

# **BIOADHESIVE DRUG DELIVERY SYSTEMS**

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## INTRODUCTION

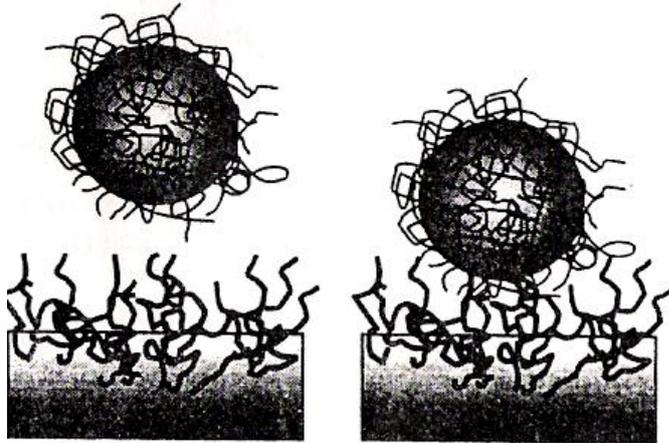
The term bioadhesion commonly defined as adhesion between two materials where at least one of the materials is of biological origin. In the case of bioadhesive drug delivery system, bioadhesion often refers to the adhesion between the excipients and biological tissue.

- ❖ When adhesion is restricted to mucous layer lining of the mucosal surface layer known as Mucoadhesion.
- ❖ For the purpose of drug delivery, the term bioadhesion is defined as the ability of the drug carrier system or the material to adhere to a biological tissue for extended period of time, leads to an increased drug concentration gradient at the absorption site and therefore improved bioavailability of systemically delivered drugs.
- ❖ In addition, bioadhesive dosage forms have been used to target local disorders at the mucosal surface (e.g. mouth ulcer) to reduce the overall required and minimize side effect that may be caused by systemic administration of drugs.
- ❖ Now, due to bioadhesion, the immobilization of drug carrying particles at the mucosal surface would result in,
  - ✓ A prolonged residence time at a site of absorption or action
  - ✓ A localization of the drug delivery system (DDS) at a given target site.
  - ✓ Increase in the drug concentration gradient due to the intestine contact of the particles with mucosal surface.
  - ✓ Possible by pass of first pass effect
  - ✓ Avoidance of presystemic elimination within GIT.
  - ✓ Depending on the particular drug, a better enzymatic flora for drug absorption.
  - ✓ Inclusion of penetration enhancers such as sodium glycocholate, sodium taurocholate and protease inhibitors in dosage form results in better absorption of peptides and proteins.

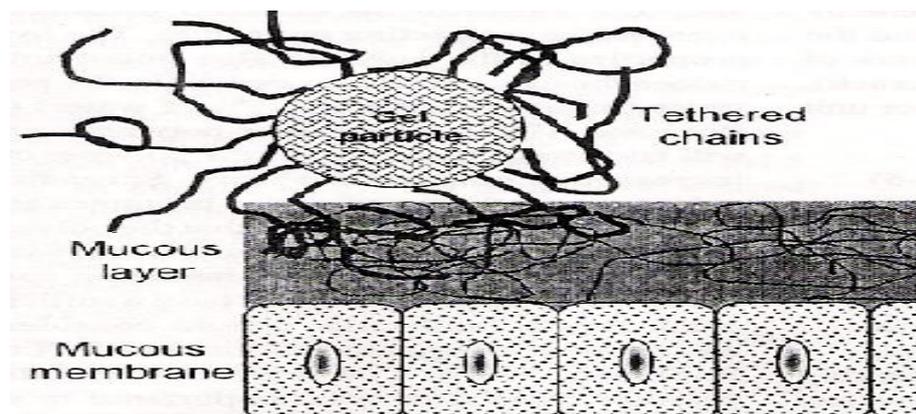
## MECHANISM OF BIOADHESION

The process involved in the formation of bioadhesive bonds has been described in three steps –

- Wetting and swelling of polymer to permit intimate contact with biological tissue.
- Interpenetration of bioadhesive polymer chain and entanglement of polymer and mucin chains.
- Formation of weak chemical bonds between entangled chain.



Interpenetration of Bioadhesive and Mucous Polymer Chains



## BIOLOGICAL MEMBRANE

- ◆ Membranes of internal tracts of the body are covered with a thick gel like structure known as mucin and mucin is synthesized by goblet cells and special exocrine glands with mucous cell acini.
- ◆ This bioadhesive mucin consists of highly hydrated, cross-linked, linear, flexible and random coil glycoprotein molecules with net negative charge.
- ◆ The cell surface membrane also possesses a net negative charge due to the presence of charged groups. Thus the binding of mucin to cell surfaces, which is a result of interaction between the two surfaces with same net charge, indicates that *adhesive forces dominate the electrostatic repulsive forces* between the two surfaces.

## Composition and characteristic of mucous

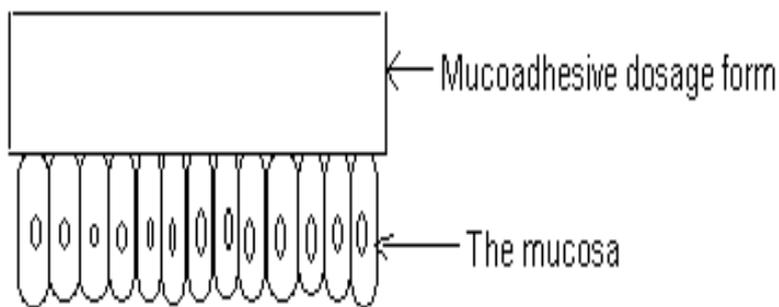
- Mucins are synthesized by the goblet cells and special exocrine glands
- Mucin is of glycoprotein family, having mol.wt.1-40 dalton

### *Mucin network is negative because of*

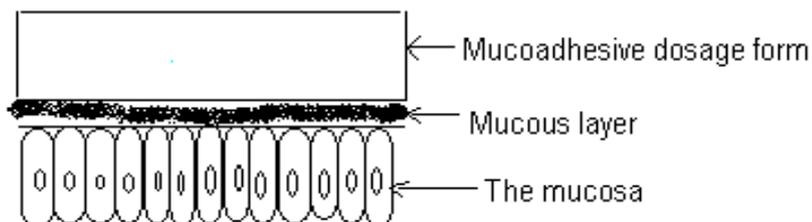
- Presence of sialic acid which has pKa of 2.6
- Presence of charged groups.

## Two basic steps have been identified for mucoadhesion.

- (1) Contact stage :- An intimate contact is formed between the mucoadhesive and mucous membrane.

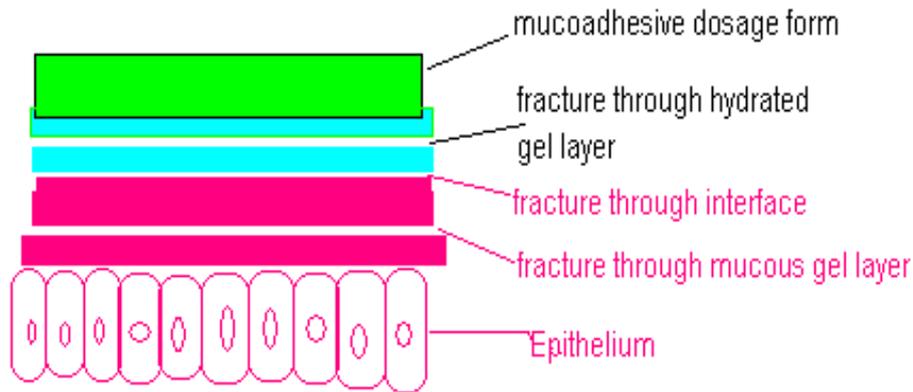


- (2) Consolidation stage :-



It has been proposed that if strong or prolonged adhesion is required, with larger formulations exposed to stresses such as blinking or mouth movements, then a second "consolidation" stage is required. The mucoadhesive, the mucosa, and the interfacial region, consisting of mucous.

Adhesive joint failure may occur at weakest components of the joint. The strength of the adhesive joint will depend on the cohesive nature of the weakest region.



### (Possibilities in mucoadhesion failure)

To understand the above problem there are two theories of how this gel strengthening occurs.

- (1) Macromolecular interpenetration effect
- (2) Rheological synergy study :-

- ◆ The rheological synergy study suggests that as soon as mucus and mucoadhesive interpenetrate, they are likely to interact and form a surface gel layer that will substantially inhibit any further interpenetration.
- ◆ The theory proposed that consolidation arises from the ability of dry or partially hydrated mucoadhesive materials to swell and hydrate mucous gel, and it is water movement rather macromolecular interpenetration.

### MECHANISM OF HYDROGEL HYDRATION:-

- ⊕ Swelling is an affinity consequence of the affinity of polymeric components for water. Polymers swell because of an imbalance between the chemical potential of solvent within the polymer and that in the surrounding medium. Thus solvent moves as a result of polymeric "osmotic pressure" until equilibrium is achieved and the internal and external chemical potentials are equivalent.
- ⊕ For low- molecular weight hydrophilic polymers the equilibrium state is a solution; for high molecular weight crossed linked polymers it can be a water swollen gel.
- ⊕ The extent and rate of swelling are affected by the degree of crsslinking and chain length.
- ⊕ If the surrounding medium contains solute, the rate of swelling decreases, particularly if the solute is large and cannot enter the hydrogels network.

## THEORIES OF BIOADHESION

- (1) **Electronic theory:** - According to this theory, electron transfer occurs upon contact of an adhesive polymer with a mucous glycoprotein due to difference in

their electronic structure. This results in formation of electrical double layer at the interface.

- (2) **Adsorption theory:** - After an initial contact between two surfaces, the material adheres because of surface forces acting between the atoms in the two surfaces.
- (3) **Wetting theory:** - Predominantly applicable to liquid bioadhesive systems. The thermodynamic work of adhesion is a function of surface tension of the surface in contact as well as interfacial tension. The interfacial energy is responsible for the contact between the two surfaces and adhesive strength.
- (4) **Fracture theory:** - It attempts to relate the difficulty of separation of two surfaces after adhesion.
- (5) **Diffusion theory:** - The polymer chains and mucus mix to a sufficient depth to create a semipermanent adhesive bond.

## FACTORS AFFECTING MUCOADHESION

### (1) POLYMER RELATED FACTORS :-

#### 1) Molecular weight:-

- There is certain molecular weight at which bioadhesion is at a maximum.
- The interpenetration of polymer molecules is favorable for low molecular weight polymers, whereas entanglements are favored for high molecular weight polymers.
- It seems that the bioadhesive forces increase with the molecular weight of the bioadhesive polymer up to 100000, and that beyond this level there is not much effect.

#### 2) Concentration of active polymer

- Bremecker relates that there is an optimum concentration of polymer corresponding to the best bioadhesion.
- In highly concentrated systems, the adhesive strength drops significantly. In fact, in concentrated solutions, the coiled molecules become solvent-poor, and the chains available for interpenetration are not numerous.
- This result seems to be of interest only for more or less liquid bioadhesive forms

#### 3) Degree of hydration

- Depending on the degree of hydration adhesive properties are different. It is maximum at a certain degree of hydration.
- When the degree of hydration is high, adhesiveness is lost probably due to formation of slippery, non-adhesive mucilage in an environment of large amount of water at or near the interface.

#### 4) Charge on polymer

- Mucosal surface is negatively charged. So positively charged polymer might facilitate the mucoadhesive process. Perhaps the initial step of mucoadhesion of a positively charged polymer to the biologic surface is through electrostatic attraction, followed by mechanical interlinking of polymer chains, van der Waal forces, H bonds and other

forces. Chitosan have bioadhesion due to electrostatic attraction between positively charged D- glucosamine residue of chitosan and negatively charged sialic acid residues.

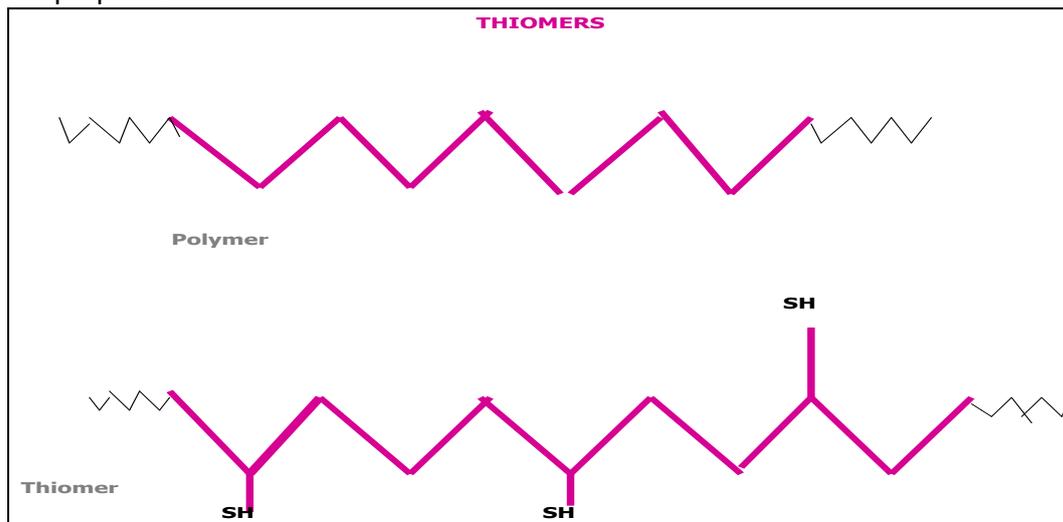
### 5) Flexibility of polymer chain

### 6) Spatial confirmation

### 7) Swelling

### 8) Presence of functional group

- Non-invasive delivery of hydrophilic macromolecular drugs such as peptides, nucleic acids & polysaccharides is one of the major challenges in modern pharmaceutical technologies.
- Thiomers are thiolated polymers.
- Due to immobilization of thiol groups on well established polymers like chitosan & polyacrylic acid their permeation enhancement, enzyme inhibitory & mucoadhesive properties are improved.
- The immobilization of thiol groups on microparticles improves mucoadhesive properties.



FOR EXAMPLE:-

- ✓ Chitosan – Thyoglycolic acid conjugates were synthesized and their characteristic including thiol group content and bioadhesive property evaluated.  
*Finally concluded that chitosan – Thyoglycolic acid conjugate with a 5.56 % weight exhibited better bioadhesion.*
- ✓ Surface modification of PLGA nanoparticles with Chitosan – 4 – Thiobutylamidine .

PLGA nanoparticles were prepared by emulsion solvent evaporation method.

*Immobilization of thiolated chitosan to the surface of PLGA nanoparticles via amide bonds shows 3.3 fold prolonged residence time on mucosa.*

## **(2) ENVIRONMENT RELATED FACTORS:-**

### **(1) pH**

- pH was found to have a significant effect on mucoadhesion.
- pH influences the charge on the surface of both mucus and the polymers. Mucus will have a different charge density depending on the pH because of the difference in the dissociation of the functional groups on the carbohydrate moiety and amino acids of the polypeptide backbone.
- Robinson *et al.* Observed that the pH of the medium is critical for the degree of hydration of highly cross linked polyacrylic acid polymers, increasing between pH 4 to pH 5, continuing to increase slightly at pH 6- pH 7, and decreasing at more alkaline levels. This behavior was attributed to difference in the charge density at the different pH levels.

### **(2) Applied strength**

- To place a solid bioadhesive system, it is necessary to apply a defined strength. The adhesion strength increases with the applied strength or with the duration of its application, up to an optimum level.

### **(3) Initial contact time**

- The initial contact time between the mucoadhesives and the mucus layer determines the extent of swelling and the interpenetration of the polymer chains. The mucoadhesive strength increases as the initial contact time increases.

### **(4) Swelling**

- Interpenetration of chains is easier when polymer chains are dis entangled and free of interactions. When swelling is too great, a decrease in the bioadhesion occurs, such a phenomena must not occur too early, in order to lead to a sufficient time for action of the bioadhesive system.

## **(3) PHYSIOLOGICAL FACTORS :-**

### **(1) Mucin turnover**

The natural turnover of the mucin molecules from the mucus layer is important for at least two reasons-

- The mucin turn over is expected to limit the residence time of mucoadhesive dosage form on the mucus layer.
- Mucin turnover results in substantial amount of soluble mucin molecules. These mucin molecules interact with mucoadhesive before they have a chance to interact with the mucus layer.

## (2) Disease states

- The physiological properties of the mucus are known to change during disease conditions such as the common cold, gastric ulcers etc. The exact structural changes taking place in mucus under these conditions are not yet clearly understood.

There are some other factors that influence the chemical or physical characteristics of mucin or mucoadhesive layer and will have an effect on the extent of interaction and strength of mucoadhesion.

## BIOADHESIVE POLYMERS

They are water soluble and water insoluble polymers which are swellable networks jointed by crosslinking agents.

### Characteristics of an ideal polymer .....

- Degradation products should be non toxic and non absorbable from g.i.t
- Non irritant to mucous membrane.
- Form a strong non covalent bond with mucin epithelial cell surfaces.
- Should adhere quickly to moist tissue and should possess site specificity.
- Allow easy incorporation of the drug and offer no hindrance to its release.
- Polymer must not decompose on storage or during shelf life of dosage form.
- Cost effective.

POLYMER	BIOADHESIVE PROPERTY
Carboxy methyl cellulose	+++
Carbopol 934	+++
Polycarbophil	+++
Tragacanth	+++
Poly (acrylic acid / divinyl benzene)	+++
Sodium alginate	+++

Hydroxy ethyl cellulose	+++
Gum karaya	++
Gelatin	++
Guar gum	++

POLYMER	BIOADHESIVE PROPERTY
Thermally modified starch	+
Pectin	+
PVP	+
Acacia	+
PEG	+
Psyllium	+
Amberlite – 200 resin	+
HPC	+
Chitosan	+
Hydroxy ethyl methacrylate	+

+++ :- Excellent      ++:- Fair      +:- Poor

**Summary of work on Mucoadhesive dosage Forms:-**

(1). Anti hypertensive, Antianginal, and related drugs:

Drug	Route/Purpose	Dosage form	Polymer
Captopril	Oral, SR	Tablet	Carbopol 934
Chlorthiazide	Orar, SR	Beads	POlycarbophil
Nifedipine	Buccal, SR	Patch	Sodium alginate, PEG6000 PEG 6000, carbopol
	Nasal SR	Gel	

Isosorbide dinitrate	Buccal SR	Tablet	PVP, Polyacrylic acid
Verapamil HCl	Buccal SR	Tablet	HPC-M, arbopol 934
DeltiazemHCl	Buccal SR	Tablet	Carbopol 934, PVP
Propranolol	Buccal SR Nasal SR	Patch Gel	Sodium CMC -
Nitroglycerine	Buccal SR	Tablet	-
Hydralazine	Buccal SR	Tablet	Carbopol 934, CMC
Vasopressin	Nasal SR	Solution	Sodium hyaluronate.
Dopamine	Nasal SR	Solution	HPC

## (2) Analgesic and anti-inflammatory drugs

Morphine sulphate	Oral SR	Tablet	Protein Prosobet L85, HPMC
Buprenorphine	Buccal SR	Patch	Polyisobutylene, Polyisoprene, Carbopol 934 P
Ketorolac tromethamine	Buccal SR	Tablet	-
Lignocaine HCl	Gingival SR	Film	-
Triamcinolone acetonide	Buccal SR	Tablet	HPC, Carbopol 934
Prednisolone	Buccal SR	Ointment	Carbopol, white petrolatum
Antipyrine	Rectal SR	Gel	Hydroxy ethyl methacrylate

## (3) Anti asthmatic drugs

Salbutamol sulphate	Buccal SR	Film	-
	Buccal SR	Tablet	-
Terbutaline sulphate	Buccal SR	Film	-
Beclomethasone Dipropionate	Nasal SR	Powdre	HPC
Di- isoproterenol	Oral CR	Tablet	HPC

#### (4) Anti infective drugs

Metronidazole	Oral SR Buccal SR Oral, vaginalSR	Tablet	Carbopol 934, HPMC HPMC, polyacrylic acid HPC, Carbopol 934 P
Miconazole	Buccal SR	Tablet	Drum dried starch, Polyacrylic acid
Cetyl pyridinium chloride	Buccal SR	Tablet	-
Clotrimazole	Buccal SR	Tablet	-
Gentamycin	Nasal SR	Microsphere	Starch

#### (5) Anti neoplastic drugs

Bleomycin	Vaginal SR	Disk	HPC, Carbopol 934
5- Fluorouracil	Vaginal SR	Stick	HPC, Carbopol 934
Interferon B	Nasal SR	Powder	Avicel, Human serum albumin

#### (6) Hormonal Drugs

Insulin	Oral	Tablet	HPC, Carbopol934
Insulin	Nasal	Gel Powder	Polyacrylic acid Carbopol 934
Testosterone	Buccal	Tablet	-
Calcitonin	Nasal	Gel	Polyacrylic acid

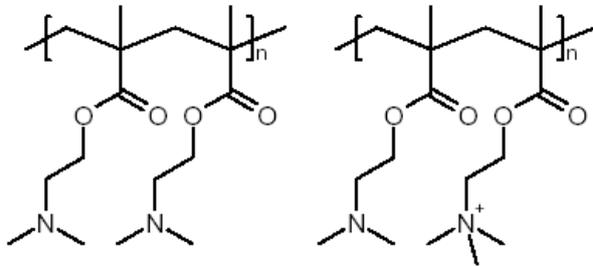
#### (7) Ophthalmic drugs

Progesterone	Occular	-	-
Pilocarpine	Occular SR	Gel	Hyaluronic acid
Tropicamide	Occular SR	Gel	Hyaluronic acid

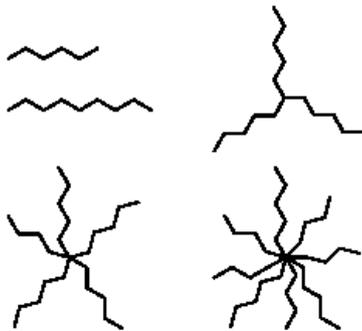
❖ **Advantage of poly ( dimethyl aminoethyl methacrylate) { PDMAEMA } over chitosan** is that it has more selectivity to mucous. While chitosan binds to both mucous and cellular surfaces.

Other advantage is that these polymers are easy to handle.

They are readily soluble and can easily be modified to suit application.



**Figure 1.** PDMAEMA and PDMAEMA<sup>+</sup> polymers.



**Figure 2.** Possible shapes of mucoadhesive polymers.

### Mucosal Permeation Enhancers

- 23-lauryl ether
- Aprotinin
- Azone
- Benzalkonium chloride
- Cetylpyridinium chloride
- Cetyltrimethylammonium bromide
- Cyclodextrin
- Dextran sulfate
- Lauric acid

## **POTENTIAL SITES FOR BIOADHESIVE DRUG DELIVERY**

The mucosal layer lines number of regions of the body including the GI tract, urogenital tract the airways, the ear, nose, eye etc. These represent the potential sites for the attachment of many bioadhesive systems and hence mucoadhesive drug delivery system include the following-

- ❖ Buccal Drug Delivery system
- ❖ Sublingual Drug Delivery system
- ❖ Oral Drug Delivery system
- ❖ Nasal Drug Delivery system
- ❖ Ocular Drug Delivery system
- ❖ Vaginal Drug Delivery system
- ❖ Rectal Drug Delivery system

### **Other classification of bioadhesive dosage form:-**

#### **Solid bioadhesive formulations**

Tablets  
Bioadhesive microparticles  
Bioadhesive inserts  
Bioadhesive wafers  
Lozenges

#### **Semisolid bioadhesive Formulations**

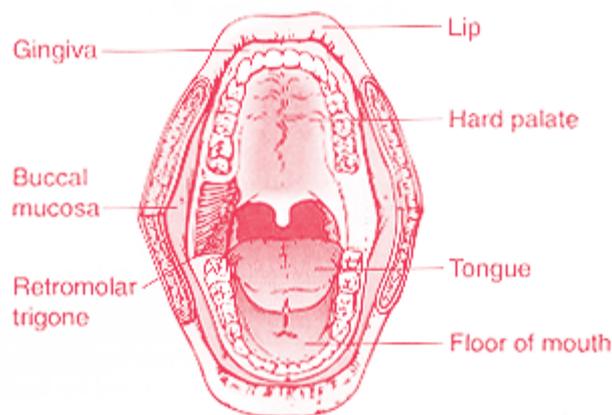
Gels  
Films

#### **Liquid bioadhesive formulations**

Suspensions  
Gel forming liquids

### **BUCCAL BIOADHESIVE DRUG DELIVERY: -**

- ➔ Oral cavity has rich blood supply and direct access to systemic circulation. The oral route is suitable for drugs which are susceptible to acid hydrolysis in the stomach or which are extensively metabolized in the liver.
- ➔ In oral cavity, buccal and gingival areas are associated with a smaller flow of saliva as compared to the sublingual region, thus the duration of adhesion of the delivery system would be longer at these areas than at the sublingual region.



### **Buccal absorption of drug**

To penetrate the mucosa to a significant degree a drug should have relatively low molecular weight and exhibit biphasic solubility patterns, that is, be soluble in both the aqueous salivary fluid and lipid membrane barrier to show penetration. High molecular weight mucopolysaccharides such as heparin and proteins such as insulin are not well absorbed. A significant amount of drug should be un-ionized at salivary pH and the drug should also not bind strongly to the oral mucosa.

### **Oral mucosa as site for drug delivery**

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

#### **1. Sublingual delivery: -**

- ➔ Which is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth.
- ➔ Sublingual mucosa is relatively permeable due to the thin membrane and large veins, hence allow rapid absorption and acceptable bioavailability of many drugs.
- ➔ 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.

#### **2. Buccal delivery: -**

- ➔ Which is drug administration through the mucosal membranes lining the cheeks (buccal mucosa)
- ➔ Buccal mucosa is significantly less permeable than sublingual mucosa, which makes it more suitable for sustained drug delivery and is generally not able to provide the rapid absorption and good bioavailabilities seen with sublingual administration.

- ➔ The buccal mucosa has an expanse of smooth muscle and relatively immobile mucosa, which makes it a more desirable region for retentive systems used for oral transmucosal drug delivery.
- ➔ Thus the buccal mucosa is more fitted for sustained delivery applications, delivery of less permeable molecules, and perhaps peptide drugs.
- ➔ Get higher patient compliance due to accessibility of the cheek lining and lack of invasive measures.

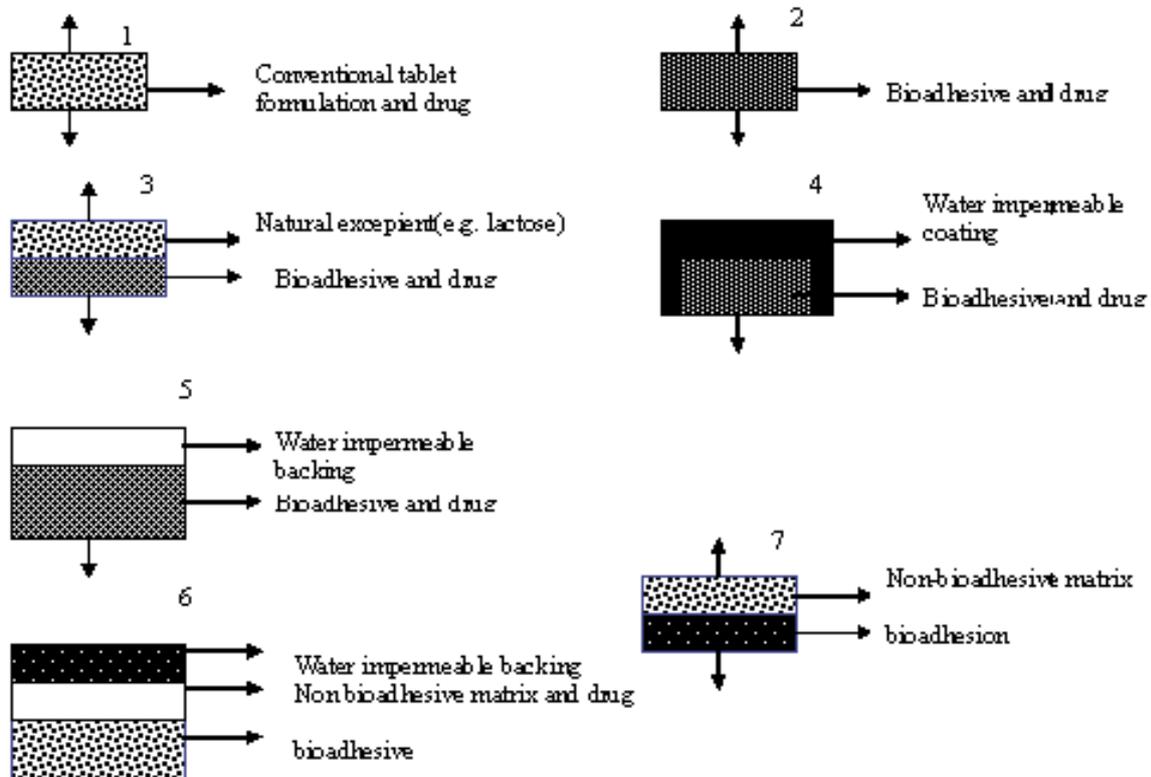
### 3. Local delivery: -

- ➔ Which is drug delivery into the oral cavity.

## TYPES OF BUCCAL BIOADHESIVE DOSAGE FORM

### BIOADHESIVE BUCCAL TABLETS

- ⇒ Bioadhesive tablets are immobilized drug delivery systems.
- ⇒ They can be formulated into monolithic partially coated or multilayered matrices.
- ⇒ Drug can be co-incorporated with an absorption enhancer, if required. Partial coating of a monolithic tablet affords the protection of every face of the tablet, which is not in contact with the mucosa.
- ⇒ In case of bi-layered tablets, drug can be incorporated in the adhesive layer, which comes in contact with the mucosal surface.
- ⇒ Following are the possible designs for buccal bioadhesive drug delivery-



**The limitations of bioadhesive tablets are: -**

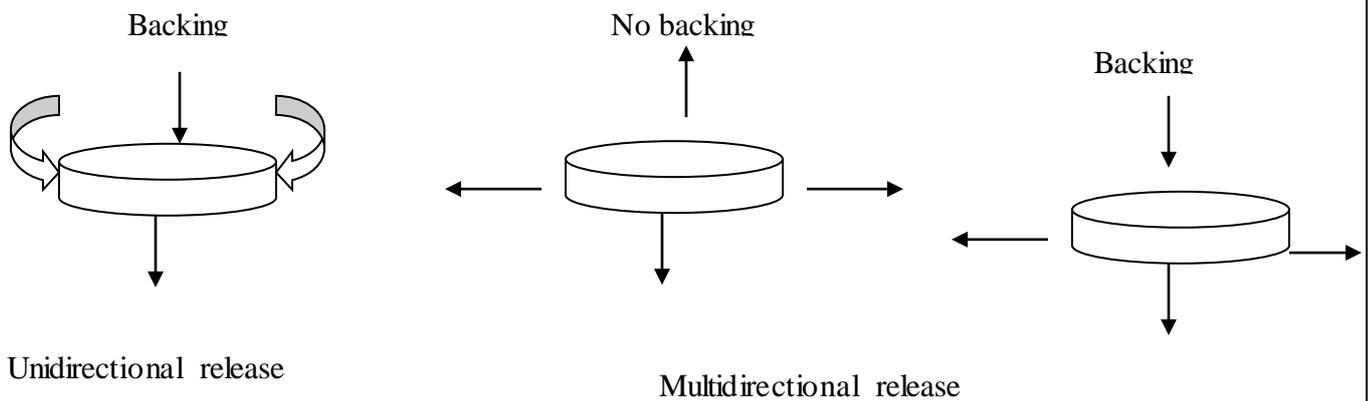
- ⇒ The small surface of contact with the mucosa.
- ⇒ Their lack of physical flexibility.
- ⇒ It is difficult to get high release rates, which is required for some drugs.
- ⇒ The extent and frequency of contact may cause irritation following chronic application on the buccal and sublingual mucosa.

e.g. of buccoadhesive tablets:-

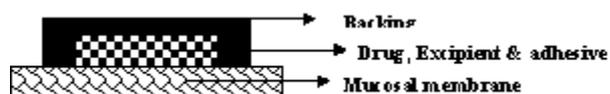
- a. Sublingual mucosal delivery of nitroglycerin - Susadrin®
- b. Buccal mucosal delivery of prochlorperazine - Buccastem®  
chewing gum buccal mucosal delivery of Nicotine – Nicorette

**BUCCAL PATCHES**

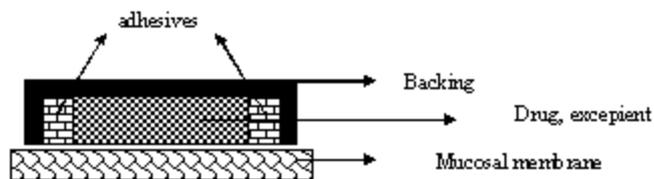
- ⇒ Adhesive patches can be designed either for unidirectional release or multidirectional release.



- ⇒ The adhesive part of the system can be used as drug carrier or as an adhesive for the retention of a drug loaded non-adhesive layer.
- ⇒ The use of an impermeable backing layer will maximize the drug concentration gradient and prolong adhesion because the system is protected from saliva.



**Matrix System**



- ⇒ Polyacrylic acid based patches have been used successfully for the delivery of opioid analgesics

### Application aids

Depending on the therapeutic aim of a buccal patch, it may be necessary to consider a design with an application aid. A good application aid should help a patient handle a thin and small patch in such a way that the patch itself does not have to be held with the fingers. As it may be difficult to put two fingers holding a patch deep into the mouth to reach an administration site deep into the distal region of the buccal cavity. An example of this is shown in the figure-



### Other buccal drug delivery systems:-

#### Lozenges

- ❖ Act typically within the mouth including the antimicrobials, corticosteroids, local anaesthetics, antibiotics and antifungal.

#### Bioadhesive liquids

- ❖ Dry mouth is treated with artificial saliva solution that is retained on mucosal surfaces to provide lubrication. These solutions contain bioadhesive polymers including sodium carboxymethyl cellulose.

#### Films

- ❖ It can reach to the base of the pocket to be treated.

#### Hollow fibers

- ❖ Burnside et al designed a microporous hollow fiber of polysulfone, intended for delivery of histrelin.
- ❖ This fiber is intended to be placed in the buccal cavity for oral mucosal drug delivery.
- ❖ The lack of intimate contact of the delivery system with the mucosa may be detrimental to peptide absorption and the delivery system does not afford protection of the drug

from the environment of the oral cavity and may subject the peptide drug to enzymatic degradation

**Oravescent:-**

- ❖ It is oral effervescent tablet, which is kept in the buccal cavity.

**Chewing gums:-**

- ❖ Chewing gum preparations like nicotine are commonly available in the market.

**Buccal spray:-**

- ❖ It is a spray, which is put into the lingual region leading to very quick drug absorption. Therefore, it is called as immediate –immediate release lingual spray.

**ADVANTAGES OF BUCCOADHESIVE DRUG DELIVERY SYSTEMS**

- Good patient compliance.
- Administration and termination of therapy is easy.
- Due to lack of langerhans cells it is tolerant to potential allergens.
- This route can administer drugs that are unstable in the acidic environment of the stomach or are destroyed at the enzymatic or alkaline environment of the intestine.
- Permits localization of the drug to the oral cavity for prolonged period of time.
- Offers an excellent route for systemic delivery of drugs having drawbacks of first pass metabolism, convenient for drugs that show poor bioavailability.
- Significant dose reduction can be achieved.
- The presence of saliva ensures relatively large amounts of water for drug dissolution unlike the rectal and transdermal routes.
- Offers a passive system for drug absorption and does not require any activation.
- Consist of non-keratinised epithelium resulting in somewhat more permeable tissue than the skin.

**LIMITATION OF BUCCOADHESIVE DRUG DELIVERY SYSTEM**

- One of the major limitations with buccal drug delivery is the low flux, which results in low drug bioavailability.
- Drugs which irritate the mucosa or have bitter or unpleasant taste or an obnoxious odor or unstable at buccal pH cannot be administered by this route.
- Only drugs with small dose requirements and drugs that are absorbed by passive diffusion can be administered by this route.
- There is a possibility of patient swallowing the dosage form.
- Eating and drinking may become restricted.
- Over hydration may lead to formation of slippery surface. Swelling and hydration of the bioadhesive polymers may disrupt structural integrity of the formulation.

**GASTROINTESTINAL BIO/MUCO ADHESIVE DRUG DELIVERY**

### **GIT as a target for drug delivery**

The target sites for bioadhesion in GIT are-

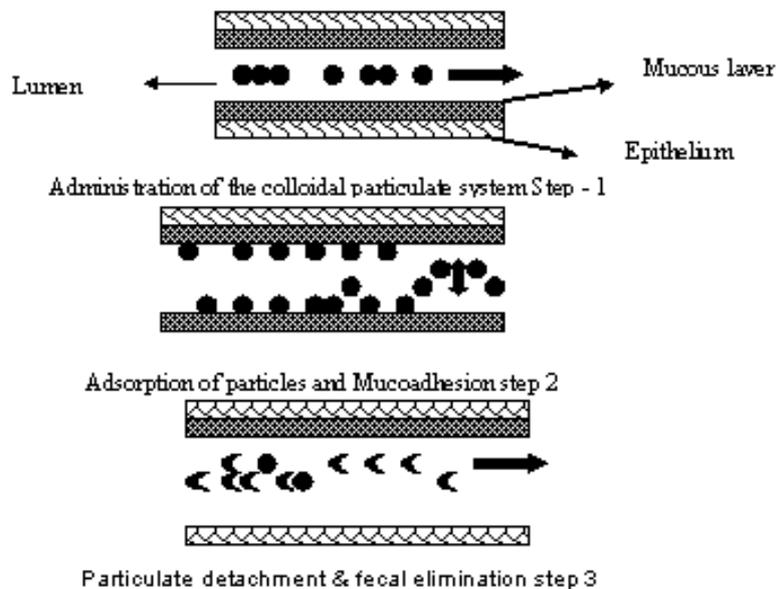
- The mucosal tissue.
  - The mucosal gel layer.
    - ◆ The thickness of the mucin gel layer varies regionally through out the GIT.
    - ◆ There is a continuous renewal of the mucosal layer by a turnover process, which limits the duration of mucoadhesion.
- The micro particles are attached to the mucosal layer through specific or non-specific interactions.

### **NON – SPECIFIC BIOADHESION**

- ❖ Non-specific bioadhesion with the intestinal membrane occurs through physiochemical interactions.
- ❖ In the GIT, particles are directly mixed with liquid materials in the stomach, which is likely to strongly decrease the adhesiveness of such polymers because of the premature hydration of the polymer, which takes place before the contact with mucosal surface.
- ❖ So the various approaches of GI bioadhesion of colloidal particles are based on the use of non-swallowable, hydrophobic polymers.
- ❖ In this case, adhesion is mainly due to inherent tendency of these small particles to develop intimate contacts with large mucosal surfaces.

### **Non-specific bioadhesion suffers from two major drawbacks-**

- ▶ Only a fraction of the dosage form administered is absorbed while remaining part is subjected to direct fecal elimination.
- ▶ Due to unspecificity of the interactions, targeting to a specialized area of the mucosa with unmodified particles is unrealistic.



### **SPECIFIC BIOADHESION**

- Specific adhesion is adhesion directly to surface of the cells of the mucosa and this involves specific ligand receptor interactions between complementary structures.
- Ideally, the adhesion takes place when the dosage form reaches the desired site.
- Different targets within GIT can be identified depending on the pharmaceutical applications. The targets are,

Mucosal glycoprotein, M-cells

Epithelial cells, Payer's patches or gut-associated lymphoid tissue etc.

### **Limitation of specific bioadhesion strategy-**

- Specific bioadhesion strategy is likely to be limited in vivo by the limited capacity of the particles to diffuse through the mucous layer before reaching cell surfaces.
- The search of ligands exhibiting a sufficient specificity and lack of toxicity at the same time may be crucial task.
- A possible alteration or a blockage of the cell membrane functions and the immunogenicity of the ligand should be considered

### **Lectin conjugates (cytoadhesion)**

- The concept is specifically based on certain materials that can reversibly bind to cell surfaces in the GIT.
- This next generation of mucoadhesives functions with greater specificity because they are based on receptor-ligand-like interactions in which the molecules bind strongly and rapidly directly onto the mucosal cell surface rather than the mucus itself.
- One such class of compounds *that has these unique requirements is called lectins*.
- Lectins have been used extensively for oral delivery in recent years because of their inherent property to provide specific binding to biological surfaces bearing sugar residues located at the surface of epithelial cells and they are resistant to acidic pH and enzymatic degradation.

- The binding of lectins is only possible if corresponding sugar moieties are available on the mucosal surface.
- Lectin-based drug delivery systems have applicability in targeting epithelial cells, intestinal M cells, and enterocytes.
- Lectins favor binding at neutral pH; it is more likely that they will be suited to small intestinal applications.
- **Toxicity is an important factor** to bear in mind, as some lectins can be toxic at certain levels.

## COLONIC BIOADHESIVE DRUG DELIVERY

- ⊕ Kakoulides et al., synthesized azo-crosslinked poly (acrylic acid) for colonic delivery as well as for adhesion specificity.
- ⊕ They evaluated in vitro degradation and ex vivo bioadhesion of the synthesized polymer. Azo- networks based on acrylic backbone crosslinked with 4,4' - divenyl benzene.
- ⊕ The study indicates that there is optimum crosslinking density to allow non-adhesive particles to reach the colon.
- ⊕ In colonic environment, the azo-network degrades to produce a structure capable of developing subsequent mucoadhesive interaction with colonic mucosa.

### Suspensions

Sucralfate suspensions adhere directly to mucosal surfaces within the GIT. This adhesion is not due to bioadhesive polymer but due to the acidification of the insoluble powder leading to the formation of an adhesive paste. Incorporation of a bioadhesive agent, however, has demonstrated enhanced invitro adhesion of sucralfate formulation within the oesophagus.

### Bioadhesive liquids

Gastric reflux of acidic materials from the stomach into the oesophagus leads to damage of the oesophageal tissue, bioadhesive liquids that coat the oesophagus after oral administration may be used to protect this mucosal surface from gastric reflux. These adhesive liquids that coat the oesophagus may be used to deliver drugs for the treatment of local disorders including motility dysfunction, fungal infections and oesophageal cancer.

### In situ gelling system

- Rectal insitu gelling and mucoadhesive Meberevine HCl solution for rectal administration by using poloxamer 407 and poloxamer 188 which are having thermogelling property. Meberevine HCl undergo first pass metabolism. It is used in the irritable bowl syndrome.

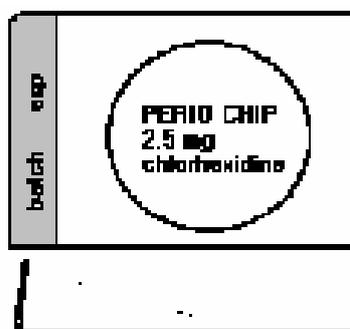
## INTRA-PERIODONTAL POCKET BIOADHESIVE DRUG DELIVERY

**FIBERS-** Commercially available delivery system (AcitsiteO) is based on a monolithic ethylene vinyl acetate fiber that delivers tetracycline

**FILMS** - It can reach to the base of the pocket to be treated. The physical properties of the film with its sufficient adhesiveness keeps it sufficiently submerged without any noticeable interference with patients eating and oral hygiene habits.

**DEGRADABLE DEVICES-** Resorbable hydroxy propyl cellulose based devices for delivery of tetracycline and chlorhexidine as well as ofloxacin have been tested clinically (in vivo retention was seen even after 24 hrs).

**PERIOCHIP** –is a film made up of degradable matrix of crosslinked-hydrolyzed gelatin. It is a subgingival delivery method.



**PERIODONTAL BIOADHESIVE GEL:** - Made with bioadhesive polymers like CMC, methyl cellulose, PVP, carbopol. This has been formulated for metronidazole.

## NASAL BIOADHESIVE DRUG DELIVERY SYSTEMS

- ❖ The key parameters in case of nasal drug delivery are–
  - Dispersion patterns.
  - Bioadhesion.
- ❖ The nasal mucosa allows effective absorption of a variety of lipophilic drug and hydrophilic drugs such as peptides and proteins.
- ❖ The major difficulty in administering these drugs intra-nasally is their low bioavailability due to enzymatic degradation, mucociliary clearance and poor mucosal membrane permeability. This problems can be overcome by co-administering penetration enhancers or/and mucoadhesive substance.
- ❖ Chitosans are biodegradable high molecular weight cationic polysaccharide having mechanism of transport enhancement by transient opening of tight junction in nasal

membrane and the property of bioadhesion, enhance the nasal absorption in human volunteers of polypeptides and other polar drugs.

### 1. Liquid Bioadhesive Technology

- A range of studies has been performed with liquid bioadhesive formulations of variable viscosity.
- Pennigton et al. has shown that an increase in viscosity of a solution by means of the bioadhesive material hydroxypropylmethyl cellulose results in a prolonged clearance time from the nasal cavity. Concentrations of 0.6, 0.9, and 1.25% HPMC resulted in clearance half-life of 0.47, 1.7, and 2.2 hrs respectively in human.

### 2. Self-Gelling Bioadhesive System

- ⇒ A problem may be encountered in therapeutic use with application of the bioadhesive liquid gel system in the nasal cavity, especially if a high concentration of the polymer is used. The formulations are not likely to be readily delivered using a normal nasal spray device but rather will have to be applied with the means of a tube.
- ⇒ To overcome this problem, bioadhesive formulation that gel upon interaction with the nasal mucosa (due to either increase in temperature, increase in ionic strength, or presence of calcium ions), so-called **environmentally responsive polymers** have been exploited for nasal drug delivery. For e.g. thermogelling polymer Pluronic F127 is a polyoxyethylene polyoxypropylene block copolymer that is liquid at a concentration of more than 25% in buffer at 4°C, whereas room temperature or at higher temperature it forms a clear viscous gel.

### 3. Bioadhesive Powder System

- Nagai and co-workers investigated the use of bioadhesive powder dosage form for the administration of peptides such as insulin to the nasal cavity.
- The bioadhesive agents studied in combination with the freeze-dried insulin includes crystalline cellulose, hydroxypropyl cellulose and Corbopol 934. All formulations tested gave significant decrease in the plasma glucose levels when administered nasally to dog and rabbit models.

### 4. Bioadhesive Microsphere System

- Illum et al first suggested the use of the bioadhesive microspheres.
- These microspheres swell when they come in contact with the nasal mucosa to form a gel and control the rate of clearance from the nasal cavity, thereby giving poorly absorbed drugs sufficient time to absorb from the nasal mucosa.

## OCULAR BIOADHESIVE DRUG DELIVERY SYSTEMS

### 1. Hydrogels

- Hydrogels-sodium hyaluronate and carbomer are the two hydrogels, providing considerable bioadhesive nature. Artificial tears for the treatment of dry eye (e.g. Viscotear®, Novartis) are the carbomer solutions that adhere on the surface of the eye providing a lubricated surface

- Carbopol is considered superior for sustained drug delivery in case of ocular drug delivery because it has similar features to mucin. E.g. negative charge, expanded nature etc.

## 2. Solid Formulations

Solid ophthalmic delivery devices are thin disks or small cylinders made with appropriate polymeric materials and fitting into the lower or upper conjunctival sac. Some inserts like now classical occusert can release the drug at a slow constant rate for one week. So, mucoadhesive polymers can be profitably used as constituents of inserts to achieve prolonged contact with the conjunctival sac and to alleviate the risk of expulsion from cul-de-sac.

## 3. Particulate Drug Delivery systems

Liposomes, microspheres and nanoparticles – are manufactured with bioadhesive polymers to show controlled drug release properties.

# EVALUATION OF BIOADHESIVE DRUG DELIVERY SYSTEM: -

### 1. IN VITRO / EX VIVO METHODS

- Methods based on measurement of tensile strength.
- Methods based on measurement of shear strength.

#### OTHER IN VITRO METHODS

- Adhesion weight method
- Fluorescent probe method
- Flow channel method
- Falling liquid film method
- Colloidal gold staining method
- Mechanical spectroscopic method
- Thumb test
- Viscometric method
- Adhesion number
- Electrical conductance

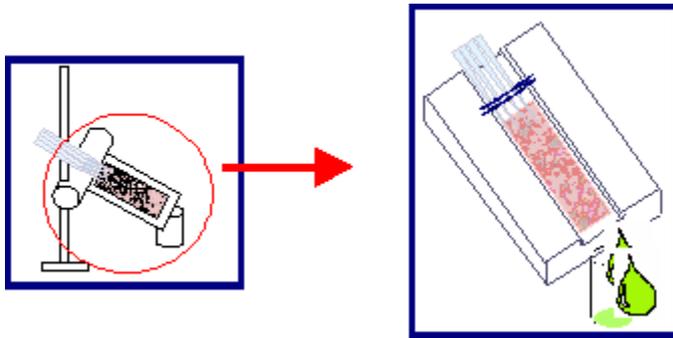
### 2. IN VIVO METHODS

- Use of radio isotopes
- Use of gamma scintigraphy

## Measurement of residence time / retention time

- Measured at site of application.
- Provides quantitative information on mucoadhesive properties.

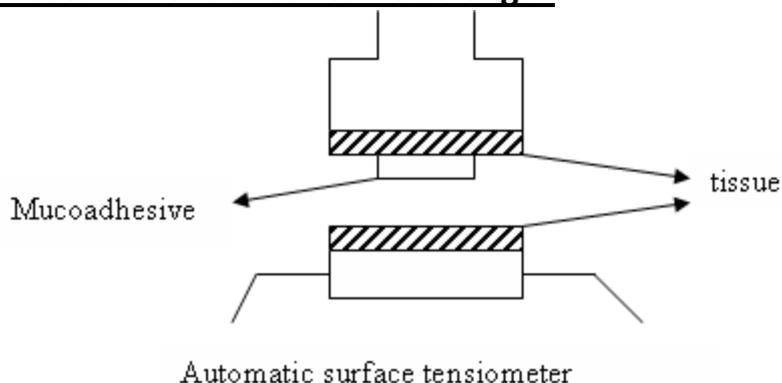
- The GI transit time of many mucoadhesives have been examined using radioisotopes e.g.  $^{51}\text{Cr}$  and the time dependent distribution of the radioactivity in the GIT is measured.
- As same, redionuclides such as  $^{99\text{m}}\text{Tc}$ ,  $^{113\text{m}}\text{In}$  or  $^{123}\text{I}$  are used and their transit through the GIT is measured by  $\gamma$  scintigraphy.



In-vitro apparatus used to measure bioadhesive retention to a particular tissue

- If we want to test the esophageal bioadhesive retention, then Longitudinal sections of *ex vivo* porcine oesophageal tissue is used and sections are equilibrated to  $37^\circ\text{C}$  in a humidity chamber immediately prior to use. The tissue is washed at a rate of  $1\text{ml}/\text{min}$  to simulate saliva flow.
- $1.5\text{ mL}$  of formulation was mixed with  $\sim 0.2\text{ MBq}$   $\text{Tc}99\text{m}$  as a radioactive label and it is spread evenly over the mounted tissue surface and washing initiated. Eluate was collected into tubes at regular intervals up to 30 minutes. The radioactivity in each tube was measured to determine the percentage of the dose washed off at each time point

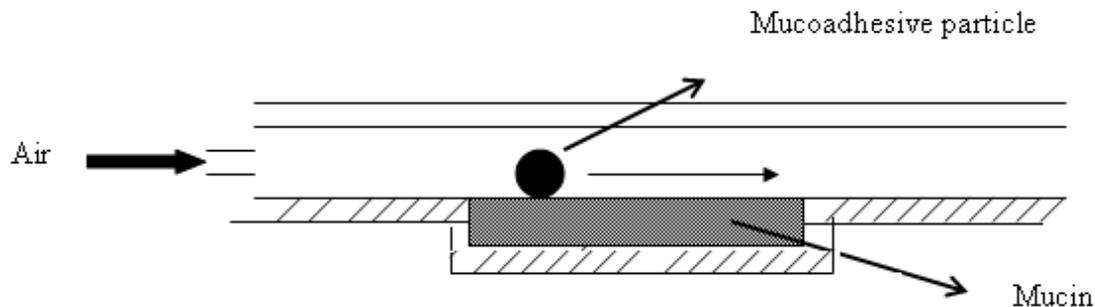
### Measurement of adhesive strength



- Three different types of stress, tensile, shear and peel stress are measured.
- For simulation of actual application conditions, the ideal substrate would be the tissue to which the mucoadhesive system will be applied and the force required to

separate mucoadhesives from mucosal tissue is measured using modified automatic surface tensiometer.

- The results from measuring tensile strength provides information regarding the effects of charge density, hydrophobicity and experimental conditions such as pH, ionic strength, mucolytic agents and applied pressure on bioadhesion.



The shear stress measures the force that causes mucoadhesive to slide with respect to the mucus layer in a direction parallel to their plane of contact.

- The shear mucoadhesive strength is measured by flow channel method where force necessary for the detachment of a particle placed on the mucin gel was determined by passing humid air through the flow cell.
- The peel test involves the application of stress over a fine line at the edge rather than over the entire area of contact sites.

### Thumb test

- Here, the adhesiveness is qualitatively measured by the difficulty of pulling the thumb from the adhesive as a function of the pressure and the contact time.
- It provides useful information on mucoadhesive potential.

### Adhesion Number

- With a mucoadhesive in the form of small particles, the adhesion number can be used as a parameter for Mucoadhesion.
- The adhesion number (Na) is,  
$$Na = (N/No) * 100$$

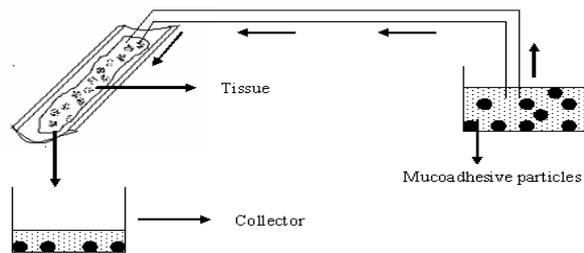
Where,

No = total no. of applied particles

N = no. of particles attached to the substrate.

- It is assumed that as the adhesion strength increases, the adhesion number also increases.

## Falling liquid film method



Small intestinal segments from rats were placed at an inclination on a tygon tube.

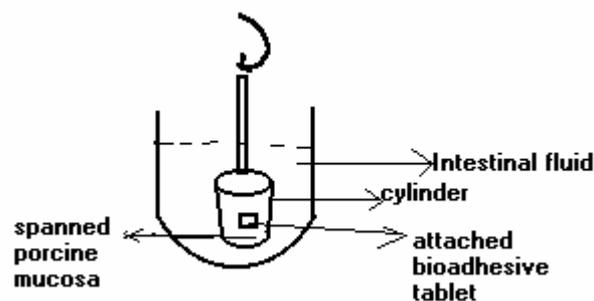
- The adhesion of particles to this surface is measured by passing the particle suspension over the surface and by comparing the fraction of particles adhered to the tissue; the adhesion strength of different polymers can be determined.

## Membrane viscosity

- The interaction between polymers and cell membranes was examined by labeling the cell membranes with fluorescent probes.
- The lipid bilayer and proteins of cell membranes were labeled with pyrene and fluorescein isothiocyanate.
- The fluorescence spectrum of pyrene and the fluorescence depolarization of fluorescein isothiocyanate were used to examine the change in membrane viscosity after interaction with polymer.

## Mucoadhesion studies

- Bernkop-schnurch and steininger et al. have established a new method to evaluate the binding to the mucosa as well as the cohesiveness of the tablet.
- The prepared tablets were attached to freshly excised intestinal porcine mucosa, which has been spanned on stainless steel cylinder (apparatus 4 cylinder, USP XXII).



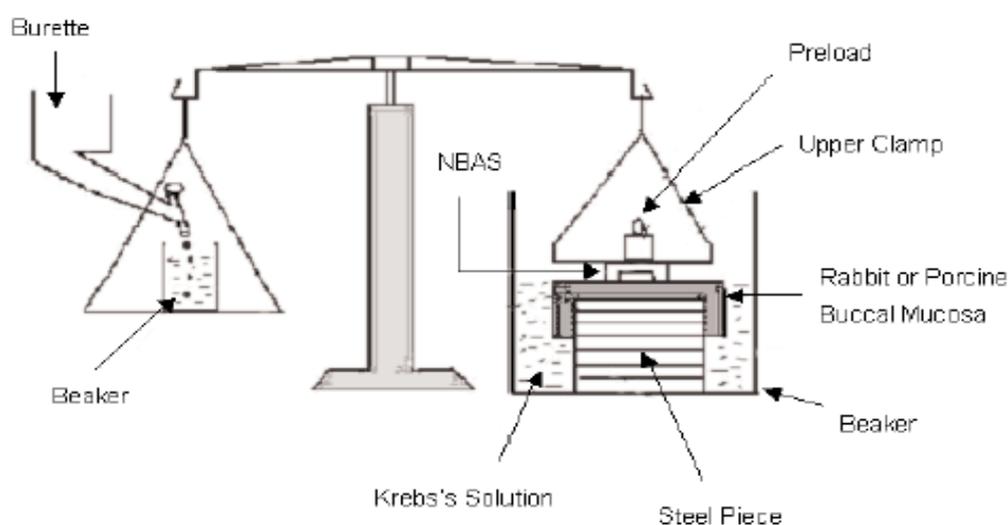
- Thereafter, the cylinder was placed in the dissolution apparatus according to the USP containing 100 mM Tris-HCl buffered saline (TBS). The fully immersed cylinder was agitated with 250 rpm. The detachment, disintegration or erosion of tablet were observed and recorded within a time period of 10h.

## In vivo evaluation methods

In vivo methods used for evaluation methods are based on administration of polymers to a laboratory animal and tracking their transit through the GI system. Administration methods include forced oral gavage, surgical stomach implantation and infusion through a loop placed in situ in the small intestine. Tracking generally followed with the help of X-ray studies, radio opaque markers and radioactive elements etc. For e.g. X- ray studies for monitoring GI transit time for bioadhesive tablet made of BaSO<sub>4</sub> and radiolabelled microspheres and nanoparticles is carried out.

## Mucoadhesive strength measurement.

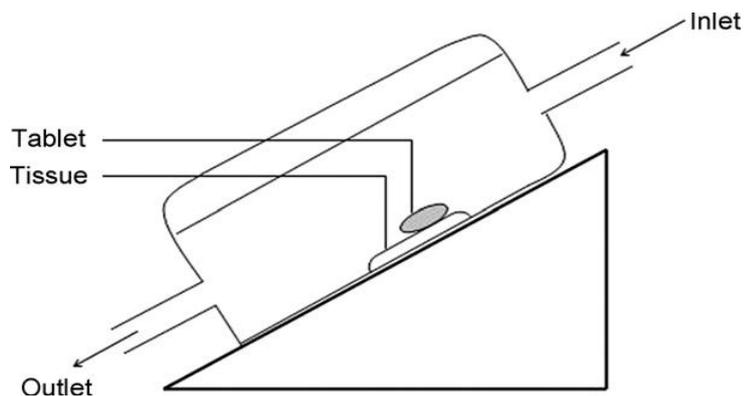
Here first tissue novel bioadhesive system (NBAS) is placed or adhered to the rabbit or porcine buccal mucosa. Whole assembly placed in the krebs solution . Then NBAS is clamped. On other side, from the burette liquid is poured and amount of liquid required to detach the NBAS from tissue is measured. An thus bioadhesive strength measured.



**Figure 5.** Mucoadhesive strength measurement device.

## Dissolutin of Buccal tablet:-

Mumtaz and Chang model for the dissolution of the buccal tablet as shown in figure. From the inlet dissolution medium is poured and from outlet it is collected. And assayed.



### Some currently available bioadhesive formulations in U.K.

PRODUCT	COMPANY	BIOADHESIVE AGENT	PHARMACEUTICAL FORM
Buccastem®	Reckitt Benckiser	PVP, Xanthum gum	Buccal tablet
Corlan pellets®	Celltech	Acacia gum	Oromucosal pellets
Suscard®	Forest	HPMC	Buccal tablet
Gaviscon liquid®	Reckitt Benckiser	Sodium alginate	Oral liquid
Orabase®	Convatech	Pectin, Gelatin	Oral paste
Corsodyl gel®	GalaxoSmithKline	HPMC	Oromucosal gel
Pilogel	Alcon	Carbomere	Eye ge
Timoptol	Merk, sharpe and Dohme	Gallan gum	Eye gel forming solution
Aci- jel	Janssen- cilag	Tragacanth	Vaginal gel
Crinone	Serono	Carbomer	Vaginal gel
Gynol	Janssen- cilag	Sod. CMC & PVP	Vaginal gel
Zidoval	3M	Carbomer	Vaginal gel
Nyogel®	Novartis	Carbomer and PVA	Eye gel

### **Study Questions:-**

- ⊕ Give the definitions and importance of BDDS.
- ⊕ Theories of bioadhesion
- ⊕ Which are the factors important to bioadhesion?
- ⊕ Give classifications of BDDS.
- ⊕ Write note on Buccal BDDS with its advantages and limitations.

- ⊕ How will you do the evaluation of bioadhesive drug delivery systems?
- ⊕ What is the importance of Transmucosal routes of drug delivery? Suggest potential sites and mechanism of adhesion? Enumerate mucosal permeation enhancers and experimental methods to evaluate them. Write a note on intraperiodental drug delivery systems. ( March- 2005)
- ⊕ What is the importance of Transmucosal routes of drug delivery? Suggest potential sites and mechanism of adhesion? Enumerate mucosal permeation enhancers and experimental methods to evaluate them. How you will approach combination drug therapy in transdermal patch? ( University Exam – 2005)
- ⊕ Write a short note on Buccal patch ( Sept-2006)