Review Article

A REVIEW ON POLYMERS USED IN MUCOADHESIVE DRUG DELIVERY SYSTEM

*,1Muthukumaran M, 2Dhachinamoorthi D, 1Chandra Sekhar K B, 3Sriram N
*,1 Jawaharlal Nehru Technological University Anantapur, Anantapur, A.P, India–515 002.
2 QIS College of Pharmacy, Vengamukkapalem, Ongole, A.P, India–523 272.
3Research Scholar, Acharya Nagarjuna University, Guntur, A.P, India-522 510.

Abstract

Mucoadhesion can be defined as a state in which two components, of which one is of biological origin are held together for extended periods of time by the help of interfacial forces mucoadhesion is the attachment of the drug along with a suitable carrier to the mucous membrane. Mucoadhesion is a complex phenomenon which involves wetting, adsorption and interpenetration of polymer chains the mucoadhesive polymers can be categorized into two broad categories, materials which undergo matrix formation or hydrogel formation by either a water swellable material or a water soluble material. Mucoadhesive drug delivery systems is one of the most important novel drug delivery systems with its various advantages and it has a lot of potential in formulating dosage forms for various chronic diseases. 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: Mucoadhesion, Oral Mucosa, Mucoadhesive Polymers.

Introduction

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.[1-4] Bioadhesive polymeric systems have been used since long time in the development of products for various biomedical applications which include denture adhesives and surgical glue[5-8]. The bioadhesive polymers can be broadly classified into two groups, namely specific and nonspecific[9]. The specific bioadhesive polymers (e.g. lectins, fimbrin) have the ability to adhere to specific chemical structures within the biological molecules while the nonspecific bioadhesive polymers (e.g. polyacrylic acid, cyanoacrylates) have the ability to bind with both the cell surfaces and the mucosal layer.

The use of mucoadhesive polymers for the development of pharmaceutical formulations dates back to 1947, when attempts were made to formulate a penicillin drug delivery system for delivering the bioactive agent to the oral mucosa using gum tragacanth and dental adhesive powders [10]. Improved results were reported when carboxymethyl - cellulose and petrolatum were used for the development of the formulation.

*** *Author for Correspondence:***

Muthukumaran M,
Jawaharlal Nehru Technological University Anantapur,
Anantapur, Andhra Pradesh,
India – 515 002.
Email: muthu_mpharm2006@yahoo.co.in

Subsequent research resulted in the development of a mucoadhesive delivery vehicle which consisted of finely ground sodium carboxymethylcellulose (SCMC), pectin, and gelatin.The formulation was later marketed as Orahesive®. Another formulation which entered into the clinical trials is Orabase®, which is a blend of polymethylene/ mineral oil base. This was followed by the development of a system where polyethylene sheet was laminated with a blend of sodium carboxymethylcellulose and poly (isobutylene) which provided an added advantage of protecting the mucoadhesive layer by the polyethylene backing from the physical interference of the external environment [11-13].

Over the years, various other polymers (e.g. sodium alginate, sodium carboxymethylcellulose, guar gum, hydroxyethylcellulose, karya gum, methylcellulose, polyethylene glycol (PEG), retene and tragacanth) have been found to exhibit mucoadhesive properties. During the period of 1980s poly (acrylic acid), hydroxypropylcellulose, and sodium carboxymethylcellulose were widely explored for the development of formulations having mucoadhesive properties. Since then the use of acrylate polymers for the development of mucoadhesive formulations have increased many-fold, various authors have investigated the mucoadhesive properties of different polymers with varying molecular architecture[14-16]. After a lot of research, the researchers are of the view that a polymer will exhibit sufficient mucoadhesive property if it can form strong intermolecular hydrogen bonding with the mucosal layer, penetration of the polymer into the mucus network or tissue crevices, easy wetting of mucosal layer and high molecular weight of the polymer chain. The ideal characteristics of a mucoadhesive polymer matrix include the rapid adherence to the mucosal layer without any change in the physical

property of the delivery matrix, minimum interference to the release of the active agent, biodegradable without producing any toxic byproducts, inhibit the enzymes present at the delivery site and enhance the penetration of the active agent (if the active agent is meant to be absorbed from the delivery site) [17].

Mechanism of Mucoadhesion

As stated, mucoadhesion is the attachment of the drug along with a suitable carrier to the mucous membrane. Mucoadhesion is a complex phenomenon which involves wetting, adsorption and interpenetration of polymer chains. Mucoadhesion has the following

Mechanism [19]

1. Intimate contact between a bioadhesive and a membrane (wetting or swelling phenomenon)
2. Penetration of the bioadhesive into the tissue or into the surface of the mucous membrane (interpenetration)[20,21]

Residence time for most mucosal routes is less than an hour and typically in minutes, it can be increased by the addition of an adhesive agent in the delivery system which is useful to localize the delivery system and increases the contact time at the site of absorption. [22] The exact mechanism of mucoadhesion is not known but an accepted theory states that a close contact between the mucoadhesive polymer and mucin occurs which is followed by the interpenetration of polymer and mucin. The adhesion is prolonged due to the formation of vandervaals forces, hydrogen bonds and electrostatic bonds. [18]

Theories of Mucoadhesion [19]

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.

The adsorption theory proposes the presence of intermolecular forces, viz. hydrogen bonding and VanderWaal'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 [23-24]

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 [25-26]. 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 [27-28].

The term "mucoadhesion" was coined for the adhesion of the polymers with the surface of the mucosal layer [29]. 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 muco polysaccharides. 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 glycoprotein 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 visco elastic nature of the mucus [24].

Factors affecting Mucoadhesion [30,31]

The mucoadhesion of a drug carrier system to the mucous membrane depends on the below mentioned factors.

- polymer based factors

Molecular weight of the polymer, concentration of polymer used of polymer chains swelling factor stereo chemistry of polymer.

- physical factors

pH at polymer substrate interface applied strength, contact time.

- physiological factors

Mucin turnover rate diseased state.

Polymers Used for Mucoadhesive Drug Delivery [19,30]

The rheology of the mucoadhesion is a typical topic and it deals with a number of forces, factors of the components, state of the material, its derived properties. Based on the rheological aspects, we can categorise the mucoadhesive polymers into two broad categories, materials which undergo matrix formation or hydrogel formation by either a water swellable material or a water soluble material. These carriers generally polymers are classified as,

Hydrophilic polymers contains carboxylic group and possess excellent mucoadhesive properties. These are PVP (poly vinyl pyrrolidine) Mc (methyl cellulose)
Scmc (sodium carboxy metyhyl cellulose) HPC (hydroxyl propyl cellulose)

Hydrogels - These swell when in contact with water and adhere to the mucus membrane. These are further classified according to their charge

Anionic polymers - carbopol, polyacrylates
Cationic polymers - chitosan
Neural/non ionic polymers- eudragit analogues [32-35]

They can also be classified as,[18]
Synthetic polymers
Natural polymers
Synthetic polymers - Cellulose derivatives, Carbopols, etc.
Natural polymers - Tragacanth, Pectin, gelatin, Sodium alginate, acacia.

Ideal Muco Polymer Characteristics

A mucoadhesion promoting agent or the polymer is added to the formulation which helps to promote the adhering of the active pharmaceutical ingredient to the oral mucosa. The agent can have such additional properties like swelling so as to promote the disintegration when in contact with the saliva. As understood earlier, that various physical and chemical exchanges can affect the polymer/ mucus adhesion, so as polymer should be carefully selected with the following properties in mind.[36]

1. Polymer must have a high molecular weight up to 100.00 or more this is necessary to promote the adhesiveness between the polymer and mucus. [36]
2. long chain polymers-chain length must be long enough to promote the interpenetration and it should not be too long that diffusion becomes a problem.[37]
3. High viscosity
4. Degree of cross linking- it influences chain mobility and resistance to dissolution. Highly cross linked polymers swell in presence of water and retain their structure. Swelling favours controlled release of the drug and increases the polymer/mucus interpenetration. But as the cross linking increases, the chain mobility decreases which reduces the mucoadhesive strength.[37]
5. Spatial conformation
6. Flexibility of polymer chain- this promotes the interpenetration of the polymer within the mucus network.[38]
7. Concentration of the polymer- an optimum concentration is required to promote the mucoadhesive strength. It depends however, on the dosage form. For solid dosage form the adhesive strength increases with increase in the polymer concentration. But in case of semi solid dosage forms an optimum concentration essential beyond which the adhesive strength decreases.[39]
8. Charge and degree of ionization- the effect of polymer charge on mucoadhesion was clearly shown by Bernkop-Schnurch and Freudl. In this work, various chemical entities were attached to chitosan and the mucoadhesive strength was evaluated. Cationic chitosan HCL showed marked adhesiveness when compared to the control. The attachment of EDTA an anionic group increased the mucoadshesive strength significantly. DTPA/chitosan system exhibited lower mucoadhesive strength than cationic chitosan and anionic EDTA chitosan complexes because of low charge. Hence the mucoadhesive strength can be attributed as anion>cat ion>nonionic.[40]
9. Optimum hydration- excessive hydration leads to decreased mucoadhesive strength due to formation of a slippery mucilage.[41,42,43]
10. Optimum Ph – mucoadhesion is optimum at low pH conditions but at higher pH values a change in the conformation occurs into a rod like structure making them more available for inter diffusion and interpenetration.[44] At very elevated pH values, positively charged polymers like chitosan form polyelectrolyte complexes with mucus and exhibit strong mucoadhesive forces.[45]
11. High applied strength and initial contact time
12. It should non toxic, economic, biocompatible preferably biodegradable

Polymer Used for Oral Mucoadhesive Drug Delivery [47]

PAA derivatives carbomer- carbopol934
Noveon- polycarbophil

These are polymers of acrylic acid cross linked with polyalkenyl ethers or divinyl glycol. They are produced from primary polymer particles of about 0.2 - 0.6 micron diameter. Each primary particle exists as a network structure of polymer chains' interconnected by cross links. Carbopol polymers along with pemulen and novel on polymers are all cross linked. They swell in water up to 1000 times their original volume to form a gel when exposed to a pH of 4.0 to 6.0. The glass transition temperature is about 105°c. due to presence of carboxylate group and an pKa of 6.0 to 0.5, repulsion between the negative charges occurs leading to increased swelling and hence increased mucoadhesive strength of the polymer.[48]

Today, a large number of companies are using carbopol polymers because of the following merits [48]

- Good tabletting formulation flowability.
- Long drug release profiles can give drug releases profiles similar to carbopol 971oNF, with better handling characterstics.
- Are safe and effective for oral administration
- Arebioadhesive and providing increased bioavailability
- Are approved by many pF the world pharmacopoeias
- Protect protein and peptides from degradation and hence increase the bioavailability of proteins or peptide based formulations.

Chitosan

It is an cationic polymer (polysaccharide),[49] it is produced by the deacetylation of chitin. Chitosan is gaining importance in the development of mucoadhesive drug delivery System because of its good biocompatibility, biodegradability and non toxic nature. It binds to the mucosa via ionic bonds between the amino group and sialic acid residues. Chitosan being linear provides greater polymer chain flexibility. Onishi and Machida showed that chitosan and its metaboloized derivatives are quickly eliminated by the kidney.[50]

Newer second generation polymers [19]
They have the following advantages
- More site specific hence called cytoadhesives.
- Are least effected by mucus turnover rates,
- Site specific drug delivery is possible.

a) Lectins
Lectins are naturally occurring proteins that are useful in biological recognition involving cells and proteins. Lectins are a class of structurally diverse proteins and glycoprotein that bind reversibly to specific carbohydrate residues.[51] After binding to the cell the lectins may either remain on the cell surface or may be taken inside the cell via endocytosis., they hence allow a method for site specific and controlled drug delivery. The lectins have many advantages but they also have the disadvantage of being immunogenic.

b) Thiolated polymers
These are thiomers which are derived from hydrophilic polymers such as polyacrylates, chitosan or deacetylated gallan gum. The presence of the thiol group increases the residence time by promoting covalent bonds with the cystiene residues in mucus. The disulphide bonds may also alter the mechanism of drug release from the delivery system due to increased rigidity and cross linking.[52] ex. chitosan iminothiolane PAA homocystiene, Paa cystiene Alginate cystiene

c) Polyox WSRA
Class of high molecular weight polyethylene molecular weight polyethylene oxide. Homopolymers having the following properties, [53]
- Water soluble
- Hydrophillic nature
- High molecular weight
- Functional group for hydrogen bonding
- Biocompatible and non toxic
- Can be formulated into tablets, films, gels, microcapsules, syrups.

Novel polymers
- Tomato lectin showed that it has binding selectivity to the small intestine epithelium.[54]
- Shajaei and Li have designed and characterized a co polymer of PAA and PEG monoethylether mono methacrylate(PAA-co-PEG) for exhibiting optimal buccal adhesion [55]
- Lele et al, investigated novel polymers of PAA complexed with PEGylated drug conjugate.[56]
- A new class of hydrophilic pressure sensitive adhesives (PSA) has been developed by corium technologies. Complex have been prepared by non covalent hydrogen bonding cross linking of a film forming hydrophilic polymer with a short chain plasticizer having reactive OH groups at chain ends.
- Bogataj et. Al prepared and studied Mucoadhesive microspheres for application in urinary bladder[57]
- Langath N et.al. Investigated the benefit of thiolated polymers for the development of buccal drug delivery systems.[58]
- Alur H.H. et.al. Studied the transmucosal sustained delivery of chlorphenazine maleate in rabbits using a novel natural mucoadhesive gum from hakes as an excipient in buccal tablets. The gum provided sustained release and sufficient mucoadhesion.[59]

Conclusion
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. The most widely studied and accepted polymers for mucoadhesion have been the hydrophilic, high molecular weight, anionic molecules like carbomers Recently the focus has been on the novel second generation polymers like the thiolated polymers, lectins and lecithin. Many potential mucoadhesive systems are being investigated which may find their way into the market in near future.

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