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Mucoadhesive Polymers: Means of Improving the Mucoadhesive Properties of Drug Delivery System

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ABSTRACT

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly & then maintain the desired drug concentration. That is why the drug delivery system should deliver dr ug at a state dictated by the needs of the body over a specified period of treatment. This idealized objective points to the two aspects most important to drug delivery, namely, spatial placement relates to targeting a drug to a specific organ or tissue while temporal delivery refers to the control of rate of drug delivery to the target tissue. Bioadhesion can be defined as the process by which a natural or a synthetic polymer can adhere to a biological substrate. When the biological substrate is a mucosal layer then the phenomena is known as mucoadhesion. The substrate possessing bioadhesive property can help in devising a delivery system capable of delivering a bioactive agent for a prolonged period of time at a specific delivery site. The current review provides a good insight on mucoadhesive polymers, the phenomenon of mucoadhesion and the factors which have the ability to affect the mucoadhesive properties of a polymer.

Keywords: Mucosa, mucoadhesion, mucoadhesive polymers, drug delivery.

INTRODUCTION

The pharmaceutical research is being steadily shifted from the development of new chemical entitles to the development of Novel Drug Delivery System (NDDS) of existing drug molecule to maximize their effectiveness in terms of therapeutic action and patient protection. Extensive

efforts have recently been focused on targeting a drug or drug delivery system in a particular region of the body for extended periods of time, not only for local targeting of drugs but also for better control of systemic drug delivery. There are various routes of drug administration like oral, parenterals, transdermal, nasal, rectal, intravaginal, ocular etc. Amongst these various routes of drug administration, oral route is the most preferred for its ease in administration and patient compliance.

Mucoadhesive polymers have recently gained interest among pharmaceutical scientists as a means of improving drug delivery by promoting dosage from residence time and contact time with the mucous membranes. The present review describes mucoadhesion, mucoadhesive polymers and use of these polymers in designing different types of mucoadhesive gastrointestinal, nasal, ocular, vaginal and rectal drug delivery systems. This also focuses on mucoadhesive drug delivery systems available in the market **[1].**

In the early 1980s, the concept of mucosal adhesives, or mucoadhesives, was introduced into the controlled drug delivery area. Mucoadhesives are synthetic or natural polymers that interact with the mucus layer covering the mucosal epithelial surface and main molecules constituting a major part of mucus. The concept of mucoadhesives has alerted many investigators to the possibility that these polymers can be used to overcome physiological barriers in long-term drug delivery. Extensive research efforts throughout the world have resulted in significant advances in understanding the various aspects of mucoadhesion. The research on mucoadhesives, however, is still in its early stage, and further advances need to be made for the successful translation of the concept into practical application in controlled drug delivery **[2].**

Mucoadhesion

Good defined mucoadhesion as the state in which two materials, at least one biological in nature, are held together for an extended period of time by interfacial forces **[3].** It is also defined as the ability of a material (synthetic or biological) to adhere to a biological tissue for an extended period of time [**4, 5]**. In case of mucoadhesion, the biological tissue is the mucous membrane. For mucoadhesion to occur, a succession of phenomena is required. The first stage involves an intimate contact between a mucoadhesive polymer and a membrane, either from good wetting of the mucoadhesive surface or from the swelling of the mucoadhesive. In the second stage, after contact is established, penetration of the mucoadhesive into the crevice of the tissue surface or interpenetration of the chains of the mucoadhesive with those of the mucus takes place. Low chemical bonds can then settle [**6]**.Mucoadhesive polymers Mucoadhesive polymers are water-soluble and water insoluble polymers, which are swellable networks, jointed by cross-linking agents. These polymers possess optimal polarity to make sure that they permit sufficient wetting by the mucus and optimal fluidity that permits the mutual adsorption and interpenetration of polymer and mucus to take place. Mucoadhesive polymers that adhere to the musin epithelial surface can be conveniently divided into three broad classes:

1. Polymers that become sticky when placed in water and owe their mucoadhesion to stickiness.
2. Polymers that adhere through nonspecific, non covalent interactions that is primarily electrostatic in nature (although hydrogen and hydrophobic bonding may be significant).
3. Polymers that bind to specific receptor site on tile self surface. All three polymer types can be used for drug delivery [**7]**.

An ideal mucoadhesive polymer has the following characteristics [**8, 9]**.

1. The polymer and its degradation products should be nontoxic and should be non-absorbable from the gastrointestinal tract.
2. It should be nonirritant to the mucous membrane.
3. It should preferably form a strong non-covalent bond with the mucin-epithelial cell surfaces.
4. It should adhere quickly to most tissue and should possess some site-specificity.
5. It should allow daily incorporation to the drug and offer no hindrance to its release.
6. The polymer must not decompose on storage or during the shelf life of the dosage form.
7. The cost of polymer should not be high so that the prepared dosage form remains competitive.

Molecular Characteristics

Investigations into polymers with various molecular characteristics conducted by many authors [**10, 11]** have led to a nurnber of conclusions regarding the molecular characteristics required for mucoadhesion.

The properties exhibited by a good mucoadhesive may be summarized as follows [**3]**:

1. Strong hydrogen bonding groups (-OH, -COOH).
2. Strong anionic charges.
3. Sufficient flexibility to penetrate the mucus network or tissue crevices.
4. Surface tension characteristics suitable for wetting mucus/ mucosal tissue surface.
5. High molecular weight.

Although an anionic nature is preferable for a good mucoadhesive, a range of nonionic molecules (e.g., cellulose derivatives) and some cationic (e.g., Chitosan) can be successfully used.

Factors Important To Mucoadhesion

The bioadhesive power of a polymer or of a series of polymers is affected by the nature of the polymer and also by the nature of the surrounding media.

1. Polymer-Related Factors

(a) Molecular Weight:

The optimum molecular weight for maximum bioadhesion depends on the type of bioadhesive polymer at issue. It is generally understood that the threshold required for successful bioadhesion is at least 100,000 molecular weight. For example, polyethylene glycol (PEG), with a molecular weight of 20,000, has little adhesive character, whereas PEG with 200,000 molecular weight has improved, and a PEG with 400,000 has superior adhesive properties. The fact that bioadhesiveness improves with increasing molecular weight for linear polymers imply two things:

- Interpretation is more critical for lower molecular weight polymers to be a good bioadhesive,
- Entanglement is important for higher molecular weight polymers.

Adhesiveness of a nonlinear structure follows a quite different trend. The adhesive strength 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. The reason for this similarity may be that the helical conformation of dextran may shield many of the adhesive groups, which are primarily responsible for adhesion, unlike the conformation of PEG.

(b) Concentration of active polymers:
There is an optimum concentration of a bioadhesive polymer to produce maximum bioadhesion. In highly concentrated systems, beyond the optimum level, however, the adhesive strength drops significantly because the coiled molecules become separated from the medium so that the chains available for interpenetration become limited.

(c) Flexibility of polymer chains:
It is critical for interpenetration and entanglement. As water-soluble polymers become cross-linked, mobility of individual polymer chains decrease and thus the effective length of the chain that can penetrate into the mucus layer decreases, which reduces bioadhesive strength.

(d) Spatial conformation:
Besides molecular weight or chain length, spatial conformation of a molecule is also important. Despite a high molecular weight of 19,500,000 for dextrans, they have similar adhesive strength to the polyethylene glycol 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.

2. Environment Related Factors
(a) Applied strength:
To place a solid bioadhesive system, it is necessary to apply a defined strength. Whatever the polymer, poly(acrylic acid / vinyl benzene poly (HEMA) or carbopol 934, the adhesion strength increases with the applied strength or with the duration of its application, upto an optimum (dchene et al., 1988).the pressure initially applied to the mucoadhesive tissue contact site can affect the depth of interpenetration. If high pressure is applied for a sufficiently long period of time, polymers become mucoadhesive even though they do not have attractive interaction with mucin.

(b) pH:
It 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. pH of the medium is important for the degree of hydration of cross-linked polyacrylic acid, showing consistently increased hydration from pH 4 to 7 and then a decrease as alkalinity and ionic strength increases.

(c) 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.

(d) Swelling:
It depends on the polymer concentration, ionic concentration, as well as the presence of water. Over hydration results in the formation of a slippery mucilage without adhesion.

3. Physiological Variables
a) Mucin Turnover:
The natural turnover of mucin molecules is important for at least two reasons. First, the mucin turnover is expected to limit the residence time of the mucoadhesive on the mucus layer. No matter, how high the adhesive strength, mucoadhesive are detached from the surface due to mucin turn over. Second, mucin turnover results in substantial amounts of soluble mucin molecules. These molecules interact with the mucoadhesive before they have a chance to interact with the mucus layer. Mucin turnover may depend on other factors such as presence of food.

b) Disease States: The physiochemical properties of mucus are known to Change during disease conditions such as common cold, gastric ulcers, and ulcerative colitis, and cystic fibrosis, bacterial and fungal infections of the female reproductive tract.

Classification of Polymers
A short list of mucoadhesive polymers is given below
1. Synthetic polymers:
(a)Cellulose derivatives (methylcellulose, ethylcellulose, hydroxy-ethylcellulose, Hydroxyl propyl cellulose, hydroxy propyl methylcellulose, sodium carboxy methylcellulose, Poly (acrylic acid) polymers (carbomers, polycarbophil), Poly (hydroxyethyl methylacrylate), Poly (ethylene oxide), Poly (vinyl pyrrolidone), Poly (vinyl alcohol), Natural polymers, Tragacanth, Sodium alginate, Karaya gum, Guar gum, Xanthan gum, Lectin, Soluble starch,Gelatin, Pectin, Chitosan.

Table1: Mucoadhesive Polymers and their Bioadhesive Property

Polymer	Bioadhesive Property
CMC Sodium	+ + +
Carbopol 934	+ + +
Polycarbophil	+ + +
Tragacanth	+ + +
Poly(acrylic acid/divinyl benzene)	+ + +
Sodium Alginate	+ + +
Hydroxy Ethyl Cellulose	+ + +
HPMC	+ + +
Gum Karaya	+ +
Gelatin	+ +
Guar Gum	+ +
Thermally Modified Starch	+
Pectin	+
PVP	+
Acacia	+
Psyllium	+
Amberlite-200 resin	+
Hydroxy Propyl Cellulose	+
Chitosan	+

+ + + = Excellent, + + = Fair, + = Poor

2. Hydrophilic Polymers:
These are the water-soluble polymers that swell indefinitely in contact with water and eventually undergo complete dissolution, e.g. Methyl Cellulose, Hydroxyl Ethyl Cellulose, Hydroxyl Propyl Methyl Cellulose, Sodium Carboxy Methyl Cellulose, Carbomers, Chitosan and Plant gums.

3. Hydrogels:
These are water swellable materials, usually a cross-link polymer with limited swelling capacity, e.g. poly (acrylic acid co acrylamide) copolymers, carrageenan, sodium alginate, guar gum and modified guar gum, etc.

4. Thermoplastic Polymers:
These polymers include the non-erodible neutral polystyrene and semi-crystalline bio-erodible polymers, which generate the carboxylic acid groups as they degrade, e.g. polyanhydrides and polylactic acid. Various synthetic polymers used in mucoadhesive formulations include polyvinyl alcohol, polyamides, polycarbonates, polyalkylene glycols, polyvinyl ethers, esters and halides, polymethacrylic acid, polymethylmethacrylic acid, Methyl Cellulose, Hydroxyl Propyl Cellulose, Hydroxyl Propyl Methyl Cellulose, and Sodium Carboxy Methyl Cellulose.

Various biocompatible polymers used in mucoadhesive formulations include cellulose-based polymers, ethylene glycol polymers and its copolymers, oxyethylene polymers, polyvinyl alcohol, polyvinyl acetate and esters of hyaluronic acid.

Various biodegradable polymers used in mucoadhesive formulations are poly (lactides), poly (glycolides), poly (lactide-co-glycolides), polycaprolactones, and polyalkyl cyanoacrylates. Polyorthoesters, polyphosphoesters, polyanhydrides, polyphosphazenes are the recent additions to the polymers.

Mucoadhesive Dosage Forms
The primary objectives of mucoadhesive dosage forms are to provide intimate contact of the dosage form with the absorbing surface and to increase the residence time of the dosage form at the absorbing surface to prolong drug action. Due to mucoadhesion, certain water-soluble polymers become adhesive on hydration **[4]** and hence can be used for targeting a drug to a particular region of the body for extended periods of time .The mucosa lines a number of regions of the body including the gastrointestinal tract, the urogenital tract, the airways, the ear, nose, and eye. These represent potential sites for attachment of any mucoadhesive system and hence, the mucoadhesive drug delivery system may include the following [**12]**.

1. Gastrointestinal delivery system.
2. Nasal delivery system.
3. Ocular delivery system.
4. Buccal delivery system.
5. Vaginal delivery System.
6. Rectal delivery system.

1. **Gastrointestinal drug delivery system**:
The idea of mucoadhesives began with the clear need to localize a drug at certain sites in the GI tract. Therefore, a primary objective of using mucoadhesive systems orally would be achieved by obtaining a substantial increase in residence time of the drug for local drug effect and to permit once-daily dosing. A number of mucoadhesive-based dosage forms, including sustained release tablets, semisolid forms, powders, and micro- and/or nanoparticles in the GI tract, have been widely studied. Nonetheless, successful systems that will be retained in the GI tract of humans for a desirable time have not yet been developed [**13,14]**. Matharu and Sanghavi [**15]**, used carbopol 934P and poly (acrylic acid) cross-linked with 0.001% ethlene glycol to prepare mucoadhesive tablets for captopril. Decrosta et al. [1**6]**, also used carbopol 934^{P} as mucoadhesive substance to prepare captopril sustained-release tablets. Captopril mixed with carbopol 934P and stearic acid (as lubricant), tableted, and could sustain the release of the drug for up to 16 h or more.

2. **Nasal drug delivery system:**
Histologically, the nasal mucosa provides a potentially good route for systemic drug delivery. With a surface area of 150 cm^2, a highly dense vascular network, and a relatively permeable membrane structure, the nasal route has good absorption potential. One of the most important features of the nasal route is that it avoids first-pass hepatic metabolism, thereby reducing metabolism. The use of dry powder formulations containing mucoadhesive polymers for nasal administration of peptides and proteins was first investigated by Nagai et al**. [16]** Mucoadhesive microspheres are another way of prolonging the residence time in the nasal cavity. Illum et al [**18]** reported that small volumes of liquid and powder particles have almost the same clearance rate. The addition of mucoadhesive excipient such as chitosan results in a decreased clearance rate. Morimoto et al. [**19]** developed a mucoadhesive system for nasal administration of nifedipine. Using a mixture of drug, PEG 400, and carbopol 931, they obtained a relatively high and sustained drug plasma concentration.

3. **Ocular drug delivery system**:
Mucin is secreted by conjunctival globlet cells, but there are no globlet cells on the cornea. On this basis, a mucoadhesive polymer will firmly attach to conjunctival mucus but only loosely, if at all, to corneal mucus [**20]** .Opthalmic dosage forms can be improved by increasing the time the active ingredients remain in contact with eye tissues. There are several mucoadhesive dosage forms that have been developed to this end: liquid systems, in situ gelling systems, dispersed, systems and solid systems [**21, 22]**.

4. **Buccal drug delivery system**:
Because of the presence a smooth and relatively immobile surface for placement of a mucoadhesive dosage form, the buccal region appears to be more suitable for sustained delivery of therapeutic agents using mucoadhesive systems. The buccal and sublingual routes avoid first-pass metabolism. These regions consist of a nonkeratinized epithelium, resulting in a somewhat more permeable tissue than the skin. Therefore, drugs with a short biological half-life requiring a sustained release effect and exhibiting poor permeability, sensitivity to enzymatic degradation, or poor solubility may be good candidates to be delivered via the oral cavity. Relevant mucoadhesive dosage forms for the oral cavity include gels, patches, tablets, and ointments [**23, 24]**, Nagai et al. [**25]** Formulated a highly viscous gel containing carbopol and hydroxypropyl

cellulose for ointment dosage forms that were maintained on the tissue for up to 8 h. Robinson et al. [**26]** showed that a three-layer buccal patch, composed of an impermeable backing membrane, a rate-limiting middle membrane, and a basement membrane containing polycarbophil, can remain in place for up to 15 h in humans, regardless of eating or drinking.

5. **Vaginal drug delivery system:**

Recently, vaginal mucoadhesive preparations have been developed as a new type of controlled release form for the treatment of both topical and systemic diseases. For drugs that are susceptible to gut or hepatic metabolism or which cause GI side effects, vaginal delivery may offer a number of advantages over the other routes of administration. The greatest advantage of such dosage forms is the possibility of maintaining them in the vagina for extended periods of time including daytime and nighttime, thereby enabling lower dosing frequencies. The vagina is a fibromuscular tube connecting the uterus to the exterior of the body. The surface area of the vagina is increased by numerous folds in the epithelium and by microridges covering the epithelial cell surface[**26]** .Among the polymers, polyacrylic acid and hydroxypropyl methyl cellulose are the ideal excipient in mucoadhesive strength. In general, traditional vaginal dosage forms include solutions, suspensions, gels, microparticles, suppositories, creams, foams, and tablets [**26-32]** and all have a relatively short contact time. Robinson et al. reported on a system of treatment using a gel containing the mucoadhesive polycarbophil that remained on vaginal tissue for 3-4 days and hence served as a platform for delivery of drug such as progesterone.

6. Rectal drug delivery system:

Another way to deliver the drug by using mucoadhesive polymers is through the mucous membrane of the rectum. Hydrogels administered rectally have proven to be useful for drug delivery. Leede et al. [**33]** proposed that hydrogels using hydroxy ethyl methacrylate cross-linked with ethylene glycol dimethacrylate and including antipyrine and theophyiline as model drugs provided rate-controlled drug delivery.

Factor Affecting Mucoadhesion

Based on the theories of the adhesion, it can be summarized that the mucoadhesive property of a polymer can be tailored by changing the parameters which has the capacity to alter the interaction among the polymer and the mucosal layer. In this section, attempts will be made to analyze some of the parameters which can tailor the mucoadhesive property of a given polymer. Polymers usually diffuse into the mucosal layer and thereafter adhere to the layer by forming intermolecular entanglements. With the increase in the molecular weight (MW) of the polymer chain there is an increase in the mucoadhesiveness of a polymer. In general, polymers having MW = 100, 000 have been found to have adequate mucoadhesive property for biomedical applications. A typical example is polyethylene glycol (PEG). PEG of 20,000 MW shows negligible mucoadhesive property while PEG of 200,000 MW exhibits improved mucoadhesiveness and the PEG of 400,000 MW has got excellent mucoadhesiveness [**34]**.

Similarly, polyoxyethylene of 7,000,000 MW has exhibited excellent mucoadhesive property and could be tried for the development of buccal delivery systems [**35]**. Dextrans of 19,500,000 and 200,000 MW, poly (acrylic) acid of ~750,000 MW and polyethylene oxide of 4,000,000 MW also exhibit good bioadhesive property [**36].** Polymer chain length plays an important role in bioadhesiveness. With the increase in the chain length of the polymers there is an increase in

the mucoadhesive property of the polymer. Flexible polymer chains helps in the better penetration and entanglement of the polymer chains with that of mucosal layer thereby improving the bioadhesive property. The flexibility of the polymer chains is generally affected by the crosslinking reactions and the hydration of the polymer network. Higher the crosslinking density, lower is the flexibility of the polymer chains. Keeping this in mind, teethering of long flexible chains onto the polymer matrices, with high crosslinking density, appears to be an excellent idea to improve the bioadhesive property. In a recent study, this phenomenon was utilized to device tethered poly (ethylene glycol)–poly (acrylic acid) hydrogels with improved mucoadhesive properties [**37-38]**.

In addition to the reduced flexibility of the polymer chains, crosslinking results in the reduced diffusion of water into the crosslinked polymer matrix. But sufficient hydration of the polymer network is necessary for the complete opening of the inter polymeric pores within the polymer matrix in addition to the mobilization of the polymer chains [**33]**. Hence highly crosslinked polymeric matrix limits the interpenetration of polymer and mucin chains amongst themselves which in turn results in the decrease in the mucoadhesive strength [**27].** Apart from the MW and chain length of the polymer chains, spatial arrangement of the polymer chains may also play an important role. As mentioned above, dextrans of 19,500,000 and 200,000 MW exhibit good mucoadhesive properties. The efficiency of both the dextrans and PEG (MW: 200,000) have been found to possess similar bioadhesive strength [**36- 39- 40]**. Formation of hydrogen-bonds amongst the functional groups of the polymers and mucosal layer also plays an important role. In general, stronger the hydrogen bonding stronger is the adhesion. The functional groups responsible for such kind of interaction include hydroxyl, carboxyl and amino groups. Various polymers which have the ability to form strong hydrogen bonds include poly (vinyl alcohol), acrylic derivates, celluloses and starch [**40]**. Apart from the hydrogen bond formation, the presence of functional groups within the polymer structure may render the polymer chains as polyelectrolytes. The presence of charged functional groups in the polymer chain has a marked effect on the strength of the bioadhesion and can be demonstrated by cell-culture-fluorescent probe technique [**41, 42]**. Anionic polyelectrolytes have been found to form stronger adhesion when compared with neutral polymers [**43, 44]**.

In addition to the above facts, the concentration of the polymer also plays a significant role in the process of mucoadhesion. At lower concentrations of the polymer chains, there is an inadequate and unstable interaction amongst the polymer and the mucosal layer resulting in poor mucoadhesive properties. In general, polymer concentration in the range of 1-2.5 wt % may exhibit sufficient mucoadhesive property for biomedical applications. However for certain polymers, like poly (vinyl pyrrolidone) and poly (vinyl alcohol), solvent diffusion into the polymer network decreases at very high polymer concentration due to the formation of the highly coiled structure thereby limiting interpenetration of the polymer and mucin chains with the subsequent reduction in the mucoadhesive property [**45]**.

Apart from the above-mentioned physico-chemical properties of the polymeric network, various environmental factors also play an important role in mucoadhesion. As mentioned previously, mucoadhesive property is dependent on the presence of functional groups which can ionize so as to give a charge distribution on the polymer chains. The ionization of the functional group is dependent on the pH of the external medium. Hence change in the pH of the external

environment may play an important role in tailoring mucoadhesive property. As for example, chitosan (cationic polyelectrolyte) exhibit excellent mucoadhesive property in neutral or alkaline medium [**46]**. The contact time amongst the polymer matrix and the mucosal layer can also govern the mucoadhesive property. With the initial increase in the contact time there is an increase in the hydration of the polymer matrix and subsequent interpenetration of the polymer chains. The physiology of the mucosal layer may vary depending on the patho-physiological nature of the human body. The physiological factors which play an important role in governing the mucoadhesive property of a polymer matrix include texture and thickness of mucosa [**40]**.

Theories of Mucoadhesion

The phenomena of bioadhesion occur by a complex mechanism. Till date, six theories have been proposed which can improve our understanding for the phenomena of adhesion and can also be extended to explain the mechanism of bioadhesion. The theories include: (a) the electronic theory, (b) the wetting theory, (c) the adsorption theory, (d) the diffusion theory, (e) the mechanical theory and (f) the cohesive theory. The electronic theory proposes transfer of electrons amongst the surfaces resulting in the formation of an electrical double layer thereby giving rise to attractive forces. 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 such substrate surfaces are brought in contact with each other in the presence of the liquid, the liquid may act as an adhesive amongst the substrate surfaces. The adsorption theory proposes the presence of intermolecular forces, viz. hydrogen bonding and Van der Waal's forces, for the adhesive interaction amongst the substrate surfaces. The diffusion theory assumes the diffusion of the polymer chains, present on the substrate surfaces, across the adhesive interface thereby forming a networked structure. The mechanical theory explains the diffusion of the liquid adhesives into the micro-cracks and irregularities present on the substrate surface thereby forming an interlocked structure which gives rise to adhesion. The cohesive theory proposes that the phenomena of bioadhesion are mainly due to the intermolecular interactions amongst like-molecules [**27, 47]**.

Based on the above theories, the process of bioadhesion can be broadly classified into two categories, namely chemical (electronic and adsorption theories) and physical (wetting, diffusion and cohesive theory) methods **[48, 49]**. The process of adhesion may be divided into two stages. During the first stage (also known as contact stage), wetting of mucoadhesive polymer and mucous membrane occurs followed by the consolidation stage, where the physico-chemical interactions prevail [**50-51].**

As mentioned above, bioadhesion may take place either by physical or by chemical interactions. These interactions can be further classified as hydrogen bonds, Van der Waals force and hydrophobic bonds which are considered as physical interactions while the formation of ionic and covalent bonds are categorized as chemical interactions. Hydrogen bonds are formed due to the interaction of the electronegative and electropositive atoms though there is no actual transfer of electrons. Example of this kind of interaction includes formation of gelled structure when aqueous solutions of polyvinyl alcohol and glycine are mixed. Van der Waals forces are either due to presence of the dipole-dipole interactions in polar molecules or due to the dispersion forces amongst non-polar substrates. Hydrophobic bonds are formed due to the interaction of the non-polar groups when the polymers are dispersed in an aqueous solution. Freeze-thawing of

polyvinyl alcohol solution in water exhibits this kind of interaction. Ionic bonds are formed due to the electrostatic interactions amongst the polymers (e.g. instantaneous formation of gelled structure when alginate and chitosan solutions in water are mixed) while covalent bonds are formed due to the sharing of electrons amongst the atoms (e.g. crosslinking reaction amongst genipin and amino groups).

The term "mucoadhesion" was coined for the adhesion of the polymers with the surface of the mucosal layer [**52]**. The mucosal layer is made up of mucus which is secreted by the goblet cells (glandular columnar epithelial cells) and is a visco-elastic fluid. It lines the visceral organs, which are exposed to the external environment. The main components constituting the mucosa include water and mucin (an anionic polyelectrolyte), while the other components include proteins, lipids and mucopolysaccharides. Water and mucin constitute > 99% of the total composition of the mucus and out of this > 95% is water. The gel-like structure of the mucus can be attributed to the intermolecular entanglements of the mucin glycoproteins along with the non-covalent interactions (e.g. hydrogen, electrostatic and hydrophobic bonds) which results in the formation of a hydrated gel-like structure and explains the viscoelastic nature of the mucus [**36]**.

Sites for Mucoadhesive Drug Delivery Systems

The common sites of application where mucoadhesive polymers have the ability to delivery pharmacologically active agents include oral cavity, eye conjunctiva, vagina, nasal cavity and gastrointestinal tract. The current section of the review will give an overview of the above-mentioned delivery sites.

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 **[53].** The various mucoadhesive polymers used for the development of buccal delivery systems include cyanoacrylates, polyacrylic acid, sodium carboxymethylcellulose, hyaluronic acid, hydroxypropylcellulose, polycarbophil, chitosan and gellan [**36, 54]**. The delivery systems are generally coated with a drug and water impermeable film so as to prevent the washing of the active agent by the saliva [**36]**.

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 150-200 cm2. 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 mucocilliary layer in the presence of foreign particulate matter. The polymers used in the development of formulations for the development of nasal delivery system include copolymer of methyl vinyl ether, hydroxypropyl methylcellulose, sodium carboxymethylcellulose, carbopol-934P and Eudragit RL-100 [**55, 56]**.

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 **[36].** The mucoadhesive polymers used for the ocular delivery include thiolated poly (acrylic acid), poloxamer, celluloseacetophthalate, methyl cellulose, hydroxy ethyl cellulose, poly (amidoamine) dendrimers, poly (dimethyl siloxane) and poly (vinyl pyrrolidone) [**57,58]**.

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. The use of mucoadhesive polymers for the development of delivery system helps in reducing the migration of the same thereby promoting better therapeutic efficacy. The polymers used in the development of vaginal and rectal delivery systems include mucin, gelatin, polycarbophil and poloxamer [**53, 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 around the world **[35]** . The various mucoadhesive polymers which have been used for the development of oral delivery systems include chitosan, poly (acrylic acid), alginate, poly (methacrylic acid) and sodium carboxymethyl cellulose [**59]**.

Evaluation of mucoadhesive properties

Various in vivo and in vitro methods are used for testing the efficacy of the mucoadhesive nature of a polymer matrix. Commonly used in vitro/ ex vivo methods include tensile strength measurement, shear strength measurement and chip based systems whereas various imaging techniques are used for the evaluation of the delivery systems under in vivo conditions. This section will describe various methods used to study the mucoadhesive properties.

In vitro tensile strength measurement is done by dipping a filter paper in 8% mucin dispersion. There after, the mucin coated filter paper is placed in contact with the hydrated polymeric samples (in physiological solutions) for a definite period of time, followed by the determination of the maximum force required to detach the filter-paper and polymer surfaces after the mucoadhesive bonding [**60]**. Similarly, ex vivo experimentations are also done with the exception that the mucin coated filter-paper is replaced with excised mucosal tissues (e.g. buccal mucosa, intestinal mucosa, vaginal mucosa [**61, 62]**. The mucoadhesive properties can also be determined by incubating the hydrated polymer matrix surface kept in contact with a viscoelastic 30 % (w/w) mucin solution in water with the subsequent determination of the maximum detachment force required to separate the polymer matrix and mucin solution surfaces after the adhesion [**63]**.

Wash-off test may also be used to determine the mucoadhesive property of delivery systems. In the test, the mucosal tissue is attached onto a glass slide with the help of a double-sided cyanoacrylate tape. Thereafter, the delivery system is put on the surface of the tissue (exposed

mucosal surface) with the subsequent vertical attachment of the system into the USP tablet disintegrator apparatus, which contains 1 L of physiological solution maintained at 37^{o}C. The operation of the equipment gives an up-and-down movement to the tissue-delivery matrix system. In this study, the time for the complete detachment of the delivery system from the mucosal layer is determined [**1]**.

For the relative measurement of mucoadhesive nature of powder polymer samples modified Du Noiy's tensiometer may be used, while in the shear strength determination method the force required to slide the polymer matrix over the mucus layer is determined. Recently mucoadhesion studies have been reported by using BIACORE® integrated chip (IC) systems. The method involves immobilization of the polymer (powder) on to the surface of the IC with the subsequent passage of the mucin solution over the same. This results in the interaction of the mucin with that of the polymer surface. The polymer-mucin interaction is measured by an optical phenomenon called Surface Plasmon Resonance (SPR), which measures the change in the refractive index when mucin binds on the polymer surface . The in vivo experiments involve the administration of radioactive labeled delivery system with the subsequent measurement of radioactivity in the tissues, at regular intervals of time, where the delivery system is supposed to adhere. The higher the radioactivity, the higher is the mucoadhesive property of the designed delivery system [**64].**

CONCLUSION

Of late, scientists are trying to improve the bioavailability of active agents by tailoring the properties of the delivery systems instead of designing new active agents. Mucoadhesive polymers may provide an important tool to improve the bioavailability of the active agent by improving the residence time at the delivery site. The various sites where mucoadhesive polymers have played an important role include buccal cavity, nasal cavity, rectal lumen, vaginal lumen and gastrointestinal tract. Development of novel mucoadhesive delivery systems are being undertaken so as to understand the various mechanism of mucoadhesion and improved permeation of active agents. Mucoadhesive dosage forms have a high potential of being useful means of delivering drugs to the body, perhaps particularly for topical or local administration where the mechanical trauma experienced by the dosage form may be minimized.

Current use of mucoadhesive polymers to increase contact time for a wide variety of drugs and routes of administration has shown dramatic improvement in both specific therapies and more general patient compliance. The general properties of these polymers for purpose of sustained release of chemicals are marginal in being able to accommodate a wide range of physicochemical drug properties. Hence mucoadhesive polymers can be used as means of improving drug delivery through different routes like gastrointestinal, nasal, ocular, buccal, vaginal and rectal. Many potential mucoadhesive systems are being investigated which may find their way into the market in near future.

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