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ORIGINAL RESEARCH ARTICLE

Mucoadhesive Drug Delivery System: A Review

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ABSTRACT

This article gives a brief idea about bioadhesive delivery systems based on hydrogels to biological surfaces that are covered by mucus. Bioadhesion is an interfacial phenomenon in which two materials, at least one of which is biological are held together by means of interfacial forces, when the associated biological system is mucous. These systems remain in close contact with the absorption tissue, the mucous membrane, releasing the drug at the action site leading to a bioavailability increase and both local and systemic effects. Several in vitro and in vivo methodologies are proposed for studying its mechanisms. Oral mucoadhesive microcarriers were having potentiality for controlling and extending release profile so as to improve performance and patient compliance. The aim of this study was to review the mechanisms and theories involved in mucoadhesion, as well as to describe the most-used methodologies and polymers in mucoadhesive drug delivery systems.

Key words: Drug delivery, microcarrier, mucoadhesion, bioadhesion, oral hydrogels.

INTRODUCTION

The term bioadhesion refers to any bond formed between two biological surfaces or a bond between a biological and a synthetic surface. In case of bioadhesive drug delivery, the term bioadhesion is used to describe the adhesion between polymers, either synthetic or natural and soft tissues or the gastrointestinal mucosa. In cases where the bond is formed with the mucus the term mucoadhesion may be used synonymously with bioadhesion. Mucoadhesion can be defined as a state in which two components,of which one is of biological origin are held together for extended periods of time by the help of interfacial forces. Generally speaking, bioadhesion is an term which broadly includes adhesive interactions with any biological or biologically derived substance, and mucoadhesion is used when the bond is formed with a mucosal surface. Mucoadhesive drug delivery systems include the following:

Buccal delivery system, Oral delivery system, Vaginal delivery system, Rectal delivery system, Nasal delivery system, Ocular delivery system [1].

The oral route of drug administration constitutes the most convenient and preferred means of drug delivery to systemic circulation body. However oral administration of most of the drugs in conventional dosage forms has short-term limitations due to their inability to restrain and localize the system at gastrointestinal tract [2] In order to circumvent this problem, it has been proposed, successfully for several of them, to associate drugs to polymeric particulate systems because of their propensity to interact with the mucosal surface [3]. This is finally requires not only for the local targeting of drugs but also for a better control of systemic delivery [4]. The effect of a drug can now be reinforced as a result of the development of new release systems. Controlled release consists of techniques that make the active chemical agents available for a target, providing an adequate release rate and duration to produce the desired effect. Drug delivery via the buccal route, using bioadhesive dosage forms offers such a novel route of drug administration. Buccal delivery involves administration of desired drug through the buccal mucosal membrane lining of oral cavity. The mucosal lining of oral cavity offers some distinct advantages. It is richly vascularized and more accessible for the administration and removal of a dosage form. Additionally, buccal drug delivery has high

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patient acceptability compared to other non-oral routes of drug administration. Extensive first-pass metabolism and drug degradation in the harsh gastrointestinal environment can be circumvented by administering the drug via buccal route [5,6].

MUCOADHESIVE POLYMERS [7,8]:

Mucoadhesive polymers are water soluble and water insoluble polymers which are swellable networks jointed by cross linking agents. The polymers should possess optional polarity to make sure it is sufficiently wetted by the mucus and optimal fluidity that permits the mutual adsorption and interpenetration of polymer and mucus to take place.

Some of the mucoadhesive polymers along with their mucoadhesive property are summarized below:

Table: Mucoadhesive polymers with their mucoadhesive property [5]

S.No	Polymer	Mucoadhesive property
1	Carbopol 934	+++
2	Carboxymethylcellulose	+++
3	Polycarbophil	+++
4	Tragacanth	+++
5	Sodium alginate	+++
6	Hydroxyethyl cellulose	+++
7	Hydroxypropyl methylcellulose	+++
8	Gum karaya	++
9	Guar gum	++
10	Polyvinylpyrrolidone	+
11	Polyethylene glycol	+
12	Hydroxypropyl cellulose	+

Note: +++ excellent, ++ fair, +poor

Characteristics of ideal mucoadhesive polymer:

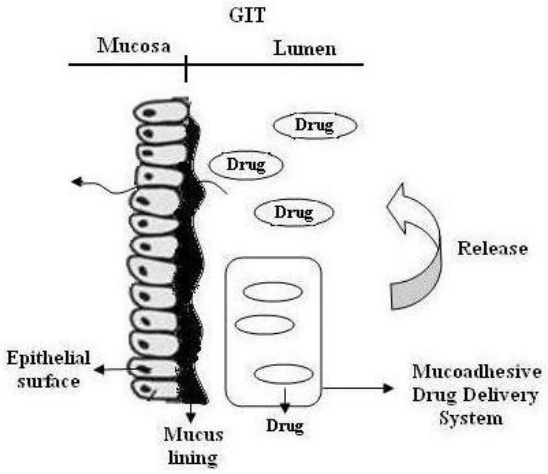
- The polymer and its degradation products should be nontoxic and nonabsorbable from the gastrointestinal tract.
- It should be nonirritant to the mucous membrane.
- It should preferably form a strong noncovalent bond with the mucin-epithelial cell surfaces.
- It should adhere quickly to soft tissue and should posses some site specificity.
- It should allow some easy incorporation of the drug and offer no hindrance to its release.
- The polymer must not decompose on storage or during shelf life of the dosage form.

MECHANISM OF MUCOADHESION:

A complete understanding of how and why certain macromolecules attach to a mucus surface is not yet available, but a few steps involved in the process are generally accepted, at least for solid systems. Several theories have been proposed to explain the fundamental mechanism of adhesion.

A General Mechanism of mucoadhesion drug delivery system is show in Figure-

Fig: Mechanism of mucoadhesion



Electronic theory

According to this theory, electron transfer occur upon contact of adhesive polymer with a mucus glycoprotein network because of difference in their electronic structures. This results in the formation of electrical double layer at the interface e.g. Interaction between positively charged polymers chitosan and negatively charged mucosal surface which becomes adhesive on hydration and provides an intimate contact between a dosage form and absorbing tissue.

Absorption theory

According to this theory, after an initial contact between two surfaces, the material adheres because of surface force acting between the atoms in two surfaces. Two types of chemical bonds resulting from these forces can be distinguished as primary chemical bonds of covalent nature and Secondary chemical bonds having many different forces of attraction, including electrostatic forces, Vander Walls forces, hydrogen and hydrophobic bonds.

Diffusion theory

According to this theory, the polymer chains and the mucus mix to a sufficient depth to create a semi permanent adhesive bond. The exact depth to which the polymer chain penetrates the mucus depends on the diffusion coefficient and the time of contact. The diffusion coefficient in terms depends on the value of molecular weight between crosslinking and decreases significantly as the cross linking density increases.

Wetting theory

The 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 substrate surfaces are

brought in contact with each other in the presence of the liquid, the liquid may act as an adhesive among the substrate surface.

Cohesive theory

The cohesive theory proposes that the phenomena of bioadhesion are mainly due to intermolecular interaction amongst like molecule. Based upon the above theories, the process of bioadhesion can broadlybe classified into two categories namely chemical (electron and absorption theory) and physical (wetting, diffusion and cohesive theory).

Fracture theory

This is perhaps the most-used theory in studies on the mechanical measurement of mucoadhesion. It analyses the force required to separate two surfaces after adhesion is established. This force,sm, is frequently calculated in tests of resistance to rupture by the ratio of the maximal detachment force, Fm, and the total surface area, A_0, involved in the adhesive interaction (eq.1):

Sm= Fm/Ao ……. (1)

Since the fracture theory is concerned only with the force required to separate the parts, it does not take into account the interpenetration or diffusion of polymer chains [9].

Mechanical theory

Mechanical theory considers adhesion to be due to the filling of the irregularities on a rough surface by a mucoadhesive liquid. Moreover, such roughness increases the interfacial area available to interactions thereby aiding dissipating energy and can be considered the most important phenomenon of the process.

FACTORS AFFECTING MUCOADHESION:

Polymer-related factors:

Molecular weight

Generally, the threshold molecular weight required for successful bioadhesion is at least 100,000. For example, polyethylene glycol (PEG) with a molecular weight (MW) of 20,000, has little adhesive character, whereas PEG with MW of 200,000 and 400,000 has improved and superior adhesive properties, respectively [10].

Spatial conformation

In general, it has been shown that the bioadhesive strength of a polymer increases with molecular weights above 100,000. Interestingly, adhesiveness of non-linear molecular structure follows a quite different trend. The adhesiveness of dextran, with a very high molecular weight of 19,500,000, is similar to that of PEG with a molecular weight of 200,000 [11].

Chain flexibility

Chain flexibility is critical for inter penetration and entanglement of mucoadhesive polymers. As water soluble polymers become cross-linked, mobility of individual polymer chains decrease andthus the effective length of the chain that can penetrate into the mucous layer decreases, which reduces bioadhesive strength. The increased chain inter penetration was attributed to the increased structural flexibility of the polymer upon incorporation of poly-ethylene glycol [12].

Hydrogen bonding capacity

Park and Robinson found that in order for mucoadhesion to occur, the desired polymers must have functional groups that are able to form hydrogen bonds. The hydrophilic functional groups responsible for forming hydrogen bonds are the hydroxyl (-OH) and carboxylic groups (-COOH). A major reason behind the selection of hydrophilic polymers for oral transmucosal drug delivery systems is the water-rich environment of the oral cavity owing to the presence of saliva [13].

Cross-linking density

The average pore size, the number average molecular weight of the cross-linked polymers, and the density of cross-linking are three important and interrelated 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 [14].

Charge

The strength of mucoadhesion of polymers with carboxyl groups was much stronger than that of those with neutral groups. Some generalizations about the charge of bioadhesive polymers have been made previously, where nonionic polymers appear to undergo a smaller degree of adhesion compared to anionic polymers [15].

Concentration

At low concentration of the polymer, the number of penetrating polymer chains per unit volume of the mucus is small and the interaction between polymer and mucus is unstable. A more concentrated polymer leads to longer penetrating chain length and better adhesion. Increased concentration of bioadhesive polymer, usually from 1.0 - 2.5 wt%, in principle, increased the binding potential [16].

Hydration (swelling)

A sufficient amount of water appears necessary to properly hydrate and expand the mucoadhesive network to expose available bioadhesive sites for bond formation by creating pores, channels or macromolecular mesh of sufficient size for diffusion of solutes or polymer chains, as well as mobilizing the polymer chain for interpenetration [17].

Environment-related factors:

pH

The pH can influence the formal charge on the surface of mucus as well as certain ionisable bioadhesive polymers. Mucus will have a different charge density depending on pH due to difference in dissociation of functional groups on the carbohydrate moiety and the amino acids of the polypeptide backbone. For example, polycarbophil does not show a strong bioadhesive property above pH 5 because uncharged rather than ionised, carboxyl groups react with mucin molecules, presumably through numerous hydrogen bonds. Moreover, bioadhesive strength increases as the initial contact time increases [18,19].

Mucin turnover rate

Estimation of mucin turnover varies widely, depending on location and method of measurement. Values ranging from a few hours to a day have been reported. However, residence times of bioadhesion that are thought to attach to mucin are typically longer than the reported mucin turnover, suggesting that the presence of bioadhesive polymer on mucin may alter the turnover of this biopolymer. The residence time of dosage forms is limited by the mucin turnover time, which has been calculated to range between 47 and 270 min in rats and 12 – 24 h in humans [20].

Physiological considerations

In many routes of administration, surface mucus is encountered by the bioadhesive before it reaches the tissue. The extent of interaction between the polymer and the mucus depends on mucus viscosity, degree of entanglement, and water content. Physiological considerations such as texture of mucosa, thickness of the mucous layer, its turnover time, and other factors, are to be considered in designing the dosage forms [21].

CONCLUSION

Mucoadhesive drug delivery system shows promising future in enhancing the bioavailability and specific needs by utilizing the physiochemical characters of both the dosage form and the mucosal lining. It has to be noted that only a moist surface can bring the mucoadhesive nature of the dosage form. Mechanism of mucoadhesion is backed up by ionic bond, covalent bond, Vander Waal bond and hydrogen bond. Ionic and covalent bonds results in very strong mucoadhesive property. Mucoadhesion commence with wetting which is described as contact stage. In the consolidation stage lot of physiochemical interaction takes place. While considering a formulation development of mucoadhesive drug delivery dosage form, several physiological factors also has to be considered at the site of action. Several synthetic and natural polymers are considered to have complying properties of mucoadhesion. While performing gastro retentive mucoadhesive in-vivo tests, it should be proved that the dosage form is no more available in the stomach after the desired period.

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