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Review Article

Pioneering and Encouraging Approach – Mucoadhesive Drug Delivery System

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ABSTRACT

A Propitious Novel Drug delivery method, Mucoadhesive drug delivery system considerably increase dosage form residence time, furthermore augmenting the affinity with the tissue and localizing the drug in a specific region. Mucoadhesive materials are used as therapeutic agents nevertheless act security blanket to damaged tissues (such as gastric ulcers or lesions of the oral mucosa) or act as lubricating agents (in the oral cavity, eye etc).The article exemplify the mechanism by which mucoadhesion can adhere to a mucous membrane with respect to the nature of the adhering surfaces and the forcing to generate a intimacy between them. Mucosal adhesion is suffixed with various theories comprising of electronic, adsorption, wetting, diffusion, fracture and mechanical. Stages of mucoadhesion include contact stage and consolidation stage. Physiology of mucous membrane, Factors affecting mucoadhesion and Chemical bonds of mucosa interaction, ionic bonds, covalent bonds, Van-der-Waal bonds and hydrogen bonds.

1. Introduction

Throughout the animal kingdom, various species have used mucous secretion in their adaptation to environments. In the earthworm, for example, mucus provides a permeable barrier allowing the passage of oxygen and carbon dioxide, yet protecting against the influx of other chemicals in the soil**[1]**. Hence forth Mucus is considered as a dynamic semi permeable barrier that enables the exchange of nutrients, water, gases, odorants, hormones, and gametes while being impermeant to most bacteria and many pathogens.The presence of a mucous layer provides a unique opportunity for sustained or prolonged drug delivery via the development of mucoadhesive dosage forms**[**2–4**]**.

This novel approach has been explored to provide prolonged drug delivery via the ophthalmic, buccal, gastrointestinal, vaginal and nasal routes[1].The use of bioadhesives has recently gained considerableattention in the area of soft tissue based mucosal delivery, and several formulations are now commercially available or under development. Such systems dramatically increase dosage form residence time, as well as improve intimacy of contact with the tissue, thereby localizing the drug in a specific region. Bioadhesion, therefore, has the potential to maintain the dosage form for a clearly defined time on the oral mucosa.

Adhesion can be defined as the bond produced by contact between a pressure sensitive adhesive and a surface. Bioadhesion may be defined as the state in which two materials, at least one of which is biological in nature, are held together for extended periods of time by interfacial forces, which may consist of valence forces, interlocking action or both. In the pharmaceutical sciences, when the adhesive attachment is to mucus or amucous membrane, the phenomenon is referred to as mucoadhesion**[**5,6**]**.

Mucoadhesion should not be confused with bioadhesion as in bioadhesion, the polymer is attached to the biological membrane and if the substrate is mucus membrane the term mucoadhesion is used.

Organs exposed to the external environment (e.g., the eyes, GI tract, respiratory tract, urinary bladder, pancreatic tract, gall bladder and the reproductive tracts) protect their epithelia by production of a mucous layer. Mucoadhesives materials could also be used as therapeutic agents in their own right, to coat or act as a blanket to protect damaged tissues (gastric ulcers or lesions of the oral mucosa) or to act as lubricating agents (in the oral cavity, eye and vagina)**[**1,8**]**.

1.1 Advantages of mucoadhesive drug delivery system**[9-15]**

Mucoadhesive delivery systems offer several advantages over other oral controlled release systems by virtue of prolongation of residence time of drug in gastrointestinal tract (GIT).

- Improved patient compliance- ease of drug administration
- Targeting and localization of the dosage form at a specific site, Rapid onset of action.
- Also, the mucoadhesive systems are known to provide intimate contact between dosage form and the absorptive mucosa, resulting in high drug flux at the absorbing tissue and improve the therapeutic performance of drug.
- Avoid of first pass metabolism.
- The residence time of dosage form at the site of absorption is prolong, hence increases the bioavailability.

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- Painless administration.
- Rapid absorption because of enormous blood supply.

1.2 Disadvantages of mucoadhesive drug delivery system[9-15]

- The dissolution of drug due to continuous secretion of saliva (0.5-2 l/day)
- Prolonged contact of the drug possessing ulcerogenic property.
- For the *in vitro* screening of drugs the oral mucosal delivery is lack of good model. This is the major drawback of this drug delivery.
- Patient acceptability in terms to taste, irritancy and mouth feel is to be checked.
- Also has smaller surface area.
- costly drug delivery system

1.3 Physiology of mucous membrane

Mucus membranes (mucosae) [Figure 1] are the moist surfaces lining the walls of various body cavities such as the gastrointestinal, mouth, nose, and respiratory tracts. They consist of a connective tissue layer (the lamina propria) 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 intestines and bronchi) or multi-layered/stratified (e.g. in the oesophagus, vagina and cornea). The former contain goblet cells which secrete mucus directly onto the epithelial surfaces; the latter contain, or are adjacent to tissues containing, specialized glands such as salivary glands that secrete mucus onto the epithelial surface. Mucus is present either as a gel layer adherent to the mucosal surface or as a luminal soluble or suspended form. The major components of all mucus gels are mucin glycoprotein's, lipids, inorganic salts and water, the latter accounting for more than 95% of their weight, making them a highly hydrated system[23]. The major functions of mucus are that of protection, Barrier, Adhesion and lubrication.

1.3.1Composition of mucus layer

Mucus is translucent and viscous secretion which forms a thin, continuous gel layer sticking to the mucosal epithelial surface. Mucus glycoproteins are high molecular weight proteins possessing attached oligosaccharide units containing, L-fructose, D-galactose, N-acetyl-D-glu-cosamine, N-acetyl-D-galactosamine and Sialic acid[30-32].

2.0 The mucoadhesive/mucosa interaction

The mucoadhesive/mucosa interactions are as below:-

2.1 Chemical bonds

For adhesion to occur, molecules must bond across the interface. These bonds can arise in the following way [16,8].

(1). Ionic bond

Where two oppositely chargedions attract each other via electrostatic interactions to form a strong bond (e.g. in a saltcrystal)[8].

(2). Covalent bonds

Where electrons are shared they impairs between the bonded atoms in order to fill the orbitals. These are also strong bonds[8].

(3). Hydrogen bonds

Here a hydrogen atom, when covalently bonded to electronegative atoms such as oxygen, fluorine or nitrogen, carries as light positively charge and is therefore is attracted to other electronegative atoms. The hydrogen can therefore be thought of as being shared, and the bond formed is generally weaker than ionic or covalent bonds[8].

(4). Van-der-Waals bonds

These are some of the weakest forms of interaction that arise from dipole–dipole and dipole-induced dipole attractions in polar molecules, and dispersion forces with non-polar substances[8].

(5). Hydrophobic bonds

More accurately described as the hydrophobic effect, these are indirect bonds (such groups only appear to be attracted to each other) that occur when non-polar groups are present in an aqueous solution. Water molecules adjacent to non-polar groups form hydrogen bonded structures, which lowers the system entropy. There is therefore an increase in the tendency of non-polar groups to associate with each other to minimize this effect[8].

2.2.Theories of adhesion

There are six general theories of adhesion, which have been adapted for the investigation of mucoadhesion [6,18-20].

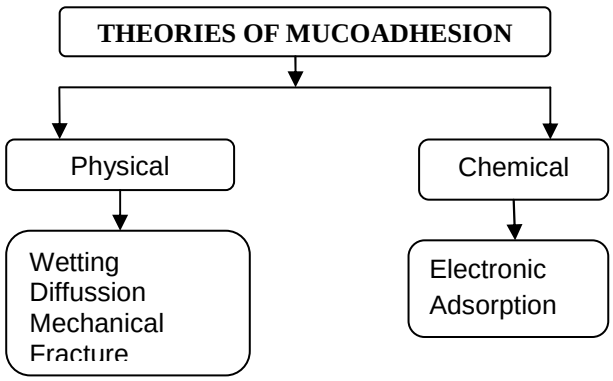

Figure No. 1: Theories of mucoadhesion

2.2.1 The electronic theory

The electronic theory suggests that electron transfer occurs upon contact of adhering surfaces due to differences in their electronic structure. The electron transfer between the mucus and the mucoadhesive projects in the formation of an electrical double layer at the interface, with subsequent adhesion due to attractive forces[20].

2.2.2. The adsorption theory

According to this theory, after an initial contact of the two

surfaces, the material will adhere because of the surface forces acting between the atoms in the two surfaces i.e. Hydrogen bonding, hydrophobic interactionsand van der Waals' forces. It has been proposed that these forces are the main contributors to the adhesive interactionbetween the adhesive polymer and mucus substrate. Additionally the chemisorptions theory, based on the assumption that an interaction across the interface occurs as a result of ionic, covalent and metallic bonding[21,22].

2.2.3. The wetting theory

Is principally 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 (S_{AB}) can be calculated from the surface energies of the solid and liquids using the equation:

$$S_{AB} = \gamma_B - \gamma_A - \gamma_{AB}$$

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

The work of adhesion (WA) represents the energy required to separate the two phases, and is given by:

$$w_A = \gamma_A + \gamma_B - \gamma_{AB}:$$

This theory explains the importance of contact angle and reduction of surface and interfacial energies to attain greater amount of mucoadhesion.

2.2.4.The diffusion theory

According to this theory, the polymer chains and the mucus co-mingle to a sufficient depth to create a semi-per meant adhesive bond**[**26**]**. Additional insight, with respect to the mechanism of interpenetration, was provided by Prager and Tirrell**[**27**]**. The bioadhesive material and glycoprotein of the biological membrane are brought in close contact. The polymer chains penetrate the mucus; the exact depth to which it penetrates to achieve sufficient bioadhesion depends on the diffusion coefficient, time of contact, and other experimental variables. The diffusion coefficient depends on molecular weight and decreases rapidly as cross-linking density increases, as shown by Peppas and Reinhart**[**28**]**. Thus thisprocess 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.

Below equationhelps to evaluate the interpenetration depth of polymer and mucin chains

$$l = (tD_b)^{1/2}$$

Where t is the contact time and D_b is the diffusion coefficient of the mucoadhesive material in the mucus. The adhesion strength for a polymer is attained when the depth of penetration is approximately equivalent to the polymer chain size. Structural similarity between the bio adhesive and the mucus promotes good mutual solubility resulting in diffusion phenomenon, hence concluded as larger the structural similarity, the stronger the mucoadhesive bond[23].

2.2.5.The mechanical theory

is based on assumption that adhesionoccurs with plugging of a liquid adhesive into irregularities on a rough substratesurface. Moreover this abrassive or rough surfaces also provide an increased interfacial 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**[15]**.

2.2.6.The fracture theory

This theory vary from the other five as it relate to evaluation of the adhesive strength to the forces required for the disentangement of the two involved surface safer established 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**[24,25].**

The fracture strength is equivalent to adhesive strength, given by the following equation;

$$cr = (E\sim/L)\ I/2$$

Where E is Young's modulus of elasticity ~ is the fracture energy, and L is the critical crack length when two surfaces are separated. The work of fracture of an elastomer network Gc is given by

$$Gc = K\ (Mc)^{1/2}$$

K is a constant dependent on density of the polymer, effective mass, length, flexibility of a single mucin chain bond, and bond dissociation energy. Gc of an elastomeric network increases with molecular weight Me of the network strands**[**24**,**25].

3.0 Mechanism of mucoadhesion

Due to relative complexity, it is likely that the process of mucoadhesion cannot be described by just one of these theories. In considering the mechanism of mucoadhesion, a whole range 'scenarios' forin-vivo mucoadhesive bond formation are possible (Figure 2)[8]. These include:

(a). Dry or partially hydrated dosage forms contacting surfaces with substantial mucus layers (typically particulates administered into the nasal cavity).

(b). Fully hydrated dosage forms contacting surfaces with substantial mucus layers (typically particulates of many

'First Generation'mucoadhesives that have hydrated in the luminal contents on delivery to the lower gastrointestinal tract).

(c). Dry or partially hydrated dosage forms contacting surfaces within/discontinuous mucus layers (typically tablets or patches in the oral cavity or vagina).

(d). Fully hydrated dosage forms contacting surfaces with thin/discontinuous mucus layers (typically aqueous semisolids or liquids administered in to the oesophagus or eye).

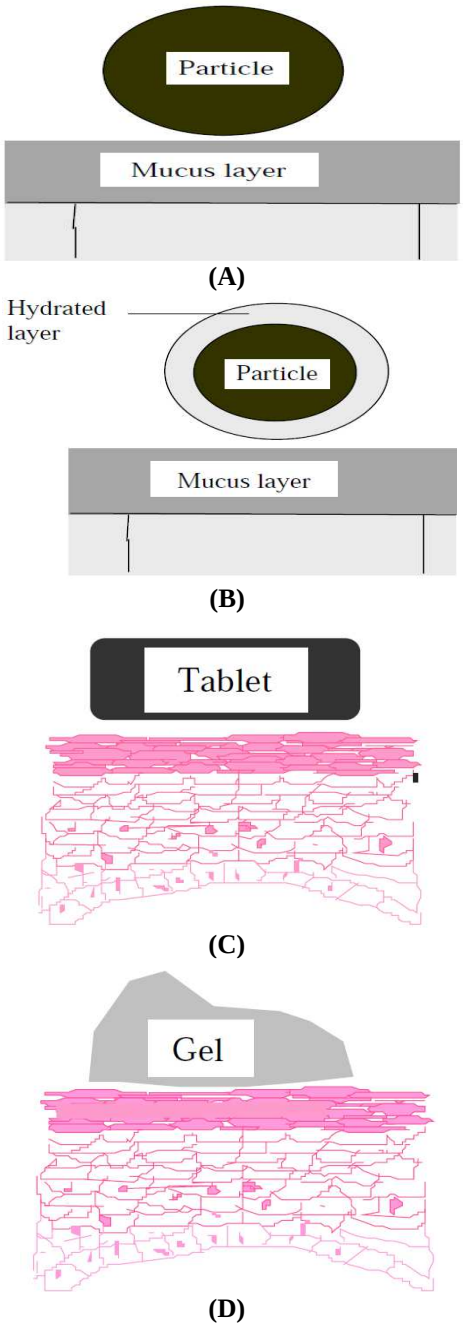

Figure No. 2: Mucoadhesion occurrence in different scenarios**[8]**

In the study of adhesion generally, two steps in the adhesive process have been identified**[33]**, which have been adapted to describe the interaction between mucoadhesive materials and a mucous membrane**[5,6]** (Figure. 3).

Step 1- Contact stage

An intimate physical contact (wetting or swelling) occurs between the mucoadhesive and mucous membrane.

Step 2-Consolidation stage

Various physicochemical interactions occur to consolidate and strengthen the adhesive joint, leading to prolonged adhesion (interpenetration)[34]**.**

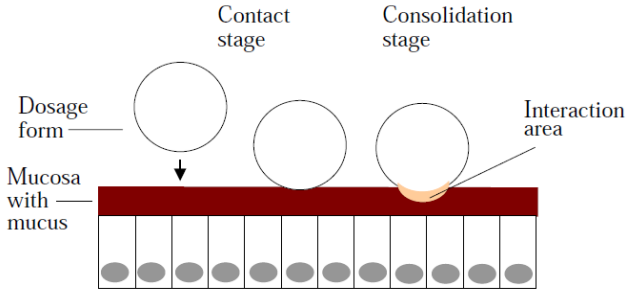

Figure No. 3: The two stages in mucoadhesion**[8]**

Step 1 - Contact stage

The mucoadhesive and the mucous membrane have initially come together to form an intimate contact. In some cases these two surfaces can be mechanically brought together, e.g. placing and holding a delivery system within the oral cavity, eye or vagina. In others the deposition of a particle is encouraged via the aerodynamics of the organ. For example within the nasal cavity or bronchi of the respiratory tract deposition onto the 'sticky'mucus coat is encouraged by processes such as inertial impaction, in order to 'filter out' particles from the air stream**[35]**.

Step 2 - Consolidation stage

It has been proposed that if strong or prolonged adhesion is required, for example with larger formulations exposed to stresses such as blinking or mouth movements, then a second consolidation stage is required. Mucoadhesive materials adhere most strongly to solid dry surfaces as long as they are activated by the presence of moisture. Moisture will effectively plasticize the system allowing mucoadhesive molecules to become free, conform to the shape of the surface, and bond predominantly by weaker van der Waal and hydrogen bonding[8,36].

Essentially, there are two theories explaining the consolidation step:

1. The diffusion theory
2. The dehydration theory**[37]**

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.

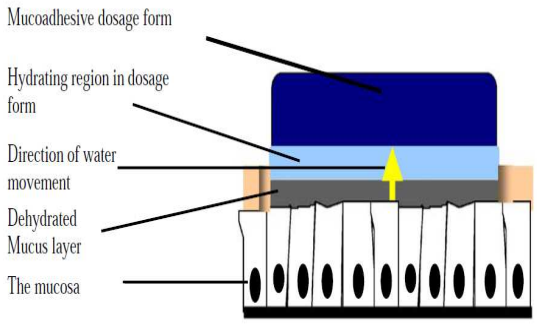

Figure No.4 The dehydration theory of mucoadhesion**[8]**

4. Factors affecting mucoadhesion

4.1 Polymer related factors

4.1.1 Molecular weight

As indicated in many studies the optimum molecular weight for maximum bio adhesion depends upon type of polymer and tissue used in mucoadhesion, circa 10^4 Da to circa $4x10^4$ Da range considered apt for mucoadhesion process. Though precise characterizesation the molecular weight of large hydrophilic polymers isvery difficult phenomenon**[8]**. For example, polyethylene glycol (PEG), with a molecular weight of 20 000, has little adhesive character, whereas PEG with 200 000 molecular weight has better, and PEG with 400 000 has superior adhesive properties**[39-41]**. The interpenetration of polymer molecules is favourable for low molecular weight polymers and lower molecular weight polymers will form weak gels and readily dissolve whereas entanglements are favours for high molecular weight polymers and these will not hydrate readily to free the binding groups to interact with a substrate**[38,8]**. Low-molecular weight polymers penetrate the mucus layer better. High molecular weight promotes physical entangling.

4.1.2 Flexibility of polymer chains

This parameter is believed to be important for interpenetration and entanglement, allowing binding groups to come together As water soluble polymers become cross-linked, the mobility of an individual polymer chain decreases and thus the effective length of the chain that can penetrate into the mucous layer decreases, which reduces mucoadhesive strength**[42-44]**. For achieving such diffusion, the polymer chain should have substantial degree of flexibility, which depends on the viscosity and diffusion coefficient. As a conclusion higher flexibility of polymer causes greater diffusion into mucus network**[38,41].**

4.1.3 Cross linking density

The cross linking density indicates the number of average molecular weight of the cross linked polymer, which determines the average pore size. When the cross linking density is higher, then the pore size becomes small, so that diffusion of water into the polymer network occurs at a lower rate, thus there is only an insufficient swelling of polymer resulting in decreased penetration of polymer into the mucin. It was reported that, this general property of polymers, in which the degree of swelling at equilibrium has an inverse relationship with the degree of cross- linking of a polymer**[45].**

4.1.4 Swelling or hydration

Hydration is required for a mucoadhesive polymer to expand and create a proper macromolecular mess 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 bio adhesive sites for hydrogen bonding and/or electrostatic interaction between the polymer and the mucus network**[46]**. Polymer swelling permits a mechanical entangle ment by exposing the Boiadhesive sites for hydrogen bonding and/or electrostatic interaction between the polymer and the mucous network**[46,47]**. However, a critical degree of hydration of the mucoadhesive polymer exists where optimum swelling and bio adhesion occurs**[48,49]**.

4.1.5 Concentration of polymer

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**[50].**

4.1.6 Spatial confirmation

Bio adhesive force is also reliant on the conformation of polymers, i.e., helical or linear. The helical conformation of polymers may shield many active groups, primarily responsible for adhesion, thus reducing the mucoadhesive strength of the polymer**[6,42,29].**

4.1.7 Hydrogen bonding capacity

Hydrogen bonding is another important factor for mucoadhesion of a polymer. For mucoadhesion to occur, desired polymers must have functional groups that are able to form hydrogen bonds**[46]**. Ability to form hydrogen bonds is due to the presence of (COOH, OH etc.). Flexibility of the polymer is important to improve its hydrogen bonding potential. Polymers such as polyvinyl alcohol, hydroxylated methacrylate and poly (methacrylic acid) as well as all their co-polymers are having good hydrogen bonding capacity**[49,51]**.

4.1.8 Charge

The degree of bioadhesive property of ionic polymer is always higher than that of non-ionic polymer**[49]**. In neutral or slightly alkaline medium, the cationic polymer reveal superior mucoadhesive property**[52]**. It has been revealed that, cationic high molecular weight polymer such as chitosan possess good bio adhesive property**[53]**.

4.2 Environment related factors

4.2.1 pH of polymer-substrate interface

pH influences the charge on the surface of both mucus and polymers[38]. Mucus will have a 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[42,43]. pH of the medium is important for the degree of hydration of cross-linked polycyclic acid, showing consistently increased hydration from pH 4 to pH 7, and then a decrease as alkalinity or ionic strength increases. However, at higher pH, the chain is fully extended due to electrostatic repulsion of the carboxyl ate anions[38,44,42,55].

4.2.2 Applied strength

While placing a buccal mucoadhesive drug delivery system, desired strength should be applied in order to provide a good bio adhesive property. Even though there is no attractive forces between polymer and mucus, then application of high pressure for sufficient long time make the polymer become Boiadhesive with mucus, hence pressure initially applied to the mucoadhesive tissue contact site can affect the depth of interpenetration[56].

4.2.3. Initial contact time

Contact time between the bioadhesive and mucus layer determines the extent of swelling and interpenetration of the bioadhesive polymer chains. Moreover, bioadhesive strength increases as the initial contact time increases[38,43]. Even though with the initial pressure the initial contact time there is rigorous effect on performance of a system[47].

4.2.4. Moistening

Moistening is required to allow the mucoadhesive polymer to spread over the surface and create a macromolecular network of sufficient size for the interpenetration of polymer and mucin molecules to increase the mobility of polymer chains. However there is a critical level of hydration for mucoadhesive polymers characterized by optimum swelling and bio adhesion[57].

4.2.5. Presence of metal ions

Interaction with charged groups of polymer and/or mucous can decrease the number of interaction sites and the tightness of mucoadhesive bonding[58].

4.3 Physiological factors

4.3.1. Mucin turnover

High mucin turnover is not beneficial for the mucoadhesive property because of following reasons:

The high mucin turns over limits the residence time of bioadhesive polymer as it detaches from the mucin layer, even though it has a good bioadhesive property. High mucin turn over may produce soluble mucin molecule[42,29], thus molecule interact with the polymer, before they interact with mucin layer[59,60,53]. Hence there will not be sufficient mucoadhesion.

4.3.2 Disease state

The physicochemical property of mucus may alter during some disease state, such as common cold, gastric ulcers, ulcerative colitis, bacterial and fungal infections etc. Thus alteration in the physiological state may affect the bio adhesive property[54,29].

4.3.3 Rate of renewal of mucosal cells

Rate of renewal of mucosal cells varies extensively from different types of mucosa. It limits the persistence of bioadhesive systems on mucosal surfaces[57].

4.3.4 Tissue movement

Tissue movement occurs on consumption of liquid and food, speaking, peristalsis in the GIT and it affects the mucoadhesive system especially in case of gastro retentive dosage form[57].

5.0 Discussion

Mucoadhesion is a multifaceted process and copious theories have been presented to elucidate the mechanisms involved. These theories include mechanical-interlocking, electrostatic, diffusion interpenetration, adsorption and fracture processes, Hence concluded as Electronic theory, Adsorption theory, Wetting theory, Diffusion theory, Fracture theory. Mucoadhesive dosage forms has inclined patient towards due to ease of drug administration and Painless administration. Most importantly there are various factors as elucidated above plays an important role in adhesion property, molecular weight of the polymer as one parameter concluded as, Low-molecular weight polymers penetrate the mucus layer better. High molecular weight promotes physical entangling. - circa 10^4 Da to circa $4x10^4$ Da range considered apt for mucoadhesion process. Higher flexibility of polymer causes greater diffusion into mucus network, further flexibility, which depends on the viscosity and diffusion coefficient. Hydration is required for a mucoadhesive polymer to expand, Polymer swelling permits a mechanical entanglement by exposing the Boiadhesive sites for hydrogen bonding and/or electrostatic interaction between the polymer and the mucous network. For Optimum Hydration pH values should between pH 4 to pH 7.

Optimum concentration is required for proper adhesion neither too low nor too high concentration supports the adhesion property. As per the spatial confirmation concerns out of helical or linear, helical conformation of polymers may shield many active groups, primarily responsible for adhesion, thus reducing the mucoadhesive strength of the polymer hence reducing the Adhesion property. The degree of ionization plays important role in bioadhesive property, ionic polymer has higher bioadhesion than that of non-ionic polymer. Thus, Mucoadhesive Drug Delivery system is considered as the preferred drug delivery system.

6.0 Conclusion

The mucoadhesive drug delivery system is a cumulative for delivering the drugs which have narrow absorption window at the target site to optimize their usefulness. Oral route is the most ancient as well as preferred by patient being convenient to take similarly in Mucoadhesive dosage forms has inclined patient towards due to ease of drug administration and Painless administration. Studies on Mucoadhesive system have focused on broad array of aspects as distended from the simple oral mucosal delivery to the nasal, vaginal, ocular and rectal drug delivery systems. The article exemplify the mechanism by which mucoadhesion can adhere to a mucous membrane with respect to the nature of the adhering surfaces and the forcing to generate a intimacy between them.

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