International Journal of Current Trends in Pharmaceutical Research
CODEN (USA): IJCTGM | ISSN: 2321-3760
Journal Home Page: www.pharmaresearchlibrary.com/ijctpr

REVIEW ARTICLE

Review article on mucoadhesive drug delivery system

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ABSTRACT

Drug actions can be improved by mucoadhesive drug delivery system. The disadvantages with the oral drug delivery are the extensive first pass metabolism, instability in acidic medium as a result inadequate absorption of the drugs. However parental route may overcome the drawback related with the oral route but these formulations have high cost, supervision is required and least patient compliance. The buccal mucosa is the main target for bioadhesion system because of a smooth and relatively immobile surface and accessibility. Mucoadhesion can be achieved by using mucoadhesive polymers. Various types of the polymers are used in mucoadhesive delivery system. Polymers are used for adhesion of the dosage form for the mucosa.

Keywords: Mucoadhesive. Mucoadhesive drug delivery.

ARTICLE INFO
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JOURNAL QR-CODE

Article History: Received 25 September 2019, **Accepted** 11 Nov 2019, **Available Online**15 Jan 2020

Citation: *Rajat Garg*, *et al.* Review article on mucoadhesive drug delivery system. *Int. J. Curnt. Tren. Pharm, Res.*, 2020, 8(1): 01-06.

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1. Introduction

Bioadhesion can be defined as the state in which two materials, at least one of which is biological in nature, are maintained together for a prolonged time period by means of interfacial forces. [(1)] Buccal routes of drug delivery offer a large number of advantages over the other route of drug administration for systemic drug delivery such as bypass of first pass effect and drug directly delivered to systemic circulation, avoidance of pre-systemic elimination within the GI tract. These factors make the buccal drug delivery a very attractive and feasible site for systemic drug delivery. 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. [2, 3] The potential use for mucoadhesive systems as drug carriers lies in its prolongation of the residence time at the absorption site, allowing intensified contact with the epithelial barrier. [4] The buccal have ability to maintain a delivery system at a particular location for an extended period of time has great appeal for both local as well as systemic drug bioavailability. The buccal mucosa are rich in blood supply and absorption occur at this place is efficient, and additionally the route also providing rapid drug transport to the systemic circulation and avoiding degradation by gastro-intestinal enzymes and first pass hepatic metabolism.[5]

Mucoadhesive Drug Delivery System in Oral Cavity [5, 6]: Drug delivery via the membranes of the oral cavity can be subdivided as follows:

Sublingual Delivery: drugs are delivered through mucosal membrane lining the floor of mouth into systemic circulation.

Buccal Delivery: drugs are delivered through mucosal membrane into systemic circulation by placing drug in between cheeks and gums.

Local Delivery: drugs are delivered into the oral cavity.

2. Theories of Mucoadhesion

There are six general theories of adhesion, which have been adapted for the investigation of mucoadhesion. [7, 8, 9]

The electronic theory suggests that electron transfer occurs upon contact of adhering surfaces due to differences in their electronic structure. This is proposed to result in the formation of an electrical double layer at the interface, with subsequent adhesion due to attractive forces.

The wetting theory is primarily applied to liquid systems and considers surface and interfacial energies. It involves the ability of a liquid to spread spontaneously onto a surface as a prerequisite for the development of adhesion. The affinity of a liquid for a surface can be found using techniques such as contact angle goniometry to measure the contact angle of the liquid on the surface, with the general rule being that the lower the contact angle, the greater the affinity of the liquid to the solid. The spreading coefficient (SAB) can be calculated from the surface energies of the solid and liquids using the equation: $SAB = \gamma_{B}\text{-}\gamma_{A}\text{-}\gamma_{AB}$

Where γ_A is the surface tension (energy) of the liquid A, γ_A is the surface energy of the solid B and γ_{AB} is the interfacial energy between the solid and liquid. SAB should be positive for the liquid to spread spontaneously over the solid.

The adsorption theory describes the attachment of adhesives on the basis of hydrogen bonding and van der Waals' forces. It has been proposed that these forces are the main contributors to the adhesive interaction. A subsection of this, the chemisorptions theory, assumes an interaction across the interface occurs as a result of strong covalent bonding.

The diffusion theory describes inter diffusion of polymers chains across an adhesive interface. This process is driven by concentration gradients and is affected by the available molecular chain lengths and their mobilities. The depth of interpenetration depends on the diffusion coefficient and the time of contact. Sufficient depth of penetration creates a semi-permanent adhesive bond.

The mechanical theory assumes that adhesion arises from an interlocking of a liquid adhesive (on setting) into irregularities on a rough surface. However, rough surfaces also provide an increased surface area available for interaction along with an enhanced viscoelastic and plastic dissipation of energy during joint failure, which are thought to be more important in the adhesion process than a mechanical effect.[9]

The fracture theory differs a little from the other five in that it relates the adhesive strength to the forces required for the detachment of the two involved surfaces after adhesion. This assumes that the failure of the adhesive bond occurs at the interface. However, failure normally occurs at the weakest component, which is typically a cohesive failure within one of the adhering surfaces.

Factor affect mucoadhesion

Molecular weight:

The mucoadhesive strength of a polymer increases with molecular weights above 100,000. Direct correlation between the mucoadhesive strength of polyoxyethylene polymers and their molecular weights lies in the range of 200,000–7,000,000. [10]

Cross-linking density:

The average pore size, the number and average molecular weight of the cross-linked polymers and the density of cross-linking are three important and inter-related structural parameters of a polymer network. Therefore, it seems reasonable that with increasing density of cross-linking, diffusion of water into the polymer network occurs at a lower rate which, in turn, causes an insufficient swelling of the polymer and a decreased rate of interpenetration between polymer and mucin. [11]

Hydration:

Hydration is required for a mucoadhesive polymer to expand and create a proper macromolecular mes of sufficient size, and also to induce mobility in the polymer chains in order to enhance the interpenetration process between polymer and mucin. Polymer swelling permits a mechanical entanglement by exposing the bioadhesive sites for hydrogen bonding and/or electrostatic interaction between the polymer and the mucus network. [11] However, a critical degree of hydration of the mucoadhesive polymer exists where optimum swelling and mucoadhesion occurs. [12]

Concentration:

The importance of this factor lies in the development of a strong adhesive bond with the mucus, and can be explained by the polymer chain length available for penetration into the mucus layer. When the concentration of the polymer is too low, the number of penetrating polymer chains per unit volume of the mucus is small and the interaction between polymer and mucus is unstable. In general, the more concentrated polymer would result in a longer penetrating chain length and better adhesion. However, for each polymer, there is a critical concentration, above which the polymer produces an "unperturbed" state due to a significantly coiled structure. As a result, the accessibility

of the solvent to the polymer decreases, and chain penetration of the polymer is drastically reduced. Therefore, higher concentrations of polymers do not necessarily improve and, in some cases, actually diminish mucoadhesive properties. One of the studies addressing this factor demonstrated that high concentrations of flexible polymeric films based on polyvinylpyrrolidone or poly (vinyl alcohol) as film-forming polymers did not further enhance the mucoadhesive properties of the polymer. [13]

Flexibility:

Mucoadhesion starts with the diffusion of the polymer chains in the interfacial region. Therefore, it is important that the polymer chains contain a substantial degree of flexibility in order to achieve the desired entanglement with the mucus. [14] The increased chain interpenetration was attributed to the increased structural flexibility of the polymer upon incorporation of polyethylene glycol. In general, mobility and flexibility of polymers can be related to their viscosities and diffusion coefficients, as higher flexibility of a polymer causes greater diffusion into the mucus network. [11]

Route of drug administration

In Mucoadhesive drug delivery system administrate the drug by various routes such as

Buccal delivery system, oral delivery system, vaginal delivery system, ocular delivery system, rectal delivery system, nasal delivery system.

Table 1: Site of mucoadhesive drug administration

S.No	Delivery system	Site of delivery system
1.	Buccal delivery system	Upper and lower site of the chicks
2.	Oral delivery system	In the oral cavity
3.	Vaginal delivery system	Place the vaginal mucosa
4.	Ocular delivery system	Place the drug upper part of the eye
5.	Rectal delivery system	Inner pace of the rectum
6.	Nasal delivery system	Inner side on the nasal cavity

Mechanism of mucoadhesion:

Mucoadhesion is complex phenomenon which allows attachment of drug molecule to the mucous layer with the aid of suitable carrier. Mucoadhesion process consists of various actions such as wetting, adsorption and interpenetration of polymer chains. Numbers of steps have been involved in the process of mucoadhesive bond formation. The first step of mucoadhesion process involves spreading, wetting, and dissolution of polymeric chain at the interface. Next step of mucoadhesion is interpenetration layer in which mechanical or physical entanglement between polymeric materials with the surface of mucosal layer occurs. The last step involves chemical interactions (hydrogen bonding, covalent bonding, ionic bonds, and Van der Waals' interactions).

3. Mechanisms 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

Overview of oral mucosa:

The oral mucosa is constructed from a furthest layer of stratified squamous epithelium (Fig 1). Under this lies a cellar film, a lamina propria pursued with the aid of the sub mucosa as the deepest layer. The epithelium is like stratified squamous epithelia found inside the remainder of the body in that it has a mitotically dynamic basal cellular layer,progressing via various isolating modera te layers to the shallow layers, where cells are shed from the outside of the epithelium. The epithelium of the buccal mucosa is around forty-50 cellular layers thick, even as that of the sublingual epithelium carries to a few degrees much less. The epithelial cells increment in length and emerge as praise as they journey from the basal layers to the shallow layers. (Amir H et.al).

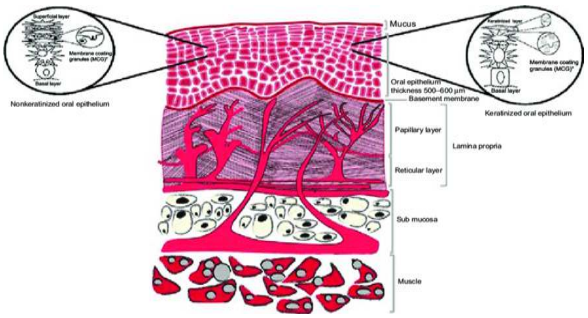

Fig 1: Anatomy of the oral mucosa

The oral hollow space might be separated into two districts, the external oral vestibule, limited via the lips and cheeks and the oral melancholy itself, the outskirts being fashioned with the aid of the tough and delicate palates, the floor of the mouth and the mainstays of the fauces and tonsils (Squier et al., 1976a). The mucosa that traces the oral cavity is probably separated into three sorts characterised by means of their function. These are masticatory mucosa, which includes the mucosa around the enamel and on the hard feel of flavour, lining mucosa which covers the lips, cheeks, fornix, alveolar manner, base

of the oral hollow, lower a few portion of the tongue and the delicate sense of taste and concentrated mucosa covering the dorsum of the tongue (Squier et al., 1976a). The oral mucosa in those regions may be essentially seen as a cover of layers, the epithelial layer, a very cell layer fashioned stratified squamous epithelium and the lamina propria, a usually a cell connective tissue layer compressing of thick connective and sinewy tissue. These two layers are isolated via a typhoon cellar membrane, a layer around 1-2/cm in thickness which lots of the time indicates up as an undulating restrict. In positive pieces of the oral hole, for example, the cheek, lips and components of the difficult experience of taste a further layer exists, the sub mucosa, whose structure is variable. This sediment consists of a unfastened greasy or granular connective tissue and incorporates the extensive veins and nerves that supply the mucosa and is available among the mucosa appropriate and underlying muscle or bone. The outside layers of the oral mucosa epithelia shape a protecting floor that's precisely excessive and impervious to physical affront and infiltration via outside materials. The shielding surface layers begin from cells inside the basal location of the epithelium which isolate and separate. The system of separation is not indistinguishable within the exclusive districts of the oral mucosa and, as an outcome; two unmistakable kinds of surface layers are perceived and alluded to as keratinised and non-keratinised. In keratinised tissue the outside layer consists of up to 20 lines of smoothed, hexagonal formed cells named squamous that are loaded up with a thick crystalline protein referred to as keratin, masterminded in interconnecting filaments through the cell phone. Keratinised tissue is probablysubdivided into ortho- and para-keratinised. In ortho-keratinised cells a dominating granular layer is to be had which is not directly found in para-keratinised tissue cells. Non-keratinised tissue includes no keratinised squamous (Squier et al., 1976a). in the grown-up human, the mucosa coating the oral pit covers a territory of round 200 cm 2 (Collins and Dawes, 1987). The thickness of human oral mucosa modifications as indicated by means of its web page. for instance, epithelial thickness of buccal mucosa (non-keratinised) is roughly 500/cm (Meyer and Gerson, 1964; Landau and Schroeder, 1977), palatal epithelium 27 t/cm, which includes a keratin layer thickness of 32/cm (Meyer and Ger-child, 1964), and gingival epithelium around 250 #m (Squier et al., 1976). Whilst all is stated in completed, non-keratinised tissue is impressively thicker than keratinised tissue, be that as it can, the floor of the mouth (non-keratinised) is slender (around 1(1(I/, tm) (Squier et al., 1976).

Composition of mucus layer:

Mucus is a translucent and vicid discharge which frames a slender, persistent gel cover disciple to the mucosal epithelial floor. The suggest thickness of this deposit differs from round 50-450µm in humans. It's far emitted with the aid of cup cells coating the epithelia or through exquisite over the top organs with mucus cellular acni. It has the following composition.

1. Water: 95 %
2. Glycoprotein's and lipids: 0.5-3.0 %
3. Mineral salts: 1%
4. Free proteins: 0.5-1 %

Functions of mucus layer:

The primary functions of mucus membrane are

1. **Protective:** Resulting especially from its hydrophobicity.
2. **Barrier:** The job of the mucus layer as an obstruction in tissue assimilation of the drugs and different substances impacts the bioavailability of drugs.
3. **Adhesion:** Mucus has solid union properties and immovably tie to the epithelial cell surface as a continuous gel layer.

At physiological pH, the mucus network may convey critical negative charges as a result of the nearness of sialic corrosive and sulfate deposits and high charge thickness to negative charge contributes fundamentally to bio adhesion. (Shojaei et. Al., 1998)

Salivary Secretion:

There are mainly three glands which secrete saliva in the oral cavity i.e. pertoid, sublingual and sub- mandibular.

Functions of Saliva:

Salivation saturates the oral cavity, helps the absorption of the food, and greases up the nourishment for rumination and swallowing, which gives assurance to the tissue from scraped area by harsh materials that may go into mouth. Salivation is constituted of 90%water and includes natural and inorganic material. Will power of salivation is maximum astounding amid the running hours. The degree of salivation delivered in the course of day is 1-1.5L but this movement is variable as per experts. The pH of the spit degrees from 5.eight to 7.four the salivation of the oral hole has a low buffering ability.

The presence of saliva in the mouth is important for two reasons:

1. Drug pervasion over the moist (mucus) layer occurs substantially more promptly than over the non-mucous films.
2. Drugs are regularly directed to the mouth in the clinical setting in a strong structure.

The medication should in this manner break down in salivation, before it tends to be ingested over the oral mucosa.

4. Evaluation Test for Mucoadhesion

Evaluation Studies of Mucoadhesive Drug Delivery System

In vitro/ex vivo tests:

1. Methods of mucoadhesive strength measurement
A) Methods determining tensile strength
B) Falling liquid film method
C) Fluorescent probe method
D) Colloidal gold mucin conjugates method
2. Swelling index
3. Thumb method
4. Electrical conductance
5. Measurement of the Residence Time

Methods of mucoadhesive strength measurement

A) Methods determining tensile strength:

There is uniform distribution of stress over the adhesive joint in tensile and shear

experiments, while the stress is focused at the edge of the joint in the peel strength. Thus the mechanical properties are measured through tensile and shear measure, while the peel strength measures the peeling force. Texture profile analyzer is one method used for measuring the force required to peel out bioadhesive films from cut out tissue in vitro. (Khan Ab et al., Rahamatullah Shaikh TR et al.) For this, a piece of animal mucous membrane was used and it was tested for the force required to pull the formulation from a model membrane which is made from disc of mucin. The texture analyzer operates in tensile test mode and is paired with a low sliding platform which is also used to determine peel strength. On a movable platform the animal skin was placed and on top of it the bioadhesive film was placed, which was later on pulled vertically to determine the peel strength.

B) Falling liquid film method:

In this method, the mucous membrane is placed in a longitudinally cut stainless steel cylindrical tube. This support is placed inclined in a cylindrical cell with a temperature controlled at 37°C in thermostatic bath. An isotonic solution is pumped through the mucous membrane by peristaltic pump and collected in a collection container. Subsequently, in the case of particulate systems, the amount remaining on the mucous membrane can be counted with the aid of a coulter counter. (Lenaerts VM.et.al, Park H.et.al)

C) Fluorescent probe method:

In this method, pyrene and fluorescein isothiocyanate are used to label the membrane lipid
bilayer and membrane proteins respectively.(Lenaerts VM.et.al) The mucoadhesive agents are mixed with cells and changes in fluorescence spectra are observed. This gives an indication of polymer binding and its role in polymer adhesion.

D) Colloidal gold mucin conjugates method:

New in-vitro method which was described for comparison of mucoadhesive property of various Hydrogels. In this technique, there is a use of red colloidal gold particles which are stabilized by the partially or fully adsorbed mucingold. Because of interaction mucoadhesive develops red colour on its surface. He mucoadhesive properties of the mucoadhesive device can be compared by measuring the intensity of red colour. (Muraleedhara KK.et.al)

2. Swelling index

The amount of swelling is calculated in % weight in the formulation. It is calculated using following formula:

Swelling index (S.I.) = (Wt-Wo/Wo)

Where,
S.I = Swelling index;
Wt = Weight of tablet at time t;
Wo = Weight of tablet before

3. Thumb method

This is used for the qualitative determination of peel adhesive strength of the polymer and is useful in the development of buccal adhesive delivery systems. The adhesiveness is measured by the strain required for pulling the thumb from the adhesive as a function of the pressure and the contact time. (Madan J et al.)

4. Electrical conductance:

The rotational viscometer was modified to determine electrical conductance of various semi-solid mucoadhesive ointments and found that the electrical conductance was low in the presence of adhesive material. (Rahamatullah Shaikh TR et al.)

5. Measurement of the Residence Time:

For determining the residence time of the buccal dosage forms the modified disintegration apparatus. 800 ml isotonic buffer pH 6.75 solution can be used as disintegration medium 3 cm long rabbit mucosa was attached to glass slide and it was vertically attached to side arm. One surface of mucoadhesive tablet was hydrated with 15 ml of isotonic phosphate buffer solution then it was taken in mucosal contact. He movement of glass slide was allowed to up and down for complete immersion. Ten times for detachment of tablet from mucosal surface can be noted. (Patel VF.et.al).

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