Review Article

Review: Polymers Used in the Mucoadhesive 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 drug 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

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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. [2] 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. [3]

This system has advantages like:

- Prolongs the residence time of the dosage form at the site of absorption.
- Due to an increased residence time it enhances absorption and hence the therapeutic efficacy of the drug.
- Excellent accessibility.
- Rapid absorption because of enormous blood supply and good blood flow rates.
- Increase in drug bioavailability due to first pass metabolism avoidance.
- Drug is protected from degradation in the acidic environment in the gastrointestinal tract.
- Improved patient compliance- ease of drug administration.
- Faster onset of action is achieved due to mucosal surface [4]

Need of mucoadhesive delivery:

Oral administration is the major route for drug delivery. Oral controlled release systems are used for controlled action of active ingredients to the targeted site. But oral controlled release systems have many problems such as first pass hepatic metabolism, enzyme degradation, swallowing problem etc. So, as compared to oral controlled release systems, mucoadhesive delivery system have several advantages like prolongation of residence time, drug targeting, intimate contact between dosage form and the absorptive mucosa. In addition, mucoadhesive dosage forms have been used to target local disorders at the mucosal surface to reduce dose and to minimize the side effects. Mucoadhesive formulations use polymers as the adhesive component. These polymers are water soluble. When polymers are used in a dry form, they attract water from themucosal surface and leads to a strong interaction which increases the retention time over the mucosal surfaces. Prolonged contact time of a drug with a body tissue through the use of a bioadhesive polymer can significantly improve the performance of many drugs. [4]

Mechanisms 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 vander Waals and hydrogen bonds.

The mechanism of mucoadhesion is generally divided into two steps

1. Contact stage
2. Consolidation step.

1 Contact stage: It explains the contact between the mucoadhesive polymer and the mucus membrane, with spreading and swelling of the formulation.

2 Consolidation step: It explains the activation and bonding of Mucoadhesive material. 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 vander Waals and hydrogen bonds [5].

Mucoadhesion theories:

Mucoadhesion is a complex process and numerous theories have been proposed to explain the mechanisms involved [6-7].

These theories include.

1. Wetting theory
2. Diffusion theory
3. Mechanical theory
4. The electronic theory
5. The adsorption theory
6. Cohesive theory

1 The wetting theory: It explains the contact angle of liquids on the substrate surface is lower, then there is a greater affinity for the liquid to the substrate surface.

2 The diffusion theory: Due to the presences of polymeric chains on the substrate surfaces, across the adhesive interface thereby forming a networked structure.

3 The mechanical theory: It 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

4 The electronic theory: Due to the transfer of electrons amongst the surfaces resulting in the formation of an electrical double layer, giving rise to attractive forces.

5 The adsorption theory: Due to the presence of intermolecular forces (hydrogen bonding) and Vander Waal' forces, results in adhesive interaction amongst the substrate surfaces.

6 The cohesive theory: The phenomena of bioadhesion are mainly due to the intermolecular interactions amongst like-molecules.

Mucoadhesive polymers:

Mucoadhesive polymers are water-soluble and water insoluble polymers, which are swellable networks, jointed by cross-linking agents by the processes such as wetting, mutual adsorption and interpenetration of polymer and mucus. .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 mucin-epithelial surface can be conveniently divided into three broad classes

1. Polymers that become sticky when placed in water and owe their mucoadhesion to stick
2. Polymers that adhere through nonspecific, non-covalent interactions that are primarily electrostatic in nature (although hydrogen and hydrophobic bonding may be significant).
3. Polymers that bind to specific receptor site on tile self-surface.[8]

An ideal mucoadhesive polymer has the following characteristics: [9, 10]

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

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. [14]

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 [13, 15]. 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 [13]. 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 mucociliary 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, hydroxy-propylmethylcellulose, sodium carboxy-methylcellulose, carbopol- 934P and Eudragit RL-100 [16-17]. 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 [13]. 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) [18-19]. 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 polymers used in the development of vaginal and rectal delivery systems include mucin, gelatin, polycarbophil and poloxamer [20-21]. 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 [22]. 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 [23]

Factors Affecting Mucoadhesion Polymers:

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. Attempts will be made to analyze some of the parameters which can tailor the mucoadhesive property of a given polymer.

1. Polymer related factors -

The adhesive bond between a bioadhesive system and mucin gel can be investigated in term of contribution of the following factors:

Molecular weight- With the increase in the molecular weight (MW) of the polymer chain there is an increase in the mucoadhesiveness of a polymer.

Chain length- With the increase in the chain length of the polymers there is an increase in the mucoadhesive property of the polymer.

Spatial arrangement- spatial conformation of a molecule is also important factor.

Flexibility- 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.

Hydration of polymer- In addition to the reduced flexibility of the polymer chains, crosslinking results in the reduced diffusion of water into the crosslinked polymer matrix. 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.

Hydrogen bonding- 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.

Charge and degree of ionization of polymer- The presence of charged functional groups in the polymer chain has a marked effect on the strength of the bioadhesion. Anionic Polyelectrolytes have been found to form stronger adhesion when compared with neutral polymers.

Polymer concentration- In general, polymer concentration in the range of 1-2.5 wt % may exhibit sufficient mucoadhesive property for biomedical applications.

2. Environmental factors -

Apart from the above-mentioned physico-chemical properties of the polymeric network, various environmental factors also play an important role in mucoadhesion.

pH - Some studies have shown that the pH of the medium is important for the degree of hydration of cross link

Applied strength – The pressure initially applied to the mucoadhesive tissue contact site can affect the depth of interpenetration. If high pressure is applied for a satisfactory longer period of time polymers become mucoadhesive even though they do not have attractive interaction with mucins.

Contact time - 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.

Swelling- Swelling depends both on polymer concentration and on water presence. When swelling is too great, decrease in bioadhesion.

3. Physiological factors- The physiological factors which play an important role in governing the mucoadhesive property of a polymer matrix include texture and thickness of mucosa.

Mucin Turnover- The mucin turnover is expected to limit the residence time of the mucoadhesive on the mucus layer. No matter how high the mucoadhesive strength is.

Disease state - The physicochemical properties of the mucus are known to change during disease conditions such as common cold, gastric ulcers, ulcerative colitis, etc. [24]

Classification of mucoadhesive polymers:

[A] Based on Origin

Synthetic mucoadhesive polymers: Cellulose derivatives, Poly (acrylic acid) polymers, Poly (hydroxyethyl methylacrylate), Poly (ethylene oxide), Poly (vinylpyrrolidone), Poly (vinyl alcohol).

Natural mucoadhesive polymers: Tragacanth, Sodium alginate, Karaya gum, Guar gum,Xanthan gum, Soluble starch, Gelatin, Pectin, Chitosan, etc.

[B] Based on Nature

Hydrophilic polymers*:* The polymers within this category are soluble in water.Matricesdeveloped with these polymers swell when put into anaqueous media with subsequent dissolution of the matrix.

Thepolyelectrolytes: extend greater mucoadhesive property. e.g.poloxamer, hydroxypropyl methyl cellulose, methyl cellulose, poly(vinyl alcohol) and poly (vinyl pyrrolidone), have also been usedfor mucoadhesive properties.

Polysaccharides and its derivatives: Numerous polysaccharides and its derivatives like chitosan,methyl cellulose, hyaluronic acid, hydroxy propylmethylcellulose, hydroxy propyl cellulose, Xanthan gum, gellangum, guar gum, and Carrageenan have found applications in ocularmucoadhesive delivery systems.

Cellulose and its derivates: Cellulose and its derivates have been reported to have surface active property in addition to its filmforming capability. Cellulose derivatives with lower surface actingproperty are generally preferred in ocular delivery systems as theycause reduced eye irritation. Of the various cellulose derivates,sodium carboxymethyl cellulose has been found to have excellentocular mucoadhesive property. Cationic cellulose derivatives (e.g.cationic hydroxyethyl celluloses) have been used in conjunctionwith various anionic polymers for the development of sustainedsystems.

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 functionalgroups like hydroxyl, amino and carboxyl groups. In addition to the drug targeting, mucoadhesive hydrogelbasedformulations for improving the bioavailability of the poorly water soluble drug. This was attributed to the increased retention time of the delivery system within the gastrointestinal tract [14]

Novel mucoadhesive polymers:

In novel mucoadhesive polymer cases, existingmucoadhesive polymers have been modified, while in others, new materials are developed.

Lectins:

Lectins are naturally occurring proteins that play afundamental 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, lectinscan 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 thatlectin 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. This phenomenon has been reported to be advantageous, given that the mucus layer provides an initial yet fully reversible binding site followed by distribution of lectin mediated drug delivery systems to the cell layer. According to the molecular structure, three groups of lectins can be distinguished

1. *Merolectins*: lectins having only one carbohydraterecognising domain;
2. *Hololectins*: lectins with two or more carbohydraterecognising domains;
3. *Chimerolectins*: lectins with additional unrelated domains.

Lectins can increase the adherence of microparticles to the intestinal epithelium and enhance penetration of drugs.

Polystyrene microparticles coated with tomato lectin were shown to be specifically adhesive to enterocytes. The use of lectins for targeting drugs to tumor tissue is currently under intensive investigation as the human carcinoma cell lines exhibit higher lectin binding capacity than the normal human colonocytes. [24]

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. Thiomersare 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.Various thiolated polymers include chitosan–iminothiolane, poly(acrylic acid)–cysteine, poly(acrylic acid)–homocysteine,chitosan–thioglycolic acid, chitosan–thioethylamidine, alginate–cysteine, poly(methacrylic acid)–cysteine and sodium carboxymethylcellulose–cysteine [25]

Bioadhesive nanopolymers as drug carriers:

Nanomedicine is defined as the use of nanometer-scale particles or systems to detect and treat diseases at the molecular level. Mucoadhesive nanopolymers, appear to be an effective solution in the challenge of achieving bioavailability with topical drugs especially in ocular drug delivery system. The justification for the development of particulate systems for the delivery of ophthalmic drugs is based on the potential entrapment of particles in the ocular surface mucus layer and the interaction of bioadhesive

polymer chains with mucin, which thereby increases the precorneal resident time of the particular drug [26]

Alginate-polyethylene glycol acrylate (alginate-PEGAc):

A novel mucoadhesive polymer, alginate-polyethyleneglycol acrylate (alginate-PEGAc) is synthesized, in which and alginate backbone carries acrylated polyethylene glycol. This polymer combines the strength, simplicity and gelation ability of alginate with the mucoadhesion properties arising from the characteristics and acrylate functionality of PEG. The strong bonding to the mucus results from a combination of PEG's ability to interpenetrate the mucus surface and a Michael-type addition reaction between an acrylate end group on a polymer and the sulfide end group of the mucin-type glycoprotein. It has development of many other multifunctional biomaterials for a variety of biotechnological and biomedical applications[27]

Poloxomer:

Poloxomer gels have been investigated as they are reported to show phase transitions from liquids to mucoadhesive gels at body temperature and will therefore allow in-situ gelation at the site of interest.

Pluronics and combination:

Pluronics have also been chemically combined with poly(acrylic acid)s to produce systems with enhanced adhesion and retention in the nasal cavity.Dihydroxyphenylalanine (DOPA), an amino acid found in mussel adhesive protein that is believed to lend to the adhesive process, has also been combined with pluronics to enhance their adhesion.

Other novel mucoadhesive polymers:

The incorporation of ethyl hexyl acrylate into a copolymer with acrylic acid in order to produce a more hydrophobic and plasticized system was considered by

This would reduce hydration rate while allowing optimum interaction with the mucosal surface, and the mucoadhesive force was found to begreater with the copolymer than with poly(acrylic acid) alone. Glyceryl monooleate/water liquid crystalline phases have also been found to be mucoadhesive using a range of mucosal surfaces, although the mechanism will differ somewhat from that of other mucoadhesives [28]

Bacterial adhesions:

Bacteria are able to adhere to epithelial surfaces of the enterocytes with the aid of fimbriae. Fimbriae are long, lectin like proteins found on the surface of many bacterial strains. Their spresence has been correlated with pathogenicity, e.g. adherence of *Escherichia coli* to the brush border of epithelial cells mediated by K99 fimbriae is a prerequisite for subsequent production and cellular uptake of *E. coli* enterotoxin. Thus, the DDS based on bacterial adhesion factors could be an efficient mechanism to increase adhesion of bioadhesive microspheres to epithelial surfaces. Another study envisaging the importance of bacterial adhesions has been carried out using “invasin”, which is a membrane protein from *Yersinia pseudotuberculosis*. Cellular uptake of polymeric nanospheres functionalized with invasion has been observed using confocal laser scanning microscopy.

Amino acid sequences:

Certain amino acid sequences have complementary parts on the cell and mucosal surfaces and when attached to microparticles can promote binding to specific cell surfaceglycoproteins. The cell surface glycoproteins are altered in the presence of disease conditions and these altered protein sequences can be targeted by the drug delivery device.

Antibodies

Antibodies can be produced against selected molecules present on mucosal surfaces. Due to their high specificity, antibody can be a rational choice as a polymeric ligand for designing site specific mucoadhesives. This approach can be useful for targeting drugs to tumor tissues [24]

Evaluation of mucoasdhesive polymers :

Mucoadhesive polymers can be evaluated by testing their adhesion strength by both in vitro and in vivo tests.

In vitro tests / exvivo the importance is layed on the elucidation of the exact mechanisms of bioadhesion. These methods are,

- methods determining tensile strength
- methods determining shear stress

- adhesion weight method
- fluorescent probe method
- flow channel method
- mechanical spectroscopic method
- falling liquid film method
- colloidal gold staining method
- viscometer method
- thumb method
- adhesion
- electrical conductance
- swelling properties
- in vitro drug release studies
- mucoretentability studies

In vivo methods

- use of radioisotopes
- use of gamma scintigraphy
- use of pharmacoscintigraphy
- use of electron paramagnetic
- resonance(EPR) oximetry
- X ray studies
- Isolated loop technique [4]

CONCLUSION

Mucoadhesive drug delivery systems, are gaining popularity day by day in the global pharma industry and a burning area of further research and development. 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 system (CDDS). There is no doubt that mucoadhesion has moved into a new area with these new specific targeting compounds (lectins, thiomers, etc.) with researchers and drug companies looking further into potential involvement of more smaller complex molecules, proteins and peptides, and DNA for future technological advancement in the ever-evolving drug delivery arena.

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