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Review Article

Mucosal Drug Delivery System

Dr. C. S. Parameswari*, Gonuguntla Sreevani

Dr. K. V. Subba Reddy Institute of Pharmacy, Kurnool, India

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ABSTRACT

Mucoadhesive drug delivery systems interact with the mucus layer covering the mucosal epithelial surface, and mucin molecules and increase the residence time of the dosage form at the site of absorption. The drugs which have local action or those which have maximum absorption in gastrointestinal tract (GIT) require increased duration of stay in GIT. Thus, mucoadhesive dosage forms are advantageous in increasing the drug plasma concentrations and also therapeutic activity. In this regard, this review covers the areas of mechanisms and theories of mucoadhesion, factors influencing the mucoadhesive devices and also various mucoadhesive dosage forms.

INTRODUCTION

Mucoadhesive drug delivery system (MDDS) represents a class of controlled drug delivery system. It involves the interaction of dosage form mucus laye4r (consists of mucosal epithelial surface and mucin molecules) causing increased residence time of dosage form at absorption site in order to attain extended release profiles of a drug. MDDS is used to localize a delivery device with in the human to enhance the drug absorption in the site specific manner. Adhesiveness polymers can adhere to the mucous epithelial surface at the target site. Delivery of drugs via the absorptive mucosa in various easily accessible body cavities like the ocular, nasal, Buccal, rectal and vaginal mucosa has the advantage by passing the hepato gastrointestinal first pass elimination associated with oral administration. Mucosal membranes can be useful sites with good accessibility for easy application of drug delivery systems especially for those with bioadhesive properties. Mucoadhesive drug delivery system utilize the property of bio adhesion of certain polymers which become adhesive on hydration and hence can be used for

***Corresponding Author:** Dr. C. S. Parameswari
Address: *Dr. K. V. Subba Reddy Institute of Pharmacy, Kurnool, India.*
Email ✉: parameswaribachu@gmail.com
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targeting a drug to a particular region of the body for extended periods of time and can be exploited for the noninvasive systemic delivery of organic and peptide based drugs with rapid absorption as well as sustained drug action.[1]

Based on different route of administration of drugs, MDDS classifies as:

1. Buccal delivery system
2. Sublingual delivery system
3. Vaginal delivery system
4. Rectal delivery system
5. Ocular delivery system
6. Nasal delivery system
7. Gastrointestinal delivery system

BIOADHESION / MUCOADHESION:

The term bio-adhesion implies attachment of a drug carrier system to a specified biological location.The biological surface can be epithelial tissue or it can be the mucus coat on the surface of a tissue.

- The adhesive attachment of the drug carrier system to a mucous coat / layer, the phenomenon is referred to as mucoadhesion.
- A bio-adhesive polymer is a synthetic or natural polymer which binds to biological substrates such as mucosal membranes.
- Such polymers are sometimes referred to as biological 'glues' because they are incorporated into drugs to enable the drugs to bind to their target tissues.

Mucoadhesive drug delivery system interact with the mucus layer covering the mucosal epithelial surface, &mucin molecules & increase the residence time of the dosage form at the site of the absorption.

- Mucoadhesive drug delivery system is a part of controlled delivery system.
- Combining the mucoadhesive with the enzyme inhibitory and enhances penetration and also improves patient compliance.[3]

MUCOSAL DRUG DELIVERY SYSTEM:

IDEAL CHARACTERISTICS:

1. Provide rapid adherence to the mucosal membrane without changing the physical property of the delivery system.
2. Should not interference with the controlled/sustained release of the active agent.
3. Should be biodegradable and should not produce any toxic by products.
4. Should enhance the penetration of the active agent.
5. The formulation stays longer at the delivery site & improve the bio availability of API.
6. The specific bioadhesive molecules can allows for the targeting of particular sites or tissues. Use of penetration enhancers allows modification of tissue permeability for absorption of macro molecules, such as peptides and proteins. Ex. Sodium glycocholate, Sodium taurocholate and L-lysophosphotidyl choline Use of protease inhibitors in the mucoadhesive dosage forms resulted in better absorption of peptides and proteins.[4]

MUCOSAL MEMBRANE:

Inner layers called mucous Covered with viscoelastic fluid. This fluid Secreted by Goblet cells and it composed of water and mucus.

Other components include proteins, lipids and mucopolysaccharides electrolytes.[5]

Table 1: General Composition Of Mucus Membrane [6]

General composition	Concentrations
Water	95%
Glycoprotein and lipids	0.5-5%
Mineral salts	1.0%
Free proteins	0.5-1%
Thickness	40 µm to 300 µm

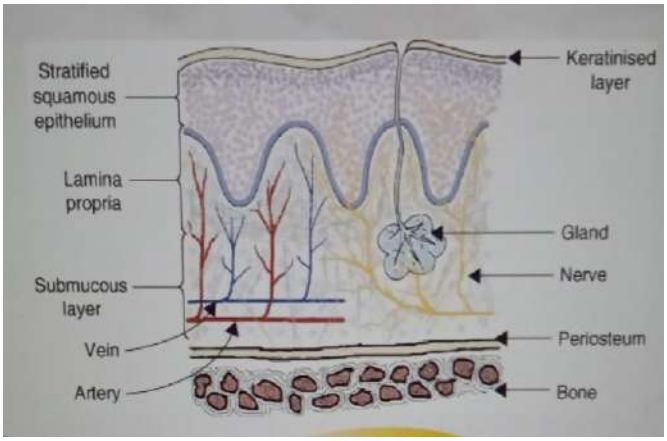

Fig No.1: General Structure Of Mucous Layer

FUNCTIONS OF MUCUS LAYER:

The primary functions of the mucus layer are:

1. PROTECTIVE: Particularly from its hydrophobicity.

2. BARRIER: In tissue absorption of the drugs and influence the bioavailability.

3. ADHESION: Mucus has strong cohesion properties.

4. LUBRICATION: keep mucosal membrane moist. [7]

THE MUCOSAL ROUTES FOR DRUG DELIVERY ARE:

Table 2: Different Routes And Formulations

ROUTES	FORMULATIONS
Buccal route	Tablets,films
Oral route	Gastroretensive ,tablets
Nasal route	Micro particles
Ophthalmic route	Gels, solutions,micro particles
Vaginal route	Gels, tablets

USE OF MDDS:

- MDDS prolong the residence time of the dosage form at the site of absorption.
- MDDS provides rapid absorption and good bio availability due to its considerable surface area and high blood flow.
- Intimate contact of the dosage form with the underlying absorption site.
- Improve therapeutic performance of drug.
- Rapid onset of action.
- High drug loading capacity.
- Controlled drug release (preferably unidirectional release)

ADVANTAGES:

- ✓ Targeting & localization of the dosage form at specific site.
- ✓ High drug flux at the absorption site.
- ✓ Ease of administration and excellent accessibility.
- ✓ Avoid of first pass metabolism.
- ✓ Termination of therapy is possible.
- ✓ Suitable for drugs with poor oral bio-availability. Suitable for drugs with shorter half life (2-8 hrs).
- ✓ Eg. Nitroglycerine (2 hrs), Isosorbide mono-nitrate (2-5hrs). It inhibits protease activity and reduces immunogenic response thus selective use of protein and peptides can be achieved.

DISADVANTAGES:

- ✓ Sometimes exerting too much force to remove the formulation may cause injury to mucosa after use.
- ✓ Some patient suffers unpleasant feeling.
- ✓ Eating and drinking may be restricted.
- ✓ Expensive therapy.
- ✓ Suitable for drug with small dose requirement only.
- ✓ Over hydration often lead to slippery surfaces affecting structural integrity of the formulation and performance.[8]

FACTORS AFFECTING MUCOADHESION:

Table 3:

A. Polymer related factors	B. Environmental related factors	C. Physiological related factors
1. Molecular weight	1. Applied strength	1. Mucin turnover
2. Flexibility	2. Initial Contact time	2. Disease condition
3. Cross linking density	3. pH	

4. Hydrogen bonding capacity		
5. Hydration		
6. Concentration		

A. POLYMER RELATED FACTORS:

1. Molecular weight: Drugs with higher mol. weight (>100,000) exhibits good mucoadhesive property.

2. Flexibility: Mucoadhesion initiates with diffusion of polymer chains in the interfacial region. Thus polymer chains must contain a optimum flexibility to achieve desired entanglement with mucus.

3. Cross-linking density: Increased cross- linking density of polymer affects the swelling efficient resulting in decrease rate of interaction between polymer and mucin.

4. Hydrogen bonding capacity: polymer must have functional group in order to form hydrogen bonds with the mucin and mucosa. Moreover hydrogen bonding facilitates flexibility of the polymer.

5. Hydration: Wetting and swelling allows a mechanical entanglement of polymer by exposing the bioadhesive sites for hydrogen bonding electrostatic interaction between polymer & mucus network.

6. Concentration: Lower the concentration polymer. lower the number of polymer interactive chains/unit volume of mucus therefore the interaction between polymer & mucus will be unstable.

B. ENVIRONMENTAL FACTORS:

1. Applied strength: To place a solid mucoadhesive system. it is necessary to apply a defined strength.

2. Initial contact Time: The mucoadhesive strength increases as the initial contact time increases.

3. pH:pH influences the charge on the surface of both mucus and the polymers.

C. PHYSIOLOGICAL FACTORS:

1. Mucin production: The mucin production is expected to limit the residence time of the mucoadhesive on the mucus layers.

2. **Diseased condition:** Physicochemical properties of mucus change during diseased states. such as common cold. gastric ulcers. ulcerative colitis. cystic fibrosis bacterial and fungal infections that may affect adhesion.[9]

TRANSMUCOSAL PERMEABILITY:

There are two routes potentially involved in drug permeation across epithelial membranes: trans-cellular route and paracellular route

Mechanism of Drug Transport

- Two major routes are involved:

[1] Transcellular - involves interchange of the cellular membranes with a polar and a lipid domain.

(2) Paracellular (intercellular)- involves the passive diffusion through the extracellular lipid domain.[10]

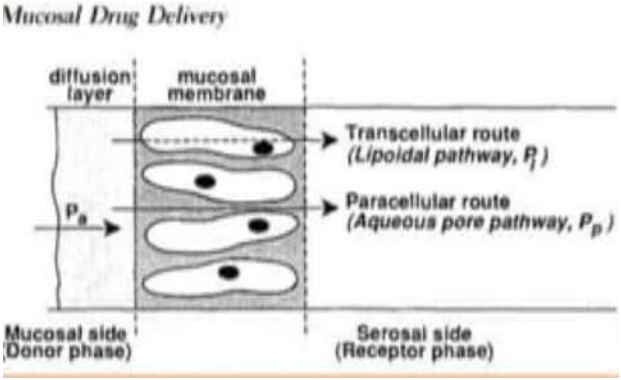

Fig no 2: Transmucosal permeability

PRINCIPLE /THEORY OF BIOADHESION OR MUCOADHESION:

They are two types:

1. Chemical: Electronic and adsorption theory

2. Physical: Wetting,diffusion,mechanical and cohesive theory

1.Electronic theory

2.Adsorption theory

3.Wetting theory

4.Diffusion theory

5.Mechanical theory

6.cohesive theory

1. ELECTRONIC THEORY:

The electron transfer between the mucus and the mucoadhesive results in the formation of a double layer of electrical charges at the mucus and mucoadhesive interface.The net result of such a process is the formation of attractive forces within this double layer.

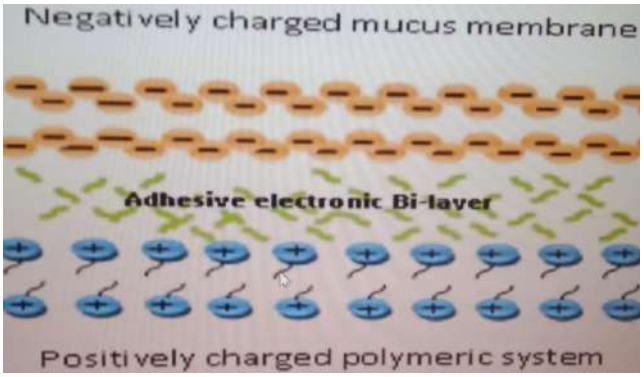

Fig.no.3:Electronic theory

2. ADSORPTION THEORY:

Adhesion occurs due to surface forces acting between the atoms present between two different surfaces.

Two types of chemical bonds resulting from these forces.

Primary: Covalent bond

Secondary: Ionic bond , hydrogen bond, & vanderwalls forces.

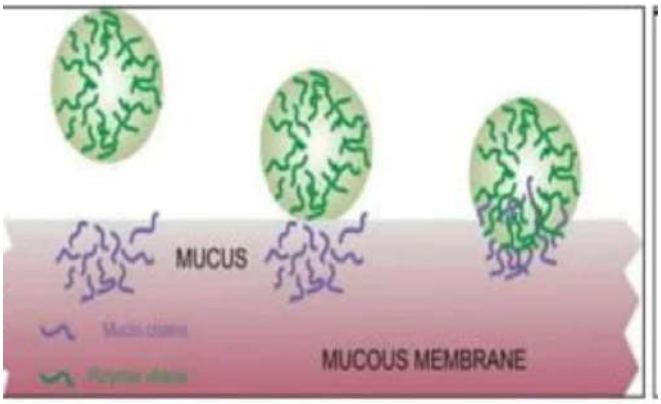

FIG.NO.4: Adsorption theory

3. WETTING THEORY:

States that if the contact angle of liquids on the substrate surface is lower then there is greater affinity for the liquid to the substrate surface.

Ability of bioadhesive polymers to spread & develop intimate contact with the mucous membrane.

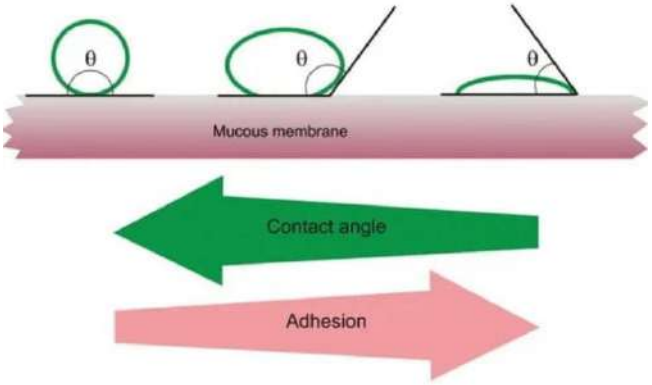

Fig. No.5: Wetting Theory

4. DIFFUSION THEORY:

The polymer chains and mucus mix at a depth to creat semi permanent adhesive bonds. Penetration of polymer chains depends on diffusion coefficient and time of contact. Physical entanglement of mucin strands and flexible polymer chains.

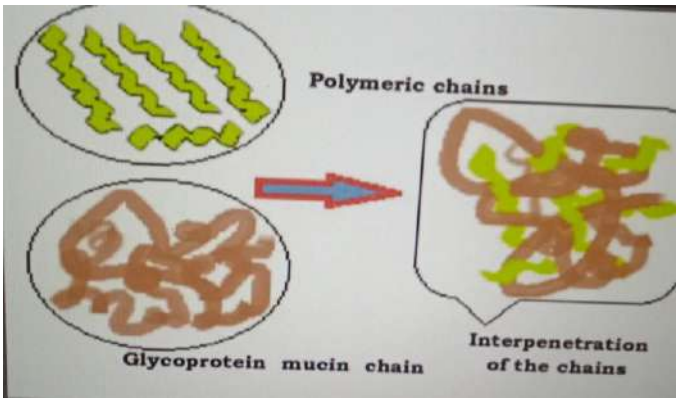

Fig no.6: Diffusion theory

5. FRACTURE THEORY:

This theory describes the force required for the separation of two surfaces after adhesion.

The major mechanism by which to determine the mechanical strength of a particular mucoadhesive, and describes the force necessary to separate the two materials after mucoadhesion has occurred.Theory only deals with the separation force, the diffusion and penetration of polymers is not accounted.

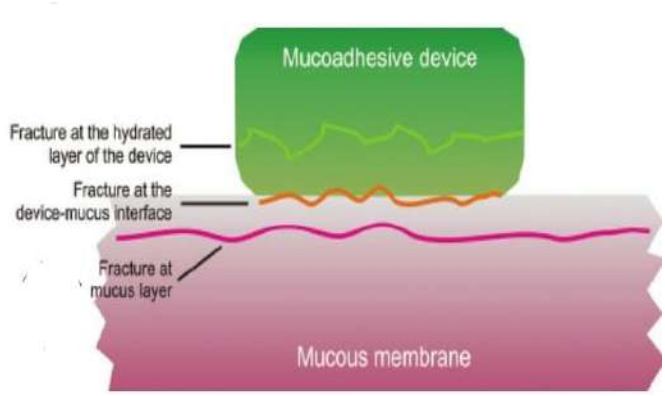

Fig no.7: Fracture theory

5. MECHANICAL THEORY:

Mechanical theory considers adhesion to be due to the filling of the irregularities and micro-cracks on a rough surface by a mucoadhesive liquid forming an inter locked structure.

6. COHESIVE THEORY:

States that process of bio adhesion occurs due to inter-molecular interactions among like molecules with in two different layer.[11]

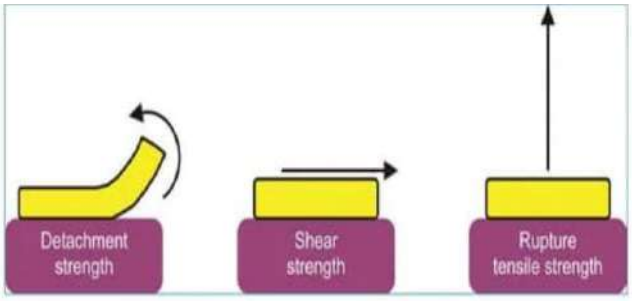

Fig.no.8: Cohesive theory

MECHANISM OF BIOADHESION:

Generally it is divided into two steps:

(a) CONTACT STAGE: The contact b/w the mucoadhesive & the mucus membrane occurs causing spreading & swelling of the formulation which allows initiating its deep contact with mucus layer.

(b) CONSOLIDATION STAGE: The mucoadhesive material are activated by the presence of moisture. Moisture allows the mucoadhesive polymer to get fragmented and promotes linking through weak vanderWaals and hydrogen bonding.[12]

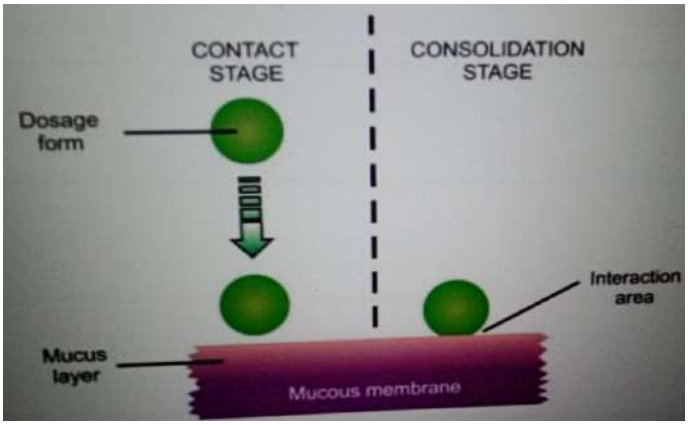

Fig.no. 9: Contact stage and consolidation stage

STEP 1: wetting and swelling of the polymer [**contact stage**].

- Wetting and swelling step occurs when polymer spreads over the surface of mucosal membrane to develop intimate contact.
- Swelling of polymer occur because the components of polymer have an affinity for water.

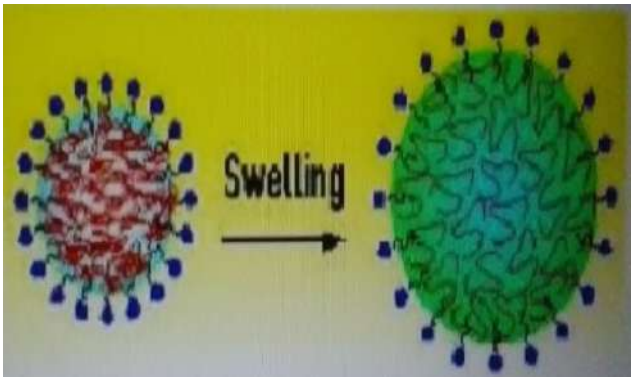

Fig.no.10: Wetting and swelling of the polymer

STEP 2: Interpretation between the polymer chains and the mucosal membrane.

- In this step the mucoadhesive polymer chain and the mucosal polymer chains intermingle and entangles to form adhesive bonds.
- Strength of bonds depends up on the degree of penetration of the two polymer groups.

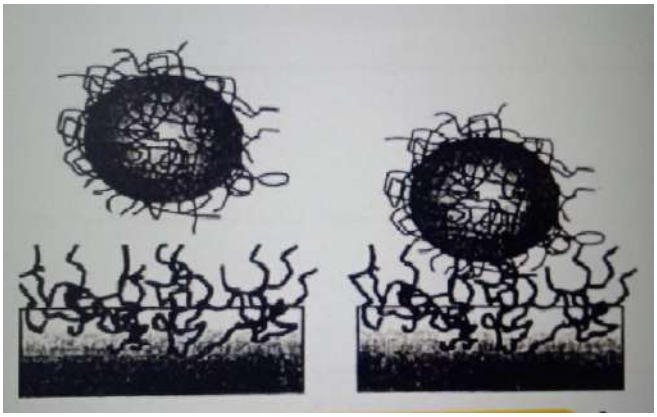

Fig.no. 11: Interpenetration of mucoadhesive and mucous polymer chain

STEP 3: Formation of bonds between the entangled chains.

- This step involves formation of weak chemical bonds between entangled polymer chains.
- Bonds includes primary bonds such as covalent bonds and secondary interactions such as vanderwalls and hydrogen bonds.[13]

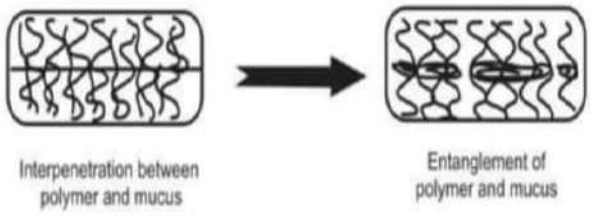

Fig.no. 12: Entanglement of Polymer and Mucus by Chemical bonds

FORMULATION DESIGN: MDDS:

➢ In case of both mucosal [local] & transmucosal [systemic] administration of conventional dosage are not able to assure therapeutic level.

CHARACTERISTIC OF IDEAL POLYMER:

- ✓ Must be non-toxic and non-absorbable from GIT.
- ✓ Must have good spreadability.
- ✓ Wetting, swelling and biodegradable properties Optimum molecular weight.
- ✓ Non-irritant to mucous membrane
- ✓ Form a strong non-covalent bond with mucin epithelial cell surface.
- ✓ Must have wetting and swelling properties .
- ✓ Must be biodegradable in the biological system.

Formulation of MDDS:

1) Mucoadhesive polymers
2) Penetration enhancers
3) Enzyme inhibitors

1. MUCOADHESIVE POLYMER: The polymer hydration & consequently mucus cohesive properties promotes mucoadhesion.Swelling should favour polymer chain flexibility & interpenetration b/w polymer& mucin chains.

Examples: Poly acrylic acid [PAA],Polyvinyl alcohol [PVA],Sodium carboxy methyl-cellulose [NACMC],Sodium alginate,HPMC,HEC,HPC.
Various co-polymer of acrylic acid such as acrylic acid, polyethylene glycol, mono methyl ether co-polymer have also been studied.

2.PENETRATION ENHANCERS: PE facilitate drug to reach the systemic circulation to exert its action . Must be non-irritant & have a reversible effect. Polymers like Chitosan & its derivatives are known to have mucoadhesive properties. Chitosan also supports paracellular transportation of drug across mucosa.

Examples of Permeation Enhancer, Benzalkonium chloride, Dextrose sulfate, Propyleneglycol, Fatty acid,. Phosphatidylcholine, Menthol, Sodium EDTA, Polysorbate 80.

3.ENZYME INHIBITORS: EI improves the Buccal absorption of drugs. particularly high molecular weight molecules such as peptides. Proteins.

Ex: Aprotinin, Bestatin, Puromycin

- ✓ Bile salts stabilize protein drugs by different mechanism affecting enzymatic activity and hence preventing the alteration of protein conformation.
- ✓ Chemical modification of chitosan with EDTA give to a polymer conjugate namely

chitosan-EDTA.very potent inhibitor of metallopeptidase very (carboxypeptidase).[14]

BUCCAL DRUG DELIVERY:

Buccal drug delivery is composed of approximately 40-50 cell layers, while sublingual layer consist of fewer cell layers. In humans, layers, while dogs, and rabbits, the Buccal mucosa measures 500-800 pm in thickness. The drug administration through the mucosal membrane lining of the cheeks (Buccal mucosa).

The Buccal region offers an attractive route of administration for the controlled systemic drug delivery. Buccal ,mucosa has an expanse of smooth muscle and relatively immobile mucosa which makes it more desirable region for retentive system. Mucoadhesive dosage forms in the Buccal cavity includes: Adhesive tablets,adhesive gels,adhesive patches, adhesive ointments .[15]

Fig.no.13: Buccal drug delivery

ADVANTAGES:

- ✓ Contact with the digestive fluid is avoided.
- ✓ Well known for its good accessibility to the membrane that lines are oral cavity.
- ✓ Patient can terminate the delivery in case of emergencies.
- ✓ The novel Buccal dosage formulations exhibit better patient compliance.

DISADVANTAGES:

- ✓ Saliva is continuously secreted into oral cavity diluting the drug resulting low drug concentration.
- ✓ Taste, irirtancy, allergy, and adverse properties like discoloration erosion of teeth may limit the drug use.
- ✓ Conventional type of Buccal drug delivery system did not allow to eat, drink, or talk(in some cases)

USES OF BUCCAL DELIVERY:

The oral cavity can be used for local and systemic therapy Examples of local therapy would be the treatment of oral infections , dental caries , mouth ulcers stomatitis, gingivitis. The Buccal route is of particular interest with regard to the systemic delivery of small molecules that are subjected to first-pass metabolism.[16]

2. SUBLINGUAL DRUG DELIVERY:

The sublingual region generally shows the higher drug permeability than the Buccal region.The substance is fastly absorbed via the blood vessels below the the tongue rather than the digestive tract. This route is been used for delivery of drugs having rapid onset of action.

Eg. Nitroglycerine.

The latest developments have been applied to the treatment of angina pectoris, cancer, and in the cure of smoking.

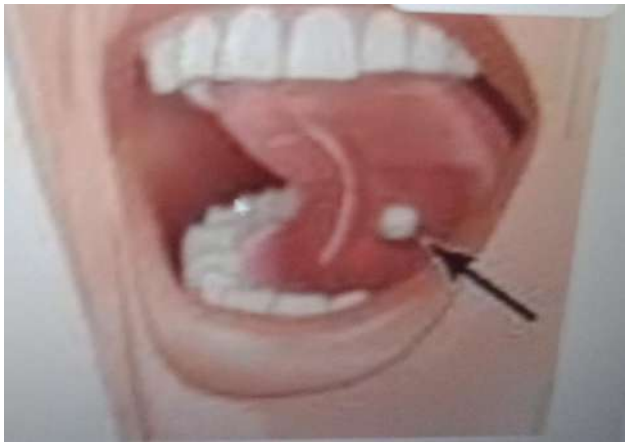

FIG.NO.14: Sublingual drug delivery

ADVANTAGES:

- Fast onset of action is achieved
- Avoids first pass metabolism
- Low dosage give high efficacy as hepatic first pass metabolism is avoided.

- Large contact surface of the oral cavity contributes to rapid absorption

DISADVANTAGES:

The sublingual administration of drugs interferes with drinking, eating and talking.[17]

3. NASAL DRUG DELIVERY:

The nasal route is an ideal alternative to the parentrals for administering drugs intended for systemic effect, in view of the rich vascularity of the nasal membranes and the ease of intranasal administration. Besides avoidance of hepatic first-pass elimination. Controlled release can been thoroughly tested in humans for other application and Most have already GRAS [generally regarded as safe] status.

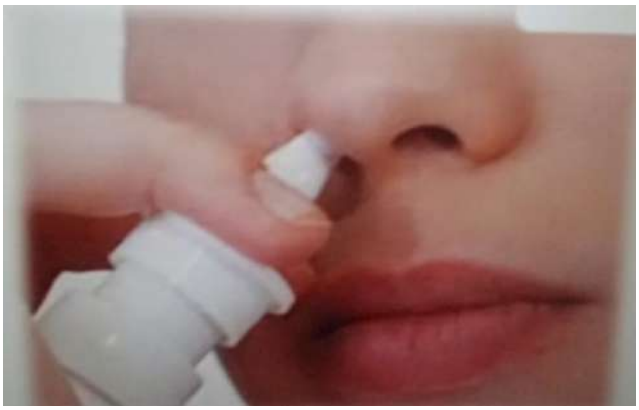

FIG.NO.15: Nasal drug delivery

4. OCULAR DRUG DELIVERY:

Various strategies were developed to enhance the bio-availability. ophthalmic drugs by prolonging the contact time between the formulations and the corneal/conjunctive epithelium. Viscous semi-solid preparations, like gels and ointments, provide a sustained contact with the eye, but they induce sticky sensation, blurred vision, irritation and reflex blinking due to discomfort Mucoadhesive concept is now implemented as new approach to optimize the ocular dosage form.

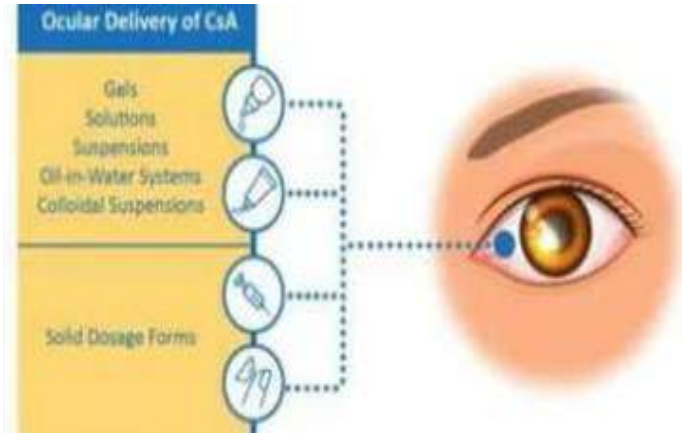

FIG.NO.16: Ocular drug delivery

2.VAGINAL AND RECTAL DRUG DELIVERY: Vaginal Bioadhesive preparations have been development . a new type of controlled-release form for the treatment of both topical and systemic diseases.The greatest advantage of such dosage forms is the possibility of maintaining them in the vagina for extended periods of time including daytime and nighttime, thereby enabling lower dosing frequencies. Drugs administered rectally as a suppository.[18]

MUCOADHESIVE DOSAGE FORM:

Table-4:

SOLIDS	SEMISOLIDS	LIQUIDS
Tablets	Gels & Ointments	Suspensions
Matrix tablets	Films	Gel forming liquid
	Patches	

SOLIDS:

TABLETS:

Generally they are prepared by direct compression, but wet granulation techniques also be used. To get sustained release and more mucoadhesion, tablets can be coated with water impermeable materials. **Example:** ethyl-cellulose, hydrogenated castor oil.

- Multilayered tablets might be designed by successively adding and compressing the ingredients layer by layer.
- Sometimes mucoadhesive micro spheres are also formulated, prior to direct compression

into tablets so as to get enhanced action and prolonged drug release.

- Adhesive tablets: Unlike conventional tablets, bioadhesive tablets allow drinking and speaking without major discomfort.

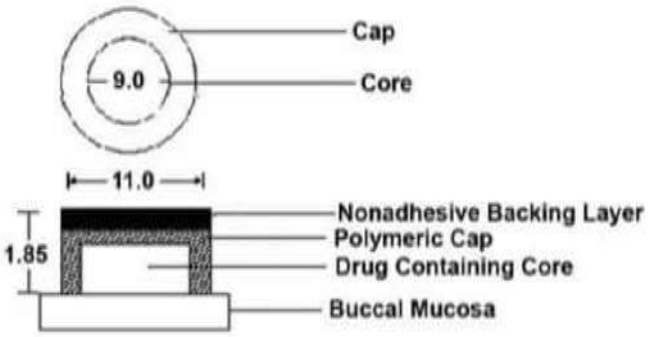

FIG.NO.17: Tablets

Eg: Prochlorperazine maleate Buccal tablet
Glyceryl trinitrate Buccal tablet
Fentanyl Buccal tablet
Miconazole Buccal tablet

MATRIX TABLETS:

(a) monolithic
(b) two layered tablets

IN MONOLITHIC TABLETS:

Mixture of drug + swelling bioadhesive polymer bidirectional release and outer side coated with impermeable hydrophobic substance.

IN TWO LAYERED MATRIX TABLETS:

Comprises of an inner layer based on bioadhesive polymer and an outer non- bioadhesive layer containing the drug for a bi-directional release but only local action. In case of systemic outer layer is inert and acts as a protective layer.

SEMI SOLIDS:

PATCHES:

Buccal patch is a non-dissolving thin matrix modified release dosage form composed of one or more polymer films or layers containing drug and/or other excipients. The patch contains a mucoadhesive polymer which bonds to release in oral the oral mucosa, or teeth for mucosa, oral cavity or both. Mucoadhesive Buccal patches can be prepared either by solvent casting or direct milling. The size of the patches can vary from 1 to 15cm^2. The smaller the size, the more convenient and comfortable are the patches. Patches may be An impermeable backing layer may also be applied to control the direction of drug release, prevent drug loss, and minimize deformation and disintegration of the device.

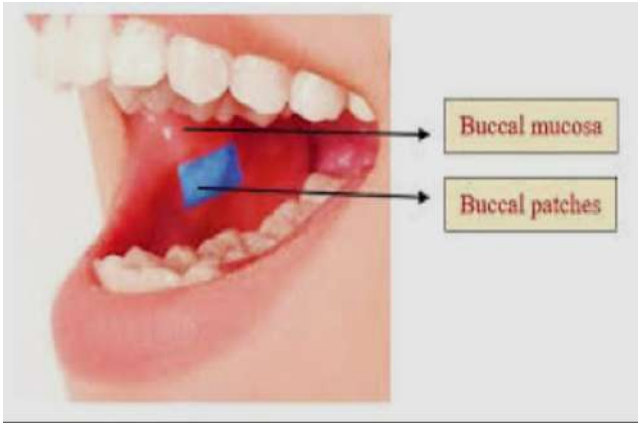

Fig.no.18: Patches

FILMS:

films are the recently formulated dosage form for Buccal administration which are preferred over mucoadhesive Buccal tablets in terms of flexibility and comfort and can also avoid the comparatively short residence time of oral gels on the mucosa, which are easily removed by saliva. Besides, the Buccal films also take care of the wound surface in local delivery for oral infections, thus reduce pain and do effective treatment.They are generally prepared by a solvent casting method.[19]

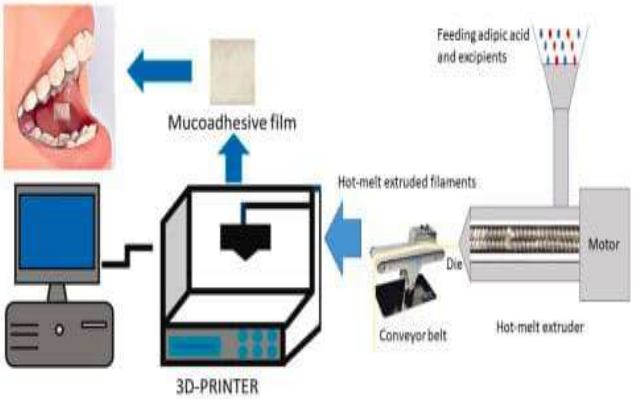

Fig.no.19: Films

Manufacturing methods of Buccal patches/ films:

Hot melt extrusion

Solvent casting

1. Hot melt extrusion of films: In hot melt extrusion ,blend of pharmaceutical ingredients is molten and then forced through an orifice to yield a more homogeneous material in different shapes such as granules, tablets, or films. Hot melt extrusion has been used for the manufacture of controlled release matrix tablets, pellets and granules, as well as oral disintegrating films.

2. Solvent casting: • In this method, all patch excipients including the drug co-dispersed in an organic solvent and coated onto a sheet of release liner. After solvent evaporation a thin layer of the protective backing material is laminated onto the sheet of coated release liner to form a laminate that is die-cut to form patches of the desired size and geometry.The solvent casting method is carried by two methods (Casting and direct milling method).

Casting method:

Water soluble ingredient is dissolve in water (H_20) and API and other agent are dissolving in suitable solvent so as to form a clear solution.

⇩

Followed by both the solution are mixed

⇩

Resulting solution in cast as a film is and allowed to dry

⇩

Film is coated

In this, patches are manufactured without the use of solvents. Drug are mechanically mixed by direct milling or by kneading, usually without the presence of any liquids. After the mixing process, the resultant material is rolled on a release liner until the desired thickness is achieved. The backing material is then laminated as previously described. While there are only minor or even no differences in patch performance between patches fabricated by the two processes, the solvent-free process is preferred because there is no possibility of residual solvents and no associated solvent-related health issues

Direct milling:

API and Excipients are blended by direct milling

⇩

Blended mixture is rolled with the help of roller.

⇩

Followed material is laminated

⇩

inally film is collected.

GELS AND OINTMENTS:

Gels and ointments are semisolid dosage forms with the advantages of uncomplicated dispersion throughout the oral mucous. But, dosing from semisolid dosage forms not much as exact as from tablets, patches, or film.

e.g. polymer 407, sodium car-boxy methyl cellulose

- They change from liquid to semisolid.
- HPMC has been used as an adhesive ointment ingredients.[20]

EVALUATION OF BUCCAL DOSAGE FORMS:

1. weight variation: Weight variation: Collect l10 tablets from each formulation of varying concentration of polymer. Weigh the tablets individually from all the selected formulations;

calculate the a weight and comparing the individual tablet weights to the average.

2. Thickness: Collect 3 tablets/patch from each batch of formulation and the thickness of the tablets were measured with the help of vernier caliper. The average thickness is calculated.

3. Friability; of the tablets was determined by using Roche Friability. From each batch, 6 tablets were weighed accurately which was WI then placed in the Friability and rotated at 25 rpm for 4 min. After completing the rotation weight of tablets were weighed which is W2. The percentage Friability was determined.[21]

Mucoadhesive polymers can be characterized by testing their adhesion strength by

A. *in vitro*

B. in vivo tests

A. *IN VITRO* TESTS:

1. Tensile strength test: It measures the force required to break the adhesive bond between a mucous membrane and the polymers. The instruments usually employed are modified .

This method is used to measure the mucoadhesive strength.[22]

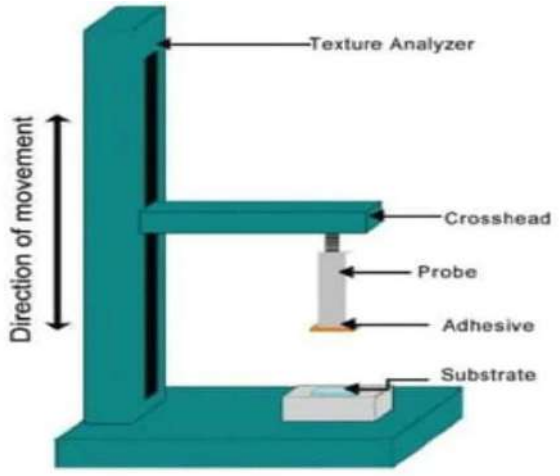

Fig.no.20: Tensile strength

2.Shear Strength Test: Shear stress measures the force that causes the bio- adhesive to slide over the mucus layer in parallel to their place of contact of adhesion.

3.Adhesion weight method: In this method the weight of adherent particle was determined by flowing a suspension of an ion exchange resin particles over the inner mucosal surface of a section of animal intestine [guinea pig].

- This method has limited value due to poor data bioavailability.
- But it was possible to determine the effect of particle size and charge on the adhesion with everted intestine after 5 minutes contact.

4.Fluorescent probe method: For the determination of the bioadhesive potential of large number of polymer, the fluorescent method is used.

- In the technique labeling the lipid bi layer and membrane protein with the fluorescent probe [pyrene and fluorescence isothiocynate].
- Addition of polymers to this substrate surface compresses the lipid bi layer or protein causing a change in fluorescence, as compared to control cells.

5.Flow channel method: This method was developed by mikos and peppas.

- A 2% w/w aqueous solution of bovine sub maxillary mucin, thermostatic at 37° c is filled in a glass made up of thin channel.
- Humid air at 37°c was passed through glass channel.
- The adhesion property is calculated by placing a particle of bioadhesive polymer on the mucin gel and its static and dynamic behaviour is monitored at frequent intervals using a camera.

6.Falling sphere method: The falling sphere method was used for characterize the mucoadhesive strength.

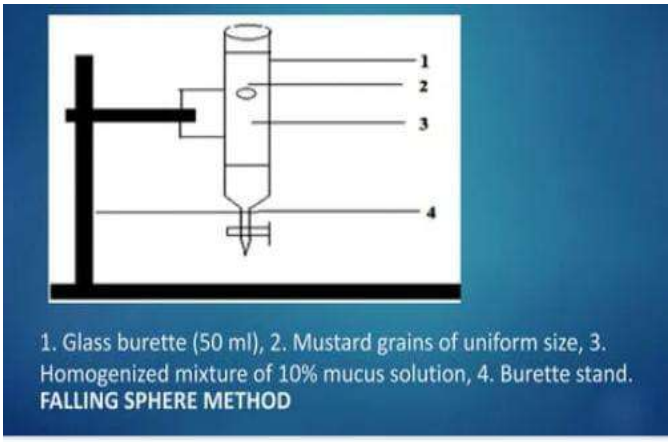

Fig.no.21: Falling sphere method

7.Colloidal gold staining method: The technique employed red colloidal gold particles which were stabilized by adsorbed mucin molecules [mucin-gold conjugates].

- Upon interaction with the mucin -gold conjugates, bioadhesive hydrogels developed a red colour the surface.
- Thus the interaction between them could easily be quantified either by the measurement of the intensity of red colour on the hydrogel surface or by the measurement of the decrease in concentration of the conjugates from the absorbance changes at 525 nm.

8. Viscometric method: Hassan and Gallo used simple viscometer to quantify the mucin polymer bond.

- Viscosites of 15% w/v percin gastric mucin dispersion in 0.1N HCL or 0.1N acetate buffer were measured with brook field viscometer.
- The brook field viscometer measure the bio-adhesion bond strength in the presence or absence of neutral, anionic, and cationic polymers.

9.Adhesion number: With a mucoadhesive in the form of small particles, the adhesion number can be used for mucoadhesion.

The adhesion number is typically represented by the following equation:

Na= (N/No) ×100

Where, Na is the adhesion number

No is the total number of applied particles

N is the number of particles attached to the substrate

As the adhesion strength increases, the adhesion number also increases.

10.Electrical conductance: The semisolid mucoadhesive ointments are tested by electrical conductance method.

- For measuring the electrical conductance we use a modified rotational viscometer.
- In this method the artificial membrane in the artificial saliva is used, the adhesion of orabase ,carbopol,cudispert,guar gum and methyl cellulose is calculated.
- In the presence of adhesive the conductance is comparatively low,as the adhesive was removed, value increased to final value,which corresponds to the conductance of saliva, which indicates the absence of adhesion.

11.Thumb test: 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.[23]

B. IN VIVO TESTS:

The common *in vivo* tests to monitor bio-adhesion include:

1. **Gamma scintigraphy:**

Gamma scintigraphy is a technique where by the transit of a dosage form through its intended site of delivery can be non-invasively imaged *in vivo* via the judicious introduction of an appropriate short lived gamma emitting radioisotope .the observed transit of the dosage form can then be correlated with the rate and extent of drug absorption . the study emphasized the importance of *in vivo* studies,because although chitosan exhibits an outstanding mucoadhesion capacity *in vitro,*the retention time at the absorption site in the human gastro intestinal tract was relatively short and not sufficient reproducible.

2. **X-ray studies:**

In this method administration of dosage form with a radio opaque substances and subsequently locating the administered dosage form by means of X-RAY. Aim is to figure out the in-vivo mucoadhesive capacity of dosage form, generally used for oral mucoadhesive tablets.[24]

APPLICATIONS:

Vaccine delivery for treatment of diseases like; hepatitis, influenza,pertussis [whooping cough], ricin toxoid , birth control.

Microsphere in vaccine delivery have specific application like improved antigenicity by adjuvant action,modulation of antigen release,stabilization of antigen.

Passing targeting of leaky tumour vessels, active targeting of tumour cells, antigens, by intravenous / intra-arterial application.

Chemo embolization:[an endovascular therapy] involves selective arterial embolization of tumour along with local delivery of chemotherapeutic agent.

Imaging: various cells, cell lines, tissues and organs can be imaged using radio labeled micro spheres.

Release of **proteins,hormones** and peptides over extended period of time.

Targeting of drug at particular site of action.

Gene therapy with DNA plasmids and delivery of insulin.

Preparation of Topical porous micro-spheres.

Preparation of Surface modified Microsphere.[25]

CONCLUSION

The mucoadhesive dosage forms offer prolonged contact at the site of administration, low enzymatic activity, and patient compliance. The formulation of mucoadhesive drug delivery system depends on the selection of suitable polymer with excellent mucosal adhesive properties and biocompatibility. Now researchers are looking beyond traditional polymers,in particular next-generation mucoadhesive polymers (lectins,thiols,etc.);these polymers offer greater attachment and retention of dosage forms.However, these novel mucoadhesive formulations require much more work, to deliver clinically for the treatment of both topical and systemic diseases.

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