

Review Article

MUCOADHESIVE DRUG DELIVERY SYSTEM: A REVIEW

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Abstract

Helicobacter pylori colonizes and grows in human gastric epithelial tissue and mucus. Its presence is associated. Mucoadhesive delivery systems are being explored for the localization of the active agents to a particular site. This review aims to provide an overview of the various aspects of mucoadhesion, mechanism, factors affecting mucoadhesion, sites of mucoadhesive drug delivery system, characteristics and the classification of polymers used for mucoadhesive drug delivery system.

Keywords: Mucoadhesive drug delivery system, Mucoadhesion, Polymer

INTRODUCTION

The basic rationale of controlled drug delivery system is to optimize the biopharmaceutical, pharmacokinetics and pharmacodynamic properties of drug in such a way that its utility is maximized through reduction in the side effects and treatment in the shortest possible time by the most suitable route. Over the Past 30 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention is being paid on development of oral controlled release drug delivery systems. The goal in designing controlled release drug delivery system is to reduce the frequency of the dosing, reducing the dose and providing uniform drug delivery [1].

Microspheres form an important part of such novel drug delivery systems. They are designed to control the drug release from the dosage form to improve bioavailability, reduce the adverse action and prolong the action of drug, reduce absorption difference in patients, reduce the dosing frequency and adverse effects during prolonged treatment. Microsphere carrier systems made from the naturally occurring biodegradable polymers have attracted considerable attention for several years in sustained drug delivery. However, the success of these microspheres is limited due to the short residence time at the site of absorption. It would therefore be advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membranes. This can be achieved by coupling bioadhesion characteristics to microspheres and developing bioadhesive microspheres [2].

MUCOADHESIVE DRUG DELIVERY SYSTEM

Over the past few decades, mucosal drug delivery has received a great deal of attention. Mucoadhesive dosage forms may be designed to enable prolonged retention at the site of application, providing a controlled rate of drug release for improved therapeutic outcome. Application of dosage forms to mucosal surfaces may be of benefit to drug molecules not amenable to the oral route, such as those that undergo acid degradation or extensive first-pass

metabolism. Mucoadhesive drug delivery gives rapid absorption and good bioavailability due to its considerable surface area and high blood flow. Drug delivery across the mucosa bypasses the first-pass hepatic metabolism and avoiding the degradation of gastrointestinal enzymes. Thus mucosal drug delivery system could be of value in delivering a growing number of high-molecular-weight sensitive molecules such as peptide and oligonucleotides. 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 [3].

For drug delivery purposes, the term bioadhesion implies attachment of a drug carrier system to a specified biological location. The biological surface can be epithelial tissue or the mucus coat on the surface of a tissue. If adhesive attachment is to a mucus coat, the phenomenon is referred to as mucoadhesion. Leung and Robinson (1988) described mucoadhesion as the interaction between a mucin surface and a synthetic or natural polymer. Mucoadhesion should not be confused with bioadhesion; in bioadhesion, the polymer is attached to the biological membrane and if the substrate is mucus membrane the term mucoadhesion is used [4].

MUCUS MEMBRANE

Mucous membranes (mucosae) are the moist surfaces, lining the walls of various body cavities such as the gastrointestinal 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 intestine and bronchi) or multilayered/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 as either a gel layer adherent to the mucosal surface or as a luminal soluble or suspended form.

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 mean thickness of this layer varies from about 50-450 μm 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%), glycoprotein 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 [5]:

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

Function of mucus layer

The primary functions of the mucus layer are: Protective, barrier, adhesion and lubrication.

Protective: Resulting particularly from its hydrophobicity and protecting the mucosa from the diffusion of hydrochloric acid from the lumen to the epithelial surface.

Barrier: The mucus constitutes a diffusion barrier for molecules and especially against drug absorption.

Adhesion: Mucus has strong cohesive properties and firmly binds to the epithelial cells surface as a continuous gel layer.

Lubrication: Mucosal layer keeps the mucosal membrane moist.

Continuous secretion of mucus from the goblet cells is necessary to compensate for the removal of mucus layer due to digestion, bacterial degradation and solubilization of mucin molecules. At physiological pH, the mucus network may carry a significant negative charge because of the presence of sialic acid and sulphate residues contributing significantly to the bio-adhesion [6,7].

The mucoadhesive / mucosa interaction

For adhesion to occur, molecules must bond across the interface. These bonds can arise in the following ways:

i. Ionic bonds- where two oppositely charged ions attract each other via electrostatic interaction to form a strong bond (e.g. in a salt crystal).

ii. Covalent bonds- where electrons are shared, in pairs, between the bonded atoms in order to 'fill' the orbitals in both. These are also strong bonds.

iii. Hydrogen bonds- here a hydrogen atom, when covalently bonded to electronegative atoms such as oxygen, fluorine or nitrogen, carries a slight positive charge and is therefore 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.

iv. Van-der-Waals bonds- these are 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.

v. Hydrophobic bonds- 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 [6,7,8].

MECHANISM OF MUCOADHESION

The mechanism of mucoadhesion is generally divided into two steps: the contact stage and the consolidation stage. The first stage is characterized by the contact between the mucoadhesive and the mucus membrane, with spreading and swelling of the formulation, initiating its deep contact with the mucus layer. 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 [9].

THEORIES OF MUCOADHESION

It is reported that, although the chemical and physical basis of mucoadhesion are not yet well understood. There are six classical theories adapted from studies on the performance of several materials and polymer-polymer adhesion which explain the phenomenon. Contact angle and time plays a major role in mucoadhesion [10,11,12].

Electronic Theory

Electronic theory is based on the assumption that both mucoadhesive and biological materials possess opposing electrical charges. According to electronic theory, attractive electrostatic forces between glycoprotein mucin network and the bioadhesive material occurs. Because of different electronic properties of the mucoadhesive polymer and the mucus glycoprotein, electron transfer between these two surfaces occurs. Electron transfer occurs between the two forming double layer of electric charges at the interface. This theory describes adhesion occurring by means of electron transfer between the mucus and the mucoadhesive system arising through differences in their electronic structure. Thus it results in the formation of double layer of electric charges at the mucus and the mucoadhesive interface with subsequent adhesion due to attractive forces [12].

Wetting Theory

The wetting theory is perhaps the oldest established theory of adhesion. It is best applied to liquid or low-viscosity bioadhesives. It explains adhesion as an embedding process, whereby adhesive agents penetrate into surface irregularities of the substrate and ultimately harden, producing many adhesive anchors. Free movement of the adhesive on the surface of the substrate means that it must overcome any surface tension effects present at the interface. The wetting theory calculates the contact angle and the thermodynamic work of adhesion [13,14,15].

The work done is related to the surface tension of both the adhesive and the substrate, as given by Dupre's equation:

$$A = \gamma_b + \gamma_s - \gamma_{bt}$$

where A is the specific thermodynamic work of adhesion and γ_b , γ_s , and γ_{bt} represent, respectively, the surface tensions of the bioadhesive polymer, the substrate, and the interfacial tension. The adhesive work done is a sum of the surface tensions of the two adherent phases, less the interfacial tensions apparent between both phases [6,16].

Adsorption Theory

According to the "adsorption theory", after an initial contact between two surfaces, the materials adhere because of surface forces acting between the chemical structures at the two surfaces. Primary and secondary chemical bonds of the covalent and non-covalent (electrostatic and Vander Waals' forces, hydrogen, and hydrophobic bonds) types are formed upon initial contact between the mucus and the mucoadhesive polymer. The formation of secondary chemical bonds greatly depends on properties of the polymer. Chemisorption can occur when adhesion is particularly strong [3,16].

Diffusion Theory

The diffusion theory states that interpenetration and entanglement of both polymer and mucin chains are responsible for mucoadhesion. The bond strength increases with the increase in the degree of the penetration. The more structurally similar a mucoadhesive to the mucosa, the greater is the mucoadhesion. It is believed that an interpenetration layer of 0.2-0.5 micrometer is required to produce an effective bond. It is believed that the adhesion force increases with the degree of penetration of the polymer chains. This penetration rate depends

on the diffusion coefficient, flexibility and nature of the mucoadhesive chains, mobility and contact time. The penetration depth (l) can be estimated by the following formula:

$$l = (t D_b)^{1/2}$$

where, t is the time of contact and D_b is the diffusion coefficient of the bio adhesive material in the mucus. The adhesion strength for a polymer is reached when the depth of penetration is approximately equivalent to the polymer chain size [3,17].

Fracture Theory

The fracture theory analyses the force that is required for the separation of two surfaces after adhesion. The maximum tensile strength produced during detachment can be determined by dividing the maximum force of detachment (F_m) by the total surface area (A_o), involved in the adhesion interactions.

$$S_m = F_m/A_o$$

The fracture theory analyzes the force required to separate two 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. 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. Consequently, it is appropriate for use in the calculations for rigid or semi-rigid bioadhesive materials, in which the polymer chains do not penetrate into the mucus layer [6,16].

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.

Lee et al. (2000) had described that it is unlikely that the mucoadhesion process is the same for all cases and therefore it cannot be described by a single theory. In fact, all theories are relevant to identify the important process variables [6,18].

FACTORS AFFECTING MUCOADHESION

1. Polymer related factors:
 - i. Molecular weight
 - ii. Concentration of active polymer
 - iii. Flexibility of polymer chains
 - iv. Spatial conformation
 - v. Cross linking density
 - vi. Hydration and Swelling
 - vii. Charge
2. Environment related factors:
 - i. pH of polymer - substrate interface
 - ii. Applied strength and Initial contact time
3. Physiological factors:
 - i. Mucin turns over
 - ii. Disease state

1. Polymer related factors:

- i. **Molecular weight:** With the increase in the molecular weight (MW) of the polymer chain there is an increase in the mucoadhesiveness of a polymer. In general, it has

been shown that the bioadhesive strength of a polymer increases with molecular weights above 100,000 [19].

- ii. **Concentration of active polymer:** 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 [20,21].
- iii. **Flexibility of polymer chains:** Bioadhesion 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. In general, mobility and flexibility of polymers can be related to their viscosities and diffusion coefficients, where higher flexibility of a polymer causes greater diffusion into the mucus network [7,22].
- iv. **Spatial conformation:** Besides molecular weight or chain length, spatial conformation of a polymer is also important. Despite a high molecular weight of 19,500,000 for dextrans, they have adhesive strength similar to that of polyethylene glycol (PEG), with a molecular weight of 200,000. The helical conformation of dextran may shield many adhesively active groups, primarily responsible for adhesion, unlike PEG polymers, which have a linear conformation [14].
- v. **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 [19,22].
- vi. **Hydration and Swelling:** A sufficient amount of water appears to be necessary for properly hydrating and expanding 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 [23].
- vii. **Charge:** 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. It has been shown that some cationic polymers are likely to demonstrate superior mucoadhesive properties, especially in a neutral or slightly alkaline medium. Additionally, some cationic high-molecular-weight polymers, such as chitosan, have shown to possess good adhesive properties [21,24].

2. Environment related factors:

- i. **pH:** The pH at the bioadhesive to substrate interface can influence the adhesion of bioadhesives possessing ionizable groups. Many bioadhesives used in drug delivery are polyanions possessing carboxylic acid functionalities. If the local pH is above the pK of the polymer, it will be largely ionized; if the pH is below the pK_a of the polymer, it will be largely unionized. The approximate pK_a for the poly(acrylic acid) family of polymers is between 4 and 5. The maximum adhesive strength of these polymers is observed around pH 4–5 and decreases gradually above a pH of 6. A systematic investigation of the mechanisms of mucoadhesion clearly showed that the protonated carboxyl groups, rather than the ionized carboxyl groups, react with mucin molecules, presumably by the simultaneous formation of numerous hydrogen bonds [25].
- ii. **Applied strength and Initial contact time:** Mucoadhesion may be affected by the initial force of application. Higher forces lead to enhanced interpenetration and high bioadhesive strength. In addition, greater the initial contact time between bioadhesive and substrate, greater is the swelling and interpenetration of polymer chains [26].

2. **Physiological factors:** Physiological variables such as mucin turnover and disease state can also affect mucoadhesion. The rate of mucus turnover can be affected by disease states and also by the presence of a bioadhesive device. In addition, the nature of the surface presented to the bioadhesive formulation can vary significantly depending on the body site and the presence of local or systemic disease [3,27].

SITES FOR MUCOADHESIVE DRUG DELIVERY SYSTEMS [6,7]

The common sites of application where mucoadhesive drug delivery systems have the ability to deliver pharmacologically active agents include oral cavity, eye conjunctiva, vagina, nasal cavity and gastrointestinal tract.

The buccal cavity has a very limited surface area of around 50 cm^2 but the easy access to the site makes it a preferred location for delivering active agents. The site provides an opportunity to deliver pharmacologically active agents systemically by avoiding hepatic first-pass metabolism in addition to the local treatment of the oral lesions. The sublingual mucosa is relatively more permeable than the buccal mucosa (due to the presence of large number of smooth muscle and immobile mucosa), hence formulations for sublingual delivery are designed to release the active agent quickly while mucoadhesive formulation is of importance for the delivery of active agents to the buccal mucosa where the active agent has to be released in a controlled manner. This makes the buccal cavity more suitable for mucoadhesive drug delivery [28].

Like buccal cavity, nasal cavity also provides a potential site for the development of formulations where mucoadhesive polymers can play an important role. The nasal mucosal layer has a surface area of around $150\text{--}200\text{ cm}^2$. 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 [29]. Ophthalmic mucoadhesives is another area of interest. Due to the continuous formation of tears and blinking of eye lids there is a rapid removal of the active medicament from the ocular cavity, which results in the poor bioavailability of the active agents. This can be minimized by delivering the drugs using ocular insert or patches [30,31,32].

The vaginal and the rectal lumen have also been explored for the delivery of the active agents both systemically and locally. The active agents meant for the systemic delivery by this route of administration bypasses the hepatic first-pass metabolism. Quite often the delivery systems suffer from migration within the vaginal/rectal lumen which might affect the delivery of the active agent to the specific location [33,34].

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 [35].

ADVANTAGES OF MUCOADHESIVE DRUG DELIVERY SYSTEM

- Prolongs the residence time of the dosage form at the site of absorption, hence increases the bioavailability.
- Excellent accessibility, rapid onset of action.
- Rapid absorption because of enormous blood supply and good blood flow rates
- Drug is protected from degradation in the acidic environment in the gut
- Improved patient compliance

DISADVANTAGES OF MUCOADHESIVE DRUG DELIVERY SYSTEM

- Occurrence of local ulcerous effects due to prolonged contact of the drug possessing ulcerogenic property
- One of the major limitations in the development of oral mucosal delivery is the lack of a good model for in vitro screening to identify drugs suitable for such administration.
- Patient acceptability in terms to taste, irritancy and mouth feel is to be checked

POLYMERS USED FOR MUCOADHESIVE DRUG DELIVERY

Mucoadhesive delivery systems are being explored for the localization of the active agents to a particular location/ 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. Mucoadhesive polymers are water-soluble and water insoluble polymers. Mucoadhesive polymers that adhere to the mucin-epithelial surface can be conveniently divided into three broad classes:

- Polymers that become sticky when placed in water and owe their mucoadhesion to stickiness.
- Polymers that adhere through nonspecific, non-covalent interactions those are primarily electrostatic in nature (although hydrogen and hydrophobic bonding may be significant).
- Polymers that bind to specific receptor site on the cell surface [9,36].

CHARACTERISTICS OF AN IDEAL POLYMER FOR MUCOADHESIVE DRUG DELIVERY [4,37,38,39]

1. Cationic and anionic polymers bind more effectively than neutral polymers.
2. Poly-anions are better than polycations in terms of binding/ potential toxicity, and further, that water-insoluble polymers give greater flexibility in dosage form design compared with rapidly or slowly dissolving water-soluble polymers.
3. Anionic polymers with sulfate groups bind more effectively than those with carboxylic groups.
4. Degree of binding is proportional to the charge density on the polymer.

5. Highly binding polymers include carboxyl methyl cellulose, gelatin, hyaluronic acid, carbopol and polycarbophyl.
6. The polymer and its degradation products should be non-toxic and non-absorbable from GIT.
7. Non-irritant to mucous membrane.
8. Preferably form a strong non-covalent bond with the mucin-epithelial cell surfaces.
9. Adheres quickly to moist tissue and should possess some site specificity.
10. Allows easy incorporation of the drug and offer no hindrance to its release.
11. The polymer must not decompose on storage or during the shelf life of the dosage form.
12. The cost of the polymer should not be high so that the prepared dosage form remains competitive.

The properties exhibited by a good mucoadhesive polymer may be summarized as follows:

- a. Strong hydrogen-bonding groups i.e. $[-OH, -COOH]$ etc.
- b. Strong anionic charges
- c. Sufficient flexibility to penetrate the mucus network or tissue crevices
- d. Surface tension characteristics suitable for wetting mucus/ mucosal tissue surface
- e. High molecular weight.

CLASSIFICATION OF MUCOADHESIVE POLYMERS

Mucoadhesive delivery systems are being explored for the localization of the active agents to a particular location/ 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. Some common classes of mucoadhesive polymers are:

Hydrophilic polymers

The polymers within this category are soluble in water. Matrices developed with these polymers swell when put into an aqueous media with subsequent dissolution of the matrix. The polyelectrolytes extend greater mucoadhesive property when compared with neutral polymers [40]. Anionic polyelectrolytes, e.g. poly (acrylic acid) and carboxymethyl cellulose, have been extensively used for designing mucoadhesive delivery systems due to their ability to exhibit strong hydrogen bonding with the mucin present in the mucosal layer [41]. Chitosan provides an excellent example of cationic polyelectrolyte, which has been extensively used for developing mucoadhesive polymer due to its good biocompatibility and biodegradable properties [42]. Chitosan undergoes electrostatic interactions with the negatively charged mucin chains thereby exhibiting mucoadhesive property [40].

The ionic polymers may be used to develop ionic complex with the counter-ionic drug molecules so as to have a drug delivery matrix exhibiting mucoadhesive property. Mucoadhesive microcapsules can be designed by using orifice-ionic gelation method. This technique has been used to design a delivery system of gliclazide, an anti-diabetic drug, using sodium alginate, sodium carboxymethyl cellulose, carbopol 934P and hydroxy propylmethyl cellulose. The delivery system showed the release of gliclazide for an extended period of time due to its mucoadhesive properties [43]. Non-ionic polymers, e.g. poloxamer, hydroxypropyl methyl cellulose, methyl cellulose, poly (vinyl alcohol) and poly (vinyl pyrrolidone), have also been used for mucoadhesive properties. The hydrophilic polymers form viscous solutions when dissolved in water and hence may also be used as viscosity modifying/enhancing agents in the development of liquid ocular delivery systems so as to increase the bioavailability of the active agents by reducing the drainage of the administered formulations. These polymers may be directly compressed in the presence of drugs so as to

have a mucoadhesive delivery system. Numerous polysaccharides and its derivatives like chitosan, methyl cellulose, hyaluronic acid, hydroxypropyl methylcellulose, hydroxypropyl cellulose, xanthan gum, gellan gum, guar gum, and carrageenan have found applications in ocular mucoadhesive delivery systems [40].

Hydrogels

Hydrogels can be defined as three-dimensionally crosslinked 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 groups. In general, with the increase in the crosslinking density there is an associated decrease in the mucoadhesion. Thielmann et al. reported the thermal crosslinking of poly (acrylic acid) and methyl cellulose. They reported that with the increase in the crosslinking density, there was a reduction in the solubility parameters and swelling which resulted in a reduction of mucoadhesion. Hydrogels prepared by the condensation reaction of poly (acrylic acid) and sucrose indicated an increase in the mucoadhesive property with the increase in the crosslinking density and was attributed to increase in the poly (acrylic acid) chain density per unit area. [44]. Acrylates have been used to develop mucoadhesive delivery systems which have the ability to deliver peptide bioactive agents to the upper small intestine region without any change in the bioactivity of the peptides [45]. In addition to the drug targeting, mucoadhesive hydrogel based formulations for improving the bioavailability of the poorly water soluble drug.

Thiolated polymers

These are the special class of multifunctional polymers called thiomers which are modified existing polymers by the addition of thiol group. These are hydrophilic macromolecules exhibiting free thiol groups on the polymeric backbone. Thiomers are capable of forming intra-and interchain disulphide bonds within the polymeric network leading to strongly improved cohesive properties and stability of drug delivery systems such as matrix tablets. Due to the formation of strong covalent bonds with mucus glycoproteins, thiomers show the strongest mucoadhesive properties of all so far tested polymeric excipients via thioldisulphide exchange reaction and an oxidation process [9].

The presence of free thiol groups in the polymeric skeleton helps in the formation of disulphide bonds with that of the cysteine-rich sub-domains present in mucin which can substantially improve the mucoadhesive properties of the polymers [46]. Few examples are chitosan–iminethiolane, poly(acrylicacid)–cysteine, poly(acrylicacid)–homocysteine, chitosan–thioglycolicacid, chitosan–thioethylamidine, alginate–cysteine, poly(methacrylic acid)–cysteine and sodium carboxymethylcellulose–cysteine.

Lecithin based polymers

Lectins are naturally occurring proteins that play a fundamental role in biological recognition phenomena involving cells and proteins. Lectins belong to a group of structurally diverse proteins and glycoproteins that can bind reversibly to specific carbohydrate residues. After initial mucosal cell-binding, lectins can either remain on the cell surface or in the case of receptor-mediated adhesion possibly become internalized via a process of endocytosis. Such systems could offer duality of function in that lectin based platforms could not only allow targeted specific attachment but additionally offer a method of controlled drug delivery of macromolecular pharmaceuticals via active cell-mediated drug uptake [9]. The specific affinity of lectins towards sugar or carbohydrate residues provides them with specific cyto-

adhesive property and is being explored to develop targeted delivery systems. Lectins extracted from legumes have been widely explored for targeted delivery systems [47].

CONCLUSION

The mucoadhesive dosage forms offer prolonged contact at the site of administration, and better patient compliance. The formulation of mucoadhesive drug delivery system is highly dependable upon the selection of suitable polymer with excellent mucosal adhesive properties and biocompatibility. Now researchers are looking beyond traditional polymers, in particular next-generation or the 'intelligent' mucoadhesive polymers which offer greater attachment and retention of dosage forms at the desired site. With the advent of newer mucoadhesive polymers, the mucoadhesive systems would play great role in the development of new pharmaceuticals and clinically for the treatment of both topical and systemic diseases.

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