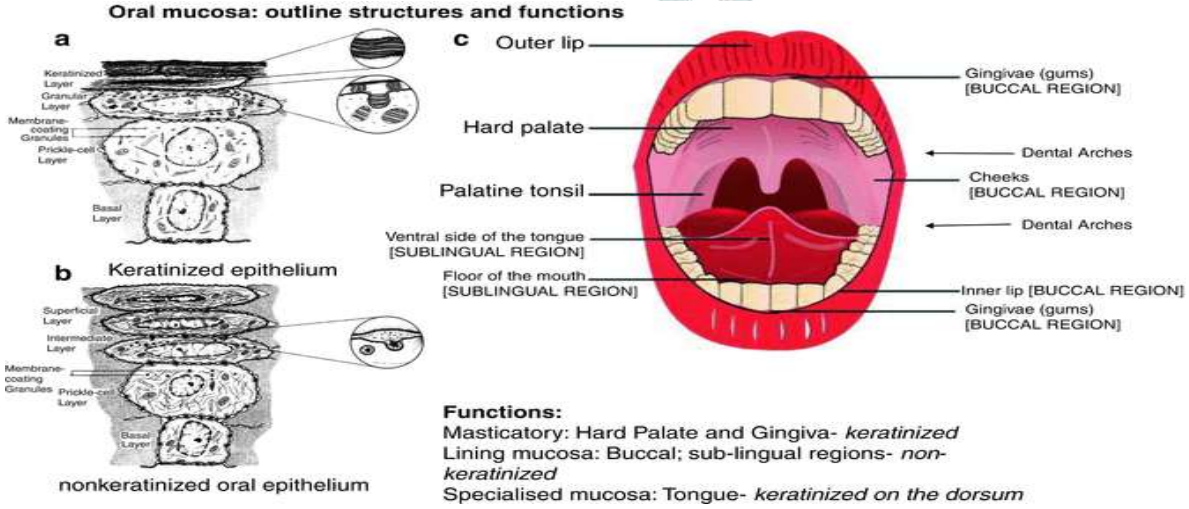
• the repeated secretion of saliva (0.5-2 l/day) results in successive dilution of the drug.

• Swallowing of saliva can also certainly lead to the release of dissolved drug and, eventually, the involuntary removal of the dosage form [17].

• These are a number of the problems that are related to current buccal drug delivery system.

Structure: The oral cavit is made up of cheeks, lips, rigid and smooth palates and tongue. The main difference between the oral mucosa and skin as compared with the gastrointestinal (GI) tract lining recline in the organization of the different epithelia. Lastly, a single layer of cells forms the simple epithelial tissue, the skin and the oral cavity have various layers of cells with different degrees of differentiation. In oral cavity, the masticatory mucosa has a keratinized or cornified epithelium, and enfold the stress-enduring parts such as the gingival and the hard palate, giving chemical resisting and mechanical force. It is categorized into four layers:

keratinized layer, granular layer, prickle-cell layer, and basal layer



(Figure 1). FIG. 1: STRUCTURE OF THE MUCOSA

The edges of mucosa mucosa, which giving elasticity, in variance, is made up of non-cornified surface epithelial tissue enfold the remaining regions together with the lips, cheeks, mouth, and soft palate. It also can be further categorized into superficial layers, intermediate layers, prickle-cell layers, and basal layers. The third type of mouth is the specialized mucosa containing the both keratinized and non-keratinized layers, and is narrowing to the dorsal part of the tongue. The intercellular spaces hold water, lipids, and proteins.

Physiological Importance of Mucins and Saliva: The mucosal tissues are further enfold with mucus, which is negatively charged, and hold high glycoproteins termed mucins. These are belief to provide appreciably to the visco-elastic nature of saliva, and keep a pH in between 5.8–7.4. Mucin contains of a protein core, which is rich in O-glycosylated serine and threonine, carrying many helix-breaking proline residues. The salivary glands secreting mucus also produce saliva, which provides shielding to the soft tissues from chemical and mechanical rubbing. The average thickness of the salivary layer in the mouth difer from 0.07 to 0.10 mm. Sustained sticking of the dosage form (tablet, patch) to the mucosal layer is an important first step in successful buccal delivery of drug. The mucus plays an important role during this mucoadhesive process by buccal drug delivery systems. The interconnection between the mucus and mucoadhesive polymers commanly used in most dosage forms can be describe by theories -

Theories of Adhesion:

There are six general theories of adhesion, which have been used for the examination of mucoadhesion.[15-17, 19]

A. The Electronic Theory

The proposition of the electronic theory depends on the assumption that the bioadhesive material and the target biological material have various electronic structures. On this theory, when the two materials comes in contact with each other, there is an electron transfer occurs in balance level, results into the formation of a double layer of electric charge at the bioadhesive-biological material boundry. The Bioadhesive force is assumed to be due to attractive forces over this electrical double layer.

B. The Adsorption Theory

The adsorption theory states that the bioadhesive bond formed between an adhesive substrate and tissue or mucosa is due to Vander Waal's forces. Although these forces are individually weak, the sheer number of interactions can as a whole produce intense adhesive strength. This theory is the most widely accepted theory of adhesion.

The adsorption theory express the addition of adhesives depends on hydrogen bonding and van der Waals' forces. It has been suggest that these forces are the main suppporter to the adhesive interaction. A subsection of this, the chemisorption theory, states that an interaction across the interface occurs as a result of strong covalent bonding.

C. The Wetting Theory

The capacity of bioadhesives or mucus to extend and expand constant contact with its corresponding substrate is one important factor in bond formation. The wetting theory is essentially applied to liquid systems and examine surface and interfacial energies. It require the ability of a liquid to transmit spontaneously onto a surface as a prerequisite for the development of adhesion. The affinity of a liquid for a surface can be found using techniques such as contact angle, measure the contact angle of the liquid on the surface, with the general rule that lower the contact angle, greater will be the affinity of the liquid to the solid. The spreading Coefficient (S_{AB}) can be calculated from the surface energies of the solid and liquids using the equation:

$$S_{AB} = \gamma_B - \gamma_A - \gamma_{AB} \quad \text{.....(1)}$$

Where γ_A is the surface tension (energy) of the liquid A, γ_B is the surface energy of the solid B and γ_{AB} is the interfacial energy between the solid and liquid. S_{AB} should be positive for the liquid to spread spontaneously over the solid. The work of adhesion (W_A) represents the energy required to separate the two phases and is given by:

$$W_A = \gamma_B - \gamma_A - \gamma_{AB} \quad \text{.....(2)}$$

Greater the individual surface energies of the solid and liquid relative to the interfacial energy, the greater the work of adhesion.

D. The Diffusion Theory

The concept that interpenetration and entanglement of bioadhesive polymer chains and mucus polymer chain produce semi-permanent adhesive bonds is supported by the diffusion theory. It is believed that bond strength increases with the degree of penetration of the polymer chains into the mucus layer.

Penetration of polymer chain into the mucus network and vice versa, is dependent on concentration gradient and diffusion coefficients. Obviously, any cross- linking of either component tends to hinder interpenetration, but small chain ends can still become entangled. It has not been examine correctly how much interpenetration is required to make an effective bioadhesive bond, but it is assumed to be in the range in between 0.2-0.5 µm.

For occurring diffusion, it is important of solubility of one component in the other, the bioadhesive and mucus

membrane should be of identical chemical structure. Therefore, the strongest bioadhesive bond should form between biomaterials whose solubility parameters are similar to those of the target mucus glycoproteins. Thus, the diffusion theory assums that,for bioadhesion process, interpenetration and entanglement of polymer chains are responsible.

E. The mechanical theory

The mechanical theory states that adhesion starts from an interconnecting of a liquid adhesive into deformity on a rough surface. Although, rough surfaces also supply an raised surface area available for interaction ahead with an increased viscoelastic and plastic dissolution of energy during joint failure.

F. The Fracture Theory

This theory varry a little from the other five in that it relates the adhesive strength to the forces required for the detachment of the two involved surfaces after adhesion. This states that the defeat of the adhesive bond occurs at the boundry surface. Although, defeat normally produced at the fragile component, which is typically a cohesive defeat within one of the adhering surfaces.

Principles of Drug Movement Through The Buccal Mucosa:

Like transdermal drug movement, drugs contacting the oral mucosa must penetrate the epithelial barrier in order to gain access to systemic circulation. The epithelium represents the primary barrier to compounds, though unlike the epidermis, there is no *stratum corneum* present in the oral cavity. Two pathways achieve drug transport across the oral mucosa.[10]

- The paracellular (between cells) route, consisting of hydrophilic intercellular spaces and
- The transcellular route, through pores in the cell membranes or penetration through the lipid bilayers of cell membranes.

Hydrophilic compounds and large or highly polar molecules follow paracellular transport, whereas transcellular transport through the lipid bilayer is followed by lipophilic drugs and by small molecules through epithelial membrane pores. Buccal patches can effectively distribute a wide range of drug classes (e.g. Opioids, antifungals, hormones) with varying physiochemical properties (lipophilic, hydrophilic, 200- 10,000 Da) and at different concentrations[10]. However, small lipophilic molecules active at low plasma concentration (e. g.

potent) are the easiest to deliver. As with transdermal drug delivery studies, methods to increase overall drug permeability and to make a wider selection of compounds available and practical for buccal delivery are being investigated.

Bioadhesion:

'Bioadhesion' mention to any bond formation between two biological side or a bond between a biological and a synthetic side. In the example of bioadhesive drug delivery systems, the word bioadhesion is usually used to express the adhesion between polymers, it may be synthetic or natural and soft tissues (i.e. mucosa). The actual adhesive bond may form with either the cell layer, a mucus layer or a combination of the two. In occurence of bonds form between mucus and polymer, the word mucoadhesion is used identically with bioadhesion. In general, bioadhesion is an word used to express adhesive interconnection with any biological or biologically obtain substances and mucoadhesion is used only while expressing a bond implying mucus or a mucosal surface.[15]

Bioadhesion is the eventin between two materials, which are grip together for longer periods of time by interfacial forces. It is generally called as bioadhesion when interaction occurs between polymer and epithelial surface; mucoadhesion when occurs with the mucus layer covering a tissue. Generally bioadhesion is greater than the mucoadhesion. Although, these two words looking to be used interchangeably. It is interesting that the interaction between the layers adsorbed from whole saliva resembles the one previously reported between layers of adsorbed gastric mucin, which points to a strong contribution to the interaction of high molecular weight glycoproteins.[17]

It is doubtful that the mucoadhesive process will be the same in each case study. In the case of adhesion generally, two steps in the adhesive operation have been observed, which have been approved to express the interaction between mucoadhesive materials and a mucous membrane (Figure 3).[17]

- Step 1: Contact step: An constant contact (wetting) produced between the mucoadhesive and mucous layers.
- Step 2: Consolidation step: different physicochemical interactions produced to integrate andstrengthen the adhesive joint, resulting to longer adhesion.

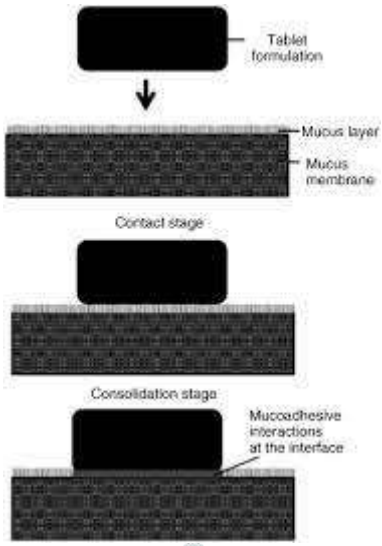


Figure 1.3 The two stages in mucoadhesion Step 1: Contact stage

The layers of Mucoadhesive and the layers of mucosa originally have to produce a close contact with each other. In some exceptions, these two surfaces can be readily lead together, e.g. placing and holding a delivery system within the oral cavity or vagina or depositing a particle within the respiratory tract. The forces promoting adsorption of small formulations such as microparticles may be sufficient to hold them on the mucosal surfaces until displaced by mucus, or cell, turnover. Adsorption will produced as a result of a decrease in surface free energy as two layers are lost and a new interface is produced.

If a particle address a surface it will undergo both repulsive forces and attractive forces. Repulsive forces arise from osmotic pressure effects as a result of the interpenetration of the electrical double layers, stearic effects and also electrostatic interactions when the surface and particle carry the same charge. Attractive forces occuring from Vander Waal's interactions, surface energy effects and electrostatic interactions if the surface and particles brings opposite charges itself. The respective power of these opposing forces will differ depending on the nature of the particle, the aqueous conditions and the gap between the particle and surface. For example, the smaller the particles, the greater the surface-area-to-volume ratio and therefore the greater the attractive forces.[18]

Step 2: Consolidation step

It has been assummed that if potent or longer adhesion is required, for example with larger formulations exposed to stresses such as blinking or mouth movements, then a second 'consolidation' stage is required. Mucoadhesive materials attach mostly to dry solid tops as long as they are start up by the presence of moisture. Moisture will successfully plasticize the system permitting Mucoadhesive molecules to enhance free, confirm to shape of the surface, and bond mostly by weaker Vander Waal's forces and hydrogen bonding. To reach potent adhesion, a change in the physical properties of the mucosa will be needed if not, it will readily fail on application of displace the stress[18].

Previous Work Done on Buccal Mucoadhesive Drug Delivery System

In 2007, Ramana et al. designed and evaluated the buccal mucoadhesive drug delivery systems of Metoprolol Tartrate using the mucoadhesive polymers i.e., Carbopol-934, hydroxy methyl propyl cellulose, hydroxyl ethyl cellulose and sodium carboxy methyl cellulose. The best mucoadhesive performance and in-vitro drug release profile were exhibited by tablets containing hydroxyethyl cellulose and Carbopol-934 in 1:2 [42]

In 2008, Kolli et al. developed the buccal mucoadhesive patch of Prochlorperazine using various concentrations of HPMC E15 and Polyester backing membrane. They concluded that the formulation containing 2500 mg of HPMC E15 and 375 µl of Propylene glycol was the optimized formulation after evaluating it in-vitro as well as ex-vivo studies [43].

In 2010, Chaudhary et al. developed the mucoadhesive buccal patches of Methotrexate. They used the backing membrane prepared by ethyl cellulose (5%) in mixture of acetone and isopropyl alcohol (60:40). Glycerol (5%) was added as plasticizer. The mucoadhesive polymers used were Sodium Alginate, carbopol-934, sodium carboxy methyl cellulose and polyvinyl pyrrolidine. The cumulative drug release of the formulation containing sodium alginate with a secondary polymer was found in order of Sodium alginate >carbopol-934 >Sodium Carboxy methyl cellulose >polyvinyl pyrroliidine at the end of 8 hours. The formulation containing Sodium Alginate (800 mg), Carbopol-934 (200 mg), glycerol (10%) and water (30 ml) waste optimized formulation [44].

In 2010, another study was also conducted by Velmurugan et al. They formulated the buccal tablets of Piroxicam using HPMC K4M and Carbopol-934 in different ratios. In this study H3 formulation comprising of piroxicam and HPMC K4M (1:3) show edoptimum drug release and satisfactory bioadhesive properties [45].

In 2011, Naga Raju et al. formulated the buccal tablets of Metoprolol\ Tartrate using different Mucoadhesive polymers such as Carbopol 934, Sodium alginate and HPMC K4M in combination. The prepared tablets were evaluated for bioadhesive strength and in-vitro drug release. In-vitro bioadhesive strength and in-vitro release studies showed that formulation containing 1:1.25 ratio of drug and polymer (Carbopol-934 and HPMC K4M) combination showed optimum bioadhesive and exhibited optimum drug release (77.33 ± 0.23) [46].

In 2011, the further study was conducted by Deshmukh et al. They formulated Propranolol hydrochloride buccal mucoadhesive gel using Natural Mucoadhesive agent obtained from the Fruits of Ficuscarica L.The formulation F1, F3, F4 and F5 showed Fickian diffusion,formulation F2 showed Anomalous (non-Fickian) diffusion [47].

In 2012, Mishra et al. formulated the buccal patches of Simvastatin.The buccal patchs were prepared from 1% eudragit-RS100 and variable amount of different polymer composite, PVP, PVA, HPMC and EC.The formulation containing eudragit-RS100 and PVP(1:1) showed themaximum and faster release [48].

In 2013, Sandhya et al. formulated buccal films of Ketorolac Tromethamine. These films were prepared by

polymers like HPMC K100M, HPMC E15, HPMC E50, Eudragit RLPO and developed by solvent casting method. Formulation F5 (HPMC E15-Polysorbate - Eudragit RLPO) exhibited best mucoadhesive performance and matrix controlled release. Swelling behaviour and duration of mucoadhesion are critical factors in the selection of satisfactory formulation [49].

In 2013, the further study was conducted on Formulation and invitro evaluation of Losartan Potassium mucoadhesive buccal tablets by Velmurugan et al. They used mucoadhesive polymers such as Carbopol - 940P, pectin, sodium CMC, Sodium alginate, HPMC K4M, HPMC K15M and HPMC K100M in alone and in combination as release retarding agent to prolong the drug release and to avoid first pass metabolism. Ex-vivo mucoadhesive strength, ex vivo residence time and in-vitro release studies showed that formulation F10 (sodium alginate and HPMC K100M) containing 1:1.25 ratio of drug and polymer combination showed satisfactory bioadhesive and exhibited optimum drug release (91.33 % after 12 hrs)

Future Perspectives

A buccal adhesive system offers untold advantages in terms of economy, accessibility, administration, withdrawal and patient compliance. Research scientists are now looking out the conventional polymers for novel drug transport systems. From the recent years, pharmaceutical experts are finding various methods to develop buccal adhesive dosage forms and to improve the bioavailability of less orally

bioavailable drugs. It is found that the second generation mucoadhesive polymer having great potential. Micro particulate or nanoparticulate systems of less bioavailable drugs are being designing in the bio adhesive systems are showing much more satisfactory results as compared to conventional buccal drug delivery systems

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Commercially Available Oral Mucoadhesive Drug Delivery Systems				
Drug	**Dosage form**	**Type of release**	**Product name**	**Manufacturer**
Zolpidem	Spray	fast	Zolpimist	NovaDel
Buprenorphine HCl and Naloxone	Tablet	fast	Sulbutex	Reckitt Benckiser
Chlorhexidine digluconate	Oromucosal gel	Controlled	Corsodyl gel	GalaxoSmith Kline
Hydrocortisone sodium succinate	Oromucosal pallets	Controlled	Corlan pellets	Celltech

Table 3: Some commercially available oral mucoadhesive drug delivery system

Conclusion

The drug delivery systems designed with the aim to enhance patient compliance and satisfaction is more cheif than ever.Therefore great work is going on to develop novel dosage forms to assure increased patient demands of more sutaible dosage forms. Oral mucosal delivery provide a suitable way of dosing medication, not only to specific populations with consume difficulties, but also to the broad population. Mucoadhesive dosage forms provide extend contact time at the site of attachment, having more patient compliance and are profit making as compare to other dosage forms. The use of mucoadhesive polymers has made this delivery system of controlled release application. There are important development have been reached in the field of mucoadhesives, but there are still many take exception to are not been sought out in this field. However, a lot of research has been done of this drug delivery system. But, these novel mucoadhesive formulations require much more research work to appreciate how to deliver drug clinically for the medicament of both systemic and topical diseases

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