IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

REVIEW ARTICLE ON MUCOADHESIVE DRUG DELIVERY SYSTEM IN ORAL CAVITY

***Chandan L. Jadhav, Prof. Rahul S. Bijwar, Asst.Prof. Suraj D. Thakare,**

Srushti S. Sulbhewar, Ayan I. Akbani

Jagadambha Institute of Pharmacy and Research, Kalamb

Abstract

The prospect of writing this review article is to present comprehensive information related to mucoadhesion and mucoadhesive drug delivery systems. The article has highlighted all the aspects of mucoadhesive drug delivery systems which will be helpful for researches and academics. The article includes detailed information about mucosa- the anatomy and physiology, the mechanisms and theories related to mucoadhesion, evaluation parameters of mucoadhesive dosage forms, mucoadhesive polymers and novel approaches related to mucoadhesive drug delivery system. The potential merits and demerits of mucoadhesive drug delivery as well as that of the polymers are also discussed.

Keywords: Mucoadhesion, theories of mucoadhesive mechanism of mucoadhesion, Route of mucoadesive drug, factor affecting mucoadesive, polymer.

Introduction

Mucoadhesive drug delivery system is drug delivery system which utilize the property of bio adhesion of certain polymers which becomes adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for extended period of time. mucoadhesion may be describes because the kingdom where on substances adheres to every different for prolong time frame with the assist of interfacial forces. when this type of substances is organic in natural the manner is referred to as bio adhesion is the manner of binding a fabric to the mucosal layer of the frame. Utilizing herbal and artificial polymer, mucoadhesive drug delivery is the way of managed drug released which lets for intimates contact between the polymers and the target tissue. Mucoadhesive drug delivery system is delivery system are delivery system which makes use of the assets of bio adhesion of positive polymers which grow to be adhesive on hydration and subsequently are able used for targeted delivery of the drug to particular region of body for prolong time period. The concept of mucoadhesion becomes introduced with inside the control released drug delivery

within the early 1980s. eight control released system provides continuous drug released at a predetermine rate. In recent years' considerable interest has been shown in the use of bio adhesive polymers and copolymers in controlled drug delivery.

This interest is due to the following potential applications of bio adhesive drug delivery system:

a) Adhesion to specific site of the body, such as the oral and nasal cavities, resulting in an enhanced drug bioavailability.

b) The formation of an optimum contact with the adhesion surface, increasing drug absorption.

c) The prolonging of the residence time of the dosage of within ten gastrointestinal tracts. this would reduce the need for multiple dosing, resulting better patient compliance.
The biological surface can be epithelial tissue or the mucus coat on the surface a tissue. If adhesive attachment is to a mucus coat, the phenomenon is referred to as mucoadhesion. Mucoadhesion should not be confused with bio adhesion; in bio adhesion, the polymer Is attached to the biological membrane and if the substrate is mucus membrane the term mucoadhesion is used.[1][2]

MUCOADHESIVE ORAL DRUG DELIVERY SYSTEMS

Oral route is the most preferred route for the delivery of any drug. Drug delivery via the membranes of the oral cavity can be subdivided as:

a) Sublingual delivery:

This is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth.

b) Buccal delivery:

This is drug administration through the mucosal membranes lining the cheeks (buccal mucosa). [2]
c) Local delivery:

This is drug delivery into the oral cavity Within the oral mucosal cavity, the buccal region offers an attractive route of administration for controlled systemic drug delivery. Buccal delivery is the administration of drugs through the mucosal membrane lining the cheeks. Although the sublingual mucosa is known to be more permeable than the buccal mucosa, the latter is the preferred route for systemic transmucosal drug delivery. This is because the buccal mucosa has an expanse of smooth muscle and relatively immobile mucosa, which makes it a more desirable region for retentive systems. Thus, the buccal mucosa is more appropriate for sustained direction of drug delivery. [3]

ADVANTAGES OF ORAL MUCOADHESIVE DRUG DELIVERY SYSTEMS

a) Prolongs the residence time of the dosage form at the site of absorption, hence increases the bioavailability.

b) Excellent accessibility, rapid onset of action.

c) Rapid absorption because of enormous blood supply and good blood flow rates

d) Drug is protected from degradation in the acidic environment in the GIT.

e) Improved patient compliance. [4]

DISADVANTAGES OF MUCOADHESIVE DRUG DELIVERY SYSTEMS

a) Occurrence of local ulcerous effects due to prolonged contact of the drug possessing ulcerogenic property.

b) One of the major limitations in the development of oral mucosal delivery is the lack of a good model for in vitro screening to identify drugs suitable for such administration.

c) Patient acceptability in terms to taste and irritancy.

d) Eating and Drinking is prohibited. [4]

Structure of Mucous Membrane

Mucous membrane as shown in Fig. 1 is the main site of administration for bio adhesive systems. A mucosa consists of two to three layers:

a) epithelium,

b) lamina propria

c) layer of smooth muscle called the muscularis.

d)They are characterized by a layer of epithelium, whose surface is covered by mucus.[5,6] Mucin, a glycoprotein of mucus, is responsible for the structure of mucus membrane. Thickness of mucus can vary from 50-500 µm in the stomach to less than 1 µm in the mouth cavity. [7, 8]

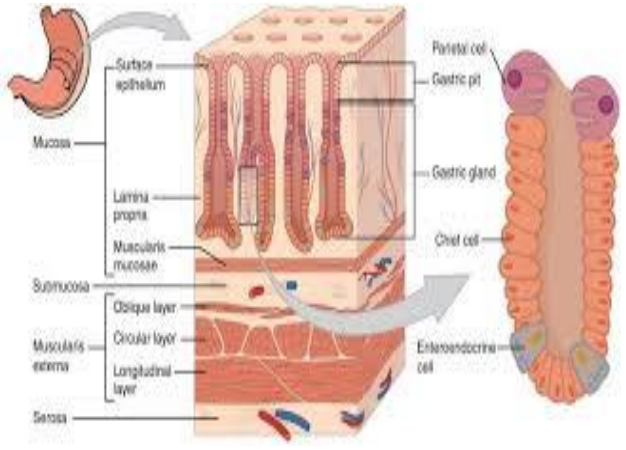

Fig. 1: Composition of mucous membrane.

Composition of mucus layer

The mucus consists of glycoproteins, fats, salts and about 95% of water by mass, making it a highly hydrophilic system. Mucus glycoproteins are high molecular weight proteins possessing attached oligosaccharide units containing, L-fucose, D-galactose, N-acetyl-D-glucosamine, N-acetyl-D-galactosamine and Sialic acid. [35]

Functions of mucus layer

Mucous membranes have absorptive, secretory, and protective functions. Mucous layer is protective because of its hydrophobicity. [4]

a) It influences the bioavailability of drugs as it hinders the tissue absorption of drugs and other substrates.

b) It strongly bonds with the epithelial cell surface as a continuous gel layer i.e. helps in mucoadhesion

c) It has key part in the lubrication of the mucosal membrane and maintenance of moisture. [9]

d) They are often covered with mucus secreted by goblet cells, multicellular mucous glands, or both. The mucus traps bacteria and foreign particles, which keeps them from invading the tissues and aids in their removal from the body. [10]

MUCOADHESION THEORIES

Six theories have been presented to explain mucoadhesion phenomenon. Mucoadhesion is defined as the interaction between a mucoadhesive polymer and mucosal layer, and these theories describe various steps of the interaction between two substrates. In the following, these theories are presented:

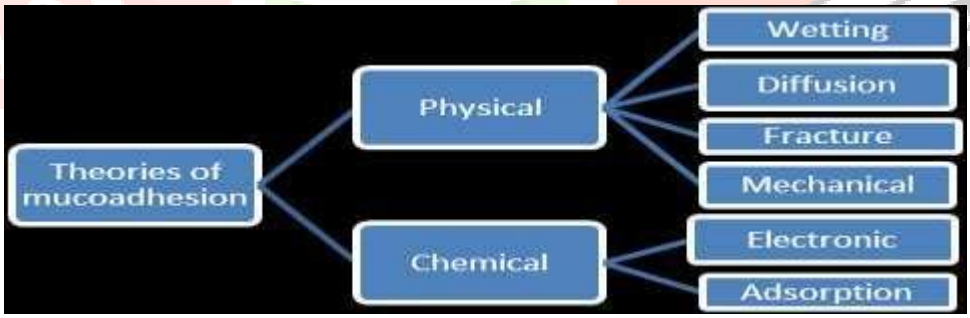

Fig. 2: Theories of mucoadhesion

A. Wetting Theory

This theory assumes the penetration of a mucoadhesive polymer into the irregularities of the absorbing surface, which becomes hardened and leads to mucoadhesion. The affinity toward the surface can be determined by measuring the contact angle. [11]

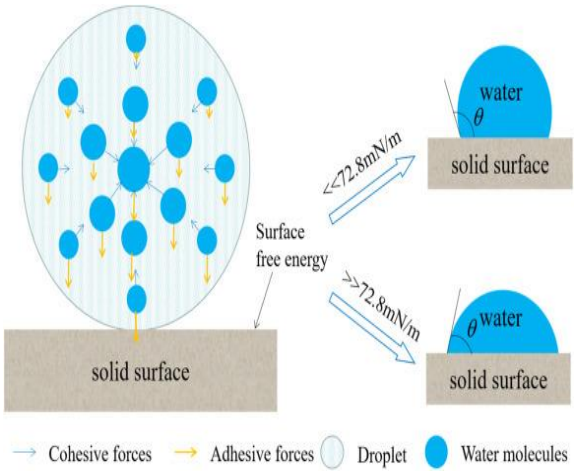

Fig. 3: Contract angle of wetting theory

B. Absorption Theory

According to this theory, adhesion is the result of interaction between the adhesive polymer and mucus substrate through two different types of chemical bonding, involving H-bonding and Van der Waals forces. After an initial contact, the adhesion of the two surfaces is due to the force between the atoms of the two surfaces. [12]

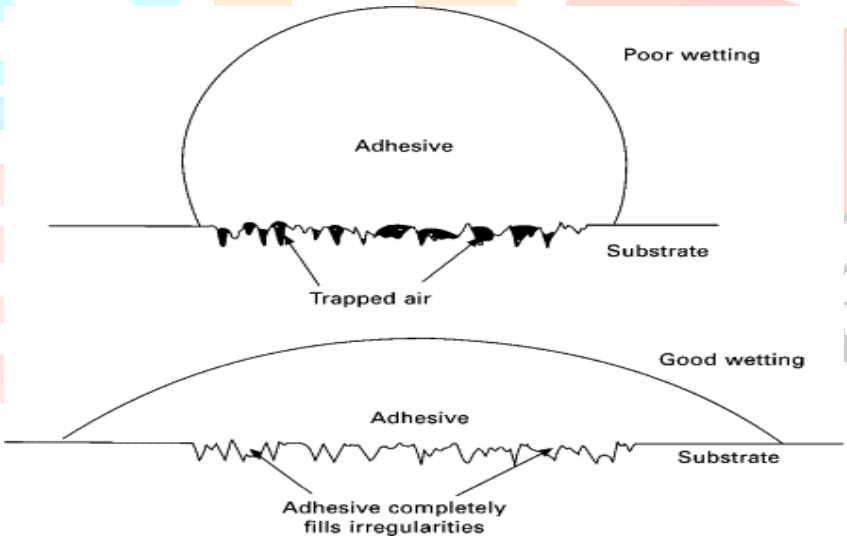

Fig. 4: Absorption theory

C. Electronic Theory

According to this theory, adhesion is the result of interaction between the adhesive polymer and mucus substrate through two different types of chemical bonding, involving H-bonding and Van der Waals forces. After an initial contact, the adhesion of the two surfaces is due to the force between the atoms of the two surfaces. [13]

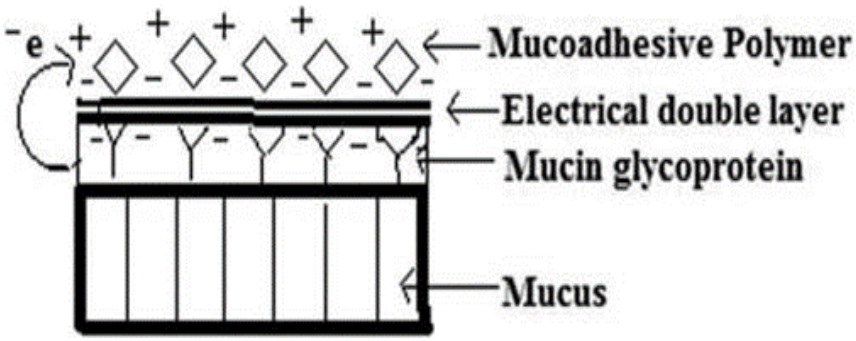

Fig. 5: Electronic theory

D. Mechanical Theory

In this theory the adhesion of two surfaces occurs, because the rough surface is filled by a mucoadhesive fluid. This step is an influential in mucoadhesion processes, although irregularities increase the area of the interface. [14]

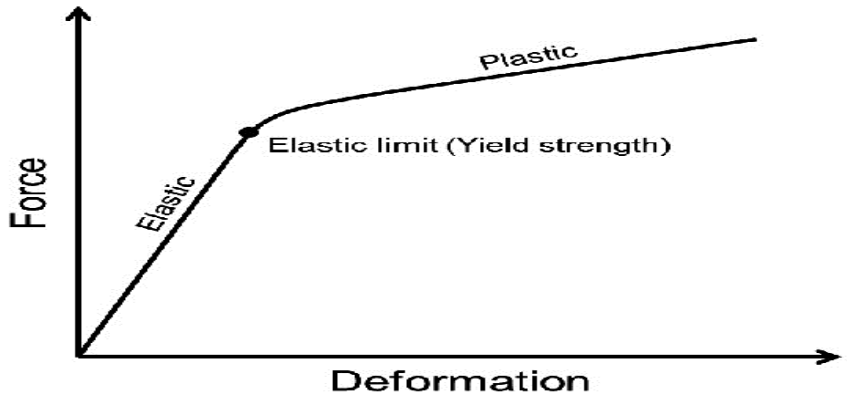

Fig. 6: Mecanical theory

E. Fracture Theory

According to this theory, the force that causes the bond of adhesion between two surfaces and the force which is needed to detach them are related. This assumption determines the amount of force required to separate the polymer from the mucus, through following equation: $\sigma = \sqrt{(E*\varepsilon)/L}$ where σ is the fracture strength, E is Young's modulus of elasticity, is the energy of fracture, and L is the critical length of crack. [15]

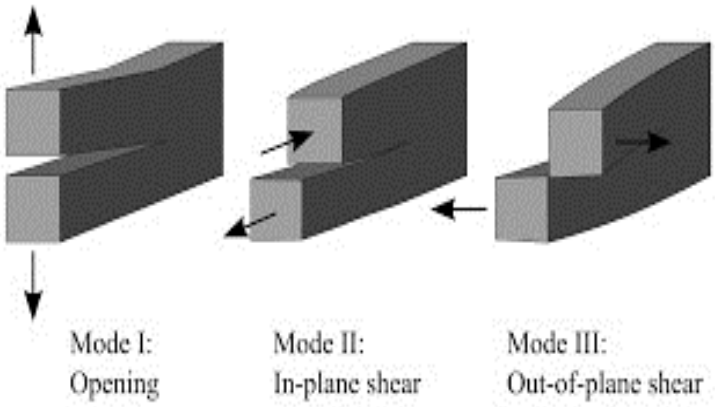

Fig.7: Fracture theory mode

F. Diffusion Theory

The diffusion theory is based both on the concentration gradient and the time of penetration of the polymer chain in the glycoprotein network of the mucus. The diffusion is a two-way process. One is the formation of a layer of interpenetration, and the other one is the achievement of an effective adhesion, which occurs when the interpenetration layer thickness reaches about 0.2-0.5 µm. The formation of this layer depends on factors like concentration gradient, molecular weight of adhesive macromolecules, hydrodynamic size, mobility, flexibility, and the length of the polymer chains. [16]

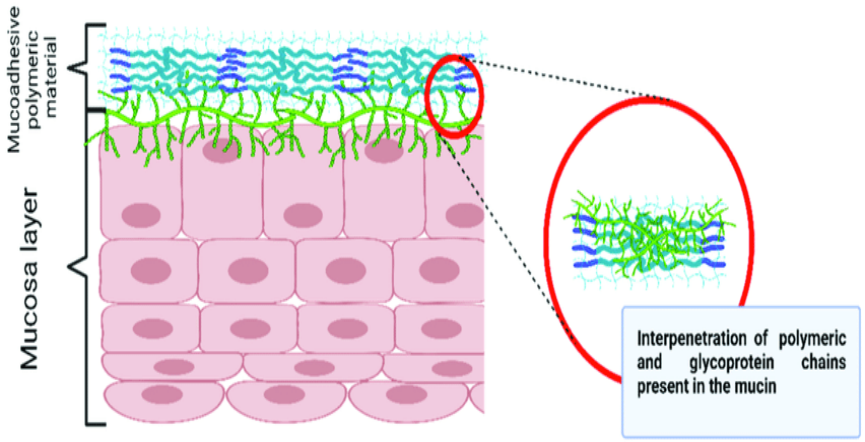

Fig.8: Diffusion mucus layer

MECHANISMS OF MUCOADHESION

The mechanism of mucoadhesion is generally divided in two steps,

a. Contact stage

b. consolidation stage

The first stage is characterized by the contact between the mucoadhesive and the mucous membrane, with spreading and swelling of the formulation, initiating its deep contact with the mucus layer. In some cases, such as for ocular or vaginal formulations, the delivery system is mechanically attached over in other cases, the deposition is promoted by the aerodynamics of the organ to the membrane, the system is administered, such as for the nasal route. 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 van der Waals and hydrogen bonds. Essentially, there are two theories. a.diffusiontheory

b. The dehydration theory. [17]

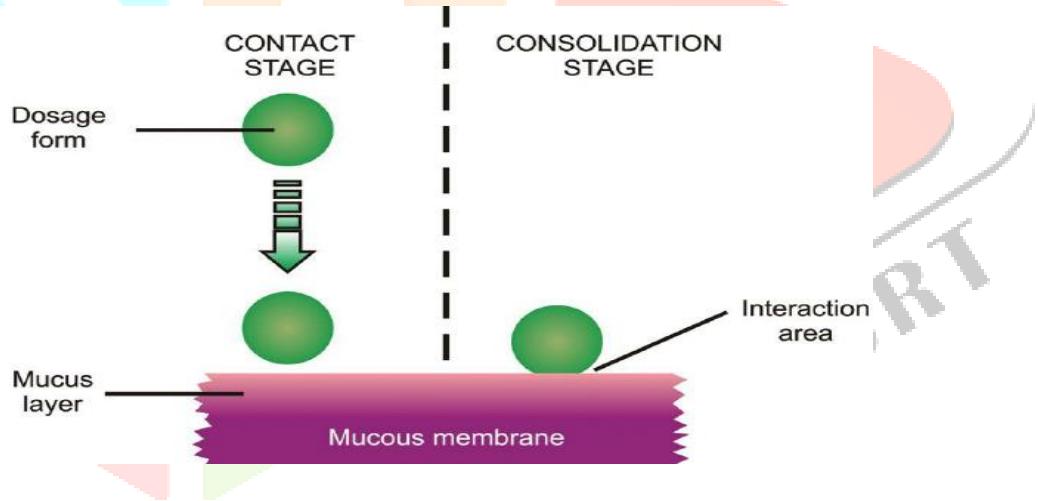

Fig. 9: Two steps of mucoadhesion.

According to diffusion theory, the mucoadhesive molecules and the glycoproteins of the mucus mutually interact by means of interpenetration of their chains and the building of secondary bonds. For this to take place the mucoadhesive device has features favouring both chemical and mechanical interactions. According to dehydration theory, materials that are able to readily gelify in an aqueous environment, when placed in contact with the mucus can cause its dehydration due to the difference of osmotic pressure. [17]

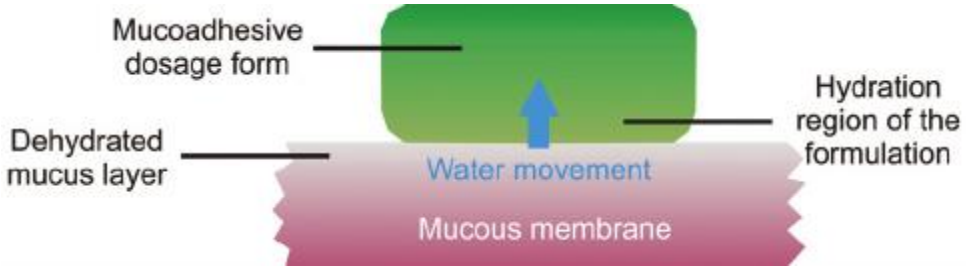

Fig.10: Dehydration theory of mucoadhesion.

ROUTES OF MUCOADHESIVE DRUG DELIVERY SYSTEMS

Mucoadhesive drug delivery system includes:

A. Buccal and sublingual delivery system;

B. Nasal delivery system;

C. Ocular delivery system;

D. Vaginal and rectal delivery system

E. Gastrointestinal delivery system.

A. Buccal and sublingual delivery system

The buccal cavity has a surface area of about 45 cm 2 but the accessibility of the site makes it preferable for delivering therapeutic moieties. Delivery through this site avoids hepatic first-pass metabolism and also aids in local remedy of the oral infections. [18] The buccal cavity offers low enzymatic activity. [19,20] Moreover; it can be instantly discontinued in cases of toxicity by removing the dosage form.[22] The sublingual mucosa is comparatively more permeable than the buccal mucosa; hence used for immediate release formulations. [21]

B. Nasal drug delivery system

The nasal mucosa has a surface area of about 150-200 cm2 but the residence time in the nasal mucosa is between 10 to 30 min. [23] This short time is due to the surged activity of the mucociliary layer triggered by foreign particles.[24] Nasal cavity avoids first-pass as it has highly vascularized surface area and blood conduits directly from the nose into the systemic circulation. The utmost use here is of intranasal active ingredients in solution form which contain sympathomimetic vasoconstrictors for prompt relief from nasal congestion. [18,20]

C. Ophthalmic drug delivery systems

There is a prompt removal of active pharmaceutical ingredient from the ocular cavity due to myriad reasons like constant tear formation, blinking of eyes as well as lacrimal drainage which results in the reduced bioavailability of the active ingredients and this can be declined by delivering the medicaments using ocular inserts or patches. Also, the holding capacity of eye is only about 30µl. This problem can be solved by using various types of dosage forms including liquid drops, gels, ointments and solid ocular inserts to improve retention time. Another interesting delivery system is in situ gelling polymer that experience a phase transition

due to ionic change, pH change or temperature change after application. Mucoadhesive polymers would only adhere to conjunctival mucus membrane in vivo. [20,23]

D. Vaginal and rectal drug delivery

Vaginal and rectal routes have been explored for the delivery of the active agents both locally and systemically. These routes have some advantages due to its enormous surface area, heavy blood supply, relatively high permeability to many drugs and self-insertion. Also, it avoids hepatic first-pass, resulting in decreased hepatic side effects and avoids pain, tissue damage, and infection. Furthermore, residence time in the vagina is much higher than at other absorption sites such as the mucosa of rectum or intestine.[11,20,23]

E. Gastrointestinal drug delivery

Gastrointestinal mucosa is also an important site for the development of mucoadhesive dosage forms for increasing GI transit time as well as bioavailability. [2] The probable occurrence of local ulcers as a side effect due to the intimate contact of the dosage form with GIT mucosa for extended periods of time should not be neglected. The mucus turnover, that is, the unceasing production of mucous by the gastric mucosa to replace the lost mucous through peristaltic contractions and the dilution of the stomach content also limits the possibilities of mucoadhesion as a gastro retentive force.[5,11]

FACTORS AFFECTING MUCOADHESIVE DRUG DELIVERY SYSTEMS

The mucoadhesive drug delivery systems are affected by polymer related factors, environmental factors, and physiological factors, which are the followings:

A. Polymer Related Factors

a. Molecular Weight

The mucoadhesion force of a mucoadhesive polymer essentially depends on its molecular weight and polymeric linearity. In general, for the linear polymers (e.g., polyethylene glycol), the mucoadhesive property is proportional to their molecular weight. However, in the case of a nonlinear polymer, the mucoadhesive force of polymer may or may not depend on its molecular weight. This is in terms of the helical or coiled structures of such polymers which may shield some of the adhesive groups which are mainly responsible for the adhesive characteristics [30].

b. Flexibility of Polymeric Chains

Mucoadhesion starts when the polymer diffuses into the interfacial area [22]. Chain flexibility is important for enlargement and interpenetration [28]. An increase in the degree of diffusion in a mucus layer leads to a stronger mucoadhesion [29].To achieve such diffusion, the polymer chain should have enough flexibility, which depends on the diffusion coefficient and viscosity [31].

c. Polymer Concentration

The concentration of the polymer is critical for forming a strong adhesive connection with the mucus. Low polymer concentrations decrease polymer chain penetration into mucus. As a result, an unstable contact arises between the polymer and the mucus. In general, the highly concentrated polymer would lead to a more infiltrating chain length with higher adhesion. [45]

d. Spatial Confirmation

The spatial conformation of a molecule is an important factor for the mucoadhesion strength. The mucoadhesive strength of a polymer depends on the spatial arrangement of polymers, i.e. whether they are helical or linear. The polymers with linear conformation have greater mucoadhesive strength than polymers with helical conformation, because helical conformation of polymer involves various active groups. Thus, their mucoadhesive strength is reduced. [36]

e. Molecular Charge of the Polymer

Non-ionic polymers have a lower degree of adhesion than anionic polymers, according to studies on their molecular charge. The anionic charge of a polymer must be strong enough to have mucoadhesion. The cationic charge on the surface of a polymer increases the interaction between polymer's surface and mucin, as the mucin has a negative charge. [37]

f. Swelling

Hydration is required for the swelling of the mucoadhesive polymers to form the desired size of macromolecules. This increases the entanglement process between polymer and mucin. The polymer concentration, ionic strength, and the presence of water are required for swelling. [38]To have a suitable swelling and mucoadhesion, an optimum level of hydration is required in the mucoadhesive polymer. [39]

g. Concentration of active polymer

Optimum concentration of active polymer is required. In remarkably concentrated system, beyond a certain optimum level, the adhesive strength declines drastically because the coiled molecules become separated from the medium so the length of chain available for permeation become limited. When the concentration of polymer is very less, the number of penetrating polymer chains per unit volume of the mucous is small and the interaction between polymers and mucous becomes erratic. [45]

h. Cross linking density

The average pore size, the average number molecular weight of cross-linked polymers and the density of cross linking are three important and inter-related structural parameters of a polymer network. Higher the cross linking density, smaller is the pore size so that diffusion of water into the polymer network occurs at a slower rate, thus there is an insufficient swelling of polymer resulting in reduced penetration of polymer into the mucin.[45,46]

i. Hydrogen bonding capacity

The polymers should have functional groups like carboxylic and hydroxyl groups which can form hydrogen bonds. Polyvinyl alcohol, hydroxylated methacrylate and poly methacrylic acid and all their co-polymers are polymers with good hydrogen bonding capacity. [39]

j. Charge

The bio adhesive property of ionic polymer is always higher than that of non-ionic polymer. In neutral or slightly alkaline medium, the cationic polymer like chitosan depicts better mucoadhesive property. [45,48]

B. Environmental Related

a. Applied Strength

If the pressure is first applied to the mucoadhesive tissue contact site, it can affect interpenetration. When high pressure is applied, the polymer used becomes mucoadhesive, even if it does not have interaction capacity. [41]

b. Initial Contact Time

The initial contact time between polymer and mucin affects the mucoadhesive strength, extent of swelling, and interpenetration of polymers. The mucoadhesive strength increases by an increase in the initial contact time. [32]

c. Moistening

Moistening provides an ideal environment for the mucoadhesive polymer to distribute over the surface of mucin and creates a particle size suitable for polymer penetration into mucin. The result of moistening of polymer is to provide a close contact of particles with the mucosa, and chemical interactions between the bio adhesive polymer and mucin chains, which create a “macromolecular mesh” of adequate size, leading to changes in the rheological of two macromolecular species. So, it enhances the mobility of polymer chains to increase penetration process between polymer and mucous. [43]

d.PH of polymer substrate interface

pH has an effect on the surface charge of both mucus and polymers. The charge density of mucus will differ depending on pH, because of variation in dissociation of functional groups on carbohydrate moiety and amino acids of the polypeptide backbone, which might influence adhesion. [14]

e. Presence of metal ions

Combining with charged groups of polymers and/or mucous can reduce the number of interaction sites and the strength of mucoadhesive bonding. [65]

C. Physiological Factors

Mucin turnover, renewal rate of mucosal cells, and disease state of mucus layer are physiological variables that may affect mucoadhesion. [66]

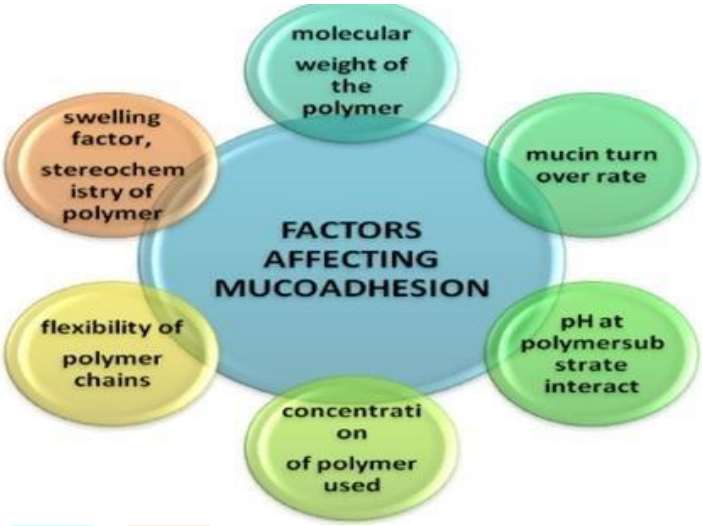

Fig.11:Factor Affecting Mucoadhesion Physiological factor

a. Mucin turnover

High mucin turnover is not beneficial for the Mucoadhesive property because of following reasons. The high mucin turnover limits the residence time of bio adhesive polymer as it detaches from the mucin layer, even though it has a good bio adhesive property. It may produce soluble mucin molecule, thus molecule interact with the polymer, before they interact with mucin layer. Hence there will not be sufficient Mucoadhesion. [66]

b. Rate of renewal of mucosal cells

Rate of renewal of mucosal cells varies extensively from different types of mucosa. It limits the persistence of bio adhesive systems on mucosal surfaces. [55]

c. Concomitant diseases

Concomitant diseases can alter the physicochemical properties of mucous or its quantity (for example, hypo and hyper secretion of gastric juice), increases in body temperature, ulcer disease, colitis, tissue fibrosis, allergic rhinitis, bacterial or fungal infection and inflammation. [44]

d. Tissue movement

Tissue movement occurs on consumption of liquid and food, speaking, peristalsis in the GIT and it affects the Mucoadhesive system especially in case of gastro retentive dosage forms. [44]

Approaches of mucoadesive drug delivery system

A. Polymeric Dosage Forms

Polymers play a vital role in mucoadhesion. They can be used to formulate various dosage forms, such as gels, films, tablets, or patches. Polymers like chitosan, sodium alginate, Carbopol, and polyethylene glycol (PEG) can provide mucoadhesive properties. These polymers can interact with the mucus layer or mucosal surfaces via hydrogen bonding, electrostatic interactions, or hydrophobic interactions. [43]

B. Gels and Hydrogels

Hydrogels and gels are two types of semi-solid adhesive systems. They should be applied to the buccal mucosa or intra-periodontal pocket to extend their residence duration and boost their absorption. Gels have the benefit of being able to make direct contact with the mucosa and releasing.
drug rapidly in the region of application, making them an ideal drug delivery mechanism for the oral cavity. In general, carbomers increase gels' efficacy as they increase residence time on mucous and prolong the duration of action. Gels have advantages over solutions as they provide longer release time and improved bioavailability. [43]

C. Micro- or Nanoparticles

Bio adhesive micro/nano particles have some advantages, such as being small particles, acceptable by the patients, and making intimate contact with the mucosal area. The small size of particles causes less local irritation at the site of adhesion and reduces uncomfortable sensations in the oral cavity. [67]

Evaluation parameter for mucoadhesive drug delivery system

In vitro/ex vivo tests:

A. Methods of mucoadhesive strength measurement

a) Methods determining tensile strength

b) Falling liquid film method

c) fluorescent probe method

d) Colloidal gold mucin conjugate method

B. Swelling index

C. Thumb method

D. Electrical conductance

E. Stability studies

F. Measurement of the Residence Time/ In Vivo Techniques

a) GI Transit using Radio-Opaque Tablets

b) Gamma Scintigraphy Technique 1 Methods of mucoadhesive strength [49]

A. Methods of mucoadhesive strength measurement

a. Methods determining tensile strength

There is uniform distribution of stress over the adhesive joint in tensile and shear experiments, while the stress is focused at the edge of the joint in the peel strength. Thus, the mechanical properties are measured through tensile and shear measure, while the peel strength measures the peeling force. Texture profile analyser is one method used for measuring the force required to peel out bio adhesive films from cut out tissue in vitro. For this, a piece of animal mucous membrane was used and it was tested for the force required to pull the formulation from a model membrane which is made from disc of mucin. The texture angler operates in tensile test mode and is paired with a low sliding platform which is also used to determine peel strength. On a movable platform the animal skin was placed and on top of it thebioadhesive film was placed, which was later on pulled verticallyto determine the peel strength. The different forces like detachment strength, shear strength and rupture tensile strength.

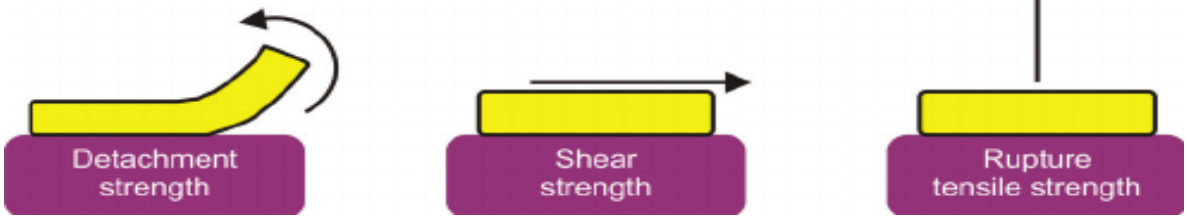

Fig. 12: Different force evaluated in mucoadhesion test.

Another method uses modified physical balance to measure mucoadhesive strength of the dosage form as shown in Fig. 13. The apparatus is made from a modified double beam physical balance wherein the right pan is replaced by a glass slide with copper wire and additional weight, to equalize the weight on both sides of pan. [49,50,51,52]

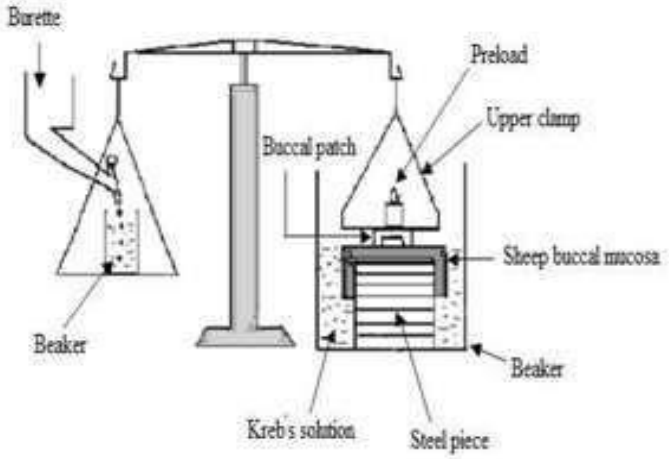

Fig.13: Measure of mucoadhesive strength

A Teflon block of specific dimensions is kept in a beaker filled with buffer of 0.1N HCl and pH 1.2, which is then placed at the bottom of the right side of the balance. Goat or rat stomach mucosa can be used as a model membrane and buffer is used as moistening fluid. One side of the formulation is fixed to the glass slide of the right arm of the balance and then the beaker is slowly lifted until contact between goat mucosa and mucoadhesive dosage form is established. A preload of 10 g is placed on the slide for 5 min (preload time) to establish adhesive bonding between mucoadhesive dosage form and the stomach mucosa. The preload and preload time are kept constant. At the end of preload time, preload is removed from the glass slide and water is then added in the plastic bottle in left side arm by peristaltic pump at a constant rate of 100 drops per min. The addition of water is stopped when mucoadhesive dosage form is detached from the goat or rat stomach mucosa. The weight of water required to detach mucoadhesive dosage form from stomach mucosa is noted as mucoadhesive strength in grams. Force of Adhesion (N) = (Mucoadhesive strength * 9.81)/1000 Bond strength (N/m2) = Force of adhesion (N)/ surface area of tablet (m2) [49,53]

b. falling liquid film method

In this method, as shown in Fig. 12, the mucous membrane is placed in a longitudinally cut stainless steel cylindrical tube. This support is placed inclined in a cylindrical cell with a temperature controlled at 37°C in thermostatic bath. An isotonic solution is pumped through the mucous membrane by peristaltic pump and collected in a collection container. Subsequently, in the case of particulate systems, the amount remaining on the mucous membrane can be counted with the aid of a coulter counter. For semi-solid systems, the non-adhered mucoadhesive can be quantified by high performance liquid chromatography.[56] This methodology allows the visualization of formation of liquid-crystalline mesophase on the mucous membrane after the flowing of the fluids and through analysis by means of polarized light microscopy.[54,55]

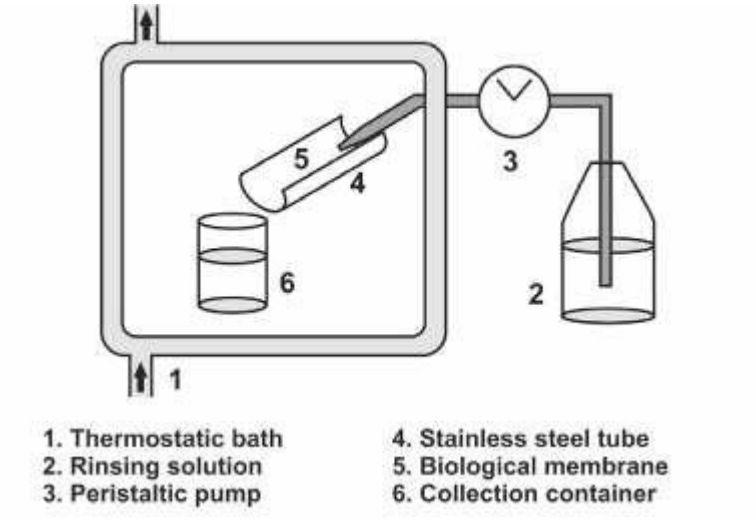

Fig.14: falling liquid film method.

c. fluorescent probe method

In this method, pyrene and fluorescein isothiocyanate are used to label the membrane lipid bilayer and membrane proteins respectively. [54] The mucoadhesive agents are mixed with cells and changes in fluorescence spectra are observed. This gives an indication of polymer binding and its role in polymer adhesion. [57]

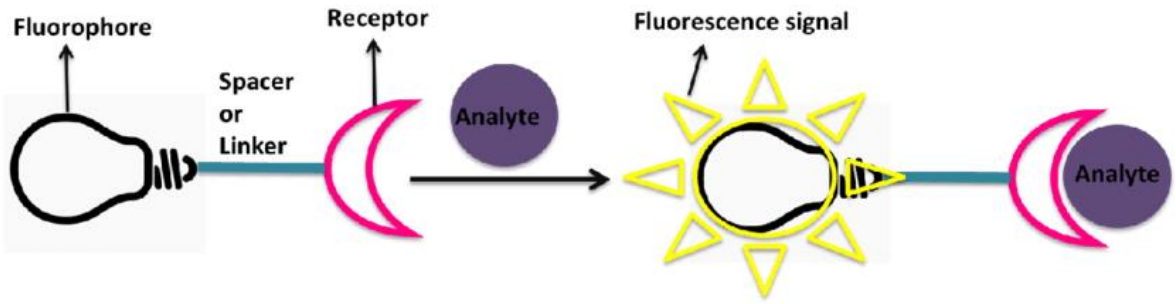

Fig. 15: Fluorescent probe diagram

d. Colloidal gold mucin conjugate method

Colloidal gold staining technique is proposed for studying bio adhesion. The method uses red colloidal gold particles, which are adsorbed on molecules of mucin to form mucin–gold conjugates. These conjugates on interaction with bio adhesive hydrogels develop a reddish tint. This can be evaluated by measuring either the intensity of red colour on the hydrogel surface or by measuring decline in the concentration of the conjugates through absorbance change at 525 nm. [54]

B. Swelling index

The amount of swelling is quantified in terms of % weight gained by the formulation. It is calculated using following formula:

Swelling index (S.I.) = (Wt.-Wo/Wo)

Where, S.I = Swelling index; Wt. = Weight of tablet at time t; Wo = Weight of tablet before placing in the beaker. [49]

C. Thumb method

This is used for the qualitative determination of peel adhesive strength of the polymer and is useful in the development of buccal adhesive delivery systems. The adhesiveness is measured by the strain required for pulling the thumb from the adhesive as a function of the pressure and the contact time. [58]

D. Electrical conductance

The rotational viscometer was modified to determine electrical conductance of various semisolid mucoadhesive ointments and found that the electrical conductance was low in the presence of adhesive material. [49]

E. Stability Studies

The success of an effective formulation can be evaluated only through stability studies. The purpose of stability testing is to obtain a stable product which assures its safety and efficacy up to the end of shelf life at defined storage conditions and peak profile. ICH guidelines can be followed in this regard. [49]

F. Measurement of the Residence Time/ In Vivo Techniques

Measurements of the residence time of mucoadhesive at the application site provide quantitative information on their mucoadhesive properties The GI transit times of many mucoadhesive preparations have been examined using radioisotopes and the fluorescent labelling techniques. [58,59]

a. GI Transit using Radio-Opaque Tablets

It is a simple procedure involving the use of radio-opaque markers, e.g. barium sulphate, encapsulated in mucoadhesive tablets to determine the effects of mucoadhesive polymers on GI transit time. [6]

b. Gamma Scintigraphy Technique

A study has reported the intensity and distribution of radioactivity in the genital tract after administration of technetium-labelled hyaluronan based biomaterial (HYAFF) tablets. The retention of mucoadhesive-radio labelled tablets based on HYAFF polymer was found to be more for the dry powder formulation than for the pessary formulation after 12 h of administration to stomach epithelium. [49,56,60]

Classification of mucoadhesive polymer

Classification of Mucoadhesive polymers

Hydrogels

On the basis of charge	On the basis of origin
A. Anionic polymers	**A) Natural polymers**
Ex. Carbopol	Ex. pectin
Cationic polymers	**B) Synthetic polymer**
Ex. chitosan	Ex. Cellulose
C)Non-ionic polymers	
Ex. HPMC, Polyethylenglycol	

Hydrogels

These swell when in contact with water and adhere to the mucus membrane.

These are further classified according to their charge. [43,68]

On the basis of charge

A) Anionic Polymers:

These polymers have negatively charged functional groups, such as carboxyl groups or sulfonic acid groups. Examples include PAA, sodium alginate, and sodium carboxymethyl cellulose (CMC). Anionic polymers can form electrostatic interactions with the positively charged mucus layer. [60]

Ex. Carbopol

Carbopol, a lightly cross-linked polyacrylic acid (PAA), is an industry standard for mucoadhesive polymers. These days, many companies use Carbopol polymers, because of some advantages such as releasing in a long period of time, being safe and effective for oral administration, increasing bioavailability, and protecting protein and peptides from degradation. The role of Carbopol in protecting peptides and protein is to change the velocity of degradation reaction. As Carbopol has a pKL value of 6.05, it makes enzymatic activity. In a study, Buprenorphine tablet, containing Carbopol 974, lactose, and PEG 3350 were made. This formulation had a sustained release profile that released their entire drug content within 2h, which is an optimum result for a sublingual tablet .Several studies have shown that insulin absorption may be greatly enhanced upon oral

delivery because of the positive properties of the thiomer polyacrylic acid cysteine, which include mucoadhesion, protection against enzymatic degradation and permeation enhancement.[60,61,62,63]

B) Cationic Polymers

These polymers have positively charged functional groups, such as amino groups. Examples include chitosan and polyethyleneimine (PEI). Cationic polymers can interact with the negatively charged mucus layer through electrostatic interactions. [69]

Ex. Chitosan

Chitosan is a cationic polymer (polysaccharide) that is gaining importance in developing mucoadhesive drug delivery systems, because of its good biocompatibility, biodegradability, and nontoxic nature. It binds to the mucosa via ionic bonds between the amino group and sialic acid residues. Onishi and Machida showed that chitosan and its metabolized derivatives are quickly eliminated by the kidney. In the study of Ayensu et al., lyophilized chitosan wafers were prepared that contained chitosan, bovine serum albumin (as a model protein), glycerol (as plasticizer), and d-mannitol (as cryoprotectant). The results indicated the usefulness of lyophilized chitosan wafers for buccal delivery of protein-based drugs. In another study, low molecular weight chitosan was optimized for a gene delivery system. AMP-loaded liposomes with chitosan improve the bioavailability and increase the effectiveness of AMP upon oral administration. Li et al. formulated KSL (KKVVFWVKFK-CONH2) peptide into polymer to swell in an aqueous medium, and so increasing medium's viscosity. This inhibits the enzyme to access the substrate, thus reducing the PLGA/chitosan composite microspheres for oral bacteria (F. nucleate). The results showed a prolonged antimicrobial and inhibitory effect for up to 80 days. In the study of Sharma et al. encapsulation of the peptide pep-H in chitosan, led to the formation of nanoparticles with a cationic surface charge, resulting in 80% reduction of intracellular M. tuberculosis load. [69]

C)Non-ionic Polymers

These polymers have no charged functional groups. They interact with the mucus layer through hydrogen bonding, hydrophobic interactions, or van der Waals forces. Examples include PEG, and HPMC. [70]

Ex. HPMC

HPMC is chemically modified cellulose polymer that is off-white in colour and considered safe for human consumption. It is most commonly used as an alternative to gelatine and gluten in vegan-friendly products.[70]

Ex. Polyethylene glycol

(PEG), acrylic acid copolymer, monomethyl ether, methacrylate and an impermeable layer. In vivo study showed that when the patch was applied in the buccal area, it remained there and released the drug for about 22 h. This study indicated that Acyclovir patch could be a good option for buccal drug delivery. [70]

On the basis of origin

A. Natural Polymer

A natural polymer is a polymer that is found in nature and is not man made all natural or organic polymers come from living organism.

Ex. Pectin

Pectin is a natural polysaccharide consisting of mainly D-galacturonic acid and glycosidic units Pectin can be used for controlled drug delivery because of its excellent biocompatibility and unique properties. For instance, pectin can easily adhere to mucosal surfaces which improve the retention time of AMPs. Krivoi rot ova et al. indicated the antimicrobial activity of nisin-loaded nanoparticles in vitro against two Gram-negative bacteria (E. coli and Klebsiella spp.) and two Gram-positive (Arthrobacter span Bacillus subtilis), using the agar-diffusion assay. Their results showed that the nisin-loaded pectin NPs possessed a higher antimicrobial activity against Gram-positive compared to Gram-negative bacteria. Furthermore, nisin-loaded pectin NPs were 100-fold more effective compared to sodium benzoate (a conventional preservative) in the killing of Gram-negative bacteria and Gram positive. These findings indicate that nisin-loaded pectin nanoparticles are an appropriate polymeric for antimicrobial delivery systems. [71]

B) Synthetic Polymer

Ex. Cellulose

cellulose is the most widely spread natural polysaccharide, there is limited number of works in literature dedicated to investigation of its blends with various synthetic polymers. Since the cellulose has three hydroxyl groups, so it easily interacts with synthetic polymers, which can form hydrogen bonds.[71]

Ideal Characteristics of Mucoadhesive Polymers

A mucoadhesion promoting agent or the polymer is added to the formulation which helps to promote the adhering of the active pharmaceutical ingredient to the oral mucosa. The agent can have such additional properties like swelling so as to promote the disintegration when in contact with the saliva. [64]

1.Polymer must have a high molecular weight up to 100.00 or more. This is necessary to promote the adhesiveness between the polymer and mucus.

2) Long chain polymers-chain length must be long enough to promote the interpenetration and it should not be too long that diffusion becomes a problem.

3)High viscosity.

4) Degree of cross linking- it influences chain mobility and resistance to dissolution. Highly cross-linked polymers swell in presence of water and retain their structure. Swelling favours-controlled release of the drug and increases the polymer/mucus interpenetration.

5)Spatial conformation.

6) Flexibility of polymer chain- this promotes the interpenetration of the polymer within the mucus network.
7) Concentration of the polymer- an optimum concentration is required to promote the mucoadhesive strength. It depends however, on the dosage form.
8) Charge and degree of ionization- the effect of polymer charge on mucoadhesion was clearly shown by Bernkop-Schnurch and Freud. Cationic chitosan HCl showed marked adhesiveness when compared to the control. The attachment of EDTA an anionic group increased the mucoadhesive strength significantly. DTPA/chitosan system exhibited lower mucoadhesive strength than cationic chitosan and anionic EDTA chitosan complexes because of low charge. Hence the mucoadhesive strength can be attributed as anion>cation>non-ionic.
9) Optimum hydration- excessive hydration leads to decreased mucoadhesive strength.
10) Optimum pH – mucoadhesion is optimum at low pH conditions but at higher pH values a change in the conformation occurs into a rod like structure making those more available for inter diffusion and interpenetration. At very elevated pH values, positively charged polymers. [64]

Conclusion

The phenomenon of mucoadhesion can be used as a model for the controlled drug delivery approaches for a number of drug candidates. There is no doubt that the oral route is the most favoured and probably most complex route of drug delivery. The buccal mucosa offers several advantages for controlled drug delivery for extended periods of time. The mucosa is well supplied with both vascular and lymphatic drainage and first-pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract are avoided.

Reference

1. Shaikh, R., Singh, T.R.R., Garland, M.J., Woolfson, A.D. and Donnelly, R.F., 2011. Mucoadhesive drug delivery systems. *Journal of pharmacy and Bio allied Sciences*, *3*(1), p.89.
2. Rao, NG Raghavendra, B. Shravani, and Mette Srikanth Reddy. "Overview on buccal drug delivery systems." *Journal of pharmaceutical sciences and research* 5, no. 4 (2013): 80.
3. Shojaei, A.H., 1998. Buccal mucosa as a route for systemic drug delivery: a review. *J Pharm Sci*, *1*(1), pp.15-30.
4. Tangri, P., Khurana, S. and Madhav, N.V.S., 2011. Mucoadhesive Drug Delivery System: Material and Method. *Int. J. Of Pham. Bio. Sci*, *2*(1), pp.34-46.
5. Khan, A.B., Mahamana, R. and Pal, E., 2014. Review on mucoadhesive drug delivery system: novel approaches in modern era. *RGUHS J Pharm Sci*, *4*(4), pp.128-141.
6. Madan J et al. Mucosal Drug Delivery System. Int J Pharm Biosci, 2010; 1: 63-70.
7. Vinod, K.R., Rohit Reddy, T., Sandhya, S. and David Banji, V.R.B., 2012. Critical review on mucoadhesive drug delivery systems. *Hygeia JD Med*, *4*(1), pp.1-5.
8. Fiebrig, I., Harding, S.E. and Davis, S.S., 1995. Methods used to develop mucoadhesive drug delivery systems: Bio adhesion in the gastrointestinal tract. *Biopolymer mixtures*, pp.373-419.
9. Mahajan, P., Kaur, A., Aggarwal, G. and Harikumar, S.L., 2013. Mucoadhesive drug delivery system: a review. *Int J Drug Dev Res*, *5*(1), pp.11-20.
10. Vivek Kumar P et al. Novel Review on Mucoadhesive Drug Delivery System; Int. J. Res. Pharm. Sci., 2014; 5(3): 205 – 215.
11. Shaikh, R., Singh, T.R.R., Garland, M.J., Woolfson, A.D. and Donnelly, R.F., 2011. Mucoadhesive drug delivery systems. *Journal of pharmacy and Bio allied Sciences*, *3*(1), p.89.
12. Ahuja, A., Khar, R.K. and Ali, J., 1997. Mucoadhesive drug delivery systems. *Drug Development and industrial pharmacy*, *23*(5), pp.489-515.
13. Dodou, D., Breedveld, P. and Wieringa, P.A., 2005. Mucoadhesive in the gastrointestinal tract: revisiting the literature for novel applications. *European journal of pharmaceutics and biopharmaceutics*, *60*(1), pp.1-16.
14. Smart, J.D., 2005. The basics and underlying mechanisms of mucoadhesion. *Advanced drug delivery reviews*, *57*(11), pp.1556-1568.
15. Ahagon, A. and Gent, A.N., 1975. Effect of interfacial bonding on the strength of adhesion. *Journal of Polymer Science: Polymer Physics Edition*, *13*(7), pp.1285-1300.
16. Zhu, Z., Zhai, Y., Zhang, N., Leng, D. and Ding, P., 2013. The development of polycarbophil as a bio adhesive material in pharmacy. *Asian journal of pharmaceutical sciences*, *8*(4), pp.218-227.
17. Akhter, M.H., Gupta, J., Faisal, M.S. and Mohiuddin, M.A., 2012. Comprehensive review on buccal drug delivery systems. *International Journal of Pharmaceutical Research and Development*, *3*(11), pp.59-77.
18. Vinod, K.R., Rohit Reddy, T., Sandhya, S. and David Banji, V.R.B., 2012. Critical review on mucoadhesive drug delivery systems. *Hygeia JD Med*, *4*(1), pp.1-5.

19. Sangeetha, S., Nagaswami Venkatesh, D., Krishan, P. and Saraswathi, R., 2010. Mucosa as a route for systemic drug delivery. *Res J Pharm Boil Chem Sci*, *1*(3), pp.178-87.
20. Thakur, V.K. and Thakur, M.K. eds., 2015. *Handbook of Polymers for Pharmaceutical Technologies, Biodegradable Polymers* (Vol. 3). John Wiley & Sons.
21. Gandhi, S.D., Pandya, P.R., Umbarkar, R., Tambawala, T. and Shah, M.A., 2011. Mucoadhesive drug delivery systems-An unusual maneuver for site specific drug delivery system. *Int J Pharm Sci*, *2*(3), pp.132-52.
22. Ilavarasan, P., Ezhumalai, K. and Rajalakshmi, A.N., 2011. Buccal patches as emerging trend. *International Journal Of Pharmacy & Technology*, *3*(2), pp.973-986.
23. Sarmento, B. and das Neves, J. eds., 2012. *Chitosan-based systems for biopharmaceuticals: delivery, targeting and polymer therapeutics*. John Wiley & Sons.
24. Shaikh, R., Singh, T.R.R., Garland, M.J., Woolfson, A.D. and Donnelly, R.F., 2011. Mucoadhesive drug delivery systems. *Journal of pharmacy and Bio allied Sciences*, *3*(1), p.89.
25. Sanzgiri, Y.D., Maschi, S., Crescenzi, V., Callegaro, L., Topp, E.M. and Stella, V.J., 1993. Gellan-based systems for ophthalmic sustained delivery of methylprednisolone. *Journal of controlled release*, *26*(3), pp.195-201.
26. Davis, S.S., 1985. The design and evaluation of controlled release systems for the gastrointestinal tract. *Journal of Controlled Release*, *2*, pp.27-38.
27. Bernkop-Schnürch, A., 2005. Mucoadhesive systems in oral drug delivery. *Drug discovery today: Technologies*, *2*(1), pp.83-87.
28. Khurana, S.H.A.F.F.I., Madhav, N.S. and Tangri, P.R.A.N.S.H.U., 2011. Mucoadhesive drug delivery: mechanism and methods of evaluation. *Int J Pharm Biosci*, *2*(1), pp.458-467.
29. Madan J et al. Mucosal Drug Delivery System. Int J Pharm Biosci, 2010; 1: 63-70.
30. Mukhopadhyay, R., Gain, S., Verma, S., Singh, B., Vyas, M. and Mehta, M., 2018. Polymers in designing the mucoadhesive films: A comprehensive review. *International Journal of Green Pharmacy*, *12*(2), pp. S330-S344.
31. Reineke, J., Cho, D.Y., Dingle, Y.L., Cheifetz, P., Laulicht, B., Lavin, D., Furtado, S. and Mathiowetz, E., 2013. Can bio adhesive nanoparticles allow for more effective particle uptake from the small intestine? *Journal of Controlled Release*, *170*(3), pp.477-484.
32. MADHAV, N.S., OJHA, A., TYAGI, Y. and NEGI, M., 2014. Mucoadhesion: a novelistic platform for drug delivery system. *International Journal of Pharmaceutics and Drug Analysis*, *2*(9), pp.773-781.
33. Zhang, Z., Liao, M., Lou, H., Hu, Y., Sun, X. and Peng, H., 2018. Conjugated polymers for flexible energy harvesting and storage. *Advanced Materials*, *30*(13), p.1704261.
34. Gandhi, J., Sarkar, I., Shah, P. and Naik, H., 2019. A comprehensive review on buccal drug delivery system. *J Pharm Sci*, *8*, pp.20-32.
35. Singh, R., Sharma, D. and Garg, R., 2017. Review on mucoadhesive drug delivery system with special emphasis on buccal route: an important tool in designing of novel controlled drug delivery system for the effective delivery of pharmaceuticals. *J Dev Drugs*, *6*(01), pp.1-12.

36. Witten, J., Samad, T. and Ribbeck, K., 2019. Molecular characterization of mucus binding. *Biomacromolecules*, *20*(4), pp.1505-1513.
37. Lalge, M., Sharma, P.K., Bhandari, A., Garud, A. and Garud, N., 2014. Mucoadhesive drug delivery system: a review. *Critical Review in Pharmaceutical Sciences*, *3*(3), pp.17-29.
38. Schonhorn, H., 1981. Adhesion and adhesives: Interactions at interfaces. *Adhesion in cellulosic and wood-based composites*, pp.91-111.
39. Schonhorn, H., 1981. Adhesion and adhesives: Interactions at interfaces. *Adhesion in cellulosic and wood-based composites*, pp.91-111.
40. Parmar, H.K., Pandya, K.K., Pardasani, L.J., Panchal, V.S. and Tandel, T., 2017. A systematic review on mucoadhesive drug delivery system. *World J Pharm Res*, *6*(9), pp.337-66.
41. Shridhar, G.S., Manohar, S.D., Bhanudas, S.R. and Anjaneri, N., 2013. Mucoadhesive buccal drug delivery: An Overview. *Journal of Advanced Pharmacy Education & Research Oct-Dec*, *3*(4), pp.319-32.
42. Lehr, C.M., Boddé, H.E., Bouwstra, J.A. and Junginger, H.E., 1993. A surface energy analysis of mucoadhesion II. Prediction of mucoadhesive performance by spreading coefficients. *European journal of pharmaceutical sciences*, *1*(1), pp.19-30.
43. Shinkar, D.M., Dhake, A.S. and Setty, C.M., 2012. Drug delivery from the oral cavity: A focus on mucoadhesive. *PDA J. Pharm. Sci. Techno*, *66*, pp.466-500.
44. Beri, C.L., Sood, R.I.C.H.A. and Hemraj, G.A., 2013. Stomach specific mucoadhesive microspheres as controlled drug delivery system-a review. *International Journal of Pharmacy and Pharmaceutical Sciences*, *5*(2), pp.21-26.
45. Khan et al. Mucoadhesive Drug Delivery System: A Review. World Journal of Pharmacy and Pharmaceutical Sciences, 2016; 5(5): 392-405.
46. Alexander, A., Sharma, S. and Khan, M.J., 2011. THEORIES AND FACTORS AFFECTING MUCOADHESIVE DRUG DELIVERY SYSTEMS: A REVIEW. *International Journal of Research in Ayurveda & Pharmacy*, *2*(4).
47. Lalge, M., Sharma, P.K., Bhandari, A., Garud, A. and Garud, N., 2014. Mucoadhesive drug delivery system: a review. *Critical Review in Pharmaceutical Sciences*, *3*(3), pp.17-29.
48. Phanindra, B., Moorthy, B.K. and Muthukumaran, M., 2013. Recent advances in mucoadhesive/bio adhesive drug delivery system: A review. *Int J Pharma Med Biol Sci*, *2*(1), pp.68-84.
49. Khan, A.B., Mahamana, R. and Pal, E., 2014. Review on mucoadhesive drug delivery system: novel approaches in modern era. *RGUHS J Pharm Sci*, *4*(4), pp.128-141.
50. Shaikh, R., Singh, T.R.R., Garland, M.J., Woolfson, A.D. and Donnelly, R.F., 2011. Mucoadhesive drug delivery systems. *Journal of pharmacy and Bio allied Sciences*, *3*(1), p.89.
51. Panicker, P.S. and Sivakumar, V., 2016. Measurement of bio adhesive strength of mucoadhesive buccal patches: Design of an in vitro assembly. *International Journal of Pharmacy Pharmaceutical Analysis*, *2*, pp.1-6.
52. Smart, J.D., Kellaway, I.W. and Worthington, H.E.C., 1984. An in-vitro investigation of mucosa-adhesive materials for use in controlled drug delivery. *Journal of Pharmacy and Pharmacology*, *36*(5), pp.295-299.

53. Carvalho, F.C., Bruschi, M.L., Evangelista, R.C. and Gremião, M.P.D., 2010. Mucoadhesive drug delivery systems. *Brazilian Journal of pharmaceutical sciences*, *46*, pp.1-17.
54. Lenaerts VM, Gurney R. Bio adhesive drug delivery systems: CRC Press.; 1989; 189-192.
55. Park, H. and Robinson, J.R., 1985. Physico-chemical properties of water insoluble polymers important to mucin/epithelial adhesion. *Journal of Controlled Release*, *2*, pp.47-57.
56. Vinod, K.R., Rohit Reddy, T., Sandhya, S. and David Banji, V.R.B., 2012. Critical review on mucoadhesive drug delivery systems. *Hygeia JD Med*, *4*(1), pp.1-5.
57. Khan, A.B., Mahamana, R. and Pal, E., 2014. Review on mucoadhesive drug delivery system: novel approaches in modern era. *RGUHS J Pharm Sci*, *4*(4), pp.128-141.
58. Madan J et al. Mucosal Drug Delivery System. Int J Pharm Biosci, 2010; 1: 63-70.
59. Junginger, H.E., Hoogstraate, J.A. and Verhoef, J.C., 1999. Recent advances in buccal drug delivery and absorption—in vitro and in vivo studies. *Journal of controlled release*, *62*(1-2), pp.149-159.
60. Xu, W., Ling, P. and Zhang, T., 2013. Polymeric micelles, a promising drug delivery system to enhance bioavailability of poorly water-soluble drugs. *Journal of drug delivery*, *2013*.
61. Shojaei, A.H. and Li, X., 1997. Mechanisms of buccal mucoadhesion of novel copolymers of acrylic acid and polyethylene glycol monomethyl ether monomethacrylate. *Journal of controlled release*, *47*(2), pp.151-161.
62. Vaidya, A.P., Wigent, R.J., Moore, J.C. and Schwartz, J.B., 2007. Protective Effect of Carbopol on Enzymatic Degradation of a Peptide-Like Substrate I: Effect of Various Concentrations and Grades of Carbopol and Other Reaction Variables on Trypsin Activity. *Pharmaceutical development and technology*, *12*(1), pp.89-96.
63. Copeland, R.A., 2023. *Enzymes: a practical introduction to structure, mechanism, and data analysis*. John Wiley & Sons.
64. Tangri P., Madhav N.V.S. (2011), Oral Mucoadhesive Drug Delivery System-A Review, Int. J. Of Bio pharm., 2(1):36-46.
65. Rathee, P., Jain, M., Garg, A., Nanda, A. and Hooda, A., 2011. Gastrointestinal mucoadhesive drug delivery system: A review. *J Pharm Res*, *4*(5), pp.1488-1453.
66. Dharmendra, S., Surendra, J.K., Sujata, M., Ashish, P. and Shweta, S., 2012. Mucoadhesive drug delivery system: A review. *International Journal of Pharmaceutical & Biological Archives*, *3*(6), pp.1287-1291.
67. Hoogstraate A, Cullender C, Senel S, Hoogstraate, A.J., Cullander, C., Senel, S., Verhoef, J.C., Boddé, H.E. and Junqinger, H.E., 1994. Diffusion rates and transport pathways of FITC-labelled model compounds through buccal epithelium. *Journal of Controlled Release*, *28*(1-3), p.274.
68. Dehghan, M.H.G., Dandge, B.H., Gaikwad, V.M. and Jagdale, S., 2010. Bio adhesive Drug Delivery Systems-Background, Applications and Trends. *Research Journal of Pharmacy and Technology*, *3*(1), pp.25-31.
69. He, P., Davis, S.S. and Illum, L., 1998. In vitro evaluation of the mucoadhesive properties of chitosan microspheres. *International journal of pharmaceutics*, *166*(1), pp.75-88.

70. Puri, V., Sharma, A., Maman, P., Rathore, N. and Singh, I., 2019. Overview of mucoadhesive biopolymers for buccal drug delivery systems. *Int J App Pharm*, *11*(6), pp.18-29.

71. González-Alvarez, M., González-Alvarez, I. and Bermejo, M., 2013. Hydrogels: an interesting strategy for smart drug delivery. *Therapeutic delivery*, *4*(2), pp.157-160.