

Mucosal Drug Delivery Systems (MDDS)

The focus of pharmaceutical research is being steadily shifted from the development of new chemical entities to the development of novel drug delivery system (NDDS) of existing drug molecule to maximize their effect in terms of therapeutic action and patient protection. Mucoadhesive systems are known to provide intimate contact between dosage form and the absorptive mucosa, resulting thereby in a high drug flux through the absorbing tissue. In addition, mucoadhesive dosage forms have been used to target local disorders at the mucosal surface to reduce the overall dosage required and to minimize the side effects that may be caused by the systemic administration of the drugs.

Ideal controlled drug delivery system:

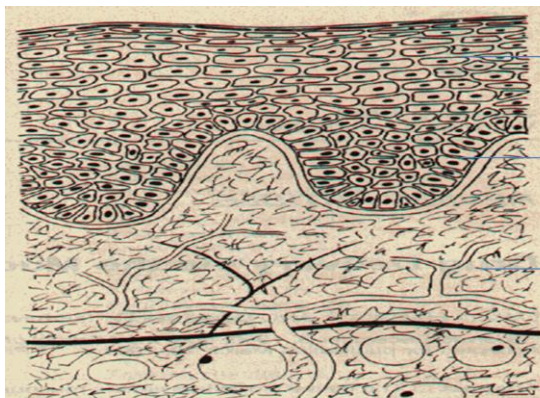
An ideal controlled drug delivery system is the one, which delivers the drug at a predetermined rate, locally or systemically, for a specified period of time.

Design of Controlled Release Drug Delivery System:

The basic goal of a controlled drug delivery is to optimize the biopharmaceutical, pharmacokinetic and pharmacodynamic properties of drug in such a way that its utility is maximized through reduction in side effects and cure or control of condition in the shortest possible quantity of drug administered by the most suitable route.

Anatomy of mucosa:

Biological membrane



Epithelium.

Lamina propria.

Muscularis mucosa.

Structure of mucosa.

Composition of mucus layer:

- Mucus is translucent and viscid secretion which forms a thin continuous gel adherent to mucosal epithelial surface.'
- Water - 95%
- Glycoprotein and lipids - 0.5-5%
- Mineral salts - 1%

- Free proteins - 0.5-1%
- All biological formulations interact with mucin layer during process of attachment, it acts as a link between the adhesive and the membrane. Mucous is a network of mucin glycoprotein that form a continuous layer that intimately cover the internal tract of body.

Advantages of Mucosal drug delivery systems

- MDDS prolong the residence time of the dosage form at the site of application or absorption.
- Intimate contact of the dosage form with absorptive mucosa.
- Prolonged contact time of a drug with a body tissue through the use of a bioadhesive polymer can significantly improve the performance of many drugs.
- Drug targeting.
- High drug loading capacity.
- Used to target local disorders at the mucosal surface to reduce dose and to minimize the side effects.
- Low enzymatic activity & avoid of first pass metabolism.
- Excellent accessibility.

Disadvantages of Mucosal drug delivery systems

- If MDDS adhere too tightly because it is undesirable to exert too much force to remove the formulation after use, otherwise the mucosa could be injured.
- Some patients suffer unpleasant feeling.
- The lack of standardized techniques often leads to unclear results.
- Costly drug delivery system.
- Medications administered orally do not enter the blood stream immediately after passage through the buccal mucosa.

Mechanism of mucoadhesion

The mechanism of mucoadhesion between hydrogels and mucosa can be described in three steps.

1. Wetting and swelling
2. Interpenetration of the bioadhesive polymer
3. Formation of weak chemical bonds.

Alternatively, mucoadhesion may be described as through contact stage and consolidation stage

- Contact stage is characterized by the contact b/w the mucoadhesive & the mucus membrane with spreading & swelling of the formulation, initiating its deep contact with mucus layer.
- In consolidation stage, the mucoadhesive material is activated by the presence of moisture

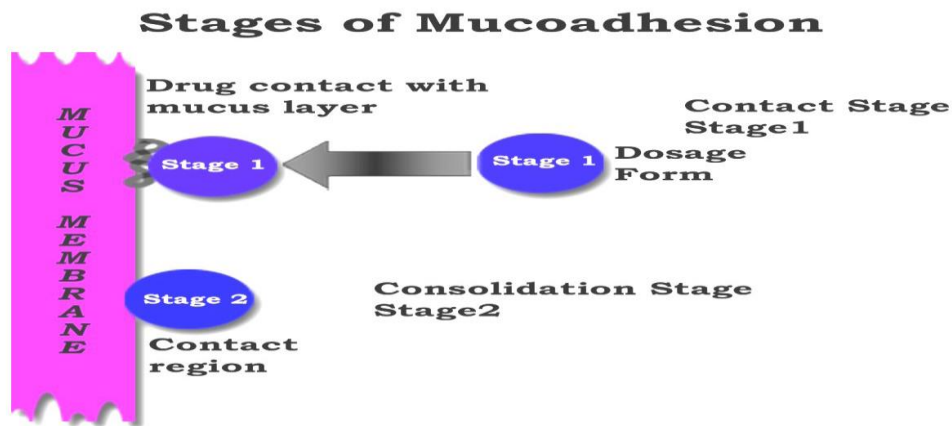


Fig. No.1. The two steps of the mucoadhesion process.

Mucoadhesion Theory

Electronic theory

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

Drug transport mechanism

Two major routes-

(1) Transcellular (Intracellular)

(2) Paracellular (intercellular)

- The transcellular route involves the crossing of the cellular membranes with a polar and a lipid domain.
- The paracellular essentially implicates the passive diffusion through the extracellular lipid domain.
- To reach the systemic circulation ,drugs must also overcome an enzymatic barrier represented by the enzymes that are present on the mucosal surface & mucosa.
- Aminopeptidase,carboxypeptidase & estrase were found in homogenates of human epithelial cell culture.

Mucosal routes for drug delivery

- Buccal / Oral route
- Nasal route
- Ocular route
- Vaginal route
- Gastrointestinal route

MUCOADHESIVE POLYMERS Properties

1. It must be loaded substantially by the active compound.
2. Swell in the aqueous biological environment of the delivery–absorption site.
3. Interact with mucus or its components for adequate adhesion.
4. When swelled they allow, controlled release of the active compound.
5. Be excreted unaltered or biologically degraded to inactive, non-toxic oligomers.
6. Sufficient quantities of hydrogen bonding chemical groups.
7. Possess high molecular weight.
8. Possess high chain flexibility.
9. Surface tension that will induce spreading into mucous layer.

Classification

Mucoadhesive polymer are classified as follows:

Source	Examples
Semi-natural/natural	Agarose, chitosan, gelatin, Hyaluronic acid, Various gums (guar, hakea, xanthan, gellan, carragenan, pectin, and sodium alginate), starch, sulfated polysaccharides.
Synthetic Cellulose derivatives	Carboxy methyl cellulose(CMC), sodium CMC, Hydroxy ethyle cellulose (HEC), Hydroxy propyl cellulose (HPC), Hydroxy propylmethyl cellulose (HPMC), Methyl cellulose (MC), methylhydroxyethylcellulose
Synthetic Poly(acrylic acid) based polymers	Carbopol, Polycarbophil, polyacrylates, poly(methylvinylether-co-methacrylic acid), poly(2-hydroxyethyl methacrylate), poly(acrylic acid-co ethylhexylacrylate), poly(methacrylate), poly(alkylcyanoacrylate), poly(isohexylcyanoacrylate), poly(isobutylcyanoacrylate), copolymer of acrylic acid and Poly ethylene glycol
Others	Poly(N-2-hydroxypropyl methacrylamide) (PHPMAm), polyoxyethylene, Poly vinyl alcohol, Polyvinyl pyrrolidone, thiolated polymers, Poloxamers

Formulation design

- In case of both mucosal (local) & transmucosal (systemic) administration, conventional dosage are not able to assure therapeutic level.
- In MDSS contain the following functional agents-
 - (1) Mucoadhesive agents
 - (2) Penetration enhancers
 - (3) Enzyme inhibitors

Mucoadhesive agents-

The polymer hydration & consequently the mucus cohesive properties that promote mucoadhesion . Swelling should favor polymer chain flexibility & interpenetration b/w polymer & mucin chains.

Examples-

- Polyacrylic acid (PAA)
- Polyvinyl alcohol(PVA)
- Sodium carboxymethylcellulose(NaCMC)
- Sodium alginate
- HPMC
- HEC
- HPC

Various copolymer of acrylic acid such as acrylic acid –polyethylene glycol monomethyl ether copolymer have also been studied.

Penetration Enhancers-

- PE are also required when a drug has to reach the systemic circulation to exert its action .
- Must be non-irritant & have a reversible effect.
- Recently chitosan & its derivatives, polymers already known for MA properties. chitosan help transportation of drug through paracellular pathway.

List of Permeation Enhancer :-

- Benzalkonium chloride
- Dextran sulfate
- Fatty acid
- Propyleneglycol
- Menthol
- Phosphatidylcholine
- Polysorbate 80
- Sodium EDTA

Enzyme inhibitors-

- Drug +enzyme inhibitors---->improving the buccal absorption of drugs, particularly peptides.

Example:

1-Aprotinin

2-Bestatin

3-Puromycin

- Bile salts stabilise protein drugs by different mechanism(effecting the activity of the enzymes,altering the conformation of the protein.
- Chemical modification of chitosan with EDTA produces polymer conjugate chitosan –EDTA that is a very potent inhibitor of metallopeptidases (carboxypeptidase)

Polymer properties desirable for mucoadhesion / Factors affecting mucoadhesion

Functional group: The mucoadhesive polymer possessing hydrophilic functional group such as COOH, OH, NH₂, and SO₄H may be more favourable in formulating targeted drug delivery system. The functionalized polymer interact with mucus not only through physical entanglement but also through

chemical bonds, resulting in formation of cross linked network. Example: Urea is well accepted hydrogen bonding disruptor which decreases mucoadhesiveness of mucin/pectin samples.

Degree of hydration Hydration is essential for the relaxation and interpenetration of polymer chains. Excess of hydration could lead to decreased mucoadhesion and/or retention due to the formation of a slippery mucilage. In this situation cross-linked polymers that only permit a certain degree of hydration may be advantageous for providing a prolonged mucoadhesive effect.

Chain length Chain length and its flexibility is critical for interpenetration and entanglement with the mucus gel. Increased chain mobility leads to increased inter diffusion and interpenetration of the polymer within the mucus network. Long polymer chains lose their ability to diffuse and interpenetrate through mucosal surfaces. Hence as the chain length decreases interpenetration increases.

Degree of cross linking The chain mobility and resistance to dissolution is significantly influenced by the degree of cross-linking within a polymer system. Cross-linked hydrophilic polymers swell in the presence of water allowing them to retain their structure. High molecular weight linear hydrophilic polymers are swellable and readily dispersible. Cross-link density increases, chain mobility decreases and hence the effective chain length, decreases, reducing mucoadhesive strength.

Polymer concentration Polymer concentration is dependent on physical state of the delivery system, with differences between semisolid and solid-state dosage form. In the semisolid state, polymer concentration is low which reduces adhesion. Hence lower number of polymer chains are available for interpenetration with mucus. On the other hand, solid dosage forms such as buccal tablets exhibit increased adhesive strength as the mucoadhesive polymer concentration increases.

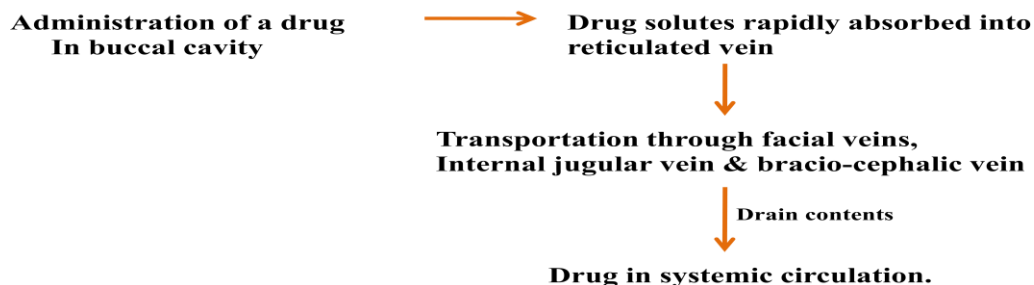
Common sites of application for mucoadhesive drug delivery platform

Mucoadhesive formulations have been widely used for their targeted and controlled release delivery to many mucosal membrane-based organelles. Such formulations may deliver active ingredient for local or systemic effect, while bioavailability limiting effects such as enzymatic or hepatic degradation can be avoided or minimised.

Buccal drug delivery

The buccal cavity offers many advantages for drug delivery application. The most significant advantage offered is high accessibility and low enzymatic activity. Additionally, buccal drug delivery can be promptly terminated in cases of toxicity through the removal of dosage form thereby offering a safe and easy method of drug utilization. Various polymers such as sodium carboxymethylcellulose, hydroxypropylcellulose and polycarbophil are used for delivery of peptides, protein and polysaccharides by this routes have been examined^{20,21,22}. Although gel and ointments are the most patient convenient; tablets, patches and films have also been examined. Furthermore buccal drug delivery is associated with high patient compliance, low levels of irritation and offers significant ease of administration^{23,24}

Mechanism of drug absorption in buccal cavity



Schematic representation of BDDS.

Ophthalmic drug delivery The delivery of therapeutic agents to the eye may be achieved using various types of dosage forms including liquid drops, gels, ointments and solid ocular inserts (both degradable and nondegradable)^{25,26}. Another interesting delivery system is in situ gelling polymer that undergoes a phase transition after application. Mucoadhesive polymers would be expected only to attach to conjunctival mucus in vivo. Additionally limited bioavailability has been experienced in vivo for carbomer and polycarbophil,²⁷ as a result of the high swelling capacity of such polymers in the neutral pH environment of the eye. Maintenance of a low viscosity in such systems through pH regulation in the range 4–5 is not acceptable as it may result in patient unease and mild lacrimation, both of which will have an effect on treatment success. User acceptance and compliance may subsequently be limited by physical and psychological barriers surrounding such dosage forms *Disadvantages of BDDS:*

- Drugs with unpleasant taste cannot be administered by this route.
- Drugs with high molecular weight cannot be administered.
- BDDS cannot be used in case of patients with recurrent vomiting & unconsciousness.
- Orally degradable drugs cannot be administered by this route.

Vaginal drug delivery systems Vaginal drug delivery offers many advantages; the avoidance of hepatic first-pass metabolism, a decrease in hepatic side effects and avoidance of pain, tissue damage, and infection commonly observed for parenteral drug delivery routes of administration. While the vagina provides a promising site for systemic drug delivery because of its large surface area, rich blood supply and high permeability, poor retention due to the self-cleansing action of the vaginal tract is often problematic. However, residence times within the vagina tend to be much higher than at other absorption sites such as the rectum or intestinal mucosa. Another important consideration is the change in the vaginal membrane during the menstrual cycle and post-menopausal period. Typical bioadhesive polymers that have been in vaginal formulations include polycarbophil, hydroxypropylcellulose and polyacrylic acid

Nasal drug delivery One of the key advantages provided by intranasal drug delivery is that the nasal cavity provides a large highly vascularised surface area through which first-pass metabolism can be avoided, as blood is drained directly from the nose into the systemic circulation. Successful nasal delivery has been obtained using solutions, powders, gels and microparticles. The most commonly employed intranasal active ingredient are solutions containing sympathomimetic vasoconstrictors for immediate relief of nasal

congestion. Local delivery of these alpha adrenergic stimulators is of particular benefit to patients with high blood pressure (or those at heightened risk of cardiovascular incident), as vasoconstriction will occur to the greatest degree within the nose. In addition to local effects, the intranasal route of drug administration has also been used to achieve a distal systemic effect. One such example is the intranasal delivery of the peptide desmopressin that exerts its action on the kidneys, mimicking the action of antidiuretic hormone, used mainly in Diabetes insipidus³

EVALUATION OF MUCOADHESIVE DRUG DELIVERY SYSTEMS

Measuring the force of attachment

The adhesive strength at bonding interface can be measured by measuring the force required to detach one entity from the other through the application of an external force. Hence the destruction of adhesive bond is usually under the application of either a shearing, tensile or peeling force^{38,39}

In vitro residence time study: The mucoadhesive properties of tablets were evaluated by in vivo residence time study as reported by Lehr et al⁴⁰. A 1-cm by 1-cm piece of porcine buccal mucosa was tied onto a glass slide (3-inch by 1-inch) using thread. Tablet was stuck onto the wet, rinsed, tissue specimen, by applying light force with a fingertip for 30 seconds. The prepared slide was hung onto one of the grooves of a USP tablet disintegrating test apparatus. The disintegrating test apparatus was operated such that the tissue specimen was given regular up and down movements in a beaker containing the dissolution medium (0.01 N HCl). At the end of 3 hour, the detachment of tablet from tissue was checked and the time of detachment was recorded as the in vivo residence time.

GI transit study using radio-opaque markers It is a simple procedure involving the use of radio-opaque markers, e.g. barium sulfate, encapsulated in bioadhesive to determine the effects of bioadhesive polymers on GI transit time. Faeces collection (using an automated faeces collection machine) and X-ray inspection provide a non-invasive method of monitoring total GI residence time without affecting normal GI motility.

Fluorescent probe method In this method the membrane lipid bilayered and membrane proteins were labeled with pyrene and fluorescein isothiocyanate, respectively. The cells were mixed with the mucoadhesive agents and changes in fluorescence spectra were monitored. This gave a direct indication of polymer binding and its influence on polymer adhesion.

Thumb test The adhesiveness is measured by the difficulty of pulling the thumb from the adhesive as a function of the pressure and the contact time. Although the thumb test may not be conclusive, it provides useful information on peel strength of the polymer.

Evaluation tests of mucoadhesive tablets

- Weight variation
- Friability
- Hardness
- Content uniformity

- Drug release study of Mucoadhesive tablets
- Swelling index
- Water sorption studies
- Mucoadhesive strength