MUCOADHESIVE DRUG DELIVERY SYSTEM: A REVIEW ARTICLE

Dakshata S. Khunepimpre*, Swapnil D. Deo, Harshal L. Tare
TSPM’s, Trimurti Institute of Pharmacy Jalgaon, Maharashtra, India

Keywords:
Mucoadhesion, Mechanisms, Theory, Applications

For Correspondence:
Dakshata S. Khunepimpre
TSPM’s, Trimurti Institute of Pharmacy
Jalgaon, Maharashtra, India

ABSTRACT

The process of Mucoadhesions involving a polymeric drug delivery system is a complex one that includes processes such as wetting, adsorption and interpenetration of polymer chains. The success and degree of Mucoadhesions bonding is influenced by various polymer based properties such as the degree of cross linking, chain length and the presence of various functional groupings. These systems in close contact with the absorption tissue, the mucous membrane, releasing the drug at the site of action leading to a bioavailability increase and both local and systemic effects. The attractiveness of mucosal targeted controlled drug delivery of active pharmaceutical ingredients, has led formulation scientists to evaluate numerous polymeric systems for such tasks. The aim of this study was to review the mechanism and theories involved in Mucoadhesions, as well as to describe the most used methodologies and polymers in mucoadhesive drug delivery system.
INTRODUCTION

Mucoadhesive Drug Delivery System

Mucoadhesive drug delivery systems are delivery systems which utilize the property of bioadhesion of certain polymers which become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for extended periods of time. Mucoadhesion is an interfacial phenomenon in which two materials, at least one of which is biological, are held together by means of interfacial forces. The attachment could be between an artificial material and biological substrate, such as adhesion between a polymer and a biological membrane. In the case of polymer attached to the mucin layer of a mucosal tissue, the “mucoadhesion” is used. (1)

Dosage forms designed for mucoadhesive drug delivery should be small and flexible enough to be acceptable for patient and should not cause irritation. A number of relevant mucoadhesive dosage forms have been developed for a variety of drugs. Several peptides, including thyrotropin releasing hormone, insulin, leuprolide and oxytocin have been delivered via the mucosal route. The development of sustain release dosage form can achieve the aim of releasing the drug slowly for a long period. The mucoadhesive dosage form will serve both the purposes of sustain release and presence of dosage form at the site of absorption. (2)

Mucous membranes are the moist surfaces, lining the walls of various body cavities such as the gastrointestinal and respiratory tracts. They consists of a connective tissue layer above which is an epithelial layer, the surface of which is made moist usually by the presence of a mucus layer. The epithelia may be either single layered (e.g. the stomach, small and large intestine and bronchi) or multilayered/stratified (e.g. in the oesophagus, vagina and cornea).

The tissue layer responsible for formation of the adhesive interface is mucus. Mucus is a translucent and viscid secretion, which forms a thin, continuous gel blanket adherent to mucosal epithelial surface. The thickness of this layer varies from about 50-450 in humans. It is secreted by the goblet cells lining the epithelia or by special exocrine glands with mucus cells acini. The composition of the mucus layer, varies substantially, depending on the species, the anatomical location and pathological states. It consists of water (95%), glycoproteins and lipids (0.5-5%), mineral salts (1%) and free proteins (0.5-1%).
Mucus glycoproteins are high molecular proteins possessing attached oligosaccharide units containing the composition. (3)

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

**Advantages**
- Prolongs the residence time of the dosage form at the site of absorption.
- To avoid first pass metabolism.
- Excellent accessibility.
- Rapid absorption because of enormous blood supply and good blood flow rates.
- Increases in drug bioavailability due to first pass metabolism avoidance.
- Improved patient compliance and ease of drug administration.
- Drug is protected from degradation in the acidic environment in the GIT.
- Faster onset of action is achieved due to mucosal surface. (4)

**DISADVANTAGE**
- If MDDS are adhere too tightly because it is undesirable too exert too much force to remove the formulation after use, otherwise the mucosa could be injured.
- Some patients suffers unpleasant feelings.
- Unfortunately, the lack of standardised 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. (5)

**Sites for mucoadhesive drug delivery system**

**Buccal drug delivery system**

The most significant advantage of buccal drug delivery is high accessibility and low enzymatic activity. 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 utilisation. Various polymers such as sodium carboxymethylcellulose, hydroxypropylcellulose and polycarbophil are used for delivery of peptides, proteins and polysaccharides by this routes have been examined. Buccal drug delivery is associated with high patient compliance, low levels of irritation and offers significant ease of administration.

**Ophthalmic drug delivery system**

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. Another inserting 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. Limited bioavailability has been experienced in vivo for carbomer and polycarbophil, as a result of high swelling capacity of such polymers in the neutral pH environment of the eye. Maintenance of a low viscosity is 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. (6)

**Nasal drug delivery system**

Nasal cavity provides a potential site for the development of formulations where mucoadhesive polymers can play an important role. The residence time of a particulate matter in the Nasal mucosa varies between 15 and 30 min, which have been attributed to the increased activity of the mucociliary layer in the presence of foreign particulate matter.

**Gastrointestinal drug delivery system**

Gastrointestinal tract is also a potential site which has been explored since long for the development of mucoadhesive based formulations. The modulation of the transit time of the delivery systems in a particular location of the gastrointestinal system by using
mucoadhesive polymers has generated much interest among researchers around the world. (7)

**Vaginal drug delivery system**

The vaginal and the rectal lumen have also been explored for the delivery of the active agents both systemically and locally. The delivery system suffer from migration within the vaginal/rectal lumen, which might affect the delivery of the active agent to the specific location. Mucoadhesive polymers helps in reducing migration. The polymers used in development of vaginal and rectal delivery systems include mucin, gelatin, polycarbophil and poloxamer. (2)

**Cervical and vulval drug delivery system**

A novel bioadhesive Cervical patch containing 5-fluorouracil for the treatment of Cervical intra epithelial neoplasia (CIN) was described by Woolfson. This patch was a bilaminar design, with a drug loaded bioadhesive film cast from a gel containing 2%w/w carbopol 981 plasticised with 1% w/which glycerine, the casting solvent was ethanol:water 30:70.

Aminolevulic acid(ALA) is commonly delivered to the vulva using creams or solutions, which are covered with an occlusive dressing. To overcome the problem of high shear forces, the authors produced a bioadhesive patch by a novel laminating procedure. The patch was extensively used in successful PDT of vulval intra epithelial neoplasia, lichen sclerosis, squamous hyperplasia, paget’s disease and vulvodynia. (8)

**MECHANISM OF MUCOADHESION**

The mechanism of Mucoadhesion is generally divided in two steps,

1) Contact stage

2) Consolidation stage

The first stage is characterised by the contact between the mucoadhesive and the mucous membrane, with spreading and swelling of the formulation, initiating its deep contact with the mucus layer. In some cases, such as for ocular or vaginal formulations, the delivery system is mechanically attached over in other cases, the deposition is promoted by the aerodynamics of the organ to the membrane, the system is administered, such as for the nasal route.
In the consolidation step, the mucoadhesive materials are activated by the presence of moisture. Moisture plasticizes the system, allowing the mucoadhesive molecules to break free and to link up by weak van der waals and hydrogen bonds. Essentially, there are two theories explaining the consolidation step:

1) The diffusion theory
2) The dehydration theory.

According to diffusion theory, the mucoadhesive molecules and the glycoproteins of the mucus mutually interact by means of interpenetration of their chains and the building of secondary bonds. According to dehydration theory, materials that are able to readily gelify in an aqueous environment, when placed in contact with the mucus can cause its dehydration due to the difference of osmotic pressure. (1)

---

**Fig.2: Stages of Mucoadhesion**

**Theories of Mucoadhesion**

- **Adsorption theory:** According to this theory, after an initial contact between two surfaces, the materials adhere because of surface forces acting between the atoms in the two surfaces. Two types of chemical bonds such as primary covalent and secondary chemical bonds (including electrostatic forces, vander waals forces and hydrogen and hydrophobic bonds) are involved in the adsorption process.

- **Electronic theory:** According to this theory, electronic transfer occurs upon contact of an adhesive polymer and the mucus glycoprotein network because of differences in their electronic structure. Due to this the formulation of an electronic double layer at the interface adhesion occurs due to attractive forces across the double layer.

- **Diffusion theory:** The diffusion mechanism is the intimate contact of two polymers or two pieces of the same polymer. During chain interpenetration the molecules of the polymer and the dangling chains of the glycoproteinic network are brought in intimate contact. Due to the concentration gradient, the bioadhesive polymer chains penetrate at
rates that are dependent on the diffusion coefficient of a macromolecule through a cross-linked network and the chemical potential gradient. Difference of the solubility parameters of the bioadhesive medium and the glycoproteins should be as close to zero as possible. Thus the bioadhesive medium must be similar chemical structure to the glycoprotein.

Fig. 3: Bioadhesion to skin

Wetting theory: Postulates that if the contact angle of liquids on the substrate surface is lower, then there is a greater affinity for the liquid to the substrate surface.

Fig. 4: Contact angle on skin

- Fracture theory: Fracture theory of adhesion is related to separation of two surfaces after adhesion. The fracture strength is equivalent to adhesive strength. (9)

Fig. 5: Hydrated layer of device

Factors Affecting Mucoadhesion

A. Polymer Related Factors
a. **Molecular weight**: The interpenetration of polymer molecules into the mucus layer is variable, for low molecular weight polymers penetration is more than high molecular weight.

b. **Concentration of active polymer**: For solid dosage forms such as tablets, the higher concentration of polymer, and the stronger the bioadhesion force.

c. **Spatial conformation**: Bioadhesive force is also dependent on the conformation of polymers, i.e., helical or linear. The helical conformation of polymers may shield many active groups, responsible for adhesion, thus reducing the mucoadhesive strength of the polymer.

d. **Degree of Hydration**: Many polymers will exhibit adhesive properties under conditions where the amount of water is limited. However in such a situation, adhesion is thought to be a result of a combination of capillary attraction and osmotic forces between the dry polymer and the wet mucosal surface which act to dehydrate and strengthen the mucus layer. Hydration is essential for the relaxation and interpenetration of polymer chains, excess hydration could lead to decreased Mucoadhesion and retention due to formation of slippery mucilage.

e. **Chain flexibility of polymer**: Chain flexibility is important for interpenetration and enlargement. As water soluble polymers become more and more cross linked, the mobility of polymer chain decreases, and cross linking density increases.

f. **Functional Group Contribution**: The attachment and bonding of bioadhesive polymers to biological substrates occurs mainly through interpenetration followed by secondary non-covalent bonding between substrates. Secondary bonding mainly arises due to hydrogen bond formation, mucoadhesive polymers possessing hydrophilic functional such as, carboxyl (COOH), hydroxyl (OH), amide (NH2) and sulphate groups (SO4H) may be more favorable in formulating targeted drug delivery platforms.

g. **Swelling**: The swelling characteristic is related to the polymer itself, and also to its environment. More the swelling of polymeric matrix higher the adhesion time of polymers.

**B. Environmental-Related Factors**

a. **pH**: pH influences the charge on the surface of both mucus and polymers. Mucus will have different charge density depending on pH, because of difference in dissociation of
functional groups on carbohydrate moiety and amino acids of the polypeptide backbone, which may affect adhesion.

**Applied strength**: To place a solid bioadhesive system it is necessary to apply a defined strength. The polymer may be the adhesion strength of those polymers increases with the increase in the applied strength.

**b. Initial contact time**: The initial contact time between mucoadhesive and the mucus layer determines the extent of swelling and the interpenetration of polymer chains. The mucoadhesive strength increases as the initial contact time increases.

**c. Selection of the model substrate surface**: The handling and treatment of biological substrate during the testing of mucoadhesive is an important factor, since physical and biological changes may occur in the mucus gel under experimental conditions.

**C. Physiological Factors**

Mucin turnover and disease state of mucus layer are Physiological variables, which may affect bioadhesion. (7)

**Ideal characteristics of mucoadhesive polymer**

- Polymer must have the maximum molecular weight upto 10,000 or more to enhance adhesiveness between polymer and mucus.
- In case of long chain polymer the chain length must be enough long that promote interpenetration.
- It should be non-irritant to the mucous membrane.
- It should form a strong non-covalent bond with the mucin epithelial cell surfaces.
- Flexibility of polymer chain must be there.
- The polymer and its degradation products should be non toxic and should be non absorbable from the gastrointestinal tract.
- The polymer must be decompose on storage or during the shelf life of the dosage form.
- It should adhere quickly to most tissue and should possess some site specificity.
- The cost of polymer should not be high so that the prepared dosage form remains competitive. (10)

**Polymers used for mucoadhesive drug delivery**

Mucoadhesive drug delivery systems are being explored for the localization of the active agents to a particular site. Polymers have played an important role in designing such
systems so as to increase the residence time of the active agent at the desired location. Polymers used in mucosal delivery system may be of natural or synthetic origin.

1) **Hydrophilic polymers:** The polymers in this category are soluble in water. The polyelectrolytes exhibit greater mucoadhesive properties when compared with neutral polymers. Anionic polyelectrolytes, e.g., poly (acrylic acid) and carboxymethylcellulose have been used for designing mucoadhesive delivery systems. Chitosan provides an excellent example of a cationic polyelectrolyte, which have been extensively used for developing mucoadhesive polymer due to its good biocompatibility and biodegradable properties. The ionic polymers may be used to develop ionic complex with the counter ionic drug molecules. Non-ionic polymers, e.g., poloxamer, methyl cellulose, methyl cellulose, poly(vinyl alcohol) and poly(vinyl pyrrolidone), have also been used for mucoadhesive properties.

Numerous polysaccharides and their derivatives like chitosan, methyl cellulose, hyaluronic acid, hydroxypropyl methyl cellulose, hydroxypropylcellulose, xanthan gum, gellan gum, guar gum and carrageenan have found applications in ocular mucoadhesive delivery systems. Cationic cellulose derivatives (e.g., cationic hydroxyethyl cellulose) have been used in conjunction with various anionic polymers for the development of sustained delivery systems.

2) **Hydrogels:** Hydrogels can be defined as three dimensionally cross-linked polymer chains which have the ability to hold water within its porous structure. The water holding capacity of the hydrogels is mainly due to the presence of hydrophilic functional groups like hydroxyl, amino and carboxyl group. If cross-linking density increase, mucoadhesion decreases. Hydrogels prepared by the condensation reaction of poly (acrylic acid) and sucrose indicated an increase in the mucoadhesive property with the increase in cross-linking density and was attributed to increase in the poly(acrylic acid) chain density per unit area. In a typical experimentation, Wood and Peppas developed a system in which ethylene glycol chains were grafted on methacrylic acid hydrogels and were subsequently functionalized with wheat germ agglutinin. Wheat germ agglutinin helped in improving the intestinal residence time of the delivery system. The mucoadhesive delivery system showed improved bioavailability of the drug when compared over the nanosuspension. This was attributed to the increased retention time of the delivery system within the gastrointestinal tract. (11)
3) **Thiolated polymers** : These are thiomers which are derived from hydrophilic polymers such as polyacrylates, chitosan or deacetylated gellan gum. The presence of the thiol group increases the residence time by promoting covalent bonds with the cysteine residue in mucus. Various thiolated polymers include chitosan-iminothiolane, poly(acrylic acid) – cysteine, poly (acrylic acid) – homocystiene, chitosan-thioglycolic acid, chitosan-thioethy lamidine, alginate-cysteine, poly(methacrylic acid) – cysteine and sodium carboxymethylcellulose – cysteine. (4,11)

4) **Lectin-based polymers** : Lectins are naturally occurring proteins that are useful biological recognition involving cells and proteins. Lectins are a class of structurally diverse proteins and glycoprotein that are bind reversible to specific carbohydrate residue. After binding to the cell the lectins may either remain on the cell surface or may be taken inside the cell via endocytosis. The various lectins which have shown specific binding to the mucosa include lectins extracted from soybean, peanut and lens culinarius. Wheat germ agglutinin have capability to bind to the intestinal and alveolar epithelium and hence could be used to design oral and aerosol delivery systems. (4,11)

**Methods of evaluation**
Mucoadhesive polymers can be evaluated by testing their adhesion strength by both in vitro and in vivo tests.

**In vitro methods**
- Methods determining tensile strength
- Methods determining shear stress
- Adhesion weight method
- Fluorescent probe method
- Flow channel method
- Mechanical spectroscopic method
- Filling liquid film method
- Colloidal gold staining method
- Viscometer method
- Thumb method
- Adhesion number
- Electrical conductance
Swelling properties
In vitro drug release studies
Muco retentability studies

In vivo methods
Use of radioisotopes
Use of gamma scintigraphy
Use of pharmacoscintigraphy
Use of electron paramagnetic resonance (EPR) oximetry
X ray studies
Isolated loop technique(4)

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

REFERENCE:
1) Priya Mahajan, Amanpreet Kaur, Geeta Aggarwal, S.L. Harikumar Rayat & Bahra Institute of pharmacy, Shauran, Kharar, District Mohali, Punjab - 140104
2) Flavia Chiva Carvalho, Marcos Luciano Bruschi, Raul Cesar Evangelista Maria Palmira Daflon Gremiao Pharmaceutical Science Postgraduate, School of Pharmaceutical Science Sao Paulo State University UNESP
3) Manohar Lalge, Peeyush Kumar Sharma, Anil Bhandari, Akanksh Garud, Navneet Garud Department of pharmaceutics, Faculty of pharmaceutical science Jodhpur National University, Namadi Jhanwar Road Jodhpur India. School of stuides Jiwaji University Gwalior India.
4) Phaninadra B, B Krishna Moorthy & M Muthukumaran corresponding Author Phaninadra B.
5) Dr. Zeenat Iqbal, Dr. Sushma Talegaonkar, Dr. Yasmin Sultana, Faculty of Pharmacy, Jamia Hamdard New Delhi, Abdul Muheem, M.pharm (Pharmaceutics), Jamia Hamdard MDDS Slideshare

6) Madan Jyotasana, Banode Sagar, Dangi Mahesh Sinhgad Collage Of Pharmacy, Pune, Maharashtra, India Accepted 16-09-2010

7) N. V. Satheesh Madhav, Abhijeet Ojha, Yogita Tyagi, Monika Negi DIT University Faculty of pharmacy, Mussoorie Diversion Road Dehradun, Uttar Pradesh, India 248009.

8) Rahamatullah Shaikh, Thakur Raghu Raj Singh, Martin James Garland, A David Woolfson & Ryan F. Donnelly Drug Delivery Group, School of Pharmacy, Queens University Belfast, Medical Biology Centre, 97 Lisburn Road Belfast B79 7BL UK

9) Sachin Shankar Lokhande, Sandeep S. Lahoti, Dr. Vedprakash Patil Pharmacy College, Paithan Road, Aurangabad 431001 (MS) India. Shri Bhagwan College Of Pharmacy, CIDCO N-6 Aurangabad 431003 (MS) India.

10) Gita Shital Shridhar, Shinkar Dattatry Manohar, Saudagar, Ravindra Bhanudas Department of Pharmaceutics, KCTSRGS College of Pharmacy, Anjaneri Nashik 422 213.

11) S. Roy, K. Pal, A. Anis, K. Pramanik & B. Prabhakar. School of Pharmacy & Technology Mangmeant, SVKMs NMIMS University Mumbai- 400056, India