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BUCCAL BIOADHESIVE DRUG DELIVERY SYSTEMS - AN OVERVIEW

Anu P Alex[1], Balaji Sadu[2], G Sushma[1], Bandla Neelima[1]

[1]Talla Padmavathi College of Pharmacy, Warangal, Andhra Pradesh, India.
[2] Dept. of Pharmaceutics, Krishna Teja Pharmacy College, Chadalawada Nagar, Tirupati, Andhra Pradesh, India.

ABSTRACT

Considerable attention has been focused in recent years on the delivery of drugs through the oral mucosa which have a high first pass metabolism or degrade in the gastrointestinal tract. Buccal delivery involves the administration of the desired drug through the buccal mucosal membrane lining of the oral cavity. Unlike oral drug delivery, which presents a hostile environment for drugs, especially proteins and polypeptides, due to acid hydrolysis and the hepatic first-pass effect, the mucosal lining of buccal tissues provides a much milder environment for drug absorption. The effective physiological removal mechanisms of the oral cavity that take the formulation away from the absorption site are the other obstacles that have to be considered. The strategies studied to overcome such obstacles include the employment of new materials that, possibly, combine mucoadhesive, enzyme inhibitory and penetration enhancer properties and the design of innovative drug delivery systems which, besides improving patient compliance, favor a more intimate contact of the drug with the absorption mucosa. This presents a brief description of advantages and limitations of buccal drug delivery and the anatomical structure of oral mucosa, mechanisms of drug permeation followed by current formulation design in line with developments in buccal delivery systems and methodology in evaluating buccal formulations.

Key words: Mucoadhesive Drug Delivery System, Suitable delivery devices, Permeation enhancers, Saliva.

INTRODUCTION

Bioadhesion can be defined as a phenomenon of interfacial molecular attractive forces in the midst of the surfaces of the biological substrate and the natural or synthetic polymers, which allows the polymer to adhere to the biological surface for an extended period of time [1-4]. The buccal region of the oral cavity is an attractive target for administration of the drug of choice. Buccal delivery involves the administration of the desired drug through the buccal mucosal membrane lining of the oral cavity. Because after oral administration many drugs show first-pass metabolism, which leads to a lack significant correlation between membrane permeability, absorption and bioavailability [5].

Difficulties associated with parenteral delivery and poor oral bioavailability provides alternative route for delivery of such drugs. These include routes such as pulmonary, ocular, nasal, rectal, buccal, sublingual, vaginal, and transdermal [6]. Among the varies transmucosal routes the mucosal lining of the oral cavity offers some distinct advantages. It is richly vascularized and more accessible for the administration and removal of a dosage form. Direct access to the systemic circulation through the internal jugular vein bypass drugs from the hepatic first pass metabolism leading to high bioavailability. Other advantages such as low enzymatic activity, suitability for drugs or excipients that mildly and reversibly damages or irritates the mucosa, painless administration, pH modifier in the formulation [7].

Various biopolymers show the bioadhesive properties and have been utilized for various therapeutic purposes in medicine. The bioadhesive polymers can be broadly classified into two groups, namely specific and nonspecific.

The specific bioadhesive polymers (e.g. fimbrinlectins) have the ability to adhere to specific chemical structures within the biological molecules while the nonspecific bioadhesive polymers (e.g.

Corresponding Author :- **Anu P Alex** Email:- annu.p.alex@gmail.com

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polyacrylicacid, cyanoacrylates) have the capability to bind with acid, cyanoacrylates have the capability to bind with both the cell surfaces and the mucosal layer. The sites of drug administration in the oral cavity include the floor of the mouth (sublingual), the gums (gingival) and the inside of the cheeks (buccal) [8].

Advantages of Drug Delivery via the Buccal lining [10,11]

1. Bypass of the gastrointestinal tract and hepatic portal system, increasing the bioavailability of orally administered drugs that otherwise undergo hepatic first-pass metabolism. In addition the drug is protected from degradation due to pH and digestive enzymes of the middle gastrointestinal tract.
2. Improved patient compliance due to the elimination of associated pain with injections; administration of drugs in unconscious or incapacitated patients; convenience of administration as compared to injections or oral medications.
3. Sustained drug delivery.
4. A relatively rapid onset of action can be achieved relative to the oral route, and the formulation can be removed if therapy is required to be discontinued.
5. Increased ease of drug administration.
6. Though less permeable than the sublingual area, the buccal mucosa is well vascularized, and drugs can be rapidly absorbed into the venous system underneath the oral mucosa.
7. In comparison to TDDS, mucosal surfaces do not have a stratum corneum. Thus, the major barrier layer to transdermal drug delivery is not a factor in transmucosal routes of administration. Hence transmucosal systems exhibit a faster initiation and decline of delivery than do transdermal patches.
8. Transmucosal delivery occurs is less variable between patients, resulting in lower inter subject variability as compared to transdermal patches.
9. The large contact surface of the oral cavity contributes to rapid and extensive drug absorption.

Limitations of Buccal Drug Delivery [10,11]

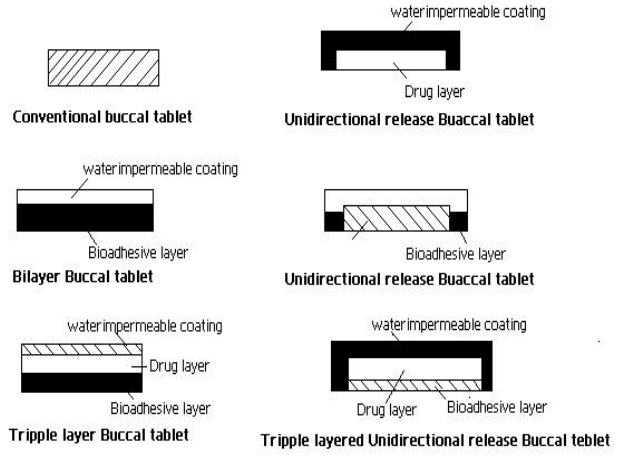
Depending on whether local or systemic action is required the challenges faced while delivering drug via buccal drug delivery can be enumerated as follows.

1. For local action the rapid elimination of drugs due to the flushing action of saliva or the ingestion of foods stuffs may lead to the requirement for frequent dosing.
2. The non-uniform distribution of drugs within saliva on release from a solid or semisolid delivery system could mean that some areas of the oral cavity may not receive effective levels.
3. 3. For both local and systemic action, patient acceptability in terms of taste, irritancy and 'mouth feel' is an issue.

Routes, mechanism and potential role of mucus

In order for a drug to be absorbed across mucosal epithelia it must first diffuse across a layer of mucus, and any associated unstirred water layer. A number of drugs, such as testosterone and the tetracycline antibiotics have been shown to be highly bound to mucus and to exhibit significantly increased diffusion coefficients and lag times in mucus compared to those which are not bound. It is not known how many drugs are similarly affected, although determining the potential role of mucus in limiting absorption is likely to become of increasing importance as the requirement to deliver therapeutics peptides and proteins via mucosal surfaces becomes of greater significance. Selected components of the absorption process are being investigated in isolation to determine the role of mucus. Diffusion of model compounds through native and partially purified mucus collected from different regions are being examined in vitro in the presence and absence of compounds known to reduce or promote structure in the mucus gel. The epithelium of the small intestine regulates some very diverse absorptive and secretory processes. Many of the secretions delivered into the intestinal lumen are synthesized and assembled within the intestinal epithelial cells. These secretions include mucus, which is provided by the goblet cells. In order for a drug (or nutrient) molecule to be absorbed it must diffuse across this layer. Factors that affect the turnover of mucus within the gastrointestinal tract and other mucosal surfaces have not been extensively investigated, although it has recently been shown that amino acids exert differential activity in promoting mucus output. The physiological mechanisms which control this junction are at present unknown, although initial studies suggest the involvement of chloride channels. It is the purpose of work in this area to establish whether amino acids promote mucus secretion at a number of different mucosal epithelia and to examine the effects on mucus output of putative antagonists to amino acids. Implications of these findings for drug delivery will be determined [9].

Fig 1. Different types of Buccal Tablets



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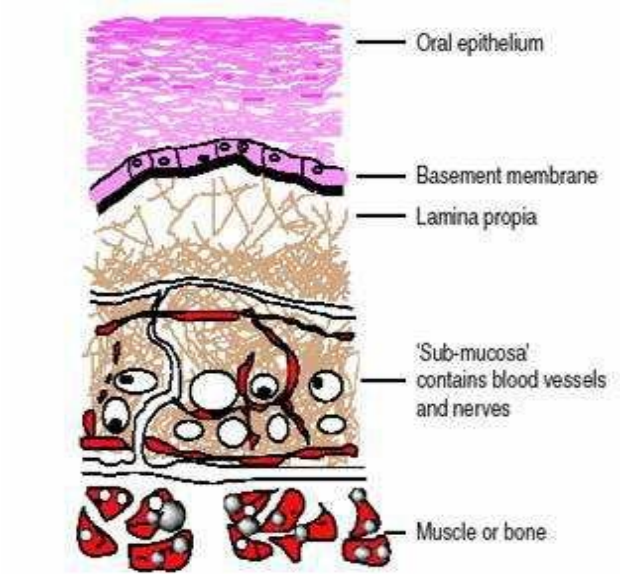
CURRENT STATUS OF BUCCAL BIOADHESIVE DOSAGE FORM

Dosage forms such as mouthwashes, erodible/chewable buccal tablets, and chewing gums allow only a short period of release, and reproducibility of drug absorption is poor. Application of bio adhesive semisolid gels reates considerable technical problems.

Bioadhesive buccal films/patches and tablets are the less developed type of dosage forms. These bio adhesive buccal films/patches and tablets were usually fabricated in different geometry, as shown in following Fig. Type I is a single-layer device, from which drug can be released multidirectionally. Type II device has aim permeable backing layer on top of the drug-loaded bioadhesive layer, and drug loss into oral cavity can be greatly decreased. Type III is a unidirectional release device, from which drug loss will be avoided and drug can penetrate only via the buccal mucosa.

Fig 2. Overview of Buccal Mucosa



A. Structure [1,2]

The oral mucosa is anatomically divided into
1) Epithelium
2) Basement membrane and Connective tissues

1) Epithelium [12,13]

The epithelium consists of approximately 40-50 layers of stratified squamous epithelial cells having thickness 500-800µm [12]. The epithelium of the oral mucosa serves as a protective covering for the tissues and a barrier to the entry of foreign materials. These functions are reflected in the organization of the epithelium in which individual epithelial cells are closely opposed and stratified so there are a number of layers that show a sequence of differentiation. The uppermost layers form a surface that is resistant to physical insuland to penetration by foreign substances [13]. Membrane Coating Granules (MCG) is spherical or oval organelles (100-300 nm in diameter). MCGs discharge their contents into the intercellular space and thus form the permeability barrier. Major MCG lipid components are cholesterol esters, cholesterol and glycosphingolipids [12]. Cells increase in size and become flattened as they progressively mature and migrate from the basal layer towards the epithelial surface, showing increasing levels of protein monofilaments and declining levels of some cytoplasmic organelles [13].

2) Basement Membrane and Connective Tissue [12, 13]

The basement membrane (BM) is a continuous layer of extracellular materials and forms a boundary between the basal layer of epithelium and the connective tissues. This basal complex anchors the epithelium to the connective tissue and supplements the barrier function of the superficial layers of the epithelium to prevent some large molecules from passing the oral mucosa.

The bulk of connective tissue consists of a collagen fiber network, the organization of which determines mechanical stability, resistance to deformation, and extendibility of the tissue. Most likely the connective tissue, along with the basemen membrane, is not considered to influence the diffusion of most compounds of pharmacological interesal though these two regions may limit the movement of some macromolecules and complexes.

B. Environment [14]

The oral cavity is marked by the presence of saliva produced by the salivary glands and mucus which is secreted by the major and minor salivary glands as part of saliva.

Role of Saliva

- Protective fluid for all tissues of the oral cavity. Continuous mineralization / demineralization of the tooth enamel.
- To hydrate oral mucosal dosage forms.

Role of Mucus

- Made up of proteins and carbohydrates. Cell-cell adhesion.
- Lubrication
- Bioadhesion of mucoadhesive drug delivery system

DESIGN OF BUCCAL DOSAGE FORM

Buccal Dosage form can be of

1. **Matrix type:** The buccal formulation designed in a matrix configuration contains drug, adhesive, and additives mixed together.
2. **Reservoir type:** The buccal formulation designed in a reservoir system contains a cavity for the drug and additives separate from the adhesive. An impermeable backing is applied to control the direction of drug

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delivery; to reduce formulation deformation and disintegration while in the mouth; and to prevent drug loss. Additionally, the formulation can be constructed to undergo minimal degradation in the mouth, or can be designed to dissolve almost immediately.

Buccal mucoadhesive dosage forms

Buccal mucoadhesive dosage forms can be categorized into three types based on their geometry.

Type I: A single layer device with multidirectional drug release. This type of dosage form suffers from significant drug loss due to swallowing.

Type II: 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: 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.

MUCOADHESION THEORIES

It is reported that, although the chemical and physical basis of mucoadhesion are not yet well understood, there are six classical theories adapted from studies on the performance of several materials and polymer-polymer adhesion which explain the phenomenon. Contact angle and time plays a major role in mucoadhesion.

Electronic theory

Electronic theory is based on the premise that both mucoadhesive and biological materials possess opposing electrical charges. Thus, when both materials come into contact, they transfer electrons leading to the building of a double electronic layer at the interface, where the attractive forces within this electronic double layer determines the mucoadhesive strength.

1. Adsorption theory

According to the adsorption theory, the mucoadhesive device adheres to the mucus by secondary chemical interactions, such as in Van der Waals and hydrogen bonds, electrostatic attraction or hydrophobic interactions. For example, hydrogen bonds are the prevalent interfacial forces in polymers containing carboxyl groups. Such forces have been considered the most important in the adhesive interaction phenomenon because, although they are individually weak, a great number of interactions can result in an intense global adhesion.

2. Wetting theory

The wetting theory applies to liquid systems which present affinity to the surface in order to spread over it. This affinity can be found by using measuring techniques such as the contact angle. The general rule states that the lower the contact angle then the greater the affinity (Figure 1). The contact angle should be equal or close to zero to provide adequate spread ability.

3. Diffusion theory

Diffusion theory describes the interpenetration of both polymer and mucin chains to a sufficient depth to create a semi-permanent adhesive bond. It is believed that the adhesion force increases with the degree of penetration of the polymer chains. This penetration rate depends on the diffusion coefficient, flexibility and nature of the mucoadhesive chains, mobility and contact time. The adhesion strength for a polymer is reached when the depth of penetration is approximately equivalent to the polymer chain size. In order for diffusion to occur, it is important that the components involved have good mutual solubility, that is, both the bioadhesive and the mucus have similar chemical structures. The greater the structural similarity, the better the mucoadhesive bond.

4. Fracture theory

This is perhaps the most-used theory in studies on the mechanical measurement of mucoadhesion. It analyses the force required to separate two surfaces after adhesion is established (Figure 2). This force, s_{um}, is frequently calculated in tests of resistance to rupture by the ratio of the maximal detachment force, F_m, and the total surface area, A_0, involved in the adhesive interaction. Since the fracture theory is concerned only with the force required to separate the parts, it does not take into account the interpenetration or diffusion of polymer chains. Consequently, it is appropriate for use in the calculations for rigid or semi-rigid bioadhesive materials, in which the polymer chains do not penetrate into the mucus layer.

5. Mechanical theory

Mechanical theory considers adhesion to be due to the filling of the irregularities on a rough surface by a mucoadhesive liquid. Moreover, such roughness increases the interfacial area available to interactions thereby aiding dissipating energy and can be considered the most important phenomenon of the process. Lee, Park, Robinson, 2000 had described that it is unlikely that the mucoadhesion process is the same for all cases and therefore it cannot be described by a single theory. In fact, all theories are relevant to identify the important process variables. The mechanisms governing mucoadhesion are also determined by the intrinsic properties of the formulation and by the environment in which it is applied. Intrinsic factors of the polymer are related to its molecular weight, concentration and chain flexibility. For linear polymers, mucoadhesion increases with molecular weight, but the same relationship does not hold for non-linear polymers. It has been shown that more concentrated

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mucoadhesive dispersions are retained on the mucous membrane for longer periods, as in the case of systems formed by in situ gelification. After application, such systems spread easily, since they present rheological properties of a liquid, but gelify as they come into contact the absorption site, thus preventing their rapid removal. Chain flexibility is critical to consolidate the interpenetration between formulation and mucus. Environment related factors include pH, initial contact time, swelling and physiological variations. The pH can influence the formation of ionizable groups in polymers as well as the formation of charges on the mucus surface. Contact time between mucoadhesive and mucus layer determines the extent of chain interpenetration. Super-hydration of the system can lead to build up of mucilage without adhesion. The thickness of the mucus layer can vary from 50 to 450 µm in the stomach to less than 1µm in the oral cavity. Other physiological variations can also occur with diseases.

BIOADHESIVE POLYMERS

Polymers that adhere to the mucin-epithelial surface can be conveniently divided into three broad categories [16]

- Polymers that become sticky when placed in water and owe their bioadhesion to stickiness;
- Polymers that adhere through non-specific, non-covalent interactions, which are primarily electrostatic in nature (although hydrogen and hydrophobic binding may be significant);
- Polymers that binds to specific receptor sites on the cell surface. All three-polymer types can be used for drug delivery.

Characteristics of Ideal buccoadhesive Polymer [17-19]

An ideal polymer for buccoadhesive drug delivery system should have the following characteristics.

1. The polymer and its degradation products should be non-toxic and non-absorbable from the GIT.
2. It should be non-irritant to the mucous membrane.
3. It should preferably form a strong non-covalent bond with the mucin epithelial cell surfaces.
4. It should adhere quickly to moist tissue and should possess some site specificity.
5. It should allow easy incorporation of the drug and offer no hindrance to its release.
6. The polymer must not decompose on storage or during the shelf life of the dosage form.
7. The cost of the polymer should not be high so that the prepared dosage form remains competitive.

Methods to study mucoadhesion

The evaluation of mucoadhesive properties is fundamental to the development of novel Bioadhesive drug delivery system. Measurement of the mechanical properties of a Bioadhesive material after interaction with a substrate is one of the most direct ways to quantify the Bioadhesive performance. Testing is essential for the development, quantification, processing and proper use of the Bioadhesive. Several methods have been developed for the determination of Bioadhesive bond strength. These tests are also important during the design and development of Bioadhesive controlled release system as they ensure compatibility, physical and mechanical stability, surface analysis, and Bioadhesive strength [20].

METHODS TO INCREASE DRUG DELIVERY VIA BUCCAL ROUTE [15]

Absorption enhancers

Absorption enhancers have demonstrated their effectiveness in delivering high molecular weight compounds, such as peptides, that generally exhibit low buccal absorption rates. These may act by a number of mechanisms, such as increasing the fluidity of the cell membrane, extracting inters/intracellular lipids, altering cellular proteins or altering surface mucin. The most common absorption enhancers are azone, fatty acids, bile salts and surfactants such as sodium dodecyl sulfate. Solutions/gels of chitosan were also found to promote the transport of mannitol and fluorescent-labelled dextrans across a tissue culture model of the buccal epithelium while Glycerol mono oleates were reported to enhance peptide absorption by a co-transport mechanism.

Prodrugs

Hussainetal delivered opioid agonists and antagonists in bitterness prodrug forms and found that the drug exhibited low bioavailability as prodrug. Nalbuphine and naloxone bitter drugs when administered to dogs via the buccal mucosa, the caused excess salivation and swallowing. As a result, the drug exhibited low bioavailability. Administration of nalbuphine and naloxone in pro drug form caused no adverse effects, with bioavailability ranging from 35 to 50% showing marked improvement over the oral bioavailability of these compounds, which is generally 5% or less.

pH

Shojaei et al evaluated permeability of acyclovir at pH ranges of 3.3 to 8.8, and in the presence of the absorption enhancer, sodium glycocholate. The in vitro permeability of acyclovir was found to be pH dependent with an increase in flux and permeability coefficient at both pH extremes (P^H3.3 and 8.8), as compared to the mid-range values (pH 4.1, 5.8, and 7.0)

Patch Design

Several in vitro studies have been conducted regarding on the type and amount of backing materials and the drug release profile and it showed

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that both are interrelated. Also, the drug release pattern was different between single-layered and multi-layered patches.

METHOD USED TO STUDY BUCCAL BIOADHESION

The test methods can be classified into two major categories:

In vitro/Ex vivo methods: The in vitro methods are based on the measurements of either tensile stress or shear stress.

Methods based on measurement of tensile strength:

In these methods the force required to break the adhesive bond between a model membrane and the test polymer is measured.

Tensinometer

This instrument consists of two jaws from flat glasses. The upper glass was fixed, but the lower glass had been mounted on a screw-elevating surface. The upper fixed glass was attached to a sensitive digital balance. Tablets from each formulation were suspended in water (pH 7) for 15 min. Then these adhesive tablets were located on the surface of lower glass and were elevated until they contact the surface of upper glass. The lower glass was then lowered until the tablet clearly was pulled free from the upper glass. The maximum tensile force needed to detach the jaws was recorded in gram/cm and mean values were calculated and recorded [21].

Modified balance method

Modified double beam physical balance was used as the Bioadhesion test apparatus. The right pan of the balance was replaced with lighter one and pan was prepared with the Teflon ring hanging by a number of metallic rings. A cylinder at whose base a tablet was attached was hung from this ring. The two sides of the balance were then balanced with a fixed weight on the right hand side. The mucus membrane was tied with mucosal side upward using a thread over a Teflon block. The block was then lowered into the jacketed beaker which was then filled with phosphate buffer such that buffer just reached the surface of the balance. The balance beam was raised by removing the fixed weight kept on the right side of the pan. This lowered the Teflon cylinder along with the tablet over the mucosa. The balance was kept in this position for a fixed time and then slowly increased on the right pan till the tablet separated from the mucus surface. The excess weight on right hand side gave the Bioadhesive strength of the tablet in grams. It was observed that assembly gave reproducible results and performed efficiently [22].

In vitro methods

1. Adhesion weight method: A system where suspension of an exchange resin particles flowed over the inner mucosal surface of a section of guinea pig intestine and the weight of adherent particles was determined. Although the method has limited value due to poor data reproducibility resulting from fairly rapid degradation and biological variation of the tissue, it was possible to determine the effect of particle size and charge on the adhesion after 5 minutes conact with the adverted intestine [23].

2. Flow channel method

Mikos and Pepp as developed this method which utilizes a thin channel made up of glass which is filled with 2% w/w aqueous solution of bovine submaxillary mucin, thermostated at 37^0C. Humid air at 37^0C was passed through glass channel. A particle of Bioadhesive polymer was placed on the mucin gel and its static and dynamic behavior was monitored at frequent intervals using a camera, thereby calculating its adhesive property [24].

3. Fluorescent probe method

In order to examine a large number of polymers for their Bioadhesive potential, the technique of labeling the lipid bilayer and membrane protein with the fluorescent probes namelypyrene and fluorescein isothiocynate, respectively, was used. Addition of polymers to this substrate surface compressed the lipid bilayer or protein causing a change in fluorescence, as compared to control cells. By using the fluorescent probes, it was possible to compare charge type and density and backbone structure and their influence on polymer adhesion. Charged carboxylated polyanions were found to have a good potential for Bioadhesive drug delivery [25].

4. Mechanical spectroscopic method

Mechanical spectroscopy was used to investigate the interaction between glycoprotein gel and polyacrylic acid, and the effect of pH and polymer chain length on this. Mortazavi et al., used a similar method to investigate the effect of carbopol 934 on the rheological behavior of mucus gel. They also investigated the role of mucus glycoprotein's and the effect of various factors such as ionic concentration, polymer molecular weight and its concentration, and the introduction of anionic, cationic and neutral polymers on the mucoadhesive mucus interface [26].

5. Thumb test

It is simple test method used to quantify mucoadhesiveness. The difficulty of pulling the thumb from the adhesive as a function of pressure and contact time gives a measure of adhesiveness. It is most likely that any mucoadhesive system is adhesive to fingers, since most mucoadhesives are non-specific and not mucin specific and like mucin the skin has also many

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hydroxyl groups for interaction with Bioadhesive systems. Although the thumb test may not be conclusive, it provides useful information on mucoadhesive Potential [27].

6. Colloidal Gold Staining

This technique employed red colloidal gold particles, which were stabilized by the absorbed mucin molecules to form mucin gold conjugates. Upon interaction with mucin-gold conjugates, Bioadhesive hydrogel developed a red color on the surface. Thus the interaction between them could easily be quantified, either by measurement of the intensity of the red color on the hydrogel surface or by the measurement of the decrease in the concentration of the conjugates from the absorbance changes at wavelength [28].

7. Electronic conductance

This method issued to test the semisolid mucoadhesive ointments. The adhesion of Orabase, carbopol, eudispert, guar gum and methylcellulose to artificial membranes in artificial saliva was studied by using a modified rotational viscometer capable of measuring electrical conductance. In the presence of adhesive the conductance was comparatively low, as the adhesive was removed, the value increased to final value, which corresponds to the conductance of saliva, which indicates the absence of adhesion [27].

REVIEW OF LITERATURE

A review of literature survey has been carried out through various Indian and international journals that are view the properties and evaluation of Polymers and related aspects. Some of the important works are revealed here, over the last few decades' pharmaceutical scientists throughout the world are trying to explore transdermal and transmucosal routes as an alternative to injections. Among the various transmucosal sites available, mucosa of the buccal cavity was found to be the most convenient and easily accessible site for the delivery of therapeutic agents for both local and systemic delivery as retentive dosage forms [29]. This review highlights the development of mucoadhesive polymers in buccal drug delivery. This article covers the anatomy of oral mucosa, mechanism of drug permeation, characteristics and properties of the desired polymers, new generation of the mucoadhesive polymers [30]. The buccal mucosa has been investigated for local drug therapy and the systemic delivery of the therapeutic peptides and other drugs that are subjected to first-pass metabolism or are unstable within the rest of the gastrointestinal tract [31]. Mucoadhesivedrug delivery systems prolong the residence time of the dosage form at the site of application or absorption and facilitate an intimate contact of the dosage form with the underlying absorption surface and thus contribute to improved and/or better therapeutic performance of drugs [32].

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