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A REVIEW ON MUCOADHESIVE DRUG DELIVERY SYSTEM WITH SPECIAL EMPHASIS ON BUCCAL ROUTE

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ABSTRACT

The two major problems in the development of new drugs are low aqueous solubility and low oral bioavailability. Although, drug delivery via oral route is most preferred for years but it also has some drawbacks. Various techniques for improving the solubility have been developed, however the success of these techniques depends on the physical and chemical properties of the drug under development. In recent years, mucoadhesive drug delivery gained high popularity in comparison to other routes of drug delivery as it can circumvent the drawbacks of conventional delivery system such as first pass metabolism, enzymatic degradation, GI toxicity of some drugs, instability in acidic or alkaline environment and poor bioavailability. Various mucoadhesive dosage forms have been developed recently including tablets, patches, films, ointments, gels etc. The objective of current review is to provide a comprehensive overview of mucoadhesive drug delivery including the mechanism and theories behind mucoadhesion, factors affecting mucoadhesion, different dosage forms, polymers used in mucoadhesive formulations, characterization techniques, marketed products and current scenario & future challenges.There are many advantages of mucoadhesive buccal drug delivery system that made this a novel drug delivery system for the local as well as systemic delivery of various drugs. The main advantage of this drug delivery system is that it prolongs the residence time of the dosage form at the site of application. Due to the high blood supply and relatively high permeability of the buccal mucosa, the buccal cavity is the best option for both local as well as systemic delivery of various drugs. The term bioadhesion can be defined as a phenomenon of interfacial molecular attractive forces in the midst layer of surface of a biological membrane and the natural or synthetic polymers, which allows the polymer to adhere the surface of that membrane for an extended as well as prolonged period

of time. In this review we have discussed the various types of mucoadhesive dosage forms along with a brief knowledge about the various types of mucoadhesive polymers.

KEYWORDS: Mucoadhesive, Solubility, Conventional delivery system, Permeability.

INTRODUCTION

The focus of pharmaceutical research is being steadily shifted from the development of new chemical entities to the development of novel drug delivery system (NDDS) of existing drug molecule to maximize their effective in terms of therapeutic action and patent protection (Berressem, 1999, Das, 2000). The development of NDDS has been made possible by the various compatible polymers to modify the release pattern of drug. In the recent years the interest is growing to develop a drug delivery system with the use of a mucoadhesive polymer that will attach to related tissue or to the surface coating of the tissue for the targeting various absorptive mucosa such as ocular, nasal, pulmonary, buccal, vaginal etc. This system of drug delivery is called as mucoadhesive drug delivery system (Shemalty 2006).

This system has advantages like;

- Prolongs the residence time of the dosage form at the site of absorption.
- Due to an increased residence time it enhances absorption and hence the therapeutic efficacy of the drug.
- Excellent accessibility.
- Rapid absorption because of enormous blood supply and good blood flow rates.
- Increase in drug bioavailability due to first pass metabolism avoidance.
- Drug is protected from degradation in the acidic environment in the gastrointestinal tract.
- Improved patient compliance- ease of drug administration.
- Faster onset of action is achieved due to mucosal surface (pranshu Tangri).

Within the oral mucosal cavity, delivery of drugs is classified into three categories:

(i) Sublingual delivery, which is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth,

(ii) Buccal delivery, which is drug administration through the mucosal membranes lining the cheeks (buccal mucosa), and

(iii) Local delivery, which is drug delivery into the oral cavity.

I. Overview of the Oral Mucosa

A. Structure

The oral mucosa is composed of an outermost layer of stratified squamous epithelium below this lies a basement membrane, a lamina propria followed by the submucosa as the innermost layer. The epithelium is similar to stratified squamous epithelia found in the rest of the body in that it has a mitotically active basal cell layer, advancing through a number of differentiating intermediate layers to the superficial layers, where cells are shed from the surface of the epithelium [(4)]. The epithelium of the buccal mucosa is about 40-50 cell layers thick, while that of the sublingual epithelium contains somewhat fewer. The epithelial cells increase in size and become flatter as they travel from the basal layers to the superficial layers.

The oral mucosal thickness varies depending on the site: the buccal mucosa measures at 500-800 μm, while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue, and the gingiva measure at about 100-200 μm. The composition of the epithelium also varies depending on the site in the oral cavity. The mucosa of areas subject to mechanical stress (the gingiva and hard palate) is keratinized similar to the epidermis. The mucosa of the soft palate, the sublingual, and the buccal regions, however, are not keratinized [(5)]. The keratinized epithelia contain neutral lipids like ceramides and acylceramides which have been associated with the barrier function. These epithelia are relatively impermeable to water. In contrast, non-keratinized epithelia, such as the floor of the mouth and the buccal epithelia do not contain acylceramides and only have small amounts of ceramide. They also contain small amounts of neutral but polar lipids, mainly cholesterol sulfate and glucosyl ceramides. These epithelia have been found to be considerably more permeable to water than keratinized epithelia.

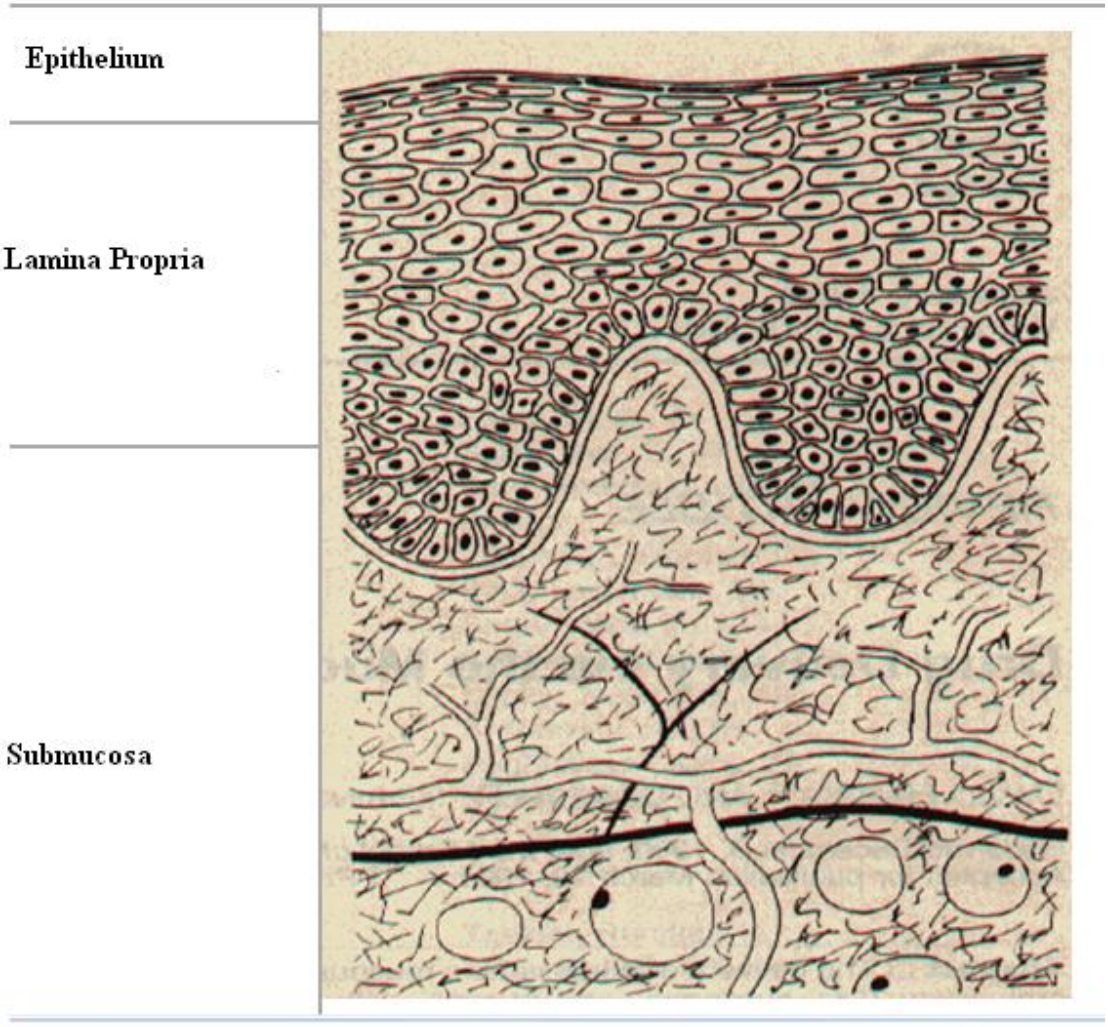

Figure 1.1Structure of the oral mucosa.

B. Permeability

The oral mucosa in general is somewhat leaky epithelia intermediate between that of the epidermis and intestinal mucosa. It is estimated that the permeability of the buccal mucosa is 4-4000 times greater than that of the skin. An indicative by the wide range in this reported value, there are considerable differences in permeability between different regions of the oral cavity because of the diverse structures and functions of the different oral mucosa. In general, the permeabilities of the oral mucosa decrease in the order of sublingual greater than buccal, and buccal greater than palatal. This rank order is based on the relative thickness and degree of keratinization of these tissues, with the sublingual mucosa being relatively thin and non-keratinized, the buccal thicker and non-keratinized, and the palatal intermediate in thickness but keratinized.

C. Environment

The cells of the oral epithelia are surrounded by an intercellular ground substance, mucus, the principle components of which are complexes made up of proteins and carbohydrates. These complexes may be free of association or some maybe attached to certain regions on the cell surfaces. This matrix may actually play a role in cell-cell adhesion, as well as acting as a lubricant, allowing cells to move relative to one another. Along the same lines; the mucus is also believed to play a role in bioadhesion of mucoadhesive drug delivery systems.In stratified squamous epithelia found elsewhere in the body, mucus is synthesized by specialized mucus secreting cells like the goblet cells, however in the oral mucosa, mucus is secreted by the major and minor salivary glands as part of saliva.Up to 70% of the total mucin found in saliva is contributed by the minor salivary glands. At physiological pH the mucus network carries a negative charge (due to the sialic acid and sulfate residues) which may play a role in mucoadhesion.

II. Buccal Routes of Drug Absorption

There are two permeation pathways for passive drug transport across the oral mucosa: paracellular and transcellular routes. Permeants can use these two routes simultaneously, but one route is usually preferred over the other depending on the physicochemical properties of the diffusant. Since the intercellular spaces and cytoplasm are hydrophilic in character, lipophilic compounds would have low solubilities in this environment. The cell membrane, however, is rather lipophilic in nature and hydrophilic solutes will have difficulty permeating through the cell membrane due to a low partition coefficient. Therefore, the intercellular spaces pose as the major barrier to permeation of lipophilic compounds and the cell membrane acts as the major transport barrier for hydrophilic compounds. Since the oral epithelium is stratified, solute permeation may involve a combination of these two routes. The route that predominates, however, is generally the one that provides the least amount of hindrance to passage.

III. Buccal Mucosa as a Site for Drug Delivery

There are three different categories of drug delivery within the oral cavity (i.e., sublingual, buccal, and local drug delivery). Selecting one over another is mainly based on anatomical and permeability differences that exist among the various oral mucosal sites. The sublingual mucosa is relatively permeable, giving rapid absorption and acceptable bioavailability of many drugs, and is convenient, accessible, and generally well accepted.The sublingual route

is by far the most widely studied of these routes. Sublingual dosage forms are of two different designs, those composed of rapidly disintegrating tablets, and those consisting of soft gelatin capsules filled with liquid drug. Such systems create a very high drug concentration in the sublingual region before they are systemically absorbed across the mucosa. The buccal mucosa is considerably less permeable than the sublingual area, and is generally not able to provide the rapid absorption and good bioavailability seen with sublingual administration. Local delivery to tissues of the oral cavity has a number of applications, including the treatment of toothaches, periodontal disease, bacterial and fungal infections, aphthous and dental stomatitis, and in facilitating tooth movement with prostaglandins.

Anatomy & Physiology of Oral Mucosa

Oral mucosal locale is adhesive in nature and goes about as a lubricant, which is permitting the cells to move comparative with each other with less grating. There are four sites are as follows:

1) Buccal cavity2) The sublingual area 3) The palate4) Gingival region

It's utilized for drug organization. The utilized site for drug organization of the four-locale referenced over that is the buccal cavity. The anatomic site for drug organization between the cheek and gingival is known as the buccal mucosa. The oral cavity is made out of three layers. The primary layer is the delineated squamous Epithelium, under this layer is basement membrane film. The storm cellular layer overlies the lamina propriety and submucosa. The constitution of the epithelium inside the various locales of the oral cavity show divergence. The epithelium in the slot sense of taste, buccal and sublingual region isn't keratinized, subsequently not containing ceramides and acyl ceramides which are related with giving a boundary work. The mucosa of the buccal & sublingual locale has just modest quantities of ceramide and subsequently more porous. When contrasted with different locales of the oral cavity. A layer of bodily fluid is available on the outer layer of the cells.

This assumes a significant part in cell to cell attachment, oral grease just as mucoadhesion of mucoadhesive drug delivery frameworks. The buccal region has a field of smooth and somewhat stable surface, which is appropriate for arrangement of a retentive framework. For buccal drug delivery, grip to the oral mucosa licenses not just the closeness of contact and the chance of further developed drug retention yet in addition the capacity of accomplish an ideal home time at the site of organization.

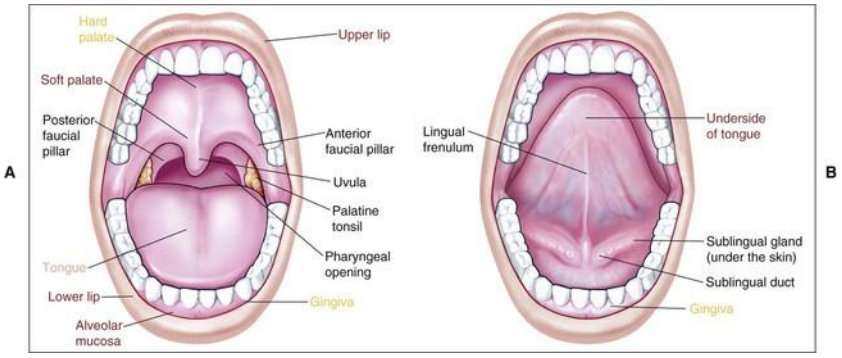

Fig. 2: Overview of Oral Mucosa.

Mucoadhesive Polymers Used In the Oral Cavity

Desired characteristics

The polymer-related factors have been briefly discussedin the previous section. Generally, some of thenecessary structural characteristics for bioadhesivepolymers include strong hydrogen bonding groups,strong anionic or cationic charges, high molecularweight, chain flexibility, and surface energy propertiesfavoring spreading on a mucus layer.

Classification

In general, adhesive polymers can be classifiedas synthetic vs. natural, water-soluble vs. waterinsoluble,and charged vs. uncharged polymers.Examples of the recent polymers classified in thesecategories are listed in Table 1. Natural bioadhesivemacromolecules share similar structural propertieswith the synthetic polymers. They are generally linearpolymers with high molecular weight, contain a substantialnumber of hydrophilic, negatively chargedfunctional groups, and form three-dimensional expanded networks. In the class of syntheticpolymers, poly (acrylic acid), cellulose ester derivatives,and polymethacrylate derivatives are the currentchoices. Chitosan and examples of various gums,such as guar and hakea (from Hakea gibbosa), areclassified as semi-natural/natural bioadhesive polymers.Poly (acrylic acid), a linear or random polymer,and polycarbophil, a swellable polymer, representwater-soluble and water-insoluble polymers, respectively.The charged polymers are divided into cationicand anionic polymers, such as chitosan and polycarbophil,respectively, while hydroxypropylcellulose isan example of uncharged bioadhesive polymers.

Table 1: Mucoadhesive polymers in buccal delivery.

Criteria	Categories	Examples
Source	Semi-natural/natural	Agarose, chitosan, gelatin, Hyaluronic acid Various gums (guar, Xanthum, gellan, carragenan,

		pectin, and sodium alginate)
	Synthetic	*Cellulose derivatives* [CMC, sodium CMC, HEC, HPC, HPMC, MC] *Poly(acrylic-acid)-based polymers* [CP, PC, PAA, Polyacrylates] *Others :*Poly(N-2-hydroxypropyl methacrylamide) (PHPMAm), polyoxyethylene,PVA, PVP
Aqueous solubility	Water-soluble	CP, HEC, HPC (waterb38 8C), HPMC (cold water), PAA, sodium CMC, sodium alginate
	Water-insoluble	Chitosan (soluble in dilute aqueous acids), EC, PC
Charge	Cationic	Aminodextran, chitosan, trimethylated chitosan
	Anionic	Chitosan-EDTA, CP, CMC, pectin, PAA, PC, sodium alginate, sodium CMC, Xanthum gum
	Non-ionic	Hydroxyethyl starch, HPC, poly(ethylene oxide)
Potential bioadhesive forces	Covalent	Cyanoacrylate
	Hydrogen bond	Acrylates [hydroxylated methacrylate, poly(methacrylic acid)], CP, PC, PVA
	Electrostatic interaction	Chitosan

There are the various drugs are given through buccal route. The list is below as

Table 2: List of Drugs investigated for buccal delivery.

Acetretin	Acyclovir
Arecoline	Buprenorphine
Buserelin	Buspirone
Captropril	Carbamazepine
Carvedilol	Diltiazem
Danazol	Ergotamine
Diclofenac sodium	Lidocaine

Fentanyl	Metoprolol tartrate
Ketoprofen	Pilocarpine
Metronidazole	Prednisolone
Nifedipine	Propranolol
Pentazocine	Theophylline
Pindolol	verapamile
Silymarin	testosterone

Mechanisms of Mucoadhesion

The mechanism of mucoadhesion is generally divided into two steps: the contact stage and the consolidation stage. The first stage is characterized by the contact between the mucoadhesive and the mucus membrane, with spreading and swelling of the formulation, initiating its deep contact with the mucus layer. In the consolidation step, the mucoadhesive materials are activated by the presence of moisture. Moisture plasticizes the system, allowing the mucoadhesive molecules to break free and to link up by weak vander Waals and hydrogen bonds.

Theories of Mucoadhesion

The process of mucoadhesion is mainly based on formation of two types of bond between bio adhesive system and mucus membrane and they are:

Chemical bond

It may include covalent bonds, Weak secondary bonds, ionic bond and hydrogen bond etc.

Mechanical bond

This bond can be arising from the physical connection between two surfaces. It is similar to that of the interlocking system.

On the basis of nature and strength of these two kinds of bonds, there are following five theories of mucoadhesion that are been postulated.

Electronic theory

According to the electronic theory, there is difference in the electronic structure of mucin surfaces and bio adhesive system which results in attaining a electronic gradient. Due to presence this electronic structure difference, the transfer of electrons occurs in these two systems (mucin surface and bioadhesive system) when they come in contact with each. As a result of this electron transfer there is the formation of an electronic bi-layer at the interface

of the two surfaces. This interfacial bi-layer exerts an attractive force in the interface of two surfaces that may produce an effective mucoadhesion.

Adsorption theory

This theory describes the involvement of both type of chemical bond, that is, primary and secondary bond in the bio adhesion mechanism. Both the surface that is mucin and drug delivery system has their own surface energy. When they come in contact, the adhesion occurs due to the surface energy and results in the formation of two types of chemical bond. Primary chemical bond such as covalent bond, which is strong in nature, thus produces a permanent bonding, whereas secondary chemical bond involves Vander-Waals forces, hydrophobic interaction and hydrogen bonding, which are weak in nature, thus produces a semi-permanent bond.

Wetting theory

This theory is based on the mechanism of spreadability of drug dosage form across the biological layer. This theory is mainly applicable to liquids or low viscous mucoadhesive system. According to this theory, the active components penetrate in to the surface irregularities and gets harden it that finally results in mucoadhesion.

Diffusion interlocking theory

This theory describes the involvement of a mechanical bond between the polymeric chain of drug delivery system and polymeric chain of mucus membrane, that is, glycol proteins. When two surfaces are in intimate contact, the polymeric chain of drug delivery system penetrates in to the glycoprotein network. According to this theory, the bioadhesion basically depends on the diffusion coefficient of both polymeric chains. The other factors that may influence the inter movement of polymeric chain are molecular weight, cross linking density, chain flexibility, and temperature in order to achieve a good bio adhesion, the bio adhesive medium should have a similar solubility with glycoprotein resulting in effective mucoadhesion.

Mucoadhesive dosage forms for buccal administration

(a) **General considerations in dosage form design**

Physiological aspects:

Constant flow of saliva and mobility of the involved tissues challenge drug delivery to the oral cavity. The residence time of drugs delivered to the oral cavity is typically short, in the range of <5–10 min. Buccal mucoadhesive formulations are expected to overcome this

problem. Bioadhesive polymers offer a means by which a delivery system is attached to the buccal mucosa, and hence, provide substantially longer retention times at the absorption site. They also provide a means to confine and maintain high local concentrations of the drug and/or excipients(s) to a defined, relatively small region of the mucosa in order to minimize loss to other regions and limit potential side effects. The buccal mucosa is a very suitable region for bioadhesive system application because of its smooth and relatively immobile surface, as well as direct accessibility. However, there are some inherent limitations associated with buccal drug delivery, including short residence time, small absorption area, and barrier properties of the buccal mucosa. The size of a buccal dosage form is restricted by the very limited area available for application of the delivery system. This size restriction, in turn, limits the amount of drug that can be incorporated in the dosage forms. In general, a buccal delivery device that is 1–3 cm^2 in size and a drug with a daily dose requirement of 25 mg or less would be preferred. In addition, an ellipsoid shape appears to be most acceptable, and the thickness of buccal delivery devices is usually limited to a few millimeters. The mucus layer covering the buccal mucosa is necessary for bioadhesive systems. Unfortunately, it not only forms a physical barrier to drug permeation, but also prevents long-term bioadhesion and sustained drug release by its short turnover time. Interestingly, the presence of bioadhesive polymers on a mucous membrane might alter the turnover of mucin, since the residence time of mucoadhesive are usually longer than the reported mucin turnover time. Nevertheless, the maximum duration for buccal drug delivery is usually limited to approximately 4–6 h, since meal intake and/or drinking may require dosage form removal.

Pathological aspects:

Many diseases can affect the thickness of the epithelium, resulting in alteration of the barrier property of the mucosa. Some diseases or treatments may also influence the secretion and properties of the mucus, as well as the saliva. Changes at the mucosal surface due to these pathological conditions may complicate the application and retention of a bioadhesive delivery device. Therefore, understanding the nature of the mucosa under relevant disease conditions is necessary for designing an effective buccal delivery system. In addition, drugs with the potential of changing the physiological conditions of the oral cavity may not be suitable for buccal delivery.

Pharmacological aspects:

A buccal dosage form may be designed to deliver a drug to the systemic circulation, or

merely indicated for local therapy of the oral mucosa. Selection of dosage forms is affected by the intended application, target site of action, drug characteristics, and the site to be treated (periodontal pockets, gingival, teeth, buccal mucosa, or systemic).

Pharmaceutical aspects:

Regardless of dosage form types, the drug must be released from the delivery system and subsequently taken up by the oral mucosa. Poor drug solubility in saliva could significantly retard drug release from the dosage form. Cyclodextrin has been used to solubilize and increase the absorption of poorly water-soluble drugs delivered via the buccal mucosa.

(b) Buccal mucoadhesive dosage forms

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.

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