



MUCOADHESIVE: A NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT

This article focuses on defining the principles of bioadhesive delivery systems based on hydrogels to biological surfaces that are covered by mucus. Mucoadhesion can be defined as the process by which a natural or a synthetic polymer can adhere to a biological substrate. There are many routes of mucoadhesive drug delivery system, oral route is the most ancient as well as preferred by patient being convenient to take. However peroral route has short comings such as hepatic first pass metabolism and enzymatic degradation in GIT which is a hindrance to the absorption of most proteins and peptides groups of drugs. The buccal mucosa is a barrier, providing protection to underlying tissue, but is more permeable than other alternative routes such as the skin. Buccal films are polymeric matrices designed to be mucoadhesive properties and usually formulated with permeability enhancers to improve bioavailability. Conventionally, buccal films for biologics are manufactured by solvent casting, yet recent developments have shown the potential of hot melt extrusion, and most recently ink jet printing as promising strategies. The research on mucoadhesives, however, is still in its early stage, and further advances need to be made for the successful translation of the concept into practical application in controlled drug delivery.

Keywords: Mucoadhesive, Mucoadhesion, Oral Mucosa

INTRODUCTION

The term 'mucoadhesive' is commonly used for materials that bind to the mucin layer of a biological membrane. Mucoadhesion can be defined as a phenomenon of interfacial molecular attractive forces amongst the surfaces of the biological substrate and the natural or synthetic polymers, which allows the polymer to adhere to the biological surface for an extended period of time. The substrate possessing bioadhesive property can help in devising a delivery system capable of delivering a bioactive agent for a prolonged period of time at a specific delivery site. Mucoadhesive polymers have been utilised in many different dosage forms in efforts to achieve systemic delivery of drugs through the different mucosa. These dosage forms include tablets, patches, tapes, films, semisolids and powders. To serve as mucoadhesive polymers, the polymers should

possess some general physiochemical features such as predominantly anionic hydrophilicity with numerous hydrogen bond-forming groups, suitable surface property for wetting mucus/mucosal tissue surfaces and sufficient flexibility to penetrate the mucus network or tissue crevices. (1,2)

Bioadhesion 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 term “mucoadhesion” is used. (3)

Mucoadhesive drug delivery systems can be delivered by various routes:-

- Buccal delivery system
- Oral delivery system
- Vaginal delivery system
- Rectal delivery system
- Nasal delivery system
- Ocular delivery system

Mechanism of mucoadhesion

The mechanism of mucoadhesion is generally divided in two steps,

1. Contact stage
2. Consolidation stage

The first stage is characterized 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 (4)

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. For this to take place the mucoadhesive device has features favouring both chemical and mechanical interactions. 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.

Theories of mucoadhesion

The phenomena of bioadhesion occurs by a complex mechanism. Till date, six theories have been proposed which can improve our understanding for the phenomena of adhesion and can also be extended to explain the mechanism of bioadhesion. The theories include:

- a) The electronic theory.
- b) The wetting theory.
- c) The adsorption theory.
- d) The diffusion theory.
- e) The mechanical theory.
- f) The cohesive theory. (5-9)

- a) **Electronic Theory** involves the formation of an electric double layer at the mucoadhesive interface by the transfer of electrons between the mucoadhesive polymer and the mucin glycoprotein network.
- b) **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. If two such substrate surfaces are brought in contact with each other in the presence of the liquid, the liquid may act as an adhesive amongst the substrate surfaces.
- c) **Adsorption Theory** proposes the presence of intermolecular forces, viz. hydrogen bonding and Vander Waal's forces, for the adhesive interaction amongst the substrate surfaces.
- d) **Diffusion Theory** assumes the diffusion of the polymer chains, present on the substrate surfaces, across the adhesive interface thereby forming a networked structure.
- e) **Mechanical Theory** explains the diffusion of the liquid adhesives into the micro-cracks and irregularities present on the substrate surface thereby forming an interlocked structure which gives rise to adhesion.
- f) **Cohesive Theory** proposes that the phenomena of bioadhesion are mainly due to the intermolecular interactions amongst like-molecules.

Based on the above theories, the process of bioadhesion can be broadly classified into two categories.

- 1) **Chemical:** ex. Electronic and adsorption theories
- 2) **Physical:** ex. Wetting, diffusion and cohesive theory methods.

The process of adhesion may be divided into two stages.

During the first stage (also known as contact stage), wetting of mucoadhesive polymer and mucous membrane occurs followed by the consolidation stage, where the physico-chemical interactions prevail

Factors affecting mucoadhesion (10)

The mucoadhesion of a drug carrier system to the mucous membrane depends on the below mentioned factors.

- ✓ Polymer based factors
 - Molecular weight of the polymer
 - Concentration of polymer used
 - Flexibility of polymer chains
 - Swelling factor
 - Stereochemistry of polymer
- ✓ Physical factors
 - pH at polymer substrate interface
 - Applied strength
 - Contact time
- ✓ Physiological factors
 - Mucin turnover rate
 - Diseased state

Advantages of Buccal Drug Delivery System

Due to larger surface area rapid disintegrating and dissolution occurs in the oral cavity. MDFs are flexible and easily transported and handled, so they are superior to oral disintegrating tablets that are brittle and fragile and require special packaging for protection during storage and transportation. As compared to liquid oral formulations, dose is more précised in form of the strips. As no is required so these dosage forms are most friendly for dysphagic patients. They are rapidly wetted due to larger surface area and can be consumed anywhere as per suitability of the individual. Drugs can absorbed directly from the highly vascularized buccal mucosa and enter the systemic circulation bypassing first-pass hepatic metabolism. This helps improving the bioavailability of the drugs that undergo extensive first pass effect. Due to least hepatic metabolism, dose is reduced leading to decrease probability of dose related side effects. Mentally ill, disabled and uncooperative patients can be easily medicated. The product can be a substitute with more clinical advantage. The manufacturing of these MDFs is cost-effective with reasonably priced end-products. MDFs are alternative to ODTs as they have to face product identification for OTC drugs. (11)

Drawbacks/limitations

Different drawbacks like high dose, difficulty in dose uniformity, hygroscopic nature of drug, and requirement of special packaging for stability and safety of product are reported.

Potential benefits of buccal films

- Buccal films provide large surface area that leads to rapid disintegration and dissolution in the oral cavity due to which it promotes the systemic absorption of Active pharmaceutical ingredient.
- No need of chewing and swallowing.
- No risk of choking.
- The film increases the systemic bioavailability of the drugs, as it bypasses the hepatic first pass metabolism.
- Drug can be protected from degradation by GI enzymes and the acidic environment.
- Rapid onset of action and minimum side effects.
- Self-administration is possible.
- Accurate dosing compared to liquid dosage forms.
- Taste masking is possible.
- Prolongs the residence time of the dosage form at the site of absorption, hence increases the bioavailability.
- Ease of administration to pediatric, geriatric patients, and also to the patients who are mentally retarded, disabled or non-cooperative.
- Good mouth feel and good stability.
- Ease of transportation, storage and consumer handling.
- Requires less excipient.
- More economical.

However, the main limitation of the buccal films is that high doses cannot be incorporated.

Manufacturing Methods

The buccal film manufacturing process includes the following techniques.

1. Solvent casting technique
2. Hot melt extrusion technique.

Film casting technique: Solvent casting method is one of the most widely used methods for the manufacturing of buccal film. It has advantages of easy preparation, being cheap and can easily be adopted at lab scale. It involves following steps. (12, 13)

- Prepare casting solution
- Deaerate the solution
- Pour the solution into a mold
- Dry the casting solution
- Cut the final dosage form containing desired amount of drug
- Packing

Hot melt extrusion technique: In this method mixture of pharmaceutical ingredients is melted. In order to achieve homogeneous mixture in various dosage form like tablets, granules, pellets or film, the melted material is pushed to pass through a small opening (14–16) Although this method is rarely used for the manufacture of film but there are certain evidence in the literature that this method can be used for film preparations.(17,18)

Finally the melt is shaped in to the film by the dies. There are certain benefits of hot melt extrusion.

- Fewer operation unit
- Better content uniformity
- An anhydrous process

Characterizations of mucoadhesive drug delivery system

1. **Chemical stabilities studies:** Chemical compatibility studies are performed to identify any possible interaction between the ingredients. Fourier transformer infra-red spectrum, differential scanning calorimetry and X-ray diffraction are the techniques usually used to conduct the compatibility studies. (19)
2. **Thickness measurements:** Electronic digital micrometer, digital vernier caliper or micro screw gauge can be used to measure the thickness of the patch. Thickness of the different location (corners and the center) is measured to assess the average thickness of the film. (14)
3. **Swelling study:** Swellability of the film is measured by placing the sample film continuing agar plate in an incubator kept at $37 + 2$ °C. Increase in diameter of the film and weight gain by the film is calculated is calculated at different time intervals (1–5 h). Swellability is calculated as (20)

$$\%S = (X_t - X_o / X_o) 100$$

Where X_o = original weight or diameter of the film and X_t = weight or diameter at time t .

- 4. Surface pH:** It is important to measure the surface pH of the films to assess the any side effect that may be produce inside the body. Acidic or basic pH can be the cause of irritation to mucosal. Initially the film is placed in 1.0 ml distilled water having pH 6.5–0.05 for 2 h. Specially designed glass tube is used for this purpose. To measure the surface pH combined glass electrode -is brought near the surface for a time interval of 1 min. (21)
- 5. Folding endurance:** Folding endurance is used to observe the flexibility of the film which is an important physical property of a buccal film. It is measured by folding the selected sample of the film at an angle of 180 and observes when it breaks. Another way to measure the flexibility of the film is to fold the film 300 times without breaking. Value of folding endurance is calculated in terms of numbers of fold without breaking the film. (22)
- 6. Moisture content:** Moisture contents of the film are calculated by finding the difference between the weights measured initially prior to the placement of film in the desiccators and after specific time interval. Calcium chloride is placed in the desiccators and the whole apparatus is kept for 24 h. Following equation is used to measure the %

$$\% \text{ moisture content} = \frac{\text{initial weight} - \text{final weight}}{\text{Initial weight}} \times 100$$
- 7. Moisture uptake:** Sample film is taken and weighed and then keep it in desiccators at room temperature. After 24 h film is taken out and expose to 84% relative humidity. Saturated solution of potassium chloride is used in desiccators till a constant weight is obtained. Following formula is used for the calculation of % moisture uptake. (23)

$$\text{Moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Final weight}} \times 100$$
- 8. Surface morphology:** Various techniques are used to observe the surface morphology. It includes SEM (scanning electron microscopy), electron microscopy and scanning tunneling microscopy. SEM is most widely used. Shape, size and number of pores present on the surface of the film are observed by SEM. (19)
- 9. In-vitro dissolution studies:** In-vitro drug release is calculated for given formulation using USP dissolution apparatus. Temperature is kept at 37 ± 0.5 °C and the rotation speed is adjusted at 50 revolutions per min and dissolution media of 900 ml is used. Samples are drawn at different time intervals. Sample is replaced with same volume of fresh medium. % drug release is observed by analyzing the sample using spectrophotometer at specified wave length. (14)
- 10. Organoleptic evaluation:** Organoleptic evaluation is done to observe and check sweetness and flavor, whether they are acceptable or not. An electronic tongue measurement is design having test sensors to observe the taste in vitro. (24)

11. Ex-vivo Permeation Studies: Ex-vivo studies are performed using modified Franz diffusion. There are two compartments one of them is donor while other is receptor compartment that has the capacity of 18 ml with 0.785 cm² area for diffusion. 37 °C temperature is maintained with the help of water jacket. Artificial mucosal membrane or mucosal membrane of animal (rabbit) is used for permeation studies. Membrane is mounted between two chambers. Phosphate buffer of pH 7.4 is used to fill the receptor compartment. Membrane is stabilize in an hour. Once the membrane is stabilized the film is placed and samples are taken. The taken volume is replaced with fresh media. (25)

Conclusion

The phenomenon of mucoadhesion can be used as model for the controlled drug delivery approaches for a number of drug candidates. The various advantages of the oral mucoadhesive drug delivery systems like prolongation of the residence time of the drug which in turn increases the absorption of the drug are important factors in the oral bioavailability of many drugs. Due to success, advantages and ease of access of drug delivery through oral mucosal tissue the buccal and sublingual routes have favourable opportunities and many formulation approaches; although the current commercially available formulation are mostly limited to tablets and films. The buccal mucosa offers several advantages for controlled drug delivery for long period of time and also favourable area for systemic delivery of orally unsatisfactory drugs and attractive alternative for non-offensive delivery of potent peptide and protein drug molecule. Mucoadhesive dosage forms extend from the simple oral mucosal delivery to the nasal, vaginal, ocular and rectal drug delivery systems. The most widely studied and accepted polymers for mucoadhesion have been the hydrophilic, high molecular weight, anionic molecules like carbomers.

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