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## Novel Mucoadhesive Polymers –A Review

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### ABSTRACT

The current article focuses on polymers used in mucosal delivery of therapeutic agents. The mucoadhesive drug delivery system is a popular novel drug delivery method because mucous membranes are relatively permeable, allowing for the rapid uptake of a drug into the systemic circulation and avoiding the first pass metabolism. Mucoadhesive polymers have been utilized in many different dosage forms in efforts to achieve systemic delivery of drugs through the different mucosa. These dosage forms include tablets, patches, tapes, films, semisolids and powders. The objective of this review is to study about novel mucoadhesive polymers and to design improved drug delivery systems.

**Keywords:** Novel drug delivery system; mucoadhesion; mucoadhesive polymers.

### INTRODUCTION

The focus of pharmaceutical research is being steadily shifted from the development of new chemical entities to the development of novel drug delivery system (NDDS) of existing drug molecule to maximize their effective in terms of therapeutic action and patent protection (Berressem, 1999, Das, 2000). The development of NDDS has been made possible by the various compatible polymers to modify the release pattern of drug. In the recent years the interest is growing to develop a drug delivery system with the use of a mucoadhesive polymer that will attach to related tissue or to the surface coating of the tissue for the targeting various absorptive mucosa such as ocular, nasal, pulmonary, buccal, vaginal etc. This system of drug delivery is called as mucoadhesive drug delivery system (Shemalty 2006). 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 (pranshu Tangri).

### MUCOADHESION

In the early 1980s, the concept of mucosal adhesives, or mucoadhesives, was introduced into the controlled drug delivery area. The concept of mucoadhesives has alerted many

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investigators to the possibility that these polymers can be used to overcome physiological barriers in long-term drug delivery (Kumar *et.al.*,2010). Mucoadhesive is defined as the ability of a material (mucoadhesive polymer) to adhere to the mucosal layer. They are held together for an extended period of time by interfacial forces. The mucosal layer is made up of mucus which is secreted by the goblet cells (glandular columnar epithelial cells) and is a viscoelastic fluid. It lines the visceral organs, which are exposed to the external environment (Roy, *et. al.*, 2009).

### 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 (Hogerstrom, *et. al.*,2003).

### MUCOADHESION THEORIES

Mucoadhesion is a complex process and numerous theories have been proposed to explain the mechanisms involved. These theories include.

- ✓ Wetting theory
- ✓ Diffusion theory
- ✓ Fracture theory
- ✓ The electronic theory
- ✓ The adsorption theory (Harsulkar, *et. al.*,2011).

### 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. 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 tile self surface.

All three polymer types can be used for drug delivery.

### Characteristics of an ideal mucoadhesive Polymer

An ideal mucoadhesive polymer has the following characteristic:

1. They 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 (Patil, *et. al.*,2006).

### 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.

#### 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.

### 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.

### 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. (Harsulkar, *et. al.*, 2011).

## CLASSIFICATION OF MUCOADHESIVE POLYMERS

### Based on Origin

#### *Synthetic mucoadhesive polymers:*

Cellulose derivatives, Poly (acrylic acid) polymers, Poly (hydroxyethyl methacrylate), Poly (ethylene oxide), Poly (vinyl pyrrolidone), Poly (vinyl alcohol).

#### *Natural mucoadhesive polymers:*

Tragacanth, Sodium alginate, Karaya gum, Guar gum, Xanthan gum, Soluble starch, Gelatin, Pectin, Chitosan, etc.

### Based on Nature

#### *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. e.g. poloxamer, hydroxypropyl methyl cellulose, methyl cellulose, poly (vinyl alcohol) and poly (vinyl pyrrolidone), have also been used for mucoadhesive properties.

### *Polysaccharides and its derivatives*

Numerous polysaccharides and its derivatives like chitosan, methyl cellulose, hyaluronic acid, hydroxy propyl methylcellulose, hydroxy propyl cellulose, Xanthan gum, gellan gum, guar gum, and Carrageenan have found applications in ocular mucoadhesive delivery systems. Cellulose and its derivatives have been reported to have surface active property in addition to its film forming capability. Cellulose derivatives with lower surface acting property are generally preferred in ocular delivery systems as they cause reduced eye irritation. Of the various cellulose derivatives, sodium carboxymethyl cellulose has been found to have excellent ocular mucoadhesive property. Cationic cellulose derivatives (e.g. cationic hydroxyethyl celluloses) have been used in conjunction with various anionic polymers for the development of sustained delivery systems.

### *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 addition to the drug targeting, mucoadhesive hydrogel based formulations 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 (S. Roy, *et. al.*, 2009).

## NOVEL MUCOADHESIVE POLYMERS

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

### **Lectins**

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. 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. (Harsulkar, *et. al.*,2011).

### 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. 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 (Sreenivas, *et. al.*,2008).

### 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 (Soumendra sahuo, *et al.*, 2011)

### Alginate-polyethylene glycol acrylate (alginate-PEGAc)

A novel mucoadhesive polymer, alginate-polyethylene glycol acrylate (alginate-PEGAc) is synthesized, in which an 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 (Davidovich-pinhas, *et.al.*,2011).

### 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.

### Pluronic and combination

Pluronic 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 pluronic 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 Shojaei et al. This would reduce hydration rate while allowing optimum interaction with the mucosal surface, and the mucoadhesive force was found to be greater 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 (Smart, 2005).

### 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 presence 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 surface glycoproteins. 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 (Harsulkar, *et. al.*, 2011).

## EVALUATION OF MUCOADHESIVE POLYMERS

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

### *In vitro* tests / *ex vivo*

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 number
- 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 (Pranshu Tangri, *et. al.*, 2011).

### Recent mucoadhesion test

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 (Vimal kumar, *et al.*, 2010).

## DEVELOPMENT ISSUES OF BIOADHESIVE DRUG DELIVERY SYSTEMS

- Novel Formulation Approaches to Oral Mucoadhesive Drug Delivery Systems

- Bioadhesive Formulations for Nasal Peptide Delivery
- Development of Bioadhesive Buccal Patches
- Vaginal Delivery of Calcitonin by Hyaluronic Acid Formulations
- Ocular Bioadhesive Drug Delivery Systems
- Bioadhesive Preparations as Topical Dosage Forms

## 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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