



Mucoadhesive drug delivery system

- » Bioadhesion can be defined as the state in which two materials, at least one of which is biological in nature, are maintained together for a prolonged time period by means of interfacial forces
- » During the 1980s, this concept began to be applied to drug delivery systems. It consists of the incorporation of adhesive molecules into some kind of pharmaceutical formulation intended to stay in close contact with the absorption tissue, releasing the drug near to the action site, thereby increasing its bioavailability and promoting local or systemic effects

Introduction

- » Type 1, adhesion between two biological phases, for example, platelet aggregation and wound healing.
- » Type 2, adhesion of a biological phase to an artificial substrate, for example, cell adhesion to culture dishes and biofilm formation on prosthetic devices and inserts.
- » Type 3, adhesion of an artificial material to a biological substrate, for example, adhesion of synthetic hydrogels to soft tissues and adhesion of sealants to dental enamel.

Classification of bioadhesion ➤³

- » For drug delivery purposes, the term bioadhesion implies attachment of a drug carrier system to a specified biological location.
- » The biological surface can be epithelial tissue or the mucus coat on the surface of a tissue.
- » If adhesive attachment is to a mucus coat, the phenomenon is referred to as **MUCOADHESION**

1. A prolonged residence time at the site of drug action or absorption.
2. A localization of drug at a given target site.
3. An increase in the drug concentration gradient due to the intense contact of particles with the mucosa
4. A direct contact with cells that is the first step before particle absorption
5. Ease of administration
6. Termination of therapy is easy.{except gastrointestinal}
7. Permits localization of drug to the oral cavity for a prolonged period of time
8. Can be administered to unconscious patients. {except gastrointestinal}

Advantages

9. Offers an excellent route, for the systemic delivery of drugs with high first pass metabolism, thereby offering a greater bioavailability
10. A significant reduction in dose can be achieved there by reducing dose related side effects
11. Drugs which are unstable in the acidic environment or destroyed by enzymatic or alkaline environment of intestine can be administered by this route. Eg. Buccal, sublingual, vaginal
12. Drugs which show poor bioavailability via the oral route can be administered conveniently
13. It offers a passive system of drug absorption and does not require any activation

14. The presence of saliva ensures relatively large amount of water for drug dissolution unlike in case of rectal and transdermal routes {buccal mucosa}
15. Systemic absorption is rapid
16. This route provides an alternative for the administration of various hormones, narcotic analgesic, steroids, enzymes, cardiovascular agents etc.
17. The buccal mucosa is highly perfused with blood vessels and offers a greater permeability than the skin
18. Less dosing frequency
19. Shorter treatment period
20. Increased safety margin of high potency drugs due to better control of plasma levels

21. Maximum utilization of drug enabling reduction in total amount of drug administered
22. Improved patient convenience and compliance due to less frequent drug administration
23. Reduction in fluctuation in steady state levels and therefore better control of disease condition and reduced intensity of local or systemic side effects

1. Drugs, which irritate the oral mucosa, have a bitter or unpleasant taste, odour, cannot be administered by this route
2. Drugs, which are unstable at target site pH cannot be administered by this route
3. Only drugs with small dose requirements can be administered {except GI}
4. Only those drugs, which are absorbed by passive diffusion, can be administered by this route
5. Eating and drinking may become restricted {buccal mucosa}
6. Swallowing of the formulation by the patient may be possible {buccal mucosa}
7. Over hydration may lead to the formation of slippery surface and structural integrity of the formulation may get disrupted by the swelling and hydration of the bioadhesive polymers

Limitations

- » Controlled release
- » Target & localised drug delivery
- » By pass first pass metabolism
- » Avoidance of drug degradation
- » Prolonged effect
- » High drug flux through the absorbing tissue
- » Reduction in fluctuation of steady state plasma level

Need of mucoadhesive dds – in short ➤¹⁰

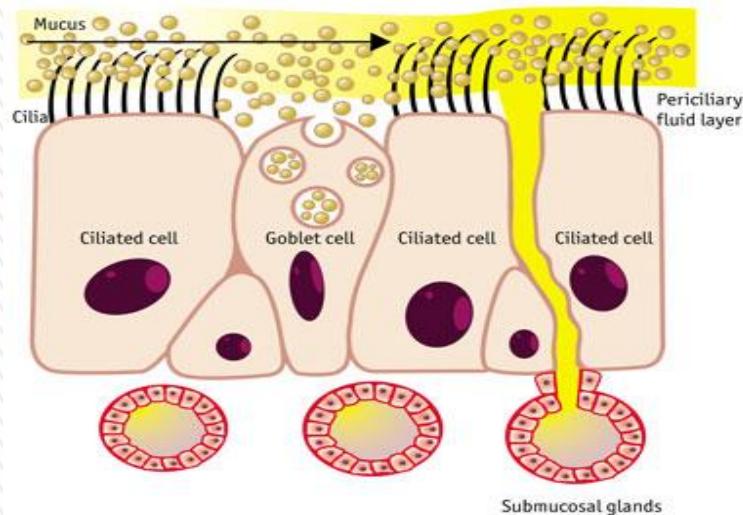
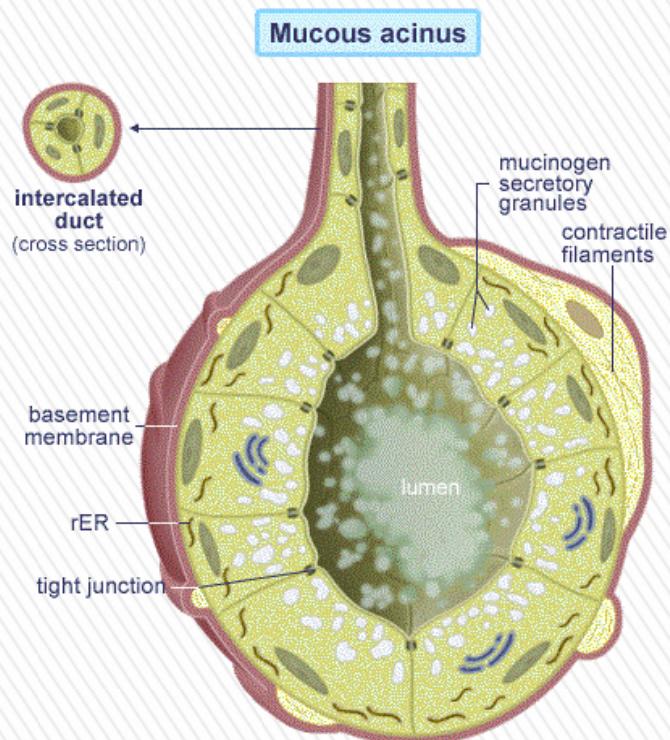
- » Mucous membranes are the moist linings of the orifices and internal parts of the body
- » They cover, protect, and provide secretory and absorptive functions
- » Mucosal membranes are relatively permeable and allow fast drug absorption.
- » They are characterized by an epithelial layer whose surface is covered by mucus.

MUCOUS MEMBRANE >¹¹

- » Mucus is a translucent and visco-elastic secretion, which forms a thin, continuous gel blanket adherent to mucosal epithelial surface.
- » The mean thickness of this layer varies from about 50-450 μm in humans.

Mucus

» It is secreted by the goblet cells lining the epithelia or by special exocrine glands with mucus cells (acini).



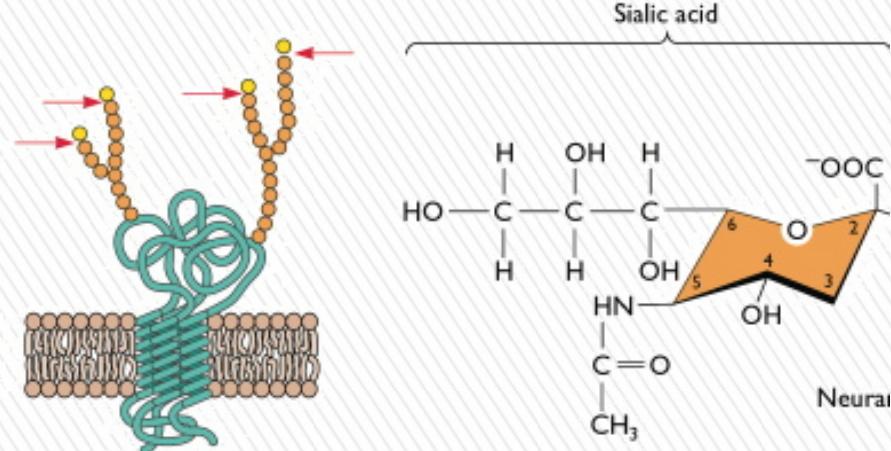
- » The primary constituent of mucus is a glycoprotein known as mucin as well as water and inorganic salts.

S.NO.	COMPOSITION	%AMOUNT
1	WATER	95
2	GLYCOPROTEINS &LIPIDS	0.5-5.0
3	MINERAL SALTS	1
4	FREE PROTEINS	0.5-1.0

- » Mucin units contain an average of about 8-10 monosaccharide residues of five different types.

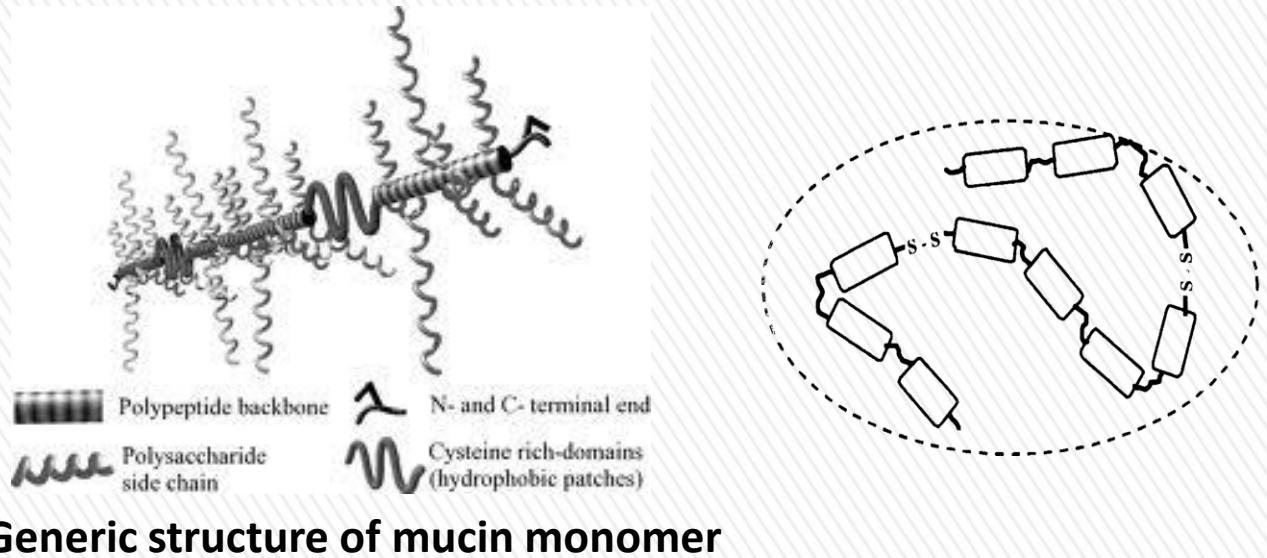
- » They are:

- a) L-fructose
- b) D-galactose
- c) N-acetyl-D-glucosamine
- d) N-acetyl-D-galactosamine
- e) Sialic acid



COMPOSITION OF MUCUS

- » Complex-high molecular weight macromolecule consisting of a polypeptide (protein) backbone to which carbohydrate side chains are attached



- » Mucin forms flexible, threadlike strands that are internally cross linked by disulphide bond

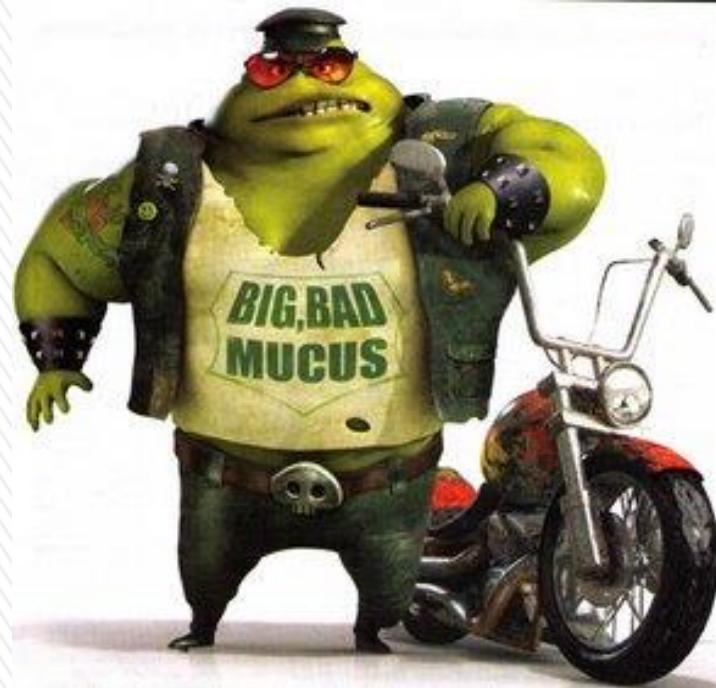
Structure of mucin

- » Protective role: The Protective role results particularly from its hydrophobicity and protecting the mucosa from the lumen diffusion of hydrochloric acid from the lumen to the epithelial surface



Functions of mucus layer

- » Barrier role: The mucus constitutes diffusion barrier for molecules, and especially against drug absorption diffusion through mucus layer depends on molecule charge, hydration radius, ability to form hydrogen bonds and molecular weight



» Lubrication role: An important role of the mucus layer is to keep the membrane moist. Continuous secretion of mucus from the goblet cells is necessary to compensate for the removal of the mucus layer due to digestion, bacterial degradation and solubilisation of mucin molecules

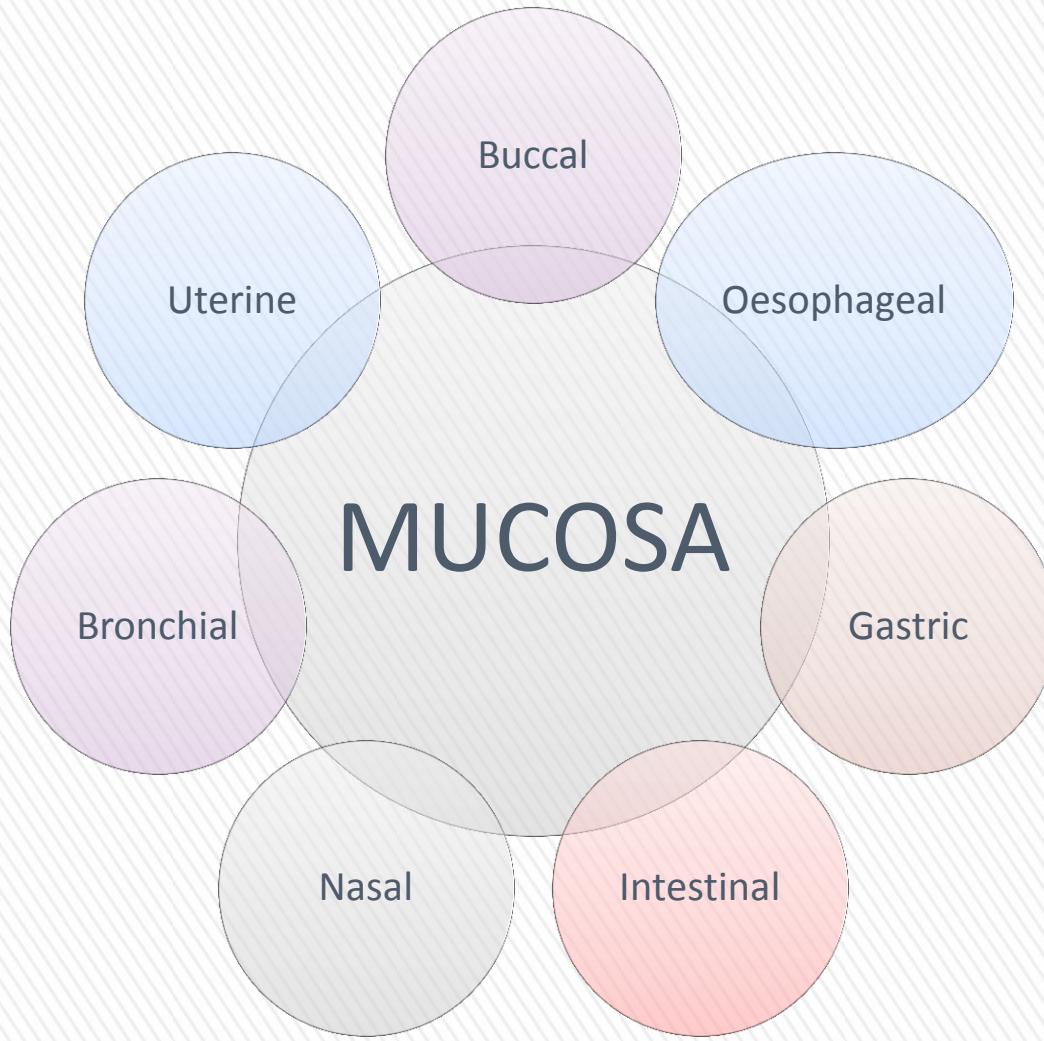


- » Adhesion role: Mucus has strong cohesive properties and firmly binds the epithelial cells surface as a continuous gel layer
- » Mucoadhesion role: At physiological pH, the mucus network may carry a significant negative charge because of the presence of sialic acid and sulphate residues and this high charge density due to negative charge contributes significantly to the bioadhe



- » There are two routes involved in drug permeation across epithelial membranes :
 - 1) Paracellular route
 - 2) Transcellular route
- » Paracellular is the transport of molecules around or between cells. Tight junctions exist between cells.
- » The intercellular tight junction is the major barrier to paracellular transport of macromolecules and polar compounds

Transmucosal drug transport



Examples of mucosa

Stages of Mucoadhesion

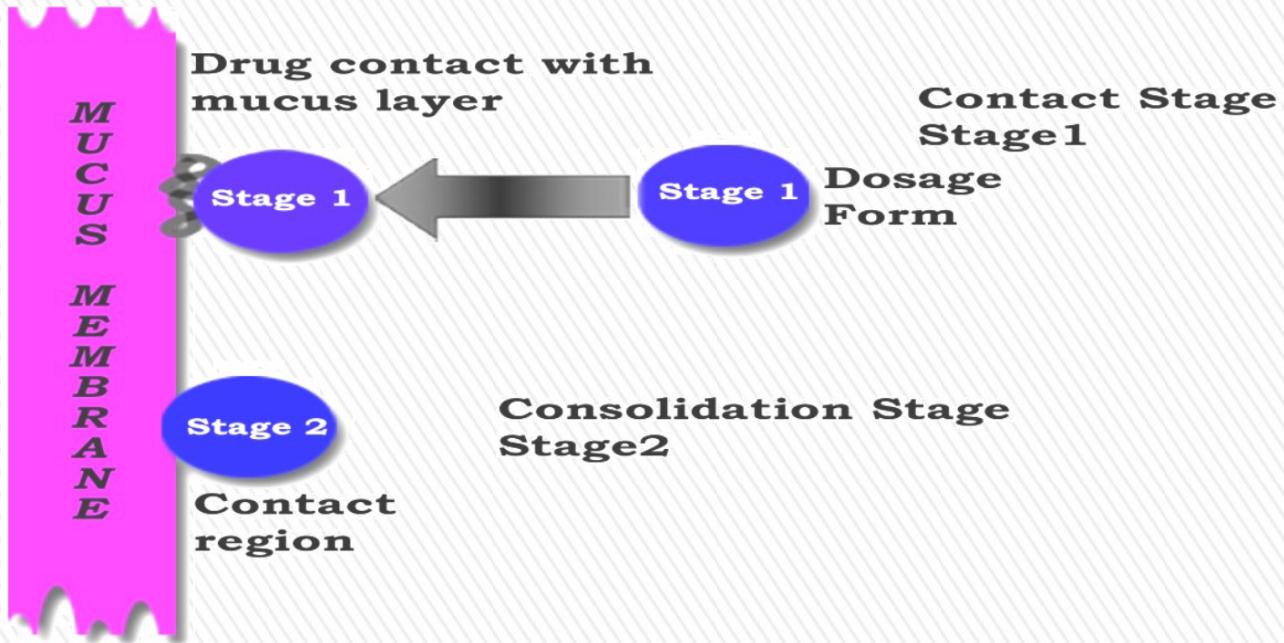


Fig. No.1. The two steps of the mucoadhesion process.

- » Stage 1: Contact stage
- » Stage 2: Consolidation stage

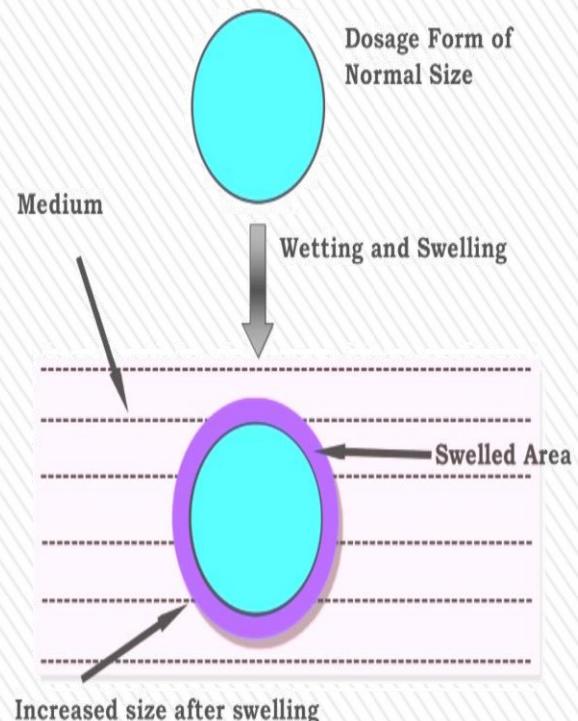
Stages of mucoadhesion

- » It is a three step process:-
- » **STEP 1:** Wetting and swelling of polymer
- » **STEP 2:** Interpenetration between the polymer chains and the mucosal membrane.
- » **STEP 3:** Formation of chemical bonds between the entangled chains.

Mechanism of mucoadhesion ➤²³

- » The wetting and swelling step occurs when the polymer spreads over the surface of the mucosal membrane in order to develop an intimate contact with the substrate.
- » This can be readily achieved by placing a bioadhesive formulation such as a tablet or paste within the cavity.
- » Bioadhesives are able to adhere to or bond with biological tissues by the help of the surface tension and forces that exist at the site of adsorption or contact.
- » Swelling of polymers occur because the components within the polymers have an affinity for water

Step 1 :-The wetting and swelling

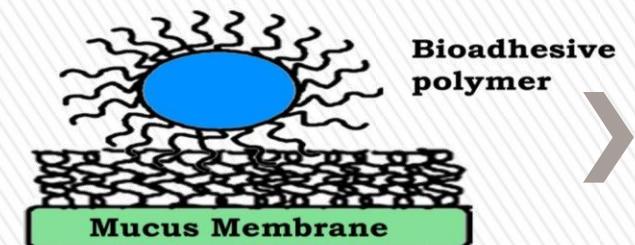
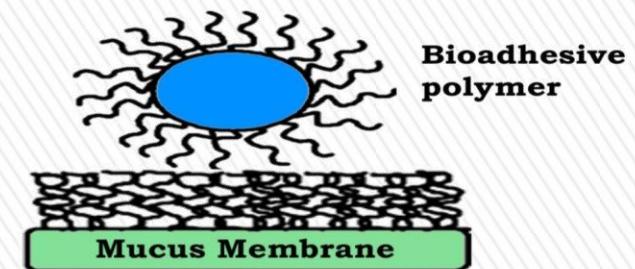
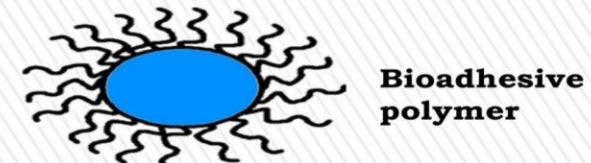


Step 1

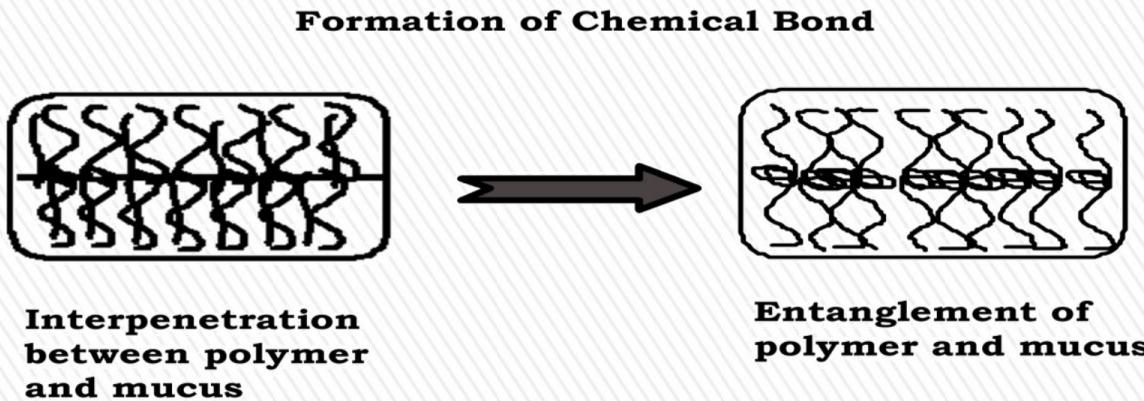
- » The surface of mucosal membranes are composed of high molecular weight polymers known as glycoproteins.
- » In this step interdiffusion and interpenetration take place between the chains of mucoadhesive polymers and the mucous gel network creating a great area of contact.
- » The strength of these bond depends on the degree of penetration between the two polymer groups.
- » In order to form strong adhesive bonds, one polymer group must be soluble in the other and both polymer types must be of similar chemical structure

Step 2

Interdiffusion and Interpenetration



- » In this step entanglement and formation of weak chemical bonds as well as secondary bonds between the polymer chains and mucin molecules occur
- » The types of bonding formed between the chains include primary bonds such as covalent bonds and weaker secondary interactions such as van der Waals Interactions and hydrogen bonds.
- » Both primary and secondary bonds are exploited in the manufacture of bioadhesive formulations

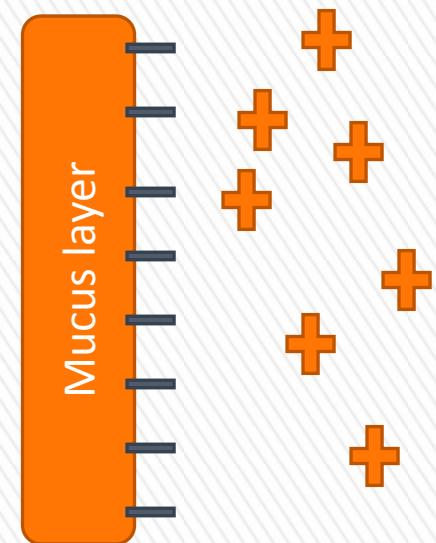


Step 3

1. Electronic theory
2. Adsorption theory
3. Wetting theory
4. Diffusion theory
5. Fracture theory
6. Mechanical theory

Theories of
mucoadhesion

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



Electronic theory

According to the adsorption theory, the mucoadhesive device adheres to the mucus by secondary chemical interactions, such as in van derWaals forces, hydrogen bonds, electrostatic attraction or hydrophobic interactions

For example, hydrogen bonds are the prevalent interfacial forces in polymers containing carboxyl group

Such forces have been considered the most important in the adhesive interaction phenomenon because, although they are individually weak, a great number of interactions can result in an intense global adhesion

Adsorption versus Absorption



Adsorption theory >

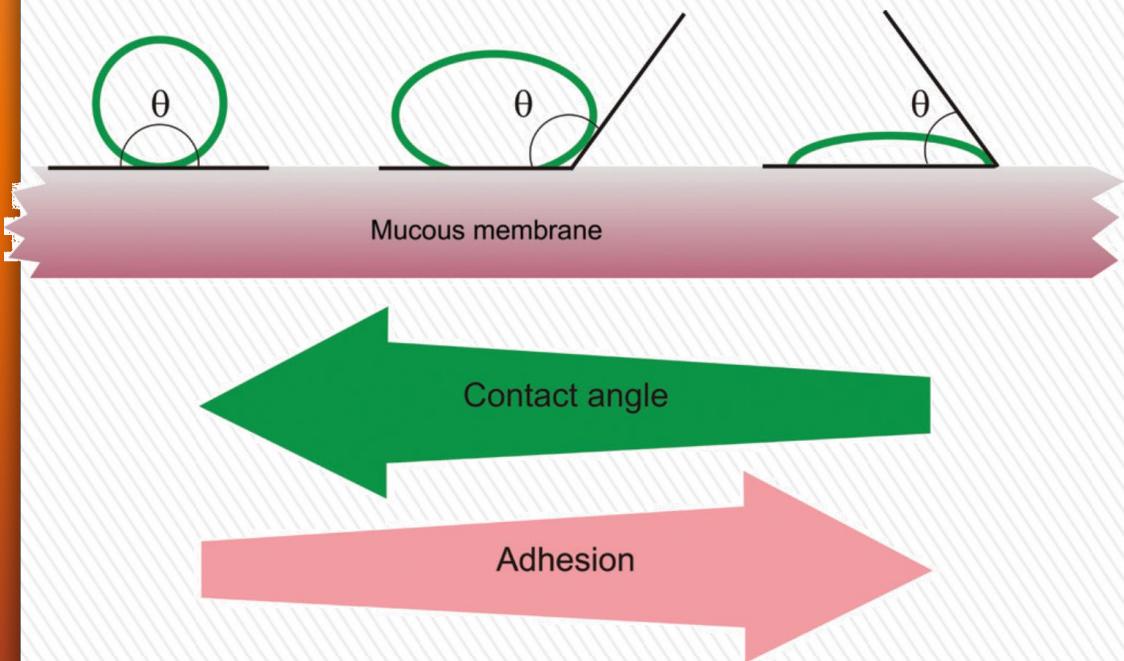
- » The wetting theory applies to liquid systems which present affinity to the surface in order to spread over it. This affinity can be found by using measuring techniques such as the contact angle. The general rule states that the lower the contact angle then the greater the affinity
- » The contact angle should be equal or close to zero to provide adequate spreadability
- » The spreadability coefficient, S_{AB} , can be calculated from the difference between the surface energies γ_B and γ_A and the interfacial energy γ_{AB} , as indicated in equation (1)

$$S_{AB} = \gamma_B - \gamma_A - \gamma_{AB}$$

Wetting theory ⁽¹⁾

- » The greater the individual surface energy of mucus and device in relation to the interfacial energy, the greater the adhesion work, W_A , i.e. the greater the energy needed to separate the two phases

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



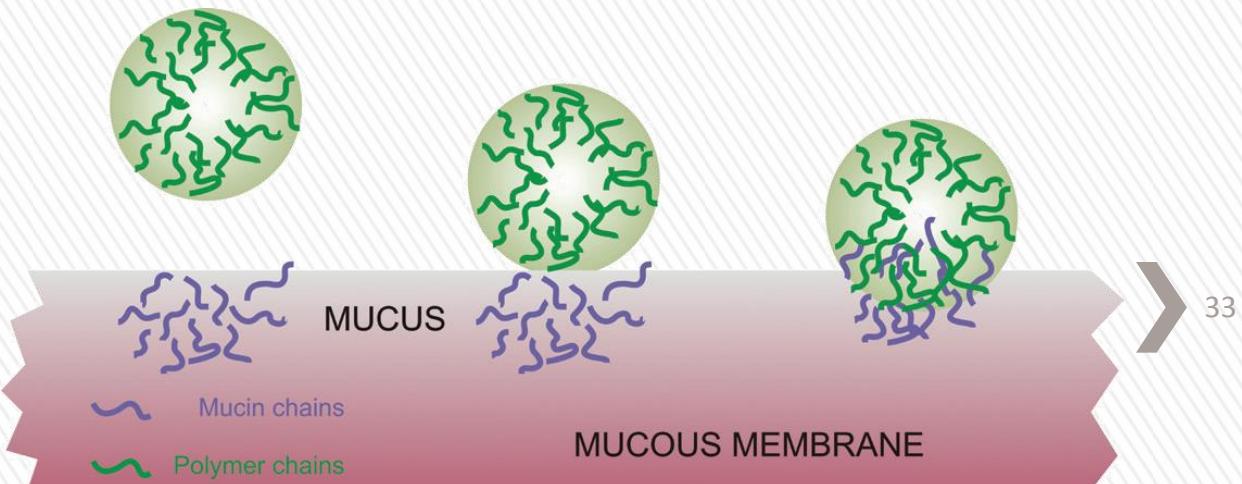
- » Diffusion theory describes the interpenetration of both polymer and mucin chains to a sufficient depth to create a semi-permanent adhesive bond
- » It is believed that the adhesion force increases with the degree of penetration of the polymer chains
- » This penetration rate depends on the diffusion coefficient, flexibility and nature of the mucoadhesive chains, mobility and contact time
- » According to the literature, the depth of interpenetration required to produce an efficient bioadhesive bond lies in the range 0.2-0.5 μm . This interpenetration depth of polymer and mucin chains can be estimated by equation 3:

$$l = (tD_b)^{1/2}$$

where t is the contact time, and D_b is the diffusion coefficient of the mucoadhesive material in the mucus

Diffusion theory

- » The adhesion strength for a polymer is reached when the depth of penetration is approximately equivalent to the polymer chain size
- » In order for diffusion to occur, it is important that the components involved have good mutual solubility, that is, both the bioadhesive and the mucus have similar chemical structures
- » The greater the structural similarity, the better the mucoadhesive bond



- » This is perhaps the most used theory in studies on the mechanical measurement of mucoadhesion.
- » It analyzes the force required to separate two surfaces after adhesion is established.
- » This force, S_m , is frequently calculated in tests of resistance to rupture by the ratio of the maximal detachment force, F_m , and the total surface area, A_0 , involved in the adhesive interaction

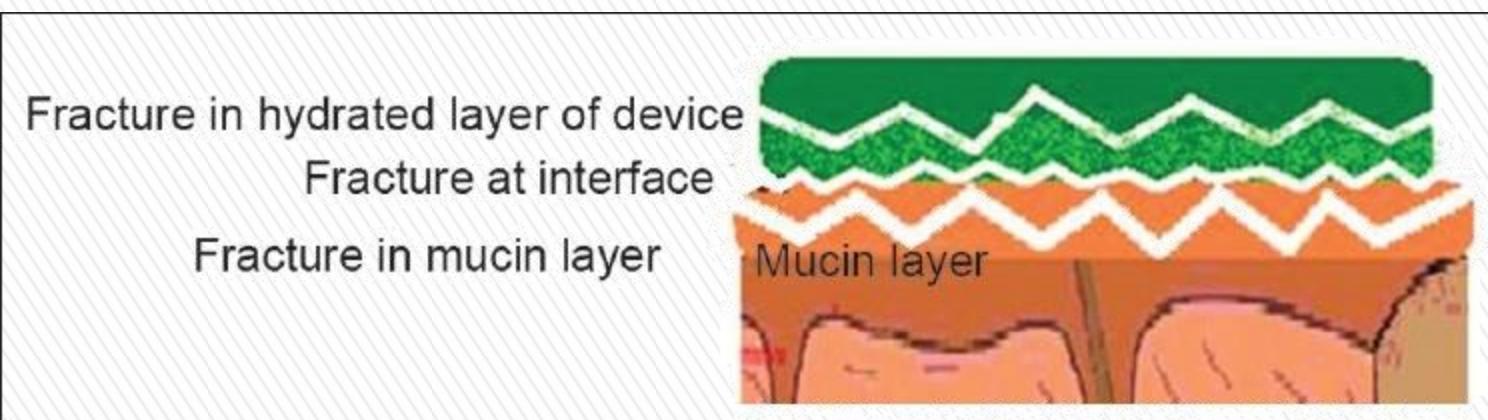
$$S_m = \frac{F_m}{A_0}$$

Fracture theory

- » the fracture force, S_f , which is equivalent to the maximal rupture tensile strength, S_m , is proportional to the fracture energy (g_c), for Young's module (E) and to the critical breaking length (c) for the fracture site, as described in equation

$$S_f \sim \left(\frac{g_c E}{c} \right)^{1/2}$$

- » Since the fracture theory is concerned only with the force required to separate the parts, it does not take into account the interpenetration or diffusion of polymer chains.
- » Consequently, it is appropriate for use in the calculations for rigid or semi-rigid bioadhesive materials, in which the polymer chains do not penetrate into the mucus layer



- » Mechanical theory considers adhesion to be due to the filling of the irregularities on a rough surface by a mucoadhesive liquid.
- » Moreover, such roughness increases the interfacial area available to interactions thereby aiding dissipating energy and can be considered the most important phenomenon of the process



Mechanical theory

Mucoadhesive interactions

Ionic bonds

Covalent bonds

van derWaals forces
of attractions

Hydrogen bonds

Hydrophobic bonds

Factors affecting mucoadhesion

- ✓ Polymer
- ✓ Environment
- ✓ Physiology

Polymer related factors

Molecular weight

Concentration of active polymer

Flexibility of polymer chains

Spatial confirmation

Cross linking density

Charge

Hydration

- » The interpenetration of polymer molecules is favorable for low molecular weight polymer
- » Entanglement of polymer chains is favoured for high molecular weight polymer
- » The mucoadhesive strength of a polymer increases with molecular weights above 1,00,000.
- » Direct correlation between the mucoadhesive strength of polyoxyethylene polymers and their molecular weights lies in the range of 2,00,000-70,00,000.

Molecular weight > 41

- » When the concentration of the polymer is too low, the number of penetrating polymer chains per unit volume of the mucus is small and the interaction between polymer and mucus is unstable.
- » In general, the more concentrated polymer would result in a longer penetrating chain length and better adhesion.
- » However, for each polymer, there is a critical concentration, above which the polymer produces an "unperturbed" state due to a significantly coiled structure.

Concentration of active polymer

- » As a result, the accessibility of the solvent to the polymer decreases, and chain penetration of the polymer is drastically reduced.
- » Therefore, higher concentrations of polymers do not necessarily improve and, in some cases, actually diminish mucoadhesive properties.
- » One of the studies addressing this factor demonstrated that high concentrations of flexible polymeric films based on polyvinylpyrrolidone or poly(vinyl alcohol) as film-forming polymers did not further enhance the mucoadhesive properties of the polymer

- » Mucoadhesion starts with the diffusion of the polymer chains in the interfacial region.
- » Therefore, it is important that the polymer chains contain a substantial degree of flexibility in order to achieve the desired entanglement with the mucus.
- » In general, mobility and flexibility of polymers can be related to their **viscosities** and **diffusion coefficients**, as higher flexibility of a polymer causes greater diffusion into the mucus network

Flexibility

- » Besides molecular weight or chain length, spatial conformation of a molecule is also important
- » Despite high molecular weight of dextran (19,500,000), they have adhesive properties same as PEG having molecular weight 2,00,000
- » The helical conformation of dextrans shields the adhesive groups
- » PEG polymers have a linear structure

Spatial conformation

- » The average pore size, the number and average molecular weight of the cross-linked polymers, and the density of cross-linking are three important and inter-related structural parameters of a polymer network.
- » Therefore, it seems reasonable that with increasing density of cross-linking, diffusion of water into the polymer network occurs at a lower rate which, in turn, causes an insufficient swelling of the polymer and a decreased rate of interpenetration between polymer and mucin

Crosslinking

density

- » Strong anionic charge on the polymer is one of the required characteristics for mucoadhesion (in acidic conditions)
- » Non-ionic polymers appear to undergo a smaller degree of adhesion compared to anionic polymers.
- » Some cationic polymers demonstrate superior mucoadhesive properties, especially in a neutral or slightly alkaline medium. Additionally, some cationic high-molecular-weight polymers, such as chitosan, have shown to possess good adhesive properties.
- » There is no significant literature about the influence of the charge of the membrane on the mucoadhesion but the pH of the membrane affects the mucoadhesion as it can influence the ionized or un-ionized forms of the polymers.

Charge

- » Hydration is required for a mucoadhesive polymer to expand and create a proper macromolecular mesh of sufficient size, and also to induce mobility in the polymer chains in order to enhance the interpenetration process between polymer and mucin.
- » Polymer swelling permits a mechanical entanglement by exposing the bioadhesive sites for hydrogen bonding and/or electrostatic interaction between the polymer and the mucus network.
- » However, a critical degree of hydration of the mucoadhesive polymer exists where optimum swelling and mucoadhesion occurs

Hydration

Environment related factors

pH of polymer - substrate interface

Applied strength

Initial contact time

Swelling

- » The pH at the bioadhesive to substrate interface can influence the adhesion of bioadhesives possessing ionizable groups.
- » Many bioadhesives used in drug delivery are polyanions possessing carboxylic acid functionalities.
- » If the local pH is above the pK_a of the polymer, it will be largely ionized; if the pH is below the pK_a of the polymer, it will be largely unionized.

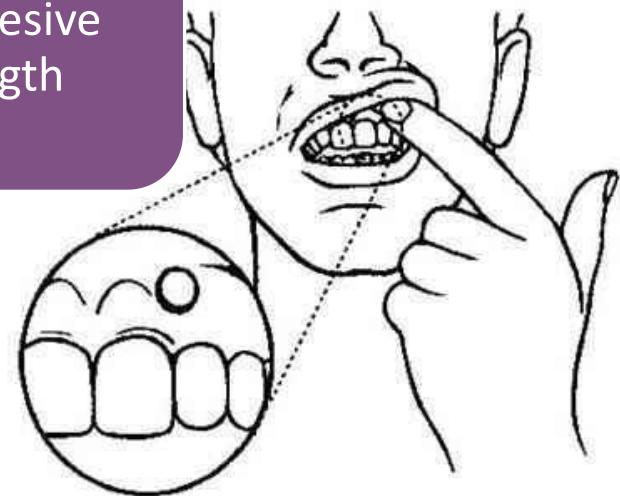
pH of polymer - substrate
interface

- » The approximate pK_a for the poly(acrylic acid) family of polymers is between 4 and 5.
- » The maximum adhesive strength of these polymers is observed around pH 4 - 5 and decreases gradually above a pH of 6.
- » A systematic investigation of the mechanisms of mucoadhesion clearly showed that the protonated carboxyl groups, rather than the ionized carboxyl groups, react with mucin molecules, presumably by the simultaneous formation of numerous hydrogen bonds

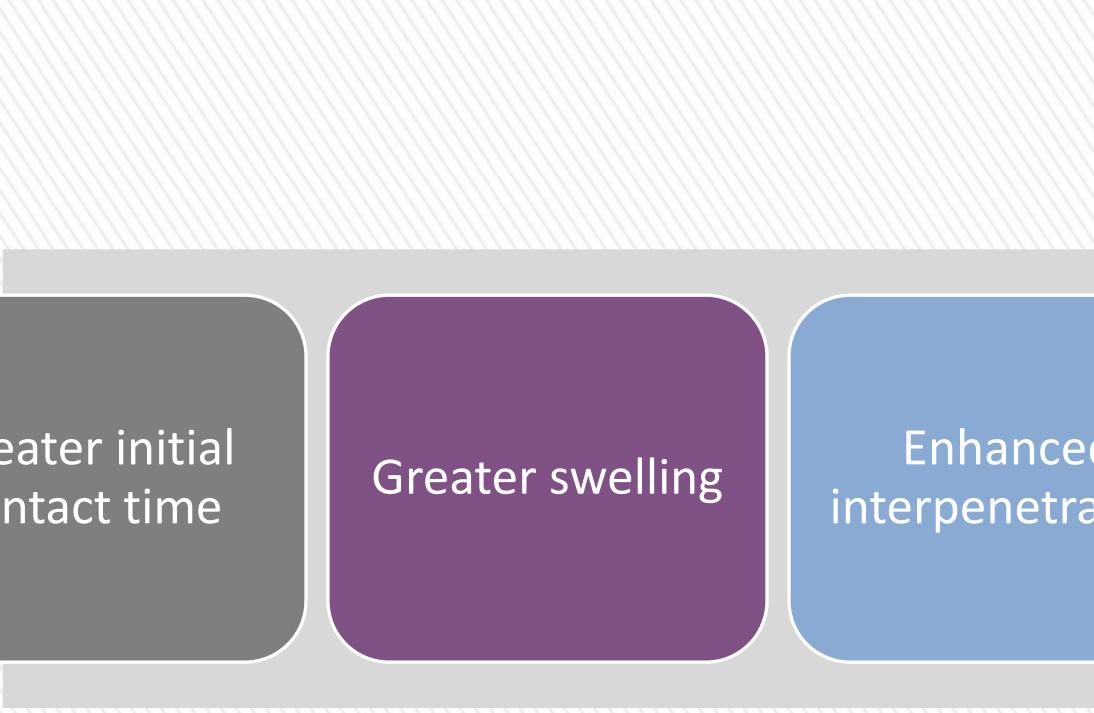
Greater applied strength

Enhanced interpenetration

Higher bioadhesive strength



Applied strength



Greater initial contact time

Greater swelling

Enhanced interpenetration

Higher bioadhesive strength

Initial contact time

- » It depends on both polymer and environment
- » Interpenetration of chains is easier as polymer chains are disentangled and free of interactions
- » When swelling is too great, a decrease in bioadhesion occurs.
- » Such phenomena must not occur too early in order to lead to sufficient bioadhesion
- » Swelling later allows easy detachment of the bioadhesive system after complete release of drug

Swelling

Physiological factors

Mucin turnover
rate

Disease states

- » It is important because:
 - > It limits the residence time of the mucoadhesive on the mucus layer
 - > Mucin turnover results in substantial amounts of free mucin molecules which interact with the mucoadhesive before it can reach the mucus layer.
- » Mucin turnover depends on presence of food
- » Mucociliary clearance in the nasal cavity – 5 mm/min
- » Mucociliary clearance in the tracheal region – 4-10 mm/min

Mucin turnover rate >

» Physicochemical properties of mucus is known to change in conditions like:

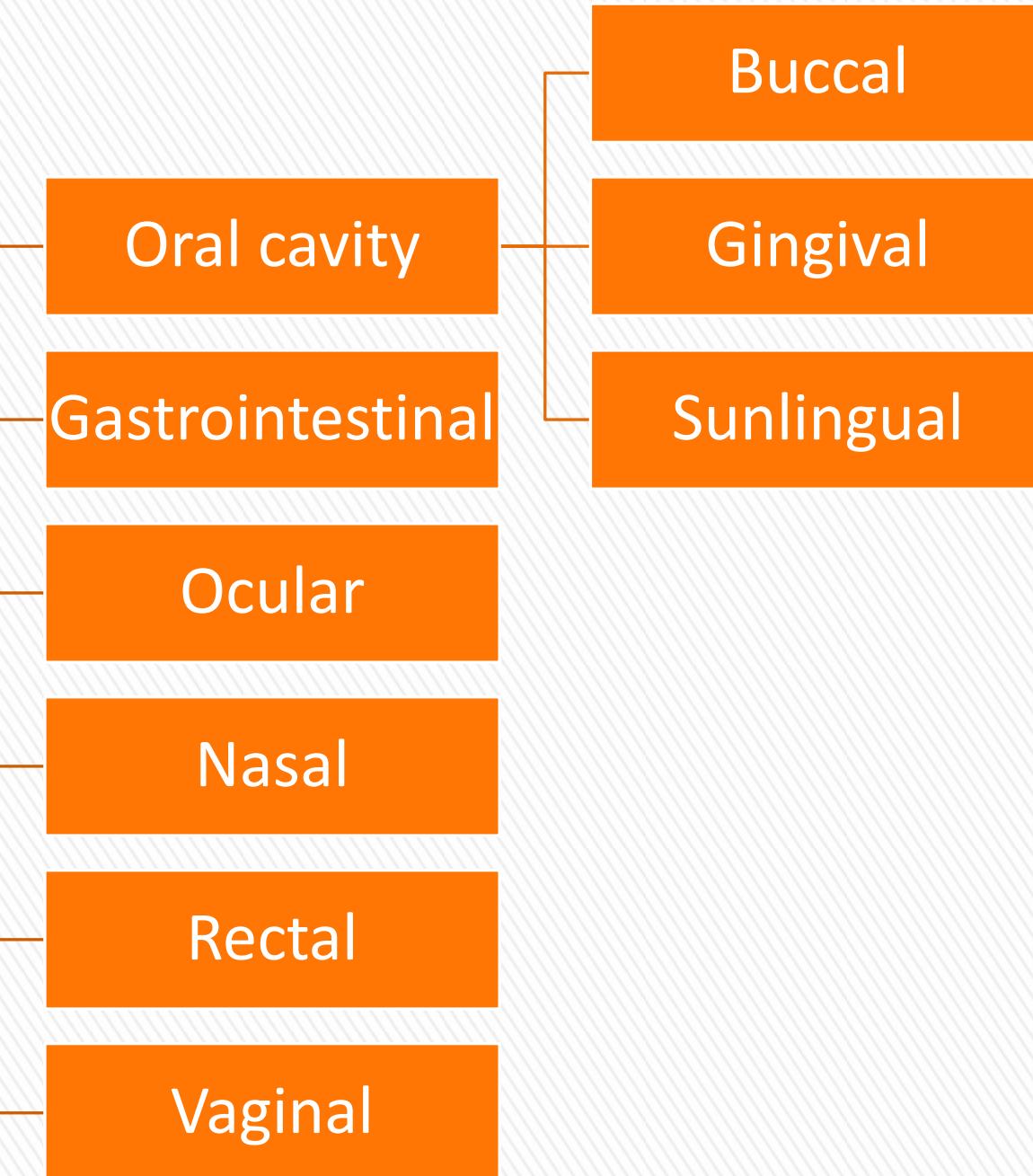
- > Common cold
- > Gastric ulcers
- > Ulcerative colitis
- > Cystic fibrosis
- > Bacterial and fungal infections of the female reproductive system
- > Inflammation of the eye

Disease states

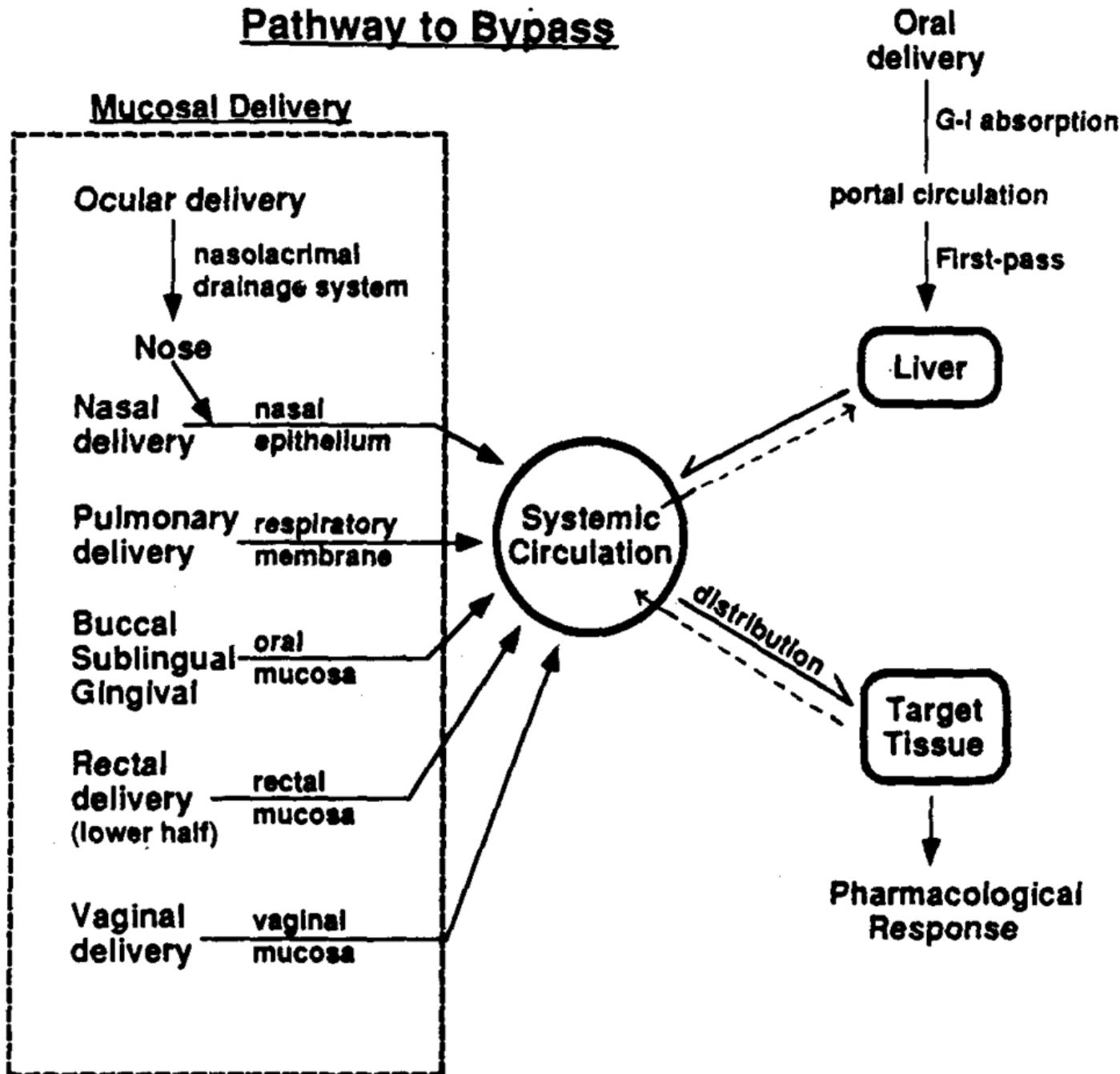
Formulation development

- ✓ Routes
- ✓ Polymers
- ✓ Permeation enhancers
- ✓ Dosage forms
- ✓ Marketed products

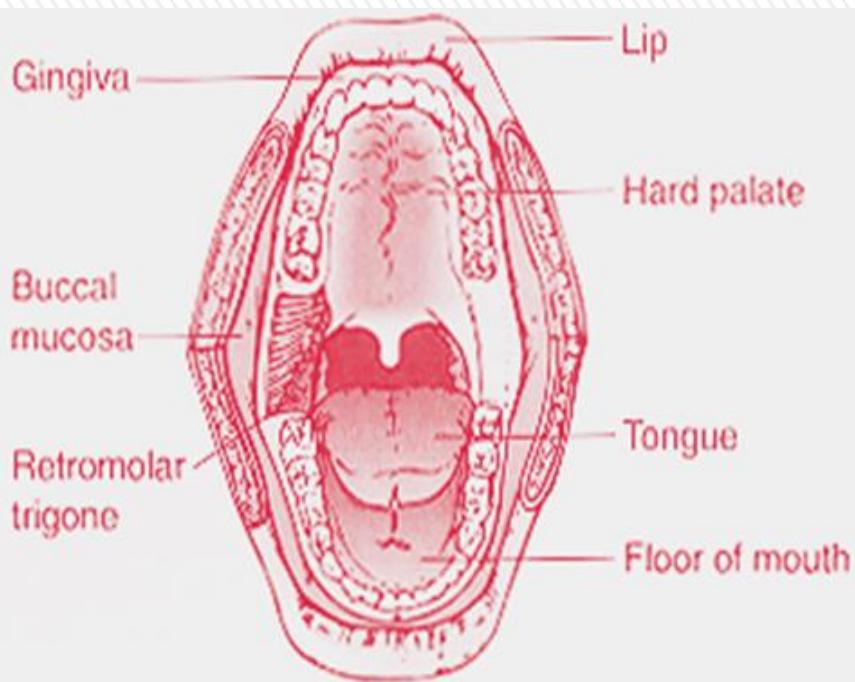
ROUTES



Pathway to Bypass



» Oral bioadhesive formulations are topical products designed to deliver drugs to the oral cavity which act by adhering to the oral mucosa and therefore can produce localised effects within the mouth



THE ORAL CAVITY

Important functions which include chewing, speaking and tasting.

Some of these functions are impaired by diseases such as ulcers, microbial infections and inflammation.

Oral cavity > 61

- » In contact with saliva dosage form swells and adheres to mucosa
- » The drug solubilises in small volume of saliva and is rapidly absorbed through reticulated vein which lies underneath the oral mucosa and is transported by facial vein, internal jugular vein and brachiocephalic vein
- » Rapid absorption.
- » Peak levels seen in 1-2 mins



- » The buccal mucosa refers to the inner lining of the lips and cheeks
- » The epithelium of the buccal mucosa is about 40-50 cells thick and the epithelial cells become flatter as they move from the basal layers to the superficial layers
- » It offers a smooth and relatively immobile surface for placement of the mucoadhesive system
- » It is suitable for sustained delivery of drugs
- » There is a limit to the size of dosage form

Buccal mucosa

» Characteristics of drugs in order to be successfully delivered by this route:

- > Short biological half live
- > Requiring sustained effect
- > Poor permeability
- > Sensitivity to enzymatic degradation
- > Poor solubility
- > Dose of drug < 25 mg

» Drugs: Triamcinolone acetonide, nitroglycerin, prednisolone, testosterone, fentanyl, fluoride

» Relevant dosage forms

- > Adhesive tablets
- > Adhesive patches
- > Adhesive gels
- > Adhesive ointments



- ❑ The sublingual mucosa surrounds sublingual gland which is a mucin-producing salivary gland located underneath the tongue
- ❑ It has higher permeability than buccal mucosa
- ❑ Faster onset of action
- ❑ Adhesive tablets
- ❑ Drugs: Nitroglycerin



Sublingual mucosa

- » Can retain dosage form for long duration
- » Drugs: Testosterone, Fluoride



Gingival mucosa

- » Increases the stay of formulation in GIT
- » Stability problems in intestinal fluids can be overcome
- » Solubility problems in intestinal fluids can be overcome
- » Can be used for drugs acting locally
- » Adhesive tablets, in-situ adhesive gels
- » Drugs: Furosemide, cinnarizine, captopril, chlorthiazide

Gastrointestinal mucosa > 68

- » Not very convenient and effective
- » If a 50 µl drop is instilled, 30 µl is lost because of overflow, 2 µl is lost per blink, hence very little drug remains for absorption after a few seconds
- » Other problems associated with this route:
 - > Loss of drug via drainage
 - > Short residence time
 - > Tear turnover
 - > Protein binding

Ocular mucosa

- » Ideal alternative to parenterals because of:
 - > High vasculature
 - > Ease of intranasal administration
 - > Avoidance of first pass metabolism
- » It is a thin vascular tissue with a surface area of 150 cm²
- » There are 2 types of mucous covering the nasal mucosa
 - > Adhering to the tips of cilia
 - > Filling the space among cilia
- » Nasal mucosa is renewed once every 10 mins
- » Total mucous production: 1500 - 200 ml/day
- » pH of nasal secretions: 5.52 - 6.5 (adults) and 5 - 6.7 (infants and young children)

Nasal mucosa

- » Relevant formulations
 - » Mucoadhesive gels
 - » Mucoadhesive powders
 - » Mucoadhesive microspheres
 - » Mucoadhesive nanoparticles
-
- » Drugs: insulin, nifedipine, beclomethasone dipropionate

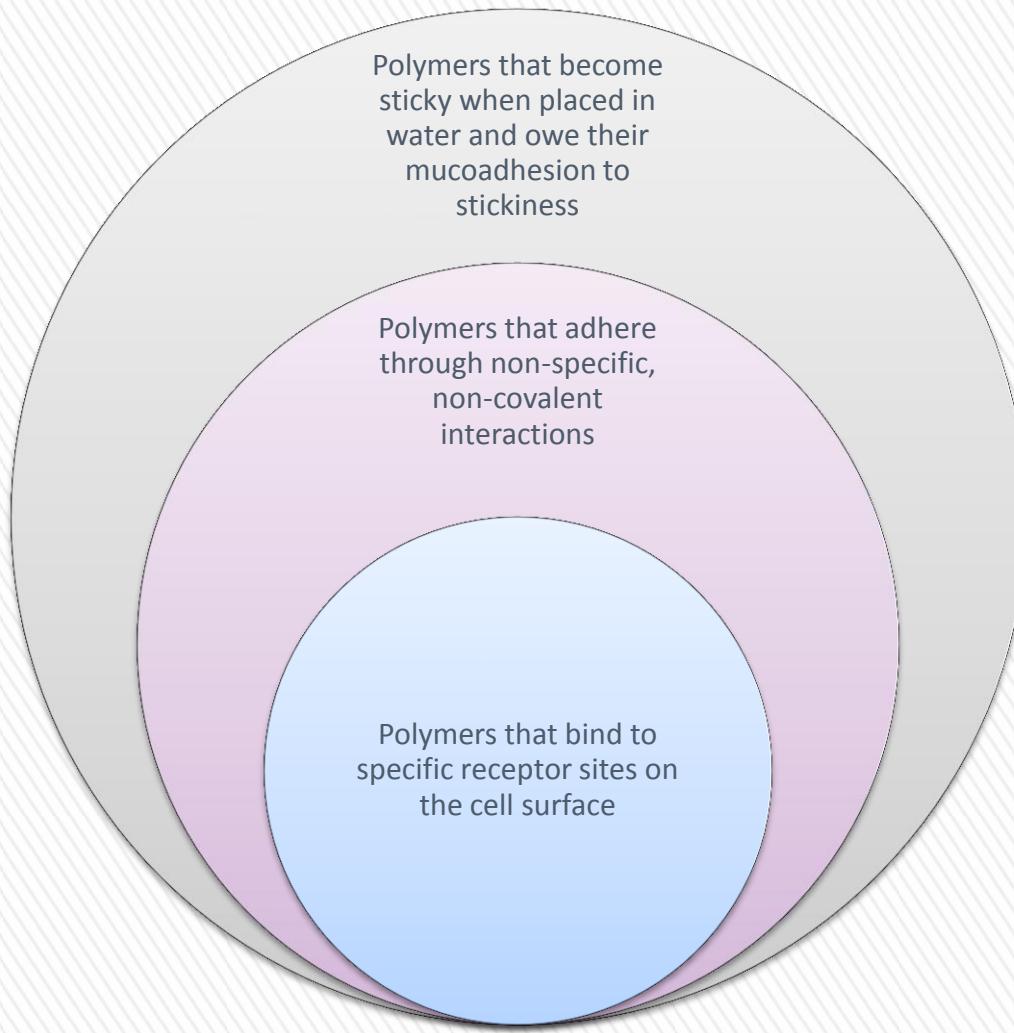
- » Hydrogels are given rectally made of mucoadhesive polymers
- » Drugs: antipyrine

Rectal mucosa

- » Ideal for drugs which:
 - > Are susceptible to gut or hepatic metabolism
 - > Cause gastric irritation
- » Can be used for both topical and systemic diseases
- » Polyacrylic acid and HPMC are ideal polymers

Vaginal mucosa

Mucoadhesive polymers



Classification of adhesive polymers

The polymer and its degradation product should be non-toxic and non-absorbable from GIT

Non-irritant to mucous membrane

Should preferably form strong non-covalent bond with mucin

Should adhere quickly to moist tissue

Site specific

Should allow easy incorporation of drug

Should not offer any hindrance to drug release

Must not decompose on storage throughout the shelf life of the formulation

Should have an optimum degree of cross-linking density, pH and hydration

Should be economic

Ideal characteristics of mucoadhesive polymer

- » Robinson et al using fluorescence technique proved that:
 1. Cationic and anionic polymers bind more effectively than non-ionic polymers
 2. Polyanions are better than polycations
 3. Anionic polymers with sulfate groups bind more effectively than those with carboxylic groups
 4. High degree of binding is proportional to the charge density of polymer
 5. Water insoluble polymers show a greater flexibility as compared to water soluble polymers
- » Highly binding polymers include CMC, gelatin, hyaluronic acid, carbopol, polycarbophil etc

Mucoadhesive
Polymers

First
Generation

Second
Generation

Classification of polymers

- » These materials are natural or synthetic hydrophilic molecules containing numerous organic functions that generate hydrogen bonds such as carboxyl, hydroxyl and amino groups, which do not adhere specifically.
- » These polymers can be subdivided into three classes: cationic, anionic and nonionic.
- » Cationic molecules can interact with the mucus surface, since it is negatively charged at physiological pH. Eg. Chitosan
- » Mucoadhesion of chitosan occurs because of the electrostatic interactions of their amino groups with the sialic groups of mucin in the mucus layer.

First generation polymers

- » In contrast, synthetic polymers derived from polyacrylic acid (carbomers) are negatively charged but are also mucoadhesive.
- » In this case, mucoadhesion results from physical-chemical processes, such as hydrophobic interactions, hydrogen and van derWaals bonds, which are controlled by pH and ionic composition.
- » Other examples of anionic polymers are CMC and alginates
- » Nonionic polymers, including HPMC, HEC and MC, present weaker mucoadhesion force compared to anionic polymers
- » There is a new class of substances being identified as bioadhesive. This class consists of ester groups of fatty acids, such as glyceryl monooleate and glyceryl monolinoleate

- » An ideal polymer should exhibit the ability to incorporate both hydrophilic and lipophilic drugs, show mucoadhesive properties in its solid and liquid forms, inhibit local enzymes or promote absorption, be specific for a particular cellular area or site, stimulate endocytosis and finally to have a broad safety range
- » These novel multifunctional mucoadhesive systems are classified as second generation polymers
- » They are an alternative to non-specific bioadhesives because they bind or adhere to specific chemical structures on the cell or mucus surface.
- » Good examples of these molecules are lectins, invasins, fimbrial proteins, antibodies, and those obtained by the addition of thiol groups to known molecules.

Second generation polymers

- » Permeation enhancers are substances added to pharmaceutical formulation in order to increases the membrane permeation rate or absorption rate of a co-administered drug.
- » They are used to improve bioavailability of drugs with normally poor membrane permeation properties without damaging the membrane and causing toxicity.
- » Enhancer efficacy depends on the physiochemical properties of the drug, administration site, nature of the vehicle and whether enhancer is used alone or in combination

Permeation enhancers

Categories and examples of membrane permeation enhancers

A. Bile salts and other steroidal detergents:

Sodium glycocholate, Sodium taurocholate, Saponins, Sodium tauro dihydro fusidate and Sodium glycol dihydrofusidate.

B. Surfactants:

1. Non- ionic: Laureth-a, Polysorbate-9, Sucrose esters and do-decyl maltoside
2. Cationic: Cetyl trimethylammonium bromide
3. Anionic: sodium lauryl sulfate

C. Fatty acids: oleic acid, lauric acid, caproic acid

D. Other enhancers:

1. Azones
2. Salicylates
3. Chelating agents
4. Sulfoxides e. g. Dimethyl Sulfoxide (DMSO)

Mucoadhesive dosage forms

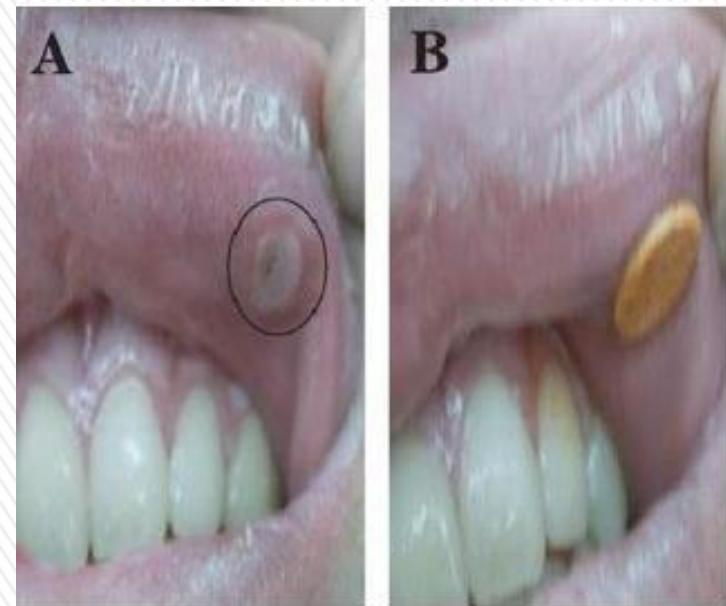
1. Tablets
2. Patches
3. Films
4. Gels and ointments
5. Novel dosage forms

- » Tablets are small, oval and flat, with a diameter of about 5-8 mm.
- » Mucoadhesive tablets allow for speaking and drinking without major discomfort.
- » They adhere to the mucosa, and are remained in position until dissolution or release is complete.
- » It facilitate absorption and improve bioavailability of the drugs due to a high surface to volume ratio and facilitates a much more intimate contact with the mucus layer.
- » Mucoadhesive tablets provides the possibilities of localized as well as systemic controlled release of drugs.



Mucoadhesive tablets >

- » They release the drug for a prolonged period so they are widely used and reduce frequency of drug administration.
- » The lack of physical flexibility is the drawback of mucoadhesive tablets, leading to poor patient compliance for long-term use
- » Made by direct compression or granulation of drug with mucoadhesive polymers.
- » Tablets for routes other than GI have to be very thin to prevent discomfort.
- » Tablets can be single layer or multi layer
- » Tablets can be coated on 3 sides to prevent drug release in bulk of the cavity



- » Patches are covered by protective layer of an impermeable backing material, a mucoadhesive surface for mucosal attachment and a drug-containing reservoir layer from which the drug is released in a controlled way.
- » Solvent casting and direct milling are two methods used to prepare adhesive patches.
- » In the first method, the intermediate sheet is prepared by casting the solution of the drug and polymer(s) onto a backing layer sheet, and subsequently allowing the solvent(s) to evaporate.



Patch

- » In the second method, formulation constituents are homogeneously mixed and compressed to the required thickness, and patches of predetermined shape and size are then cut out.
- » An impermeable backing layer may also be applied to prevent drug loss, control the direction of drug release, and reduced disintegration and deformation of the device during the application period

- » In terms of flexibility and comfort mucoadhesive films may be preferred over adhesive tablets.
- » An ideal film should be soft, elastic, flexible and yet adequately strong to withstand breakage due to stress from mouth movements.
- » It must also possess enough mucoadhesive strength in order to be attached in the mouth for the desired duration of action

Films

- » Such type of semisolid dosage forms, have the advantage of easy dispersion throughout the oral mucosa.
- » However, drug delivery from semisolid dosage forms may not be as accurate as from patches, tablets, or films.
- » Less retention of the gels at the site of application has been improved by using mucoadhesive formulations.
- » Some mucoadhesive polymers, for example, sodium carboxymethylcellulose, carbopol, hyaluronic acid, and xanthan gum are used.

Gels and ointments > 90

- » Hydrogels are used for buccal drug delivery. They are formed from polymers that are hydrated in an aqueous condition and drug molecules entrap for subsequent slow release by diffusion.
- » The application of mucoadhesive gels provides an extended retention time in the oral cavity, adequate drug penetration, as well as high efficacy and patient acceptability.

- » In case of the local delivery of medicinal agents for the treatment of periodontitis, adhesive gels have the major application which is an infectious and inflammatory disease that causes formation of pockets between the gum and the tooth, and can cause loss of teeth.
- » When mucoadhesive polymers incorporated in antimicrobial-containing formulations then these are useful for periodontitis therapy and easily introduced into the periodontal pocket with a syringe

- » Despite the limited loading capacity of drug, bioadhesive micro-and /or nanoparticles have been widely investigated for three major features:
 1. Immobilization of particles on the mucosal surface by adhesion after modification of surface properties via bioadhesive polymers.
 2. Very large specific surface between the dosage forms and the oral mucosa.
 3. Sustained release of entrapped drug, leading to higher absorption.

Novel dosage forms >

Evaluation

1. In vitro/ ex vivo
2. In vivo

- » *In vitro/ex vivo tests are important in the development of a controlled release bioadhesive system because they contribute to studies of*
 1. *Permeation*
 2. *Release*
 3. *Compatibility*
 4. *Mechanical and physical stability*
 5. *Superficial interaction between formulation and mucous membrane; and*
 6. *Strength of the bioadhesive bond.*
- » *These tests can simulate a number of administration routes including oral, buccal, periodontal, nasal, gastrointestinal, vaginal and rectal.*

In vitro/ ex vivo tests

Bioadhesion
strength

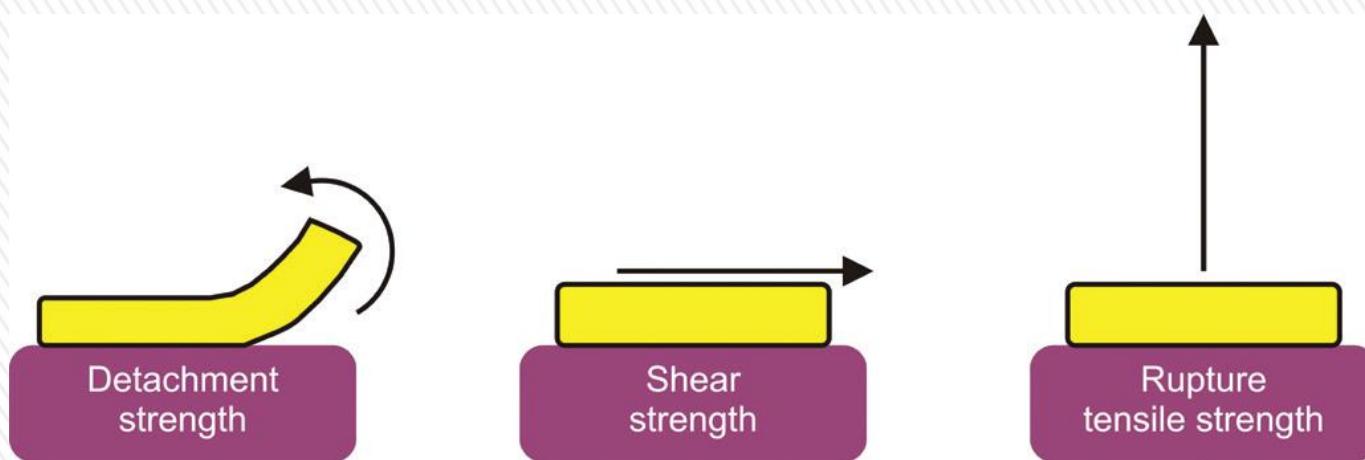
Tensile
strength

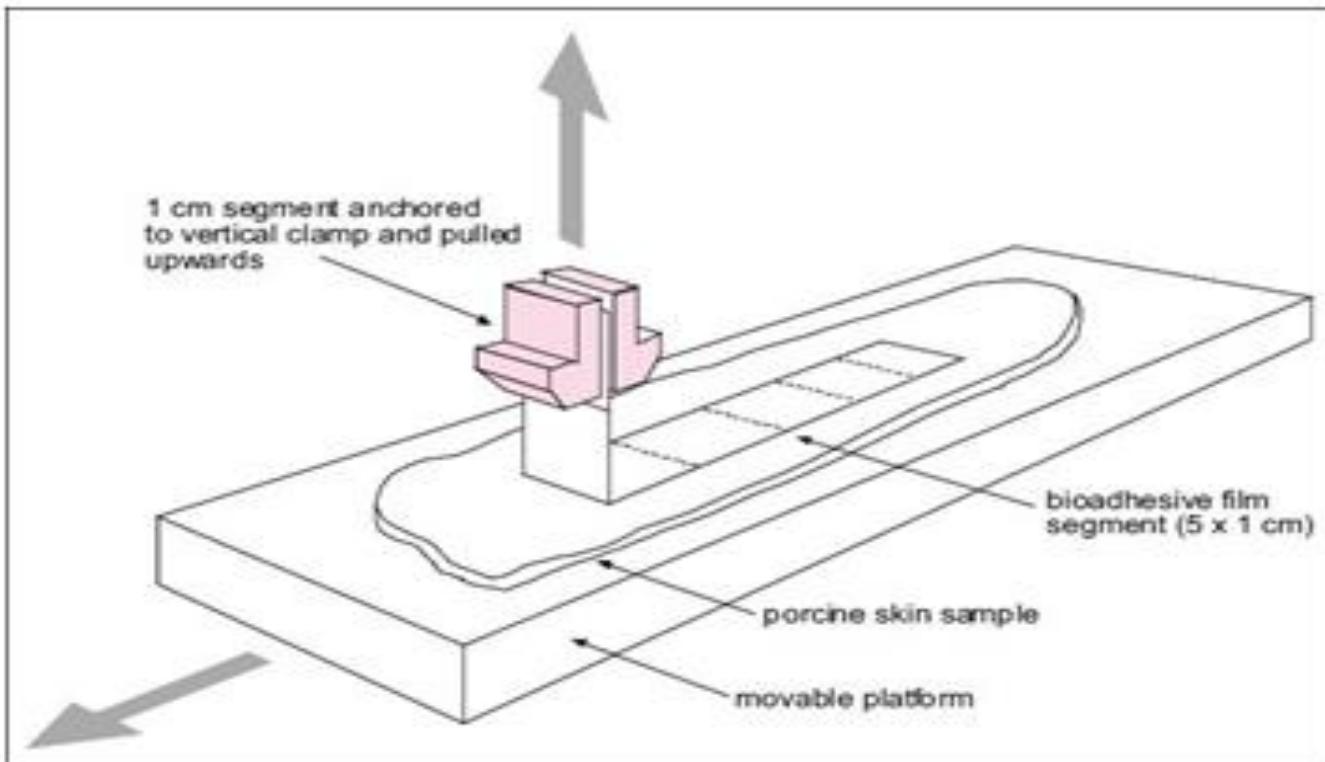
Shear
strength

Other
methods

Determination of bioadhesion

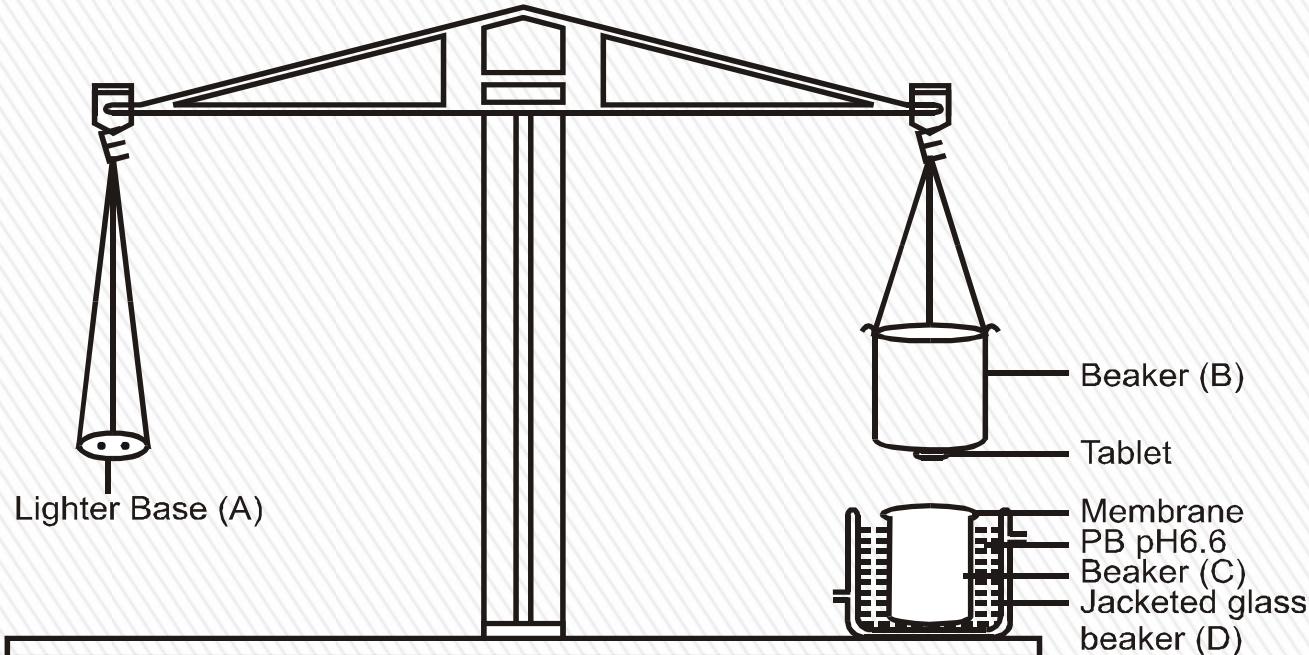
- » Depending on the direction in which the mucoadhesive is separated from the substrate, is it possible to obtain the detachment, shear, and rupture tensile strengths





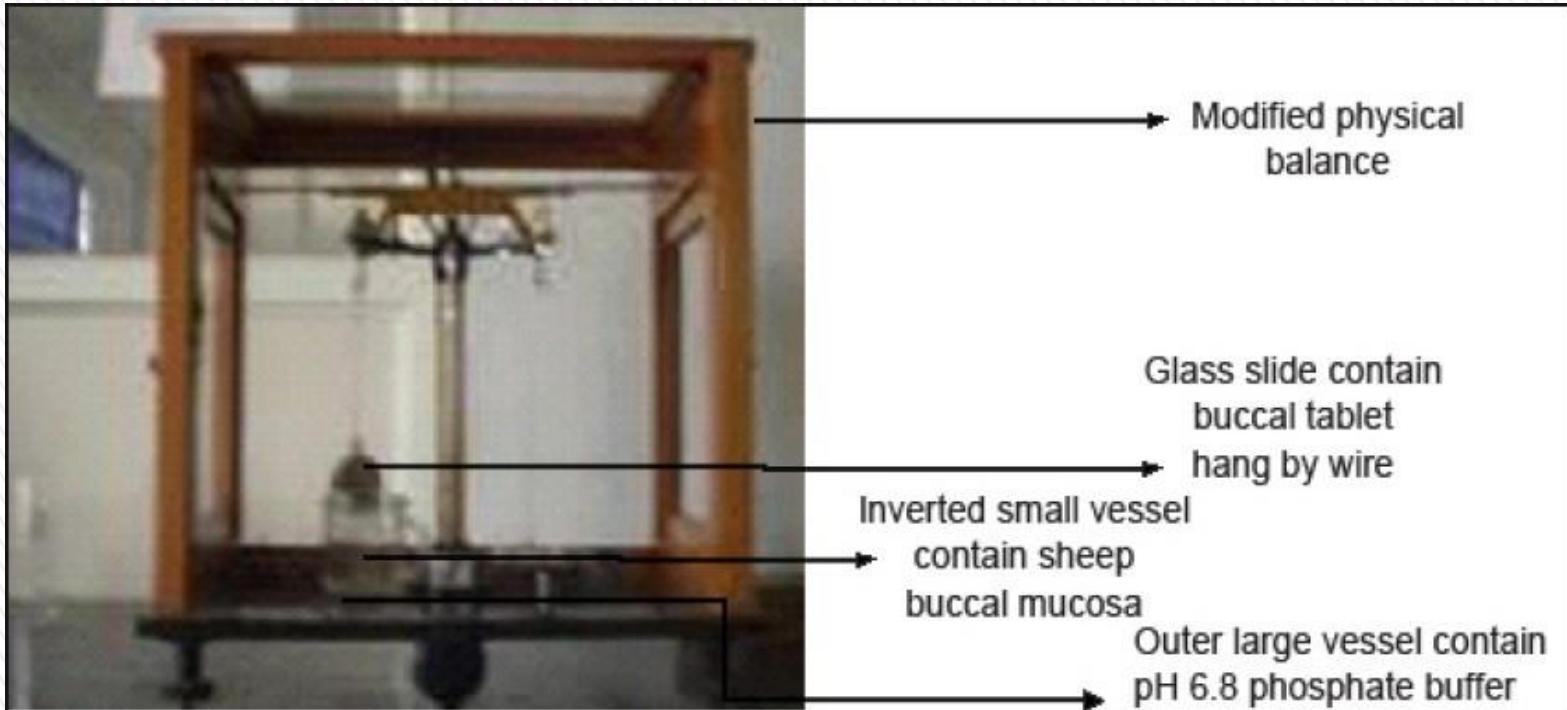
Measurement of Detachment Strength

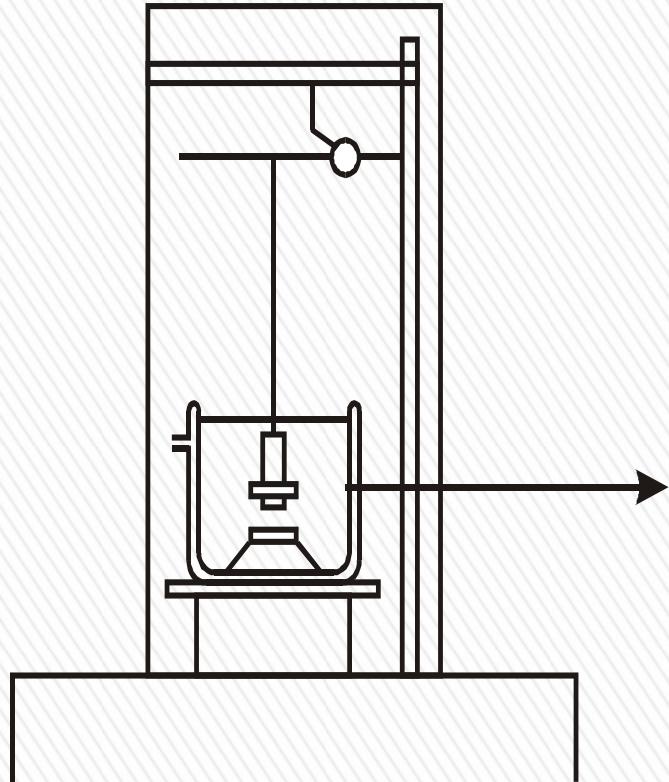
- » To measure the force required to break the adhesive bond between a model membrane and the test polymers
- » Instruments employed: modified balance or tensile testers



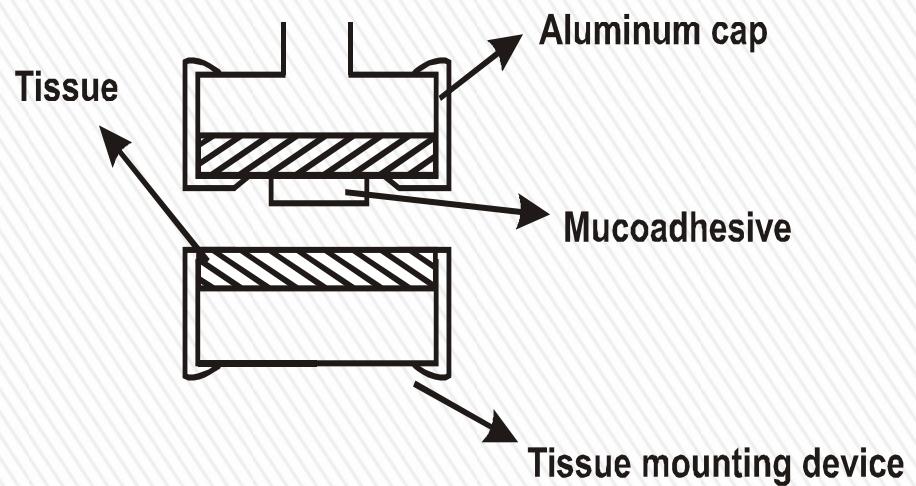
Mucoadhesion by modified balance method

Measurement of Rupture Tensile Strength





Modifier tensiometer



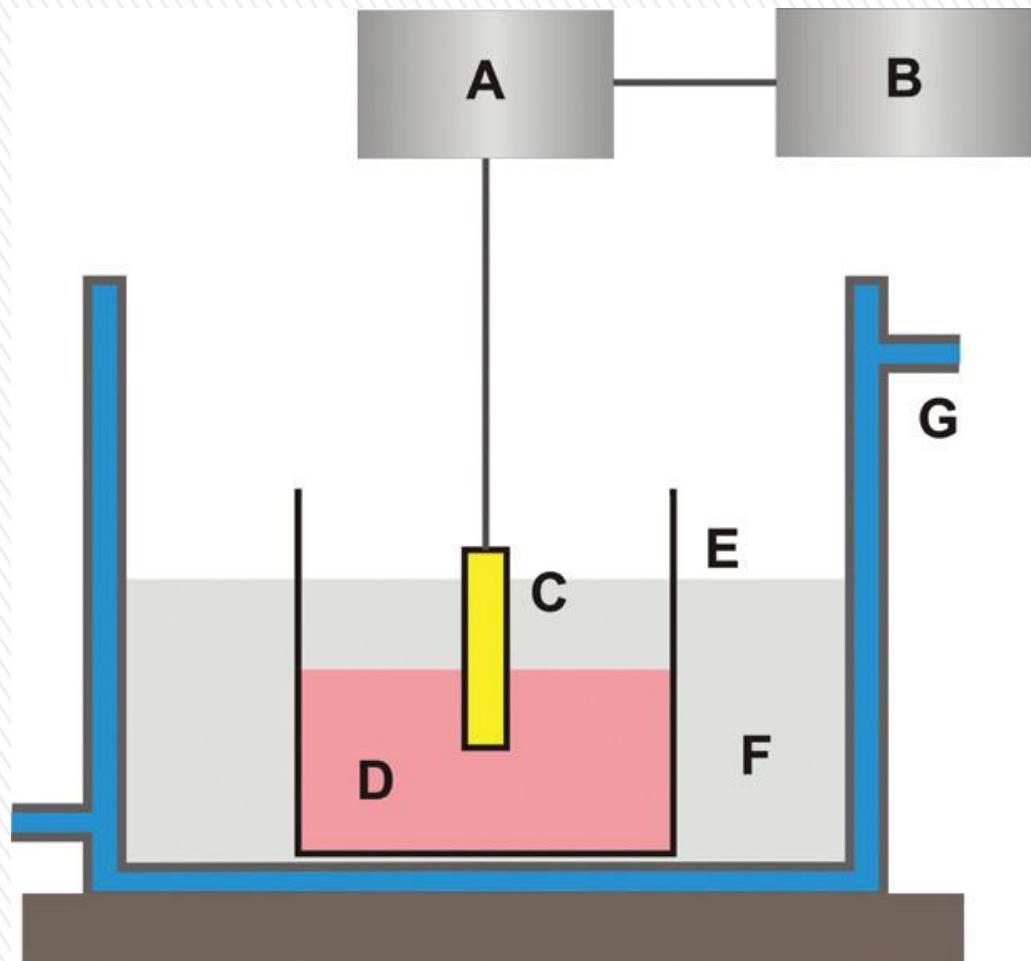
Measurement of mucoadhesive tensile strength with
an automatic surface tensiometer.

- » Equipment used: Texture analyzer or universal testing machine
- » In this test, the force required to remove the formulation from a model membrane is measured, which can be a disc composed of mucin, *a piece of animal mucous membrane.*
- » Based on results, a force-distance curve can be plotted which yields the force required to detach the mucin disc from the surface with the formulation, *the tensile work (area under the curve during the detachment process), the peak force etc.*
- » This method is more frequently used to analyze solid systems like microspheres, although there are also studies on semi-solid materials



- » This test measures the force required to separate two parallel glass slides covered with the polymer and with a mucus film
- » Eg: Wilhelmy plate method
- » Glass plate is suspended by a microforce balance and immersed in a sample of mucus under controlled temperature.
- » The force required to pull the plate out of the sample is then measured under constant experimental conditions
- » Although measures taken by this method are reproducible, the technique involves no biological tissue and therefore does not provide a realistic simulation of biological conditions

Measurement of shear strength



- A - Microforce balance
- B - Recorder
- C - Glass plate
- D - Homogenized mucus
- E - Glass recipient
- F - Water bath
- G - Water circulation

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

Other in vitro methods

- » Particles are allowed to come in contact with the mucosal membrane for a short period of time (around 5 mins)
- » The weight of particles retained is then measured
- » Good method for determination of effect of various parameters such as particle size, charge etc on mucoadhesion
- » Limitations:
 1. Poor data reproduciblity
 2. Rapid degeneration of mucosal tissue

Adhesion weight method

- » Applicable for small particles eg. Mucoadhesive microparticles
- » Particles are allowed to come in contact with the mucosal membrane for a short period of time (around 5 mins)
- » The number of particles retained is then measured

$$N_a = \frac{N}{N_0} \times 100$$

N_a – Adhesion number

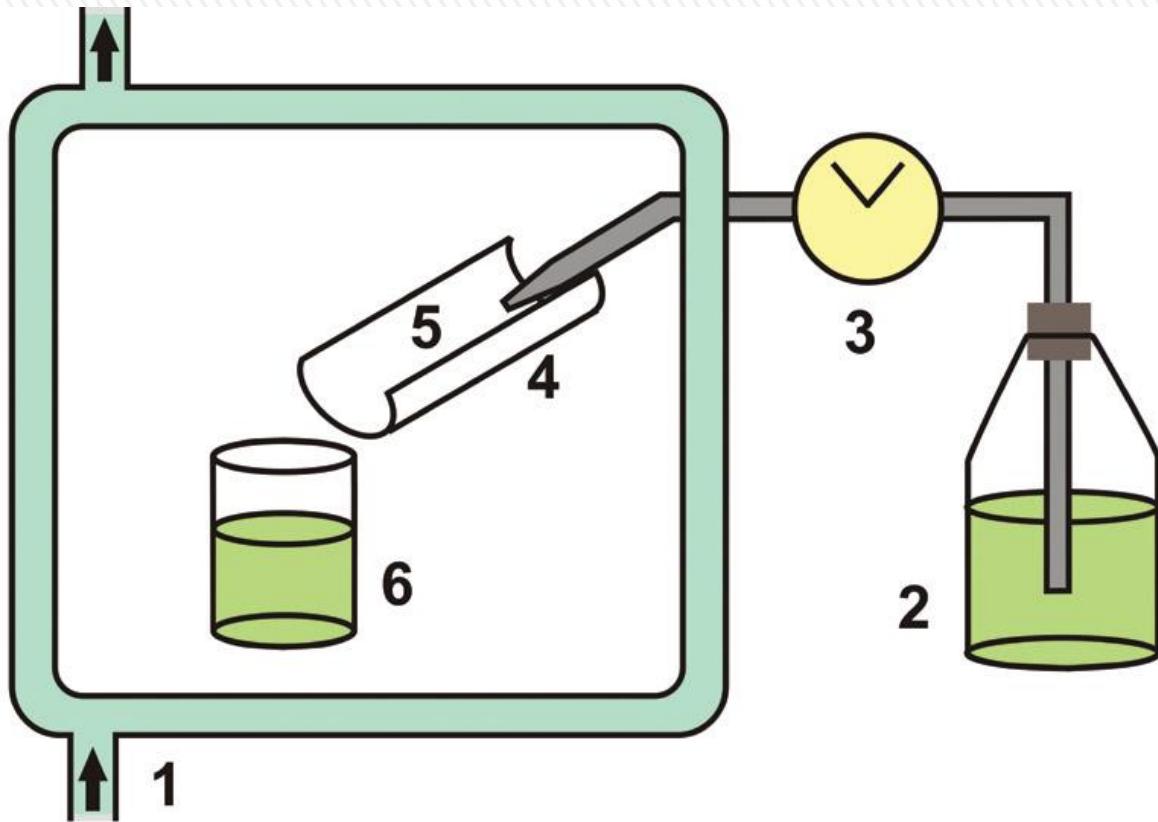
N – number of particles attached to the substrate

N_0 – total number of particles under test

Adhesion number >

- » The chosen mucous membrane is placed in a stainless steel cylindrical tube, which has been longitudinally cut.
- » This support is placed inclined in a cylindrical cell with a temperature controlled at 37 °C.
- » An isotonic solution is pumped through the mucous membrane and collected in a beaker
- » Subsequently, in the case of particulate systems, the amount remaining on the mucous membrane can be counted with the aid of a coulter counter
- » The validation of this method showed that the type of mucus used does not influence the results

Falling liquid film method



1. Thermostatic bath
2. Rinsing solution
3. Peristaltic pump

4. Stainless steel tube
5. Biological membrane
6. Collection container

- » Study polymer interaction with mucosal membrane using fluorescent probes
- » The mucus is labeled with pyrene or fluorescein isothiocyanate
- » It is then mixed with the bioadhesive material
- » The changes in fluorescence spectra is monitored

Fluorescent probe method

- » It utilises a thin channel made of glass filled with aqueous solution of mucin thermostated at 37°C.
- » Humid air at the same temperature is passed through the glass channel
- » A particle of bioadhesive polymer is placed on the mucin gel
- » Its static and dynamic behavior can be monitored at frequent intervals using a camera

Flow channel method >

- » Can be used to investigate the interaction between the bioadhesive materials and mucin
- » Can be used to study the effect of pH and chain length
- » But this method shows a very poor correlation with *in vivo* bioadhesion

Mechanical spectroscopic method >

11
3

- » Equipment: modified rotational viscometer capable of measuring electrical conductance
- » Electrical conductance as a function of time is measured
- » In presence of adhesive material, the conductance is low

Electrical conductance method

- » It employs red colloidal gold particles which were stabilized by adsorbed mucin molecules
- » Upon interaction with these mucin-gold conjugates, bioadhesive materials develop a red colour on the surface
- » This interaction can be quantified by measuring the intensity of the red colour

Colloidal gold staining number

- » It is a simple test to identify if the material is mucoadhesive
- » The adhesiveness is quantitatively measured by the difficulty of pulling the adhesive from the thumb as a function of pressure and contact time.
- » This test can be used as most mucoadhesives are not mucin specific
- » It is not a conclusive test but gives useful information on mucoadhesive potential

Thumb test



- » Viscosities of mucin dispersion can be measured by Brookfield viscometer
- » Viscosity can be measured in absence or presence of bioadhesive material
- » Viscosity components can give an idea about force of biodahesion
- » The energy of the physical and chemical bonds of the mucin-polymer interaction can be transformed into mechanical energy or work.
- » This work, which causes the rearrangements of the macromolecules, is the basis of the change in viscosity

Viscometric method >

$$\eta_b = \eta_t - \eta_m - \eta_p$$

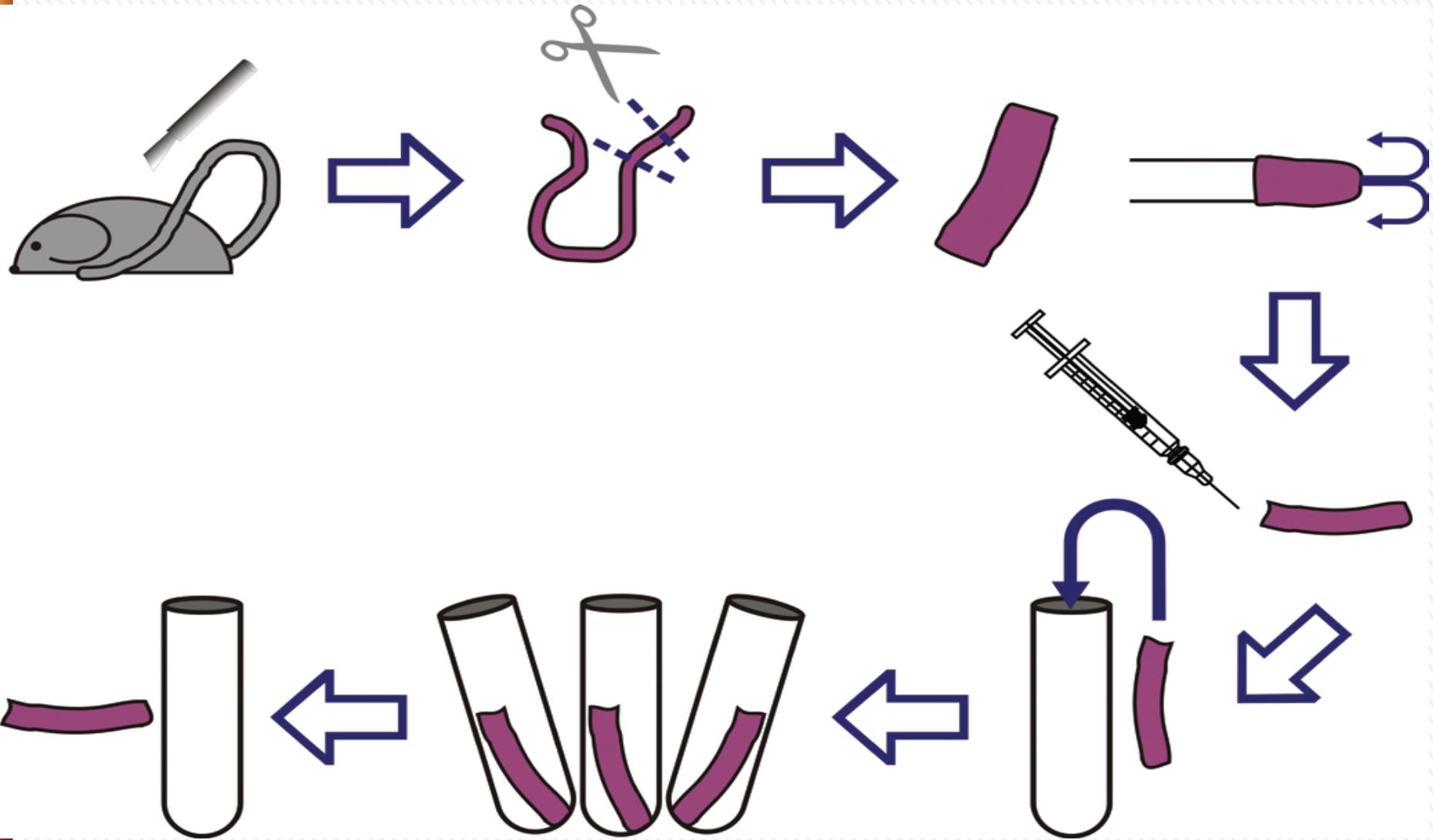
- » η_b – bioadhesion component
- » η_t - coefficient of viscosity of the system
- » η_m and η_p - coefficients of viscosity of mucin and bioadhesive polymer, respectively
- » All components should be measured at the same concentration, temperature, time and shear gradient.
- » The bioadhesion force, F , is determined by equation:

$$F = \eta_b \sigma$$

- » where σ is the shear gradient
- » The main disadvantage of this method is the breakdown of the polymer and mucin network under continuous flow

- » The everted gut sac technique is an example of an *ex vivo method*
- » It has been used since 1954 to study intestinal transport
- » It is easy to reproduce and can be performed in almost all laboratories.
- » A segment of intestinal tissue is removed from the rat, everted, and one of its ends sutured and filled with saline.
- » The sacs are introduced into tubes containing the system under analysis at known concentrations, stirred, incubated and then removed.
- » The percent adhesion rate of the release system onto the sac is determined by subtracting the residual mass from the initial mass

Using Everted gut sac of rats



Use of radioisotopes

Use of gamma scintigraphy

Use of pharmacoscintigraphy

Use of electron paramagnetic resonance(EPR) oximetry

X ray studies

Isolated loop technique

In vivo methods

In vitro drug release

In vitro drug permeation – Franz diffusion cell,
Keshary Chein cell, modified Franz diffusion cell

Histopathological evaluation of mucosa after
prolonged contact with bioadhesive material

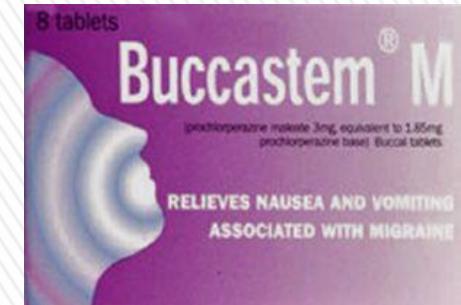
Other tests for that dosage form eg. Tablets,
microparticles etc maybe applicable

Other evaluation parameters

- » Aftach tablets – buccal triamcinolone acetonide tablets



- » Buccastem tablets,
Emedrotech buccal
tablets–
prochlorperazine



- » Aphthtab – amlexanox



Marketed formulations

Research work

- » Propranolol hydrochloride is a nonselective β -adrenergic blocking agent, used in the treatment and management of hypertension, angina, cardiac arrhythmias and acute myocardial infarction.
- » The prescribed dose of Propranolol HCl is 10-40 mg 2-3 times daily, selected dose for this study is 10 mg.
- » The F value of Propranolol HCl is about 0.1-0.5
- » Propranolol HCl undergoes extensive first pass metabolism of 40-90 %.
- » Log P value for Propranolol HCl is 3.6.
- » Freely soluble in water.

Rational of drug

selection

PREFORMULATION



FORMULATION
DEVELOPMENT



OPTIMISATION



PLAN OF WORK

STABILITY STUDIES

- » Authentication of drug: FTIR, m. p.
- » Construction of calibration curve:
 - I) UV-VIS Spectrophotometry: Phosphate buffer (pH 6.8)
 - II) HPLC
- » Flow properties of the drug: untapped bulk density, tapped bulk density, % compressibility, angle of repose and flow rate.
- » Drug-excipient compatibility studies: DSC.

» Forced degradation

PREFORMULATIO

N

RESULTS

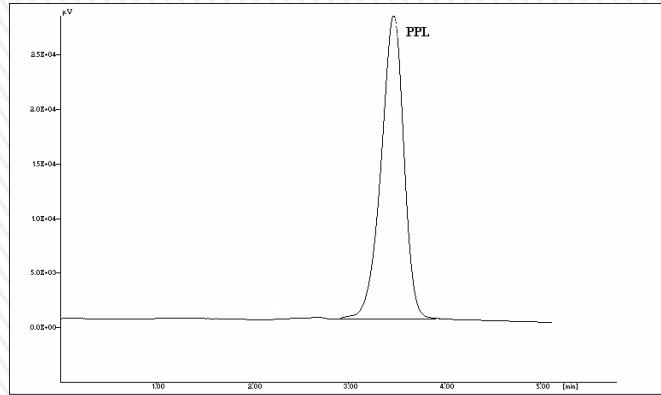
- » Calibration curves

	Slope	Coefficient of Regression (R2)
UV-VIS Spectrophotometer		
Phosphate buffer (pH 6.8)	0.0297	0.9978
HPLC		
Methanol	47970	0.9991

- » Flow properties of drug

Test	Result
Untapped bulk density	0.543 gm/mL
Tapped bulk density	0.82 gm/mL
% Compressibility	33.78 %
Angle of Repose	47.73 °
Flow Rate	12g/60 secs

Forced degradation

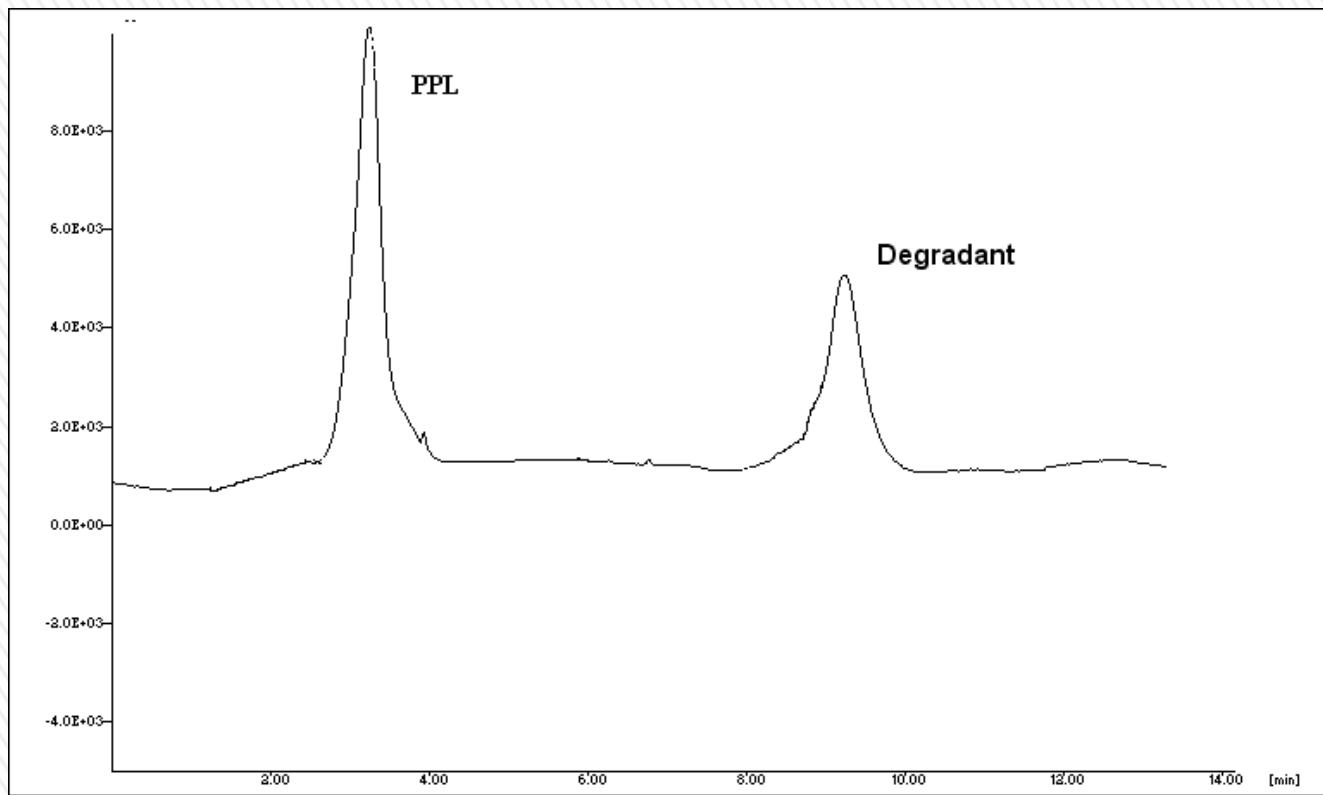


Concentration: 10 mcg/mL Retention Time: 3.680 mins

Peak Area: 442684.9 [μV.Sec]

Chromatogram of PPL Std



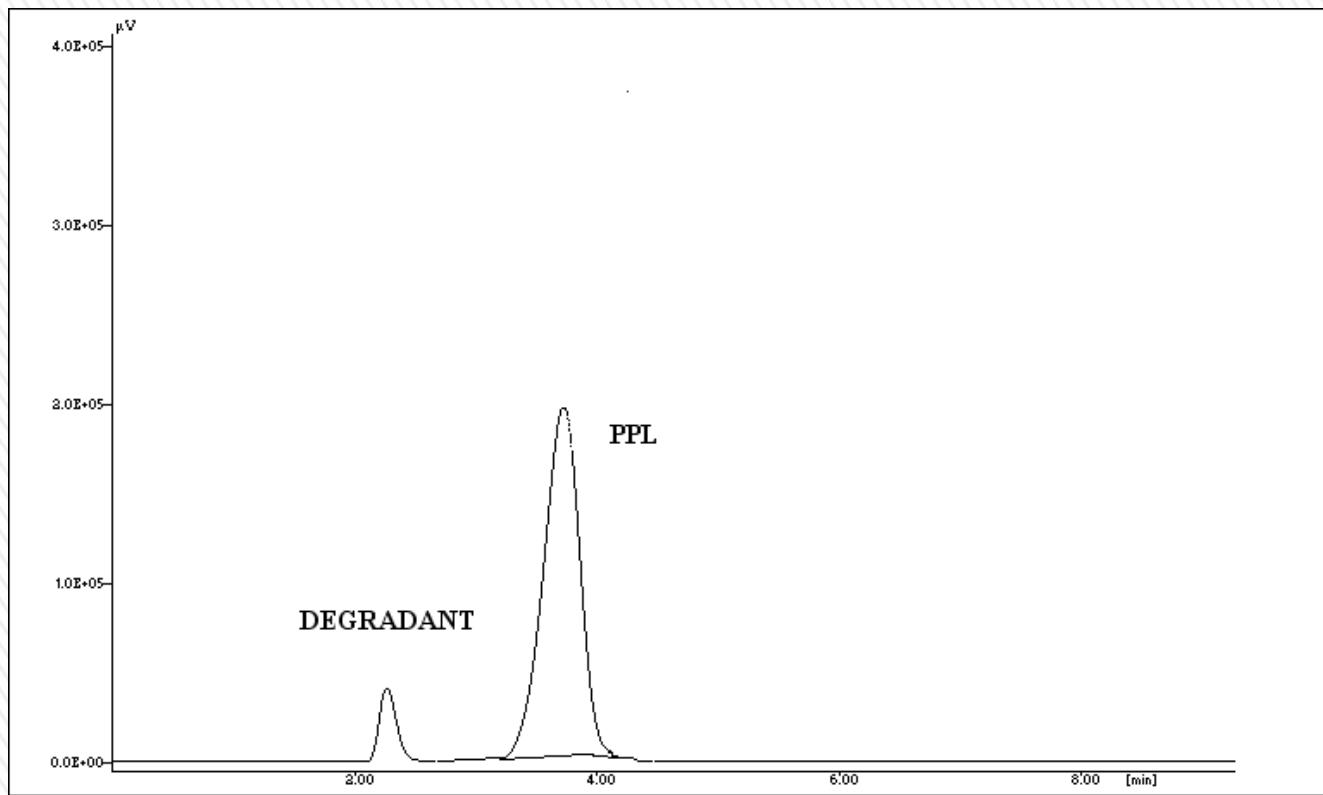


Concentration: 10 mcg/mL

Peak Area: 189406.99 [$\mu\text{V} \cdot \text{Sec}$]

Chromatogram of Base Hydrolysis of PPL

Retention Time: 3.742 mins

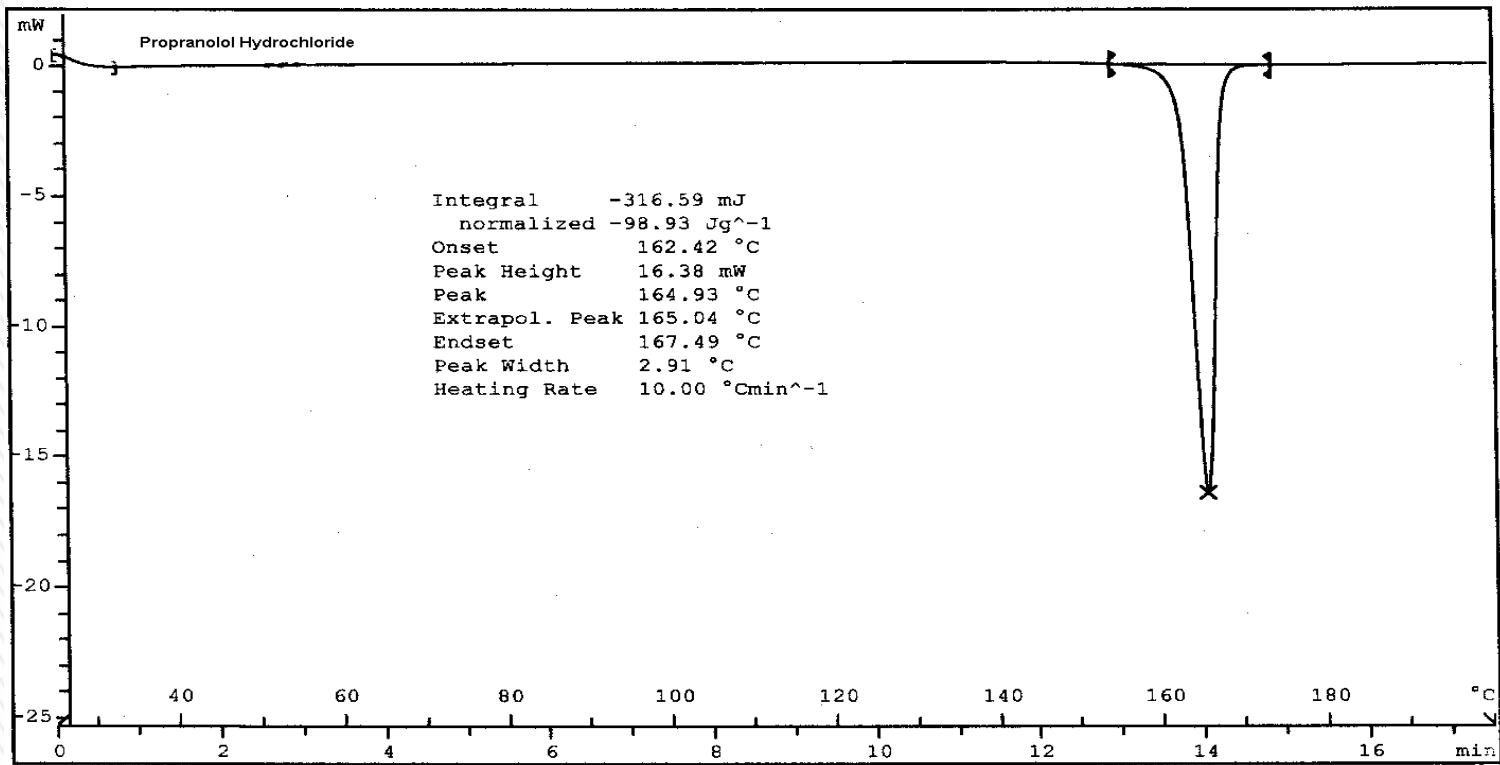


Concentration: 10 mcg/mL

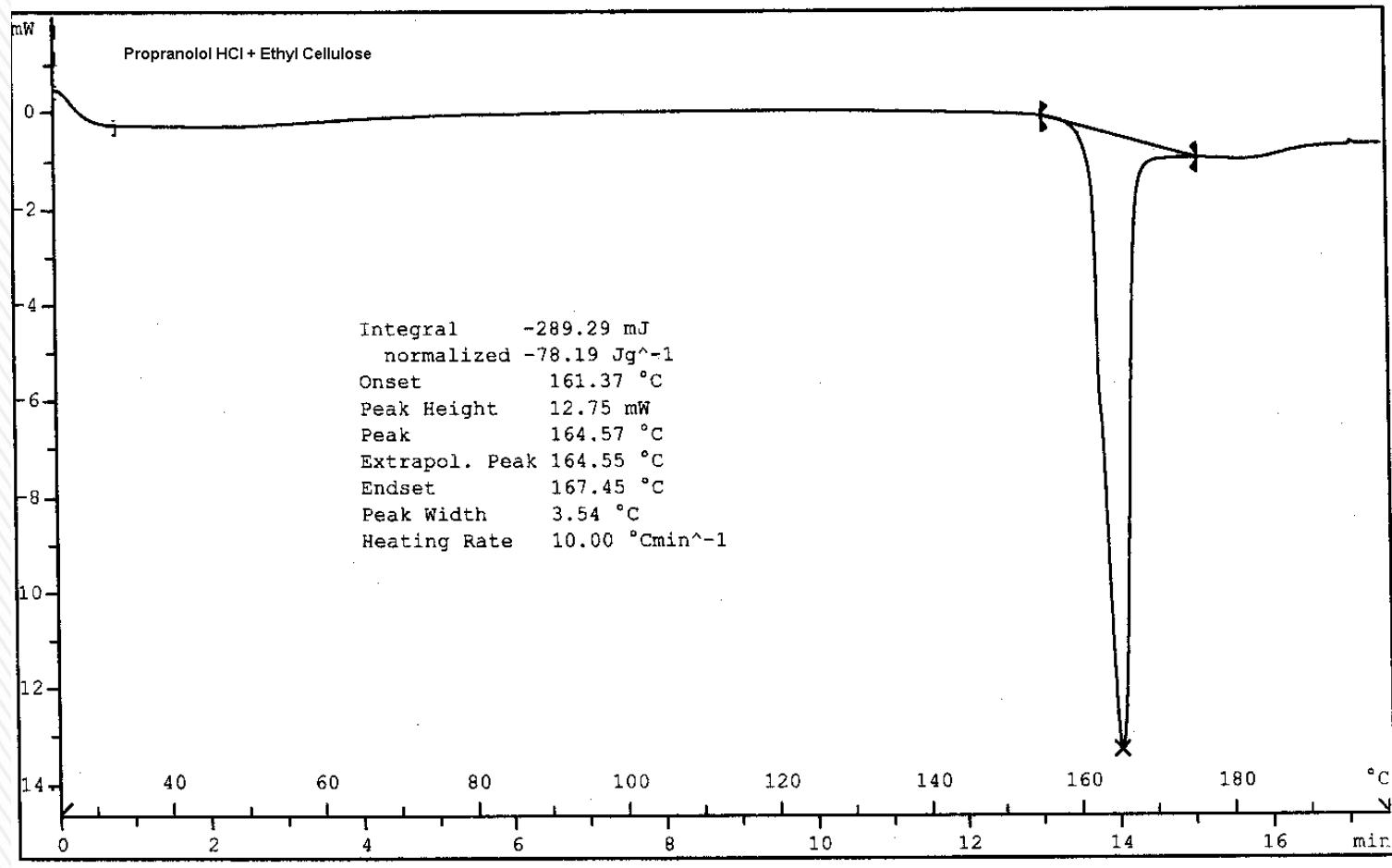
Peak Area: 360852.89 [$\mu\text{V}.\text{Sec}$]

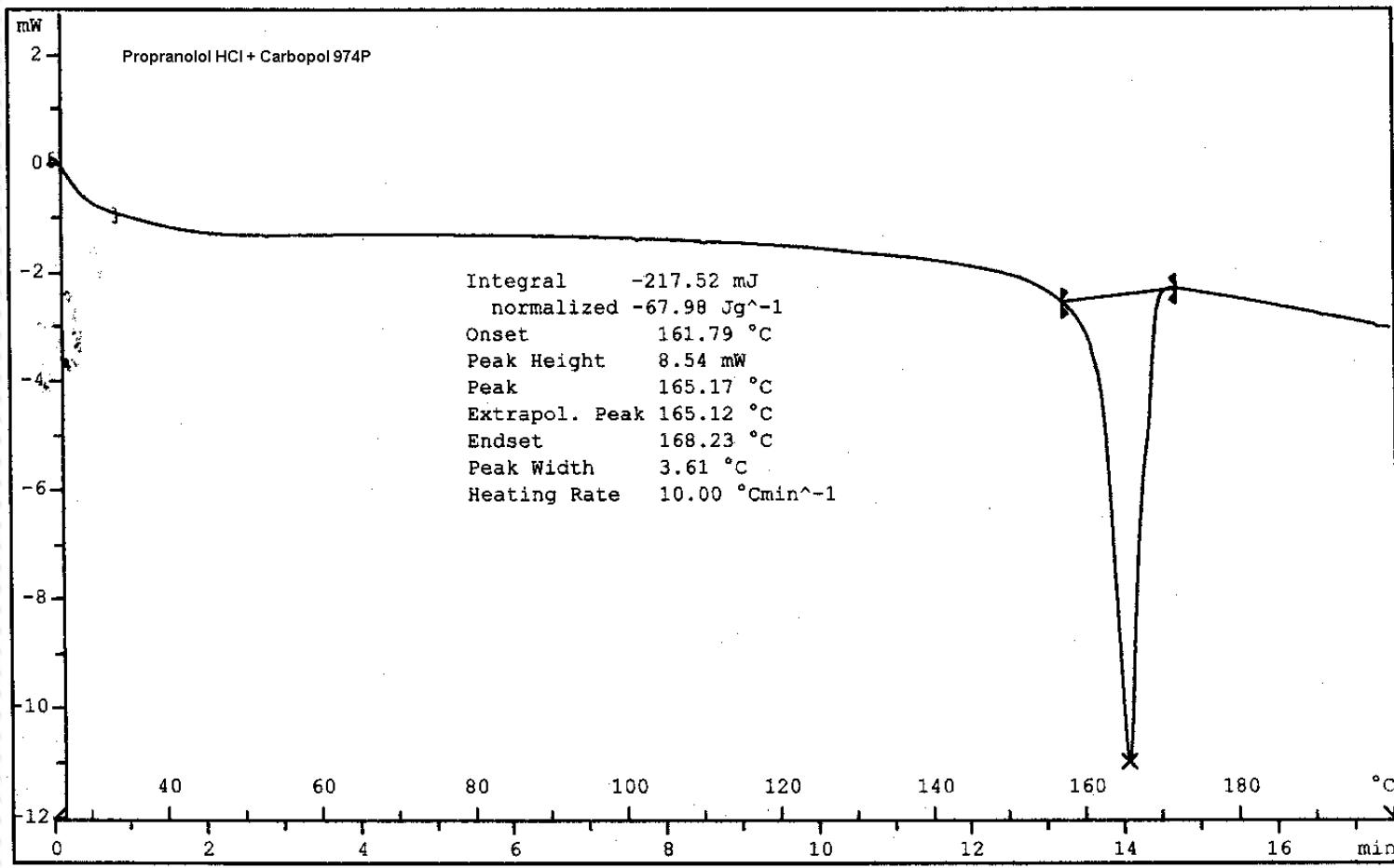
Chromatogram of Oxidative Hydrolysis of PPL

Retention Time: 3.847 mins

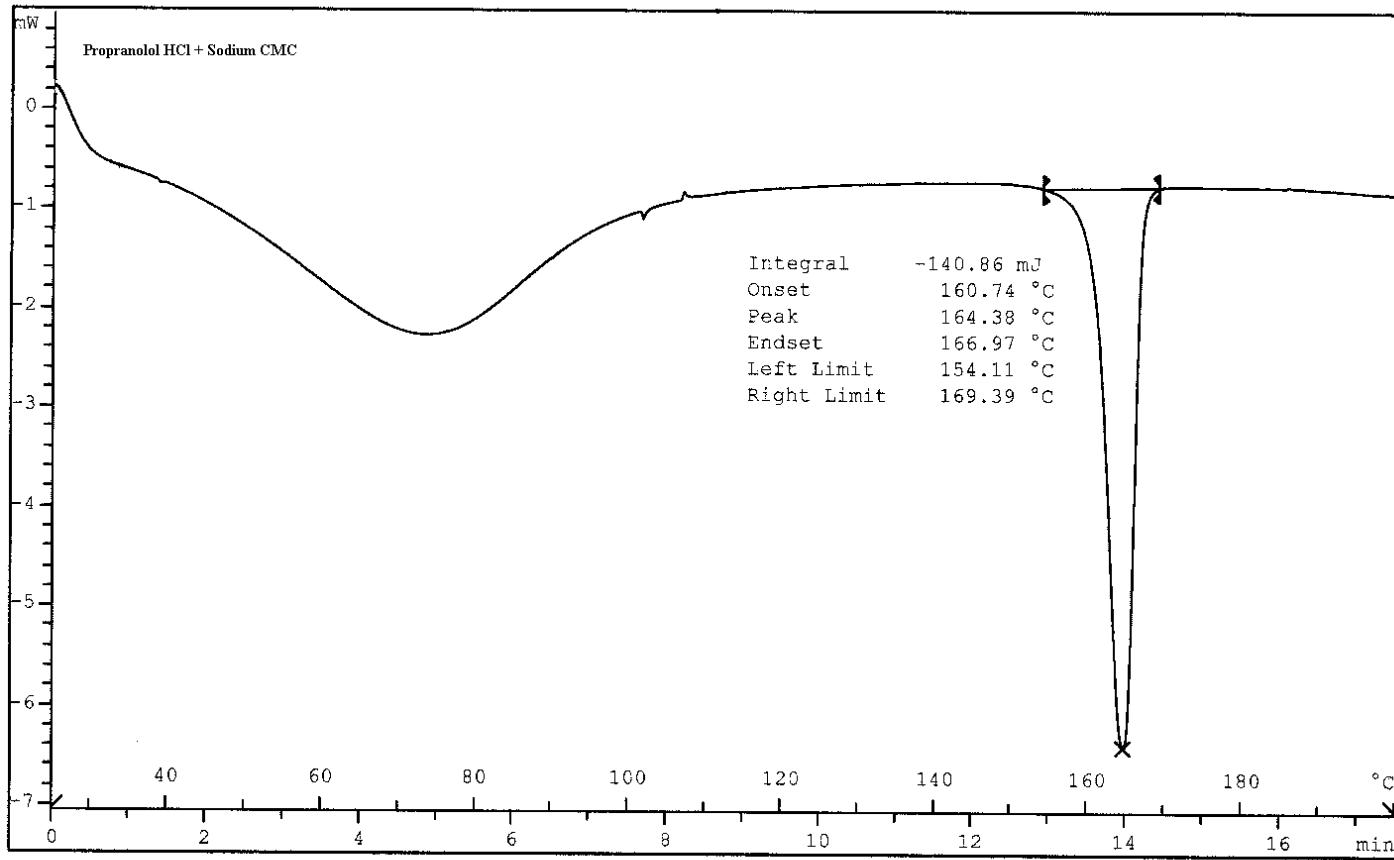


compatibility





Carbopol System



DOSE FORMULATION

- » **Preparation of tablets:** Various excipients screened for preparation of buccal mucoadhesive tablets included the following:
 - » *Diluent:* Pharmatose DCL 11
 - » *Mucodhesive polymer:* SCMC, Na. Alginate, Guar Gum, HPMC K4M, HPMC K15M, HPMC K100M, Carbopol 974P, Polycarbophil AA1 and Chitosan.
 - » *Penetration enhancer:* SLS and Bile salts.
 - » *Lubricant:* Mg St
 - » *Glidant:* Talc
 - » *Backing membrane:* EC

FORMULATION

Ingredient	Quantity per tablet (mg)					
	A1	A2	A3	A4	A5	A6
PPL	10	10	10	10	10	10
Pharmatose DCL 11	84.5	82	77	67	62	52
SCMC	2.5	5	10	20	20	30
PVP K-30	--	--	--	--	5	5
Talc	2	2	2	2	2	2
Mg. St.	1	1	1	1	1	1
TOTAL	100	100	100	100	100	100

SCMC (A1-6)
 Batches A1-4 showed poor physical strength, hence PVP K-30 was added as the binder in the dry form. The tablets showed poor hardness of 1-1.5 Kg/cm²

Ingredient	Quantity per tablet (mg)					
	B1	B2	B3	B4	B5	B6
PPL	10	10	10	10	10	10
Pharmatose DCL 11	57	32	7	52	27	2
Guar gum	50	75	100	50	75	100
PVP K-30	--	--	--	5	5	5
Talc	2	2	2	2	2	2
Mg. St.	1	1	1	1	1	1
TOTAL	120	120	120	120	120	120

These tablets had poor hardness.

Formulations of Guar Gum (B1-6) ➤

Ingredient	Quantity per tablet (mg)					
	C1	C2	C3	C4	C5	C6
PPL	10	10	10	10	10	10
Pharmatose DCL 11	57	32	7	52	27	2
Na. Alginate	50	75	100	50	75	100
PVP K-30	--	--	--	5	5	5
Talc	2	2	2	2	2	2
Mg. St.	1	1	1	1	1	1
TOTAL	120	120	120	120	120	120

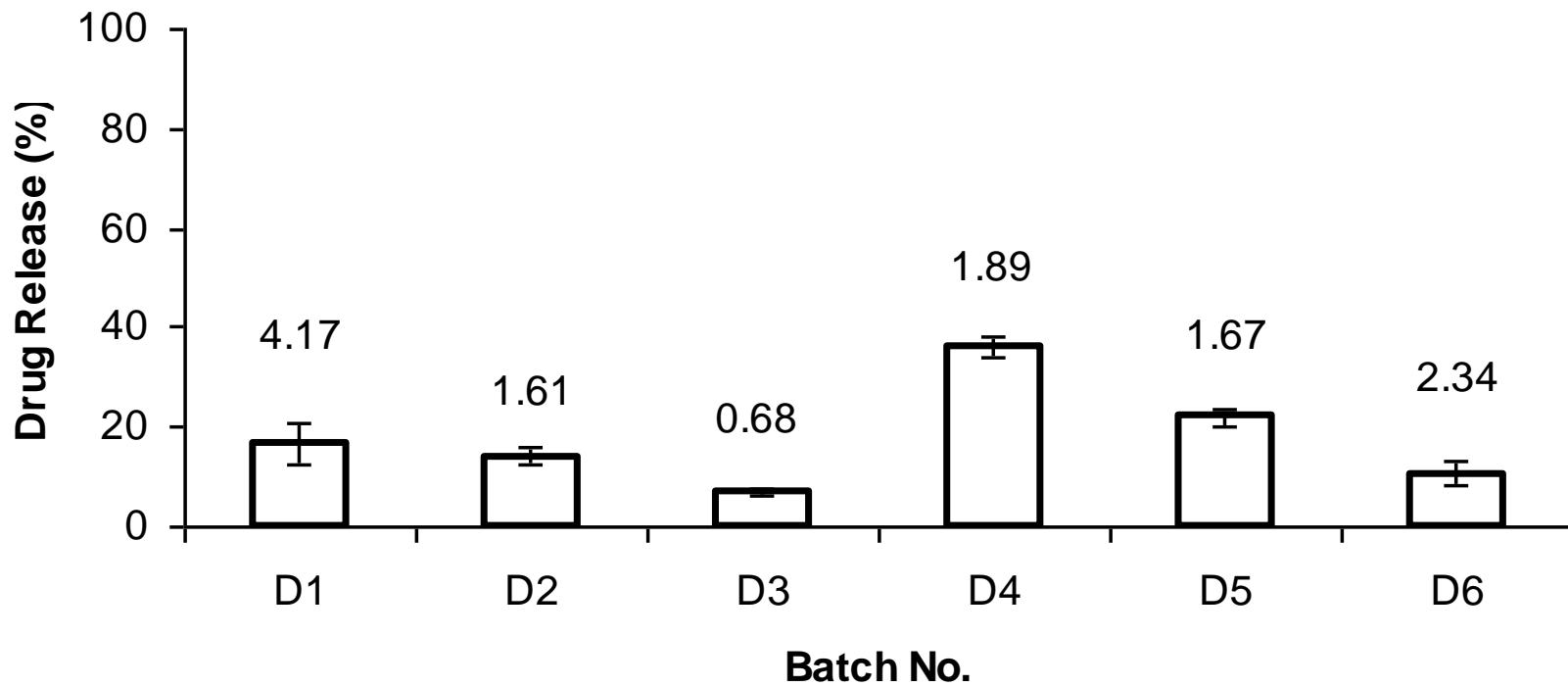
These tablets had poor integrity which could not be improved by addition of PVP K-30.

Formulations of Sodium Alginate (C 1-6)

Ingredient	Quantity per tablet (mg)								
	D1	D2	D3	D4	D5	D6	D7	D8	D9
PPL	10	10	10	10	10	10	10	10	10
Pharmatose DCL 11	82	79.5	77	82	79.5	77	82	79.5	77
HPMC K100M	5	7.5	10	--	--	--	--	--	--
HPMC K15M	--	--	--	5	7.5	10	--	--	--
HPMC K4M	--	--	--	--	--	--	5	7.5	10
Talc	2	2	2	2	2	2	2	2	2
Mg. St.	1	1	1	1	1	1	1	1	1
TOTAL	100	100	100	100	100	100	100	100	100

Tablets of HPMC K100M and K15M showed good mucoadhesive strength but those of HPMC K4M showed poor mucoadhesive strength.

HPMC (D1-9)



Dissolution data of batches D 1-6

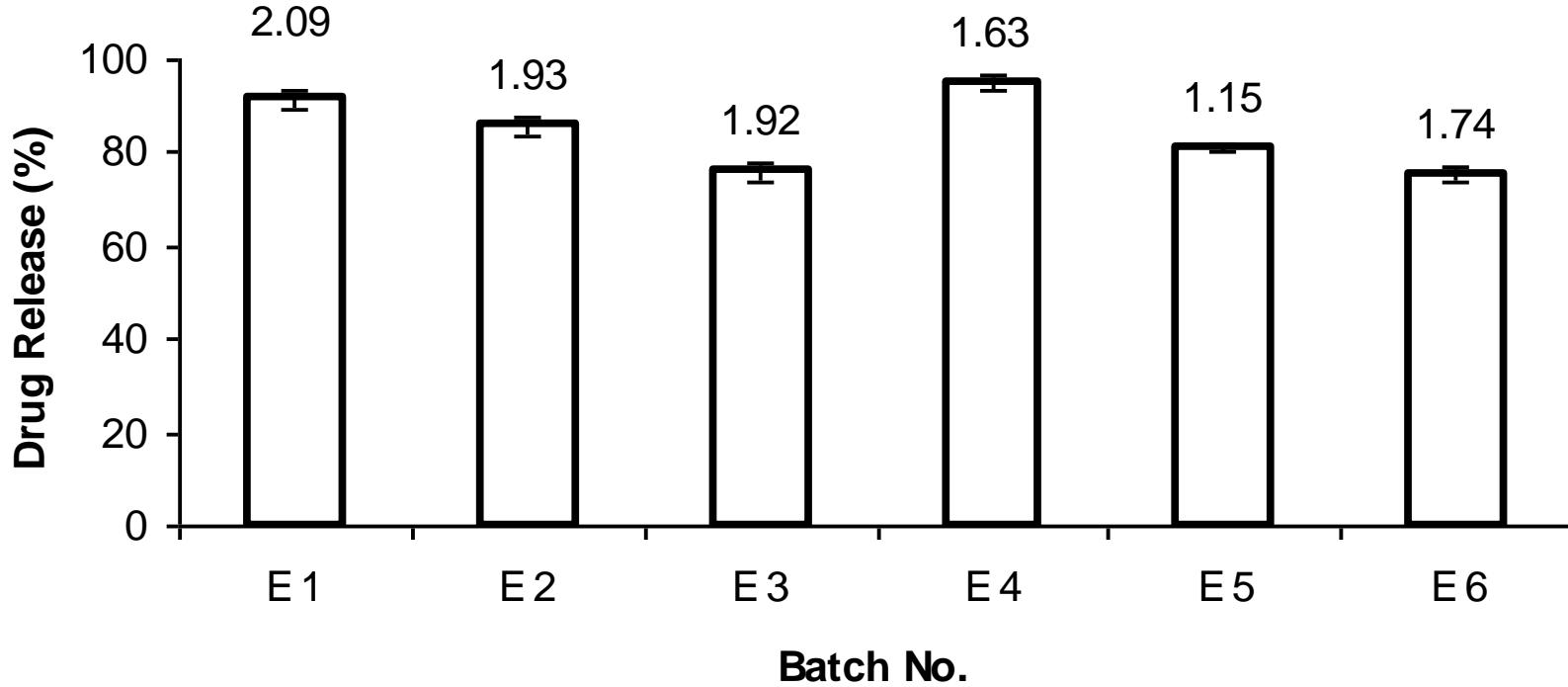
Ingredient	Quantity per tablet (mg)							
	G1	G2	G3	G4	G5	G6	G7	G8
PPL	10	10	10	10	10	10	10	10
Pharmatose DCL 11	27	17	32	27	27	32	32	27
Chitosan	80	100	80	80	80	80	80	80
PVP K-30	--	--	5	5	--	5	5	5
PEG 6000	--	--	--	5	5	--	--	5
PVP K-90	--	--	--		5	--	--	--
Water	--	--	--	--	--	Qs	--	--
2 % Acetic acid	--	--	--	--	--	--	Qs	Qs
Talc	2	2	2	2	2	2	2	2
Mg. St.	1	1	1	1	1	1	1	1
TOTAL	120	130	130	130	130	130	130	130

These batches had poor hardness and appearance.

Formulations of Chitosan (G 1-8)

Ingredient	Quantity per tablet (mg)					
	E1	E2	E3	E4	E5	E6
PPL	10	10	10	10	10	10
Pharmatose DCL 11	84.5	82	79.5	79.5	77	74.5
Carbopol 974P	2.5	5	7.5	2.5	5	7.5
PVP K-30	--	--	--	5	5	5
Talc	2	2	2	2	2	2
Mg. St.	1	1	1	1	1	1
TOTAL	100	100	100	100	100	100

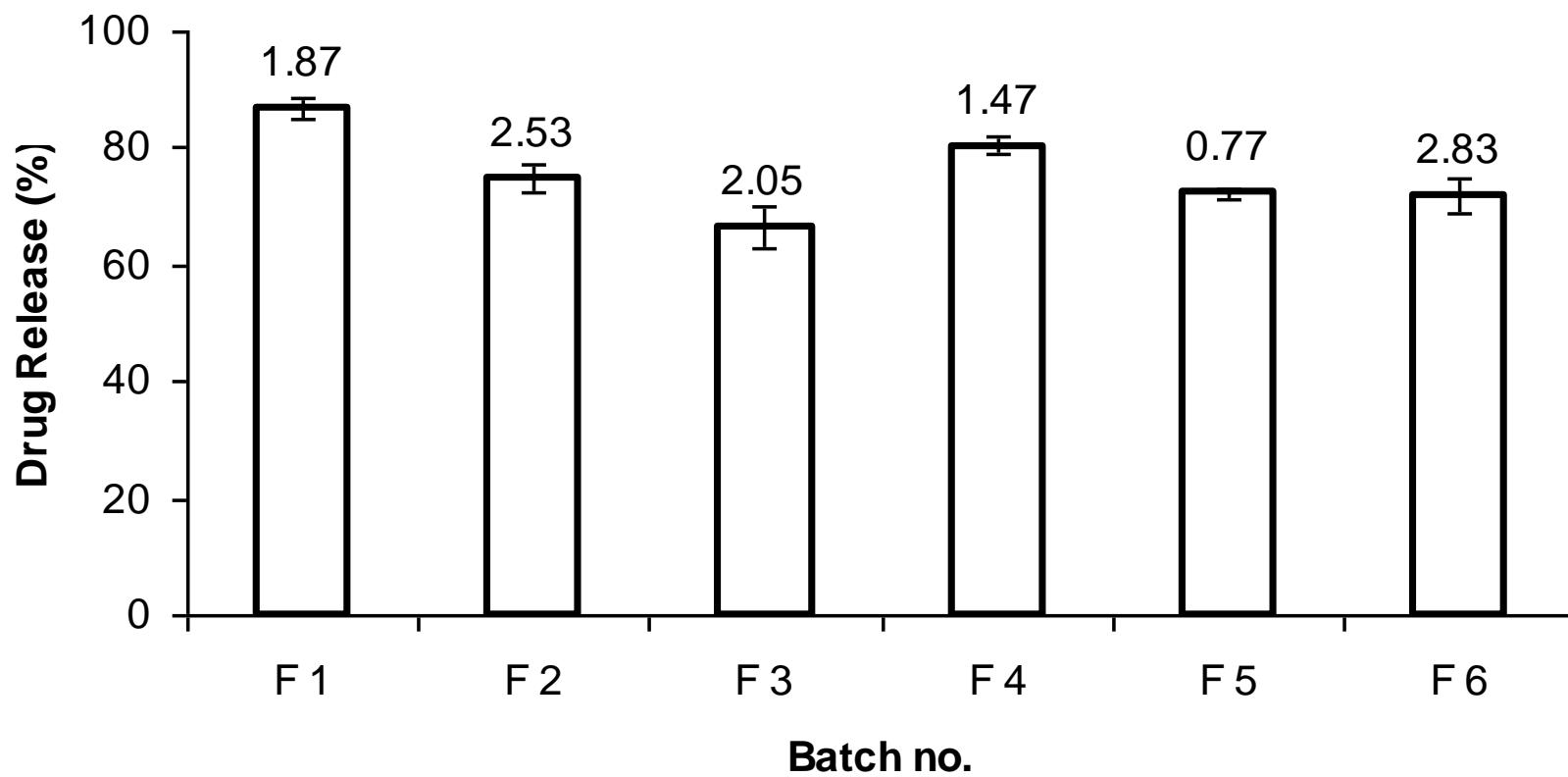
Formulations of Carbopol 974P (E 1-6)



b

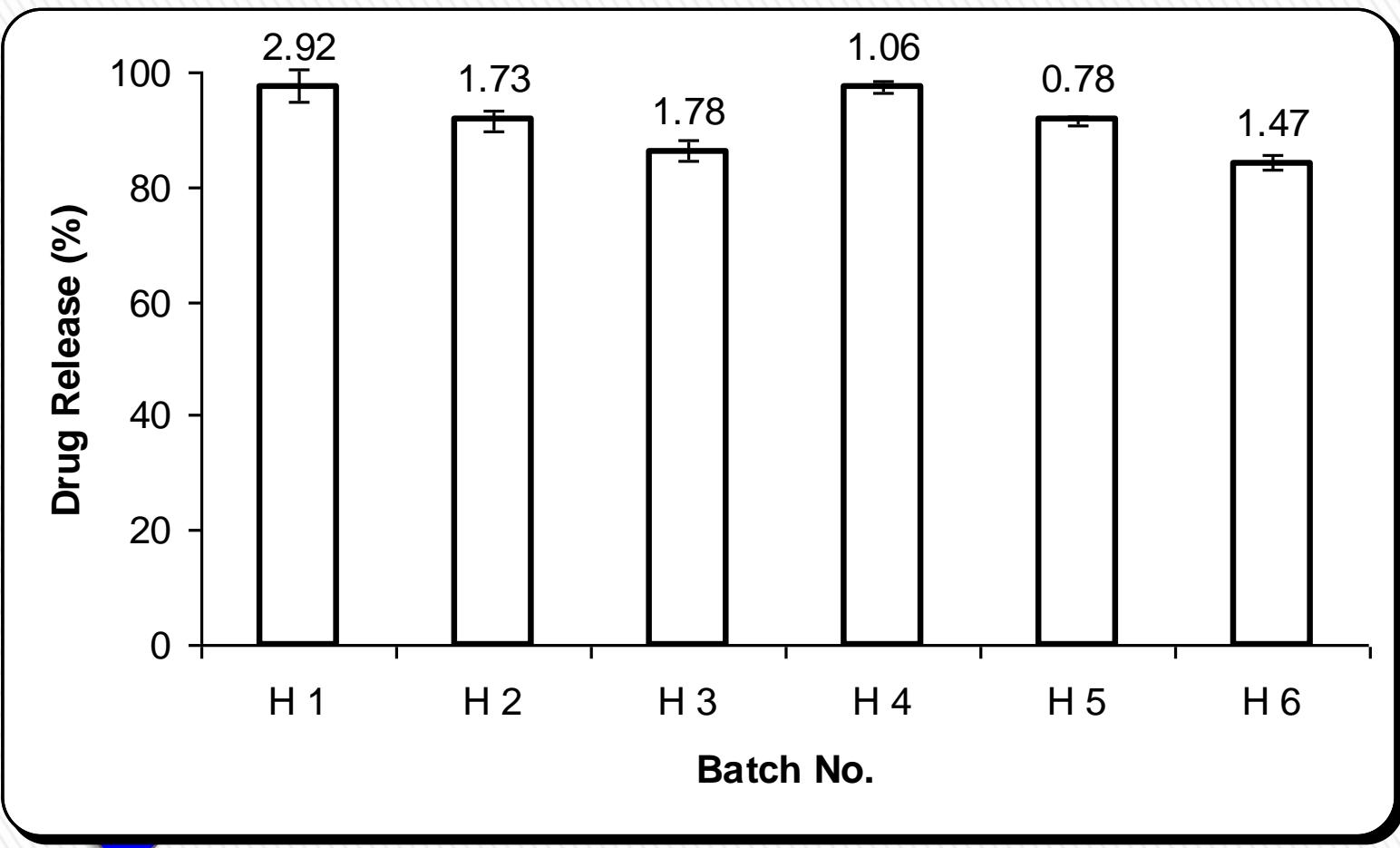
Ingredient	Quantity per tablet (mg)					
	F1	F2	F3	F4	F5	F6
PPL	10	10	10	10	10	10
Pharmatose DCL 11	84.5	82	79.5	79.5	77	74.5
Polycarbophil AA1	2.5	5	7.5	2.5	5	7.5
PVP K-30	--	--	--	5	5	5
Talc	2	2	2	2	2	2
Mg. St.	1	1	1	1	1	1
TOTAL	100	100	100	100	100	100

PC (F 1-6)



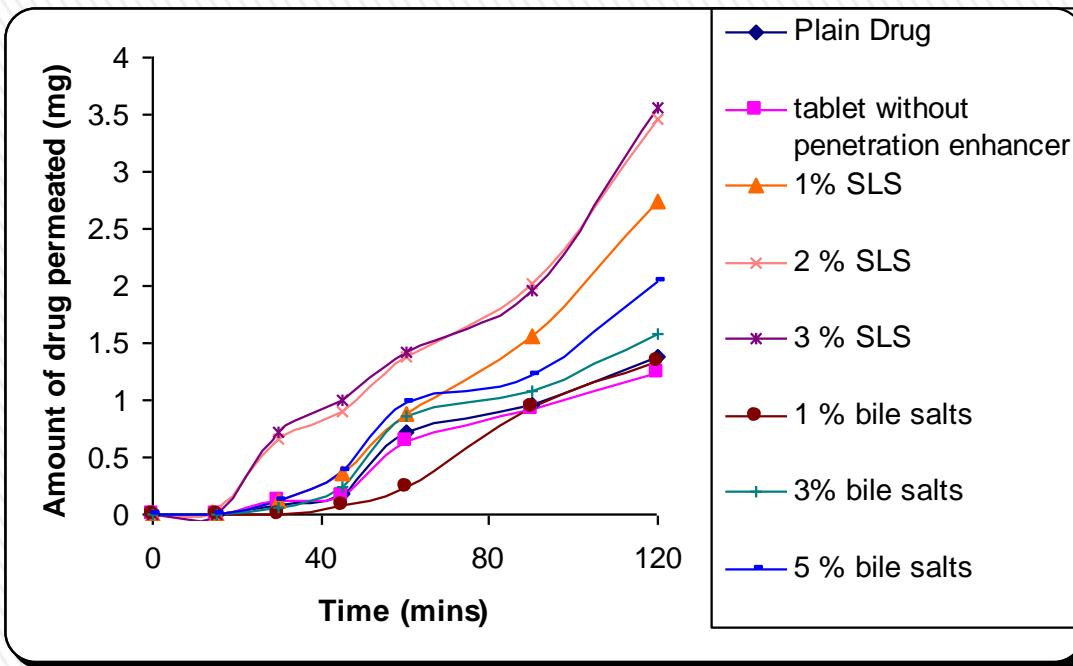
Ingredient	Quantity per tablet (mg)					
	H1	H2	H3	H4	H5	H6
PPL	10	10	10	10	10	10
Pharmatose DCL 11	77	72	62	74.5	69.5	59.5
Carbopol 974P	5	5	5	7.5	7.5	7.5
SCMC	5	10	20	5	10	20
Talc	2	2	2	2	2	2
Mg. St.	1	1	1	1	1	1
EC	60	60	60	60	60	60
TOTAL	160	160	160	160	160	160

Batches formulated with Carbopol 974P and SCMC showed desired mucoadhesive strength and good in vitro drug release



Ingredient	Quantity per tablet (mg)					
	I1	I2	I3	I4	I5	I6
PPL	10	10	10	10	10	10
Pharmatose DCL 11	73.5	72.5	71.5	73.5	71.5	69.5
Carbopol 974P	7.5	7.5	7.5	7.5	7.5	7.5
SCMC	5	5	5	5	5	5
SLS	1	2	3	--	--	--
Bile salt	--	--	--	1	3	5
Talc	2	2	2	2	2	2
Mg. St.	1	1	1	1	1	1
EC	60	60	60	60	60	60
TOTAL	160	160	160	160	160	160

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Batches I 1-3 made using SLS as the penetration enhancer showed a good increase in the amount of drug permeated. Batch I 1 showed 199.27% increase and batches I 2 & 3 containing 2 and 3 % SLS respectively showed 250.72 % & 257.97 % increase respectively as compared to that of plain drug. Batches formulated using Bile salts as the penetration enhancer though showed an increase in the amount of drug permeated as compared to the plain drug but the release achieved was lower than that achieved by using SLS.

## Ex vivo permeation of PPL via porcine buccal mucosa of batches I 1-6

# OPTIMISATION

» Batch I 2 showed good tablet appearance, physical strength, good hardness, good mucoadhesion strength optimum In-vitro drug release and acceptable Ex-vivo drug penetration, therefore this formula was optimized. A  $3^2$  factorial design was used in the present study.

» Statistical software, Statease Design-Expert® was utilized to evaluate the response. The expected responses were:

In-vitro drug release

NLT 80 % in 45 mins

Mucoadhesion strength

10 – 12 g/cm<sup>2</sup>

» The two independent variables at three levels chosen were:

| Independent variables             | +1     | 0      | -1     |
|-----------------------------------|--------|--------|--------|
| Amount of Carbopol 974P ( $X_1$ ) | 10 mg  | 7.5 mg | 5 mg   |
| Amount of SCMC ( $X_2$ )          | 7.5 mg | 5 mg   | 2.5 mg |

| Formulation code | Factor combination | Drug (mg) | X <sub>1</sub> | X <sub>2</sub> | In-vitro drug release (%) | Mucoadhesion strength (g/cm <sup>2</sup> ) |
|------------------|--------------------|-----------|----------------|----------------|---------------------------|--------------------------------------------|
| a <sub>1</sub>   | (1,1)              | 10        | 10             | 7.5            | 19.44                     | 18                                         |
| a <sub>2</sub>   | (1,0)              | 10        | 10             | 5              | 35.42                     | 15                                         |
| a <sub>3</sub>   | (1,-1)             | 10        | 10             | 2.5            | 51.53                     | 13.5                                       |
| a <sub>4</sub>   | (0,1)              | 10        | 7.5            | 7.5            | 71.24                     | 12                                         |
| a <sub>5</sub>   | (0,0)              | 10        | 7.5            | 5              | 95.22                     | 12                                         |
| a <sub>6</sub>   | (0,-1)             | 10        | 7.5            | 2.5            | 98.78                     | 7                                          |
| a <sub>7</sub>   | (-1,1)             | 10        | 5              | 7.5            | 73.8                      | 6                                          |
| a <sub>8</sub>   | (-1,0)             | 10        | 5              | 5              | 81.27                     | 4                                          |
| a <sub>9</sub>   | (-1,-1)            | 10        | 5              | 2.5            | 95.45                     | 2.5                                        |

As seen from the table, formulation a<sub>5</sub> showed high drug release with optimum mucoadhesion strength of 95.22 % and 12 g/cm<sup>2</sup> respectively. Therefore a<sub>5</sub> was devised as the optimum formulation and was subjected to stability studies.

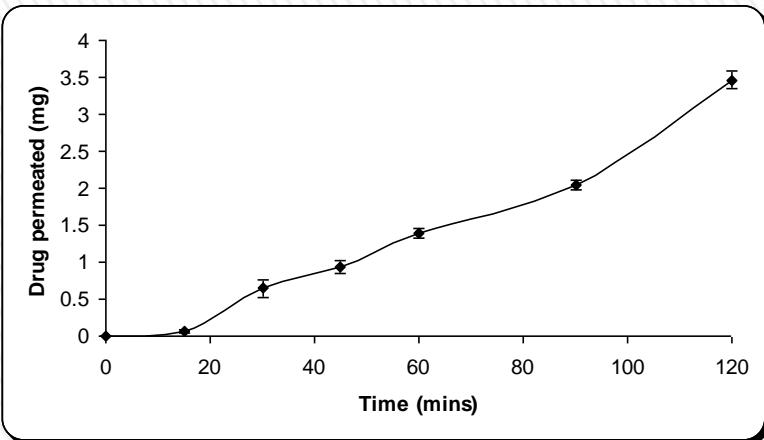
| Test                  | Result                 |
|-----------------------|------------------------|
| Untapped bulk density | $0.235 \pm 0.05$ gm/ml |
| Tapped bulk density   | $0.283 \pm 0.05$ gm/ml |
| % Compressibility     | $16.96 \pm 0.5$ %      |
| Angle of Repose       | $17.83 \pm 0.5$ °      |
| Flow Rate             | 1 g/ 20 secs           |

## EVALUATION OF OPTIMISED BATCH

Flow properties of blend ready for compression

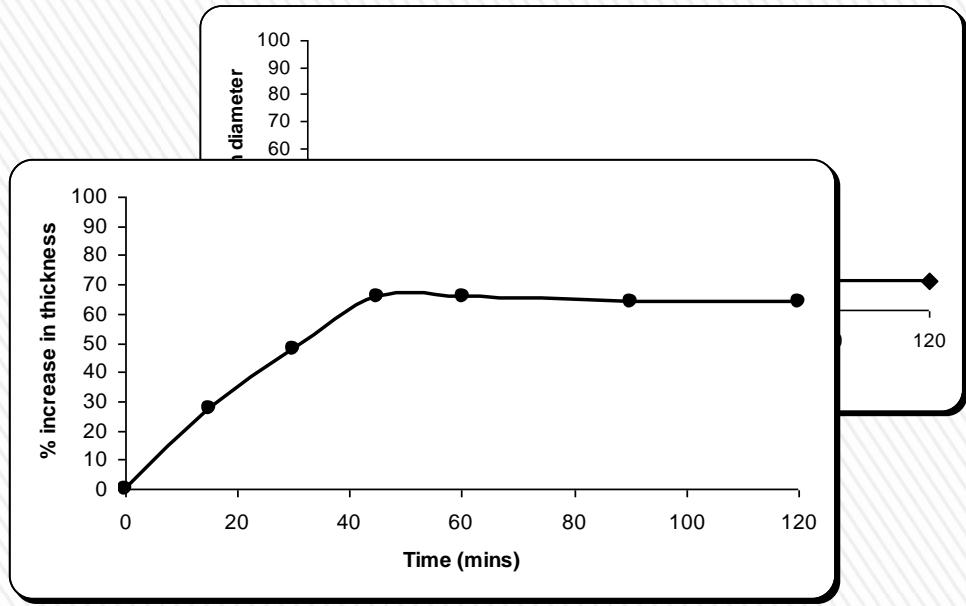
| Parameters              | Results                                                         |
|-------------------------|-----------------------------------------------------------------|
| Appearance              | Good                                                            |
| Dimensions              | Diameter -10 mm $\pm$ 0.1mm.<br>Thickness – 1.5 mm $\pm$ 0.2mm. |
| Hardness                | $3.0 \pm 0.5$ kg/cm <sup>2</sup>                                |
| Weight variation        | passes                                                          |
| Assay                   | 99.92%                                                          |
| Content Uniformity      | $10 \pm 0.5$ mg                                                 |
| Mucoadhesion strength   | $12 \pm 1.0$ g/cm <sup>2</sup>                                  |
| Surface pH              | 6 – 7                                                           |
| In-vitro residence time | More than 2 hrs                                                 |
| In-vitro drug release   | 95.22 % in 45 mins                                              |

## Evaluation of tablets of optimised batch



| Amount penetrated ( $Q_t$ )<br>μg | Time interval<br>(t)<br>secs | $dQ_t$ | $dt$ | $A \cdot dt$ | Flux ( $J_t$ )<br>μg/cm² s |
|-----------------------------------|------------------------------|--------|------|--------------|----------------------------|
| 61                                | 900                          | 61     | 900  | 4419         | 0.013                      |
| 640                               | 1800                         | 570    | 900  | 4419         | 0.129                      |
| 930                               | 2700                         | 29     | 900  | 4419         | 0.0066                     |
| 1830                              | 3600                         | 900    | 900  | 4419         | 0.204                      |
| 2040                              | 5400                         | 210    | 1800 | 7542         | 0.028                      |
| 3470                              | 7200                         | 1430   | 1800 | 7542         | 0.189                      |

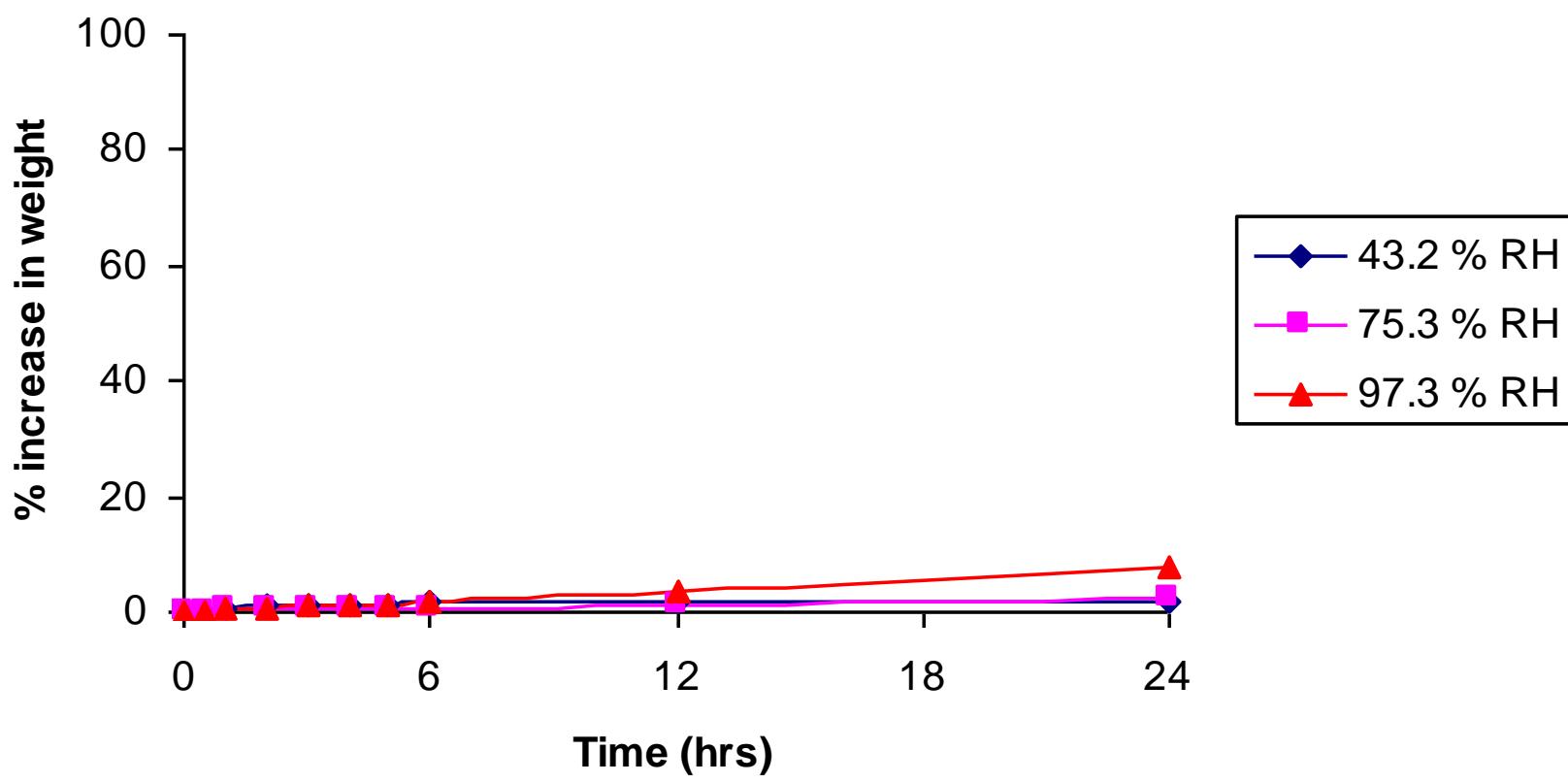
# penetration studies



# Effect of simulated saliva pH 6.8 on swelling behavior

% increase in thickness.

% increase in diameter.



| Physical Parameter                         | Tablets     | 0 day | 15 <sup>th</sup> day | 30 <sup>th</sup> day | 60 <sup>th</sup> day | 90 <sup>th</sup> day |
|--------------------------------------------|-------------|-------|----------------------|----------------------|----------------------|----------------------|
| Appearance                                 | 40°C/75% RH | +++   | +++                  | +++                  | +++                  | +++                  |
|                                            | 30°C/65% RH | +++   | +++                  | +++                  | +++                  | +++                  |
| Diameter (mm)                              | 40°C/75% RH | 10.00 | 10.00                | 10.00                | 10.00                | 10.00                |
|                                            | 30°C/65% RH | 10.00 | 10.00                | 10.00                | 10.00                | 10.00                |
| Thickness (mm)                             | 40°C/75% RH | 1.53  | 1.52                 | 1.45                 | 1.56                 | 1.45                 |
|                                            | 30°C/65% RH | 1.53  | 1.49                 | 1.53                 | 1.54                 | 1.52                 |
| Hardness (kg/cm <sup>2</sup> )             | 40°C/75% RH | 3.0   | 3.5                  | 3.0                  | 3.0                  | 3.5                  |
|                                            | 30°C/65% RH | 3.5   | 3.0                  | 3.0                  | 3.0                  | 3.0                  |
| Weight variation (mg)                      | 40°C/75% RH | 160±5 | 160±5                | 160±5                | 160±5                | 160±5                |
|                                            | 30°C/65% RH | 160±5 | 160±5                | 160±5                | 160±5                | 160±5                |
| Mucoadhesion strength (g/cm <sup>2</sup> ) | 40°C/75% RH | 12    | 12                   | 12                   | 12                   | 11                   |
|                                            | 30°C/65% RH | 12    | 12                   | 12                   | 12                   | 12                   |

| Time Interval<br>(days) | % Drug content |                | % Release in 45 mins |                | mg permeated in 120<br>mins |                |
|-------------------------|----------------|----------------|----------------------|----------------|-----------------------------|----------------|
|                         | 40°C/75%<br>RH | 30°C/65%<br>RH | 40°C/75%<br>RH       | 30°C/65%<br>RH | 40°C/75%<br>RH              | 30°C/65%<br>RH |
|                         |                |                |                      |                |                             |                |
| 0                       | 99.75          | 99.75          | 95.22                | 95.22          | 3.46                        | 3.46           |
| 15                      | 97.25          | 97.35          | 93.66                | 93.64          | 3.45                        | 3.43           |
| 30                      | 96.34          | 96.14          | 93                   | 93.33          | 3.40                        | 3.40           |
| 60                      | 93.21          | 94.1           | 91.71                | 92.25          | 3.32                        | 3.35           |
| 90                      | 92.25          | 91.25          | 90.64                | 91.47          | 3.25                        | 3.37           |

- » The conclusion arrived in this thesis indicated that the stable buccal mucoadhesive formulations of PPL could be formulated which could have good mucoadhesive strength and improved permeability.

# CONCLUSION