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Review Article

A Review on Basic Principles of Mucoadhesion: The Importance of Chitosan as a Mucoadhesive Biopolymer

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Abstract

Mucoadhesive polymers have the special functions which lead to adhesion to the mucin/ epithelial surface on the mucus-covered areas in the body such as eye, nose, vaginal and buccal cavities, and GI tract. Therefore, they provide to increase the residence time of the dosage form on the mucosa and to significantly improve the drug administration. Mucoadhesive drug delivery systems containing chitosan and its modified derivatives have many advantages for both local and systemic drug delivery. The goal of this review is to put forward the importance of chitosan as a functionalized mucoadhesive drug delivery system.

Keywords: Mucoadhesion, Mucoadhesive polymers, Mucoadhesive drug delivery systems, Chitosan.

Mukoadhezyonun Temel Prensipleri Üzerine Bir Derleme: Mukoadhezif Biyopolimer Olarak Kitosan'ın Önemi

Özet

Mukoadhezif polimerler, vücuttaki göz, burun, vajinal ve bukkal boşluklar ile gastrointestinal sistem gibi mukusla kaplı bölgelerde mukus/epitel yüzeyine yapışma özelliğine sahiptir. Bu nedenle, dozaj formunun mukozadaki kalış süresini arttırma ve buna bağlı olarak ilaç uygulamasını önemli ölçüde iyileştirme özellikleri gösterirler. Kitosan ve modifiye edilmiş türevlerini içeren mukoadhezif ilaç taşıma sistemleri hem lokal hem de sistemik ilaç taşınmasında birçok avantaj sunar. Bu derlemenin amacı, fonksiyonelleştirilmiş bir muokoadeziv ilaç taşıma sistemi olarak kitosanın önemini vurgulamaktır.

Anahtar Kelimeler: Mukoadezyon, Mukoadezif polimerler, Mukoadezif ilaç taşıma sistemleri, Kitosan.

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1. INTRODUCTION

Mucoadhesıve Bıopolymer theory was first described in the early 1980s with the application of controlled drug release systems. Mucoadhesion is defined as the ability of synthetic or natural polymers to adhere to mucosal membranes with a mucus structure, such as the nose, mouth, vagina and gastrointestinal tract [1]. Many gains have been achieved by ensuring the adhesion and penetration of the carrier system onto the mucosal membrane. The most important of these benefits are that it extends the contact time on the mucosal membrane and increases the penetration of the active ingredient and its bioavailability by protecting it biologically [2, 3].

Drug transport from the mucosal surface, the fact that the drug can be easily absorbed into the bloodstream due to the presence of dense blood vessels in the mucosal membrane structure, being painless and easy to apply to the patient, increases the importance of mucosal drug transport. In addition, the therapeutic effect of oral drug delivery, which is the most preferred method in traditional treatment, is limited due to enzymatic and chemical degradation in the gastrointestinal tract.

The therapeutic effect of oral drug administration, which is the most preferred method in traditional treatment, is limited due to enzymatic and chemical degradation in the gastrointestinal system, as well as the mucosal layer that covers and protects the epithelial tissue, preventing the drug from localizing and reducing its absorption into the circulatory system. To overcome these difficulties, biopolymers used as drug carrier systems protect the active ingredients against degradation, while problems arising from the mucosal membrane barrier can be solved by selecting biopolymers with mucoadhesive properties. Thus, a therapeutic effect can be achieved by providing a controlled and prolonged release of the active substance at the maximum dose to the targeted area. It also increases patient compliance by providing convenience as an application method and reducing the frequency of medication intake [4].

1.1 Structure and Types of Mucosal Membranes

The structure referred to as mucosal membrane or mucosa is a type of membrane that is found in the parts of the body that open to the outside and covers the surface of the internal organs. The mucosal membrane is responsible for protecting the epithelial tissue from microbial and physical damage. The most important structure that forms the mucous membrane is referred to as mucus. Mucus is a biological hydrogel that lubricates the epithelial surface in moist areas of the body, including the respiratory, gastrointestinal and reproductive tract etc. This structure not only protects the epithelial surface from physical damage with its lubricating effect, but also acts as a dynamic physicochemical semi-permeable barrier that allows the transportation and exchange of certain molecular structures such as water, gas, hormones and nutrients, while capturing and blocking foreign and harmful substances such as toxins, heavy metals, viruses and parasites [5, 6]. While mucus life or clearance time is expressed in minutes and hours, in this short period of time, the mucus layer is destroyed by shedding, excretion or digestion, and is renewed by the epithelium tissue forming a new mucus structure Therefore, biological or synthetic particles must penetrate faster than the clearance time cycle of the mucus to reach targeted areas [5, 7, 8].

Mucus has a complex structure in aqueous liquid composed of 95% water and 5% consists of 0.5-1% electrolytes, 1-2% lipids, 0.5% small proteins, 1-5% mucin which a large glycoprotein structure, enzymes and bacteria. The primary and most important component of mucus is mucin and it contains structures consisting of approximately 80% glycated proteins with different glycoprotein content [8–10]. The glycoprotein chain has a flexible and random spiral structure and a braided morphology and its molecular weight varies from 40 MDa to 0.5 MDa and is a part of the mucus secretion that is responsible for its hydration, lubrication, viscoelastic properties and adhesion to the mucosa [3, 10]. Mucin has a structure in which proline, threonine and/or serine molecules are repeated in varying numbers in the amine and carboxyl-terminated protein chain structure, and cysteine-rich parts are scattered throughout the chain. Cysteine has a negative charge that causes intramolecular repulsion as a result of ionization of the high sialic acid and sulfate content in its structure under aqueous conditions [8, 11].

Since the mucosal membrane contains different pH, enzymes, surface area, bacteria and different mucin structures depending on the tissue it is located in, it is necessary to design a transport system suitable for the targeted area [12].

Ocular/Eyes; it contains inorganic salts and tear secretion with a pH value of 7.3-7.7, due to its anatomy. The pressure created by the constant opening and closing of the eyelids removes any foreign substance that enters it. Since this makes it difficult to successfully apply topical drug delivery systems, chitosan, poly (acrylic acid), poloxomer methyl cellulose, hydroxy ethyl cellulose, poly (amidoamine) dendrimers, poly (vinyl prolidone) and thiolated bioadhesive polymers are preferred to increase the effectiveness of the drug [13–15].

Oral cavity; consists of buccal mucosa and sublingual mucosa. In local applications to the oral cavity, hepatic first pass metabolism is prevented and the pharmacological passage of the active substance into the systemic circulation system is increased. This makes it an important target tissue for drug delivery, as it causes the amount of the therapeutic agent to increase in the blood circulation and therefore the therapeutic effect to increase. The surface area of the oral cavity mucosa is small, but the drug delivery system is easy to implement. The sublingual mucosa consists of dense smooth muscles that do not move and is more permeable than the buccal mucosa. Due to this feature, while rapid release is achieved by sublingual mucosa, drug delivery through the buccal mucosa is preferred to ensure controlled release. Thiolated derivatives and bioadhesive polymers such as poly (acrylic acid), sodium carboxymethyl cellulose, hyaluronic acid, polycarbophil, chitosan and gellan are used as delivery systems [16, 17].

Gastrointestinal system; its acidic structure and chemical degradation of nutrients or drugs due to enzymatic hydrolysis reduces the bioavailability and mucosal membrane permeability of drugs. In order to protect the therapeutic agent in the acidic enzyme environment, it is used by coating it with enzyme inhibitor, conjugated polymers or lipid. The fact that it offers different drug designs, is easier than intravenous and submuscular administration, and is a natural route makes it the most researched drug delivery route. Chitosan, poly (acrylic acid), alginate and sodium carboxymethyl cellulose bioadhesive polymers and their thiolated derivatives are examples of polymers that are being developed for the gastrointestinal drug delivery systems [18–20].

Vaginal mucosa; it contains special proteins and glycogen epithelial tissue. Glycogen enzymes and bacteria break down and create an acidic environment (pH=4-5). The content of vaginal secretion constantly changes depending on age, the amount of hormones, the variety of bacteria and viruses. Vaginal formulations can be applied locally, increase permeability to the systemic circulatory system due to have dense blood vessels, which provides an advantage in the treatment of regional diseases. Gellan gum, starch, chitosan, carbomer, poloxamer and thiolated structures can be given as examples of drug carrier biopolymers [13, 21–23].

Nasal cavity; it consists of two spaces separated by a septum in the middle. There are 3 regions with different functions with special epithelial tissue, 12-14 cm deep, 5 cm high, with a surface area of approximately 150-160 cm^2. It is thought that drug transport occurs from respiratory and olfactory regions. The large surface area of the nasal cavity, low enzyme activity and rich vascular structure make nasal administration preferred for the transportation of drugs [24, 25].

Sections that comprise up the nasal cavity; respiratory region, olfactory region and vestibular region. The mucosal membrane structure of this region contains hairs called cilia, 5-10 µm in size, which serve to retain particles in the inhaled air, and a mucus secretion that moisturizes the air. Mucus secretion has a pH value of 5.5-6.5 and its transport speed is approximately 5-8 mm/minute. For this reason, since the ciliated mucosa structure has a cleaning function (mucociliary clearance) against foreign molecules and particles, the retention time of the foreign substance in the mucosa is 10-20 minutes [26–28].

In nasal drug delivery, small volumes of 25-200 µl can be used and the therapeutic agent is eliminated from the nasal cavity in a short time due to the mucociliary clearance effect and in addition, disadvantages such as the formulation may have toxic and irritating effects are encountered. But considering the advantages

such as ease of application, not causing a hepatic first-pass metabolism effect, and most importantly, providing passage to the central nervous system (CNS) without getting stuck in the blood-brain barrier (BBB) in brain targeting and having a significant therapeutic effect in the treatment of neurodegenerative diseases, the importance of nasal drug delivery is increasing Chitosan, poly (acrylic acid), sodium carboxymethyl cellulose, carbopol, gellan gum and thiolated derivatives are preferred in nasal drug delivery [25, 29–33].

1.2 Mucoadesion Mechanism

There must be three active region that provide the mucoadhesion mechanism between mucus and polymer. These regions;

1. Surface of mucoadhesive polymer

2. First layer of mucosal membrane (mucus)

3. Interface between mucosal membrane and mucoadhesive polymer

Wetting and swelling of the mucoadhesive polymer at the interface between the polymer and the mucosal membrane, with the expansion of the surface area of the polymer, the penetration of polymer chains into the membrane tissue occurs. And thus, as a result of the interaction of polymer chains and mucus, physical and/or chemical bonds are formed and mucoadhesion occurs. The mucoadhesion mechanism is explained by six theories [34–36].

1. Adsorption theory; the interaction of mucoadhesive polymers and mucus structure provides the formation of covalent and non-covalent (Van Der Waals, hydrogen and hydrophobic) bonds. Although weak (non-covalent) bonds are formed, intense binding and mucoadhesion can occur due to the formation of many interaction areas, and this theory is accepted as the basis of the mucoadhesion/bioadhesion mechanism [1, 37].

2. Diffusion theory; it refers to the formation of semi-permanent bonds as a result of the intertwining and entanglement of mucoadhesive polymer chains and mucus glycoproteins. Bond strength increases with the number of penetrating mucoadhesive polymer chains. The penetration and entanglement of the mucoadhesive polymer into the mucus structure depends on the flexibility of the polymer chains, chemical structure, concentration, diffusion coefficient and contact time [38, 39].

3. Electrostatic theory; it is explained as the formation of an electrical double layer at the interface as a result of electron exchange by electrostatic interaction with the negatively charged mucin and the positively charged polymer [1].

4. Fracture theory; the force required to separate two previously bonded surfaces from the interface is expressed as the degree of adhesion. When evaluating the breaking properties of the adhesive bond in separation experiments, it is assumed that the breakdown of the adhesive bond occurs at the bioadhesive interface [40].

5. Mechanical theory; the realization of adhesion depends on the smoothness of the two interacting surfaces and the suitability of the area required for interaction [40, 41].

6. Wetting/Wettability theory; The ability of liquid or low-viscosity mucoadhesive polymers to spread on the mucosa is expressed as surface tension. Adhesion occurs with the energy change that occurs at the surface and interface as a result of the mucoadhesive polymer coming into contact with the mucosa. Thus, the energy required to eliminate the tension at the interface indicates the mucoadhesive property of the polymer [35, 42].

1.3 Mucoadhesion-Relating Factors

It is important to consider the factors influencing the mucoadhesion mechanism for the explanation of the mucoadhesiveness [43]. These factors are presented below.

1.3.1 Polymer

The hydrophilic group content of the polymer is one of its key characteristics. Mucoadhesive polymers must have the hydrophilic groups like carboxyl, hydroxyl, amine, sulfate, etc. in order to create hydrogen bonds with mucus [1, 43].

The polymer's level of hydration is an other crucial characteristic. High chain mobility and swelling at a suitable hydration level enable mucoadhesive polymers to form a gel, which in turn enhances interpenetration and adhesion/mucoadhesion with the mucus structure [1]. The polymer concentration as well as the amount of water present in the surroundings determine the appropriate degree of hydration. Mucoadhesion may also be adversely affected by excessive swelling. Additionally, with the osmotic pressure force between the dry polymer and the wet mucosal surface, many polymers can exhibit mucoadhesive characteristics even while they exhibit minimal hydration. [44, 45].

The polymer structure is a further feature that influences adhesion to mucosa. Adhesion and mucoadhesion are determined by the polymer's molecular weight (M_w), chain length, and chain structure (conformation, modification rate). Sufficient lengthening of the chain and a high molecular weight of the polymer both influence high mucoadhesion [1, 39, 46, 47].

The polymer chains' flexibility is a further important aspect. Mucoadhesive polymers' viscosity, diffusion coefficient, and chain flexibility allow gel formation by swelling as a result of absorbing external water, and this property of the polymer has a significant effect on the mucoadhesion mechanism. Inadequate flexible polymer chains exhibit low mucus interpenetration, which results in weaker mucoadhesion bonds [43, 47].

Mucoadhesion is also influenced by polymer concentration. The forming of strong mucoadhesion interactions requires an ideal polymer concentration. Chains interpenetrate into the mucus structure promoting mucoadhesion when chain mobility achieves an optimal concentration. Mucus interpenetration reduces at very high concentrations because of the chains' limited mobility and dense spiral shape. On the other hand, the adhesion bond density is reduced at low concentrations because no polymer chain can interpenetrate adequately [47–49].

Cross-link density of the crosslinked polymer (hydrogel) is another parameter that significantly influences the mucoadhesive polymer's swelling capacity. A high cross-link structure inhibits chain mobility and reduces polymer hydration, which in effect reduces the interpenetration of the chains into the mucus structure and negatively impacts adhesion/mucoadhesion [45, 47].

The other important factor is the type of surface charge and its density of the polymer. Positively and negatively charged polymers adhere to biological surfaces more readily than uncharged ones due to their surface charge. Polymers with positive surface charges, like chitosan, also exhibit high mucoadhesiveness due to strong electrostatic interaction with the amine groups and mucin sialic groups in the mucus structure, while anionic polymers, like carbomer with a negative surface charge, show high mucoadhesive properties by forming hydrophobic interactions, hydrogen bonds, or van der walls bonds with mucus [1, 43, 50].

The acidic or basic character of the mucoadhesive polymers is indicated by its pKa value, which also influences the mucoadhesion mechanism by influencing the behavior of the ionic interaction with mucosal membrane in a pH environment [1, 45, 51].

1.3.2 External factors

The pH value of the environment influences the dissociation of functional groups, which itself effects the swelling degree of the polymer and the surface charge density of mucus. Consequently, this effects the mucoadhesion mechanism [47, 51]. Mucoadhesion is further influenced by the existence of ionic forces in the surroundings. Mucoadhesion is decreased because interaction can protect functional regions that provide adhesion through the ion effect [1, 47].

Mucoadhesion depends on the polymers that are mucoadhesive to remain on the surface of the mucosal membrane for the ideal amount of time, as well as the pressure that is generated during this time [47, 52].

Mucoadhesion is directly affected by the types of mucins found in the structure of mucus, which in turn influences the interaction between the polymer and mucus. The presence of cysteine-rich mucin glycoproteins demonstrates high mucoadhesion through the formation of disulfide bonds with thiomers, compared to adhesiveness formed by hydrogen bonding or electrostatic interactions [53].

The mucus cycle is an another crucial factor. At specific times, mucus is removed from the gel layer surface and is regenerated by keeping a specific thickness and viscosity. The particular conditions are dependent upon the location of the mucosal membrane. This cycle has an immediate impact on mucoadhesion by modifying the duration of material contact with the mucosal membrane surface. Adhesion/mucoadhesion can be enhanced and contact time can be extended by producing polymers with strong mucoadhesion capabilities [47, 52].

1.4 Mucoadhesive Polymers

The environment of the mucosal membrane can have a variety of effects on drug bioavailability, including the drug's molecule breaking down and decreasing its therapeutic efficacy, the environment's varying pH, the presence of bacteria and enzymes, and the mucus renewing itself periodically. Because to the biochemical structure of the oral mucosal barrier, it is found that when protein and peptide drugs are examined through the mucosa, their bioavailability is less than 5% [54]. Mucoadhesive polymers offer a significant potential to enhance the therapeutic effectiveness and bioavailability of drugs by preventing drug degradation and achieving controlled extended drug release by prolonging the retention time of drug on the mucosal membrane surface [35].

Chain interactions allow mucoadhesive polymer chains to penetrate into mucin chains. Mucoadhesion occurs by the chains interacting, ionic and hydrophobic interactions between polar and nonpolar groups, hydrogen bonding and/or disulfide bond formation as a result of thiolated polymer interaction, and cysteine-rich mucus glycoprotein interaction [53, 55].

The electrostatic interaction of the polymer with ionizable groups that have a cationic or anionic surface charge and the mucus structure results in the formation of an ionic bond. Due to the weakly positively charged polymer's electronegatively charged atoms (H, O, F, and N) having the ability to establish hydrogen bonds and influence the other electronegative atoms in the mucus structure, it happens. Van der Walls bond is the formation of a weak bond between the mucoadhesive polymer and nonpolar groups in the mucus structure due to induced dipole groups, and between polar groups by dipole-dipole interaction. Designing mucoadhesive polymers with thiomers that have a free thiol group in their structure creates thiolated polymers. A strong covalent bond is formed by forming a disulfide bond between thiol groups and cysteine-rich mucus glycoproteins. Thus, the retention time and bioavailability of the drug increases. Another advantage is that it exhibits rapid swelling and water uptake behavior due to its structure [55, 56].

Mucoadhesive polymers are categorized into three groups based on their sources: synthetic, semi-synthetic, and natural. Additionally, based on their surface charge, they are further divided into three groups: cationic, anionic, and nonionic. Furthermore, thiol-containing polymers are regarded as a specific category of new generation mucoadhesive polymers [53, 57–59]. This classification is presented with some examples in Figure 1.

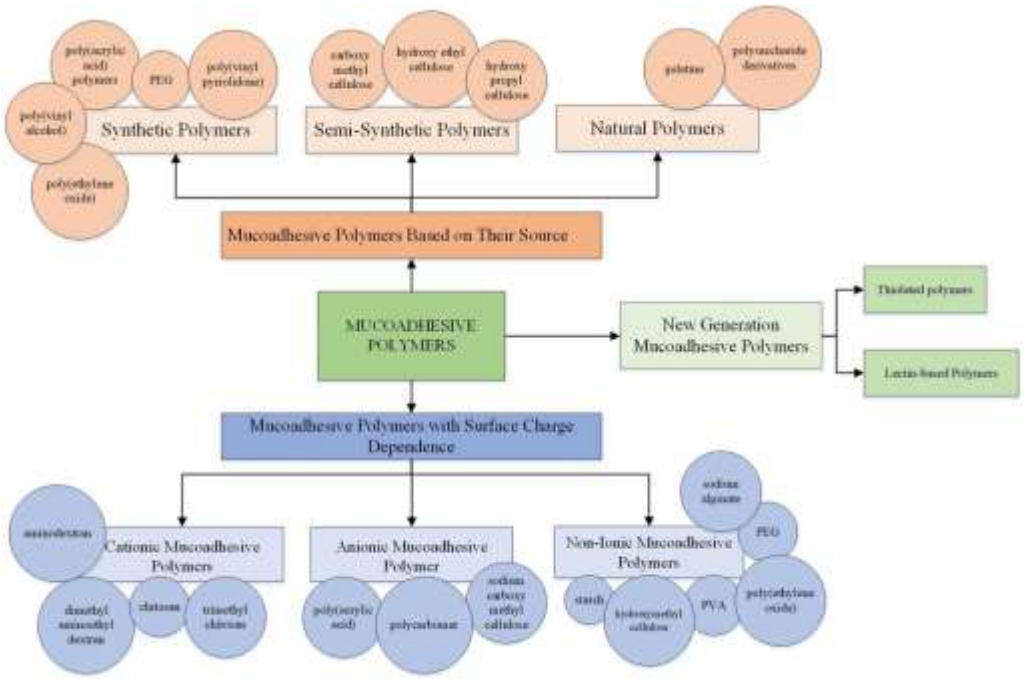

Figure 1. Classification of the mucoadhesive polymers

1.4.1 Chitosan

Chitosan is obtained by deacetylating chitin, a natural polymer produced by crustaceans such as crabs, shrimps and lobsters. Chitosan is a semi-natural biopolymer with a linear chain structure that is made up of units of D-glucosamine and N-acetyl-D-glucosamine bonded by β-(1-4) glycosidic linkages [60].

The degree of deacetylation (DD) indicates the amount of amine groups in the chitosan molecular structure, even though the hydroxyl and amine functional groups in the chitosan molecule are important for chitosan solubility. Its pKa value is approximately 6.5 due to the presence of amine groups, and when it is protonated and dissolved in acidic environments with pH less than 6.5, it forms positively charged (cationic) chitosan molecules. Chitosan is not soluble in water or most organic solvents, which restricts its application in many situations. Chitosan is modified to create chitosan derivatives, which improve its characteristics. Consequently, its physicochemical characteristics are enhanced and its range of applications is expanded through chemical modification.

The biocompatibility, biodegradability, mucoadhesiveness and nontoxic properties of chitosan and its derivatives provide their use in a wide range of pharmaceutical applications such as biomedicine, drug delivery systems, tissue engineering, bioimaging, implants, contact lenses, gene transfer, protein binding and wound healing.

In the areas of food technology, textile manufacturing [61], and water purification systems [62], it is also employed [63]. Chitosan can be created for a variety of applications since it can be used to prepare in different forms of structures, such as hydrogels, microparticles, nanoparticles, membranes, sponges, or fibers [64].

Chitosan has cationic surface charge at acidic pH value due to the the amine groups in the molecular structure that contribute to its mucoadhesiveness. The occurrence of an electrostatic interaction between positively charged chitosan molecules and the anionic characteristics of sialic acid groups in mucus structure constitute the basis of the mucoadhesion mechanism [65]. Hydrophobic interaction and the formation of hydrogen bonds also play a significant role [66, 67]. Furthermore, the cationic chitosan molecule interacts with the mucus membrane through interactions that stimulate movement throughout

mucosal cells and cause proteins linked to the close connection between cells to reorganize. As a result, the drug's penetration is increased. In this instance, it highlights how chitosan increases permeability [68, 69]. Up until an optimal value, the mucoadhesion property of chitosan increases with increasing molecular weight (M_w) and DD, and it decreases with increasing cross-linking [70].

The goal of chemically modifying the chitosan molecule is to enhance its drug retention duration, solubility, stability, hydrophobicity or hydrophilicity, usability as a drug delivery system across a broad pH range, penetrating ability, permeability, and mucoadhesiveness [67, 71]. To enhance chitosan's mucoadhesive features, modified synthetic derivatives such as Trimethyl Chitosan (TMC), Thiolated Chitosan, Chitosan with improved hydrophobicity, and PEGylated Chitosan structures can be mentioned [72, 73].

Trimethyl Chitosan (TMC): A derivative of TMC with improved water solubility due to the addition of a protonated group [$-N^{+}(CH^{3})_{3}$] to its structure, this modified polymer exhibits one of the strongest mucoadhesive properties, primarily attributed to its persistent cationic natüre. Shinde et al. [74] applied the ionic gelation method to evaluate the nanoparticle systems made from chitosan and TMC loaded with flurbiprofen as drug transport vectors via the ocular (or eye) mucosal membrane. In comparison to chitosan, the TMC nanoparticulate system exhibits increased mucoadhesive properties and longer drug release behavior. It has a greater drug loading capacity than conventional vectors and, because of its strong mucoadhesiveness, extends the duration that Flurbiprofen is retained on the mucosal membrane of the eye, enhancing its bioavailability. He and Yin [75] investigated the oral and intravenous delivery of folic acid-modified TMC nanoparticulate systems loaded with paclitaxel for the treatment of cancer. The examination of the intestinal mucosal membrane of a rabbit revealed that the folate TMC nanoparticles had a stronger mucosal adherence. Paclitaxel's anticancer impact was enhanced by the formulation, which also lengthened its half-life in the blood and enhanced its concentration in tumor cells.

PEGylated Chitosan: It is a chitosan derivative modified by poly (ethylene glycol) (PEG). In general, methyl-poly (ethylene glycol) is recommended to avoid polymer chain cross-linking. It improves chitosan's biocompatibility and durability against enzymatic degradation in addition to making it more soluble in water, which enhances the drug's bioavailability in vivo. Jintapattanakit et al [76] synthesized a TMC copolymer with PEG and evaluated its mucoadhesive properties. It was determined that the insulin-loaded nanocomplex structure's mucadephilic properties and insulin loading capability increase with a rise in positive charge. It has also been noted that, in addition to the positive charge impact, the mucoadhesive feature of the PEGylated TMC nanocomplex structure is further enhanced by the PEG chain's capacity to enter mucus.

Carboxymethyl Chitosan (CMC): It is an amphoteric derivative of chitosan due to the presence of amine (basic) and carboxyl (acidic) groups in its chemical structure. In an acidic environment, the polymer structure becomes cationic by protonating the amino groups, while in a basic environment, the polymer behaves anionicly as the carboxyl groups dissociate [77].

Acrylated Chitosan: Mucoadhesion occurs through the covalent bond between the acrylate vinyl group incorporated into the chitosan structure and the sulfhydryl groups of the glycoproteins found in the mucus structure. The use of acrylate groups in mucoadhesive polymers was first carried out by Davidovich-Pinhas and Bianco-Peled [78]. As a common feature of thiolated chitosan and acrylated chitosan, mucoadhesion occurs through covalent bonding [79–81].

Chitosan with Enhanced Hydrophobic Properties: Covalent bonding of hydrophobic alkyl chains can increase the hydrophobicity of chitosan. By making phospholipid domains in the cell membrane structure more fluid, these substances improve cell penetration. Furthermore, by reacting hydrophobically with the hydrophobic groups of lipids in the cell structure, it strengthens the mucoadhesive characteristic of chitosan when added to the structure [72, 73]. Another effect of increasing the hydrophobic feature is that as the hydration of the agent decreases, it shows higher resistance to degradation by the enzymes of its environment (such as stomach enzymes), thus increasing the stability of chitosan [82, 83]. Table 1 displays chitosan modifications with hydrophobic groups.

Table 1. Hydrophobically Modified Chitosan derivatives

Modification Type	Drug	Results	Reference
Modification of chitosan using (C6-C16) fatty acids	No specific drug reported	▪ Palmitoyl chitosan-derived tablets have improved mechanical properties and stability. ▪ Because of the strong hydrophobic interaction created by the degree of alteration and the long alkyl chain structure, it exhibits prolonged drug release.	[84]
Modification of chitosan using fatty acids (C6–C20)	pDNA	▪ By attaching to the lipophilic cell membrane, the hydrophobic alkyl chain structure increases adhesion. ▪ Comparing palmitoyl chitosan nanomicellar formulation to other fatty acid modifications, it demonstrates the highest intracellular absorption and gene transfection efficiency.	[85]
Modification of chitosan using Palmitic acid (TMC-g-PA)	Resveratrol	▪ The TMC-g-PA nanoparticulate system improves bioavailability by 3.8 times when drug release is evaluated in vitro, ▪ It may be utilized as a drug delivery vector for oral administration.	[6]
Modification of chitosan using palmitoyl quaternary ammonium	Curcumin	▪ The formulation has improved antibacterial and antioxidant effects over free curcumin, and it also demonstrates regulated and sustained drug release when taken orally.	[87]
Micellar formulation of palmitoyl glycol chitosan (PGC)	No specific drug reported	▪ PGC exhibited a therapeutic effect into the cornea, improving medication penetration, and it enhanced the micelle structure's penetration in the epithelial corneal cell line.	[88]
N-palmitoyl-N-monomethyl-N,N-dimethyl-N,N,N-trimethyl-6-O-glycolchitosan (GCPQ) polymer	SARS-COV-2 virus	▪ Studies using Vero E6 and A549 cells in vitro reveal that, at non-toxic GCPQ polymer concentrations, there is an inhibitory effect on SARS-CoV2 replication. ▪ Ex vivo treatment of the GCPQ formulation on human airway epithelial (HAE) cells confirms its inhibitory action. ▪ A prolonged retention effect is observed when the GPCQ polymer spray formulation is applied to mice nostrils in vivo. ▪ GPCQ formulation has the potential to prevent SARS-COV-2 infection and, by preventing the virus from infecting the brain, may lessen neurological problems.	[89]

O-methyl-O′-succinylpolyethylene glycol and oleic acid grafted chitosan	Camptothecin	▪ Camptothecin was stabilized by chitosan micelles. ▪ The new amphiphilic chitosan showed a controlled release in intestinal fluids. ▪ It has yielded successful results for the encapsulation of hydrophobic drugs	[90]
11-carbon and 3-carbon alkyl chains grafted hydrophobic chitosan	Carvacrol	▪ Using chitosan grafted with two distinct alkyl chain lengths, this study showed that carvacrol inhibited the formation of biofilms and their motility. ▪ Carvacrol-loaded modified chitosan nanoparticles are an efficient method for P. aeruginosa biofilm-associated infections.	[91]

Thiolated Chitosan: This derivative of chitosan is the product of modifying chitosan with substances that include a thiol group. Cysteine (Cys), thioglycolic acid (TGA), 2-iminothioline, 4-thiobutylamide (TBA), N-acetyl cysteine, isopropyl-S-acetyl thioacetamide, and glutathione are a few examples of thiolizing agents. Enhancing chitosan's mucoadhesive properties enhances its application in biomedical and pharmaceutical fields. Table 2 displays some specific studies on thiolated chitosan.

Thiolation of chitosan not only improves the mucoadhesive properties of chitosan, but also improves its permeability-increasing effect and provides in situ gelling properties. It also provides enzyme inhibition and is biodegradable due to its structure [67, 79, 92, 93]. In addition to the physical interaction, the addition of thiol groups to the structure increases the secondary interactions between the polymer and mucus. These interactions also facilitate the creation of disulfide covalent bonds, which provide mucus glycoproteins with cysteine-rich domains excellent mucoadhesiveness [69, 79].

• Permeability enhancing feature: The property that enhances permeability is caused about by the interaction between cationic chitosan and the negatively charged cell membrane, as well as the structural rearrangement of proteins involved to tight junctions. Unfortunately, limited diffusion and/or competing charge interactions with mucin prohibit it from reaching the epithelium and reduce its permeability because of the size of the chitosan chains in the mucus layer. Disulfide bonds are formed in the presence of thiol groups, which inhibit transmembrane protein tyrosine phosphatase and open tight junctions by altering their structural integrity [94–97].

• Property of in situ gelation (cross-linking): Crosslinking between the polymer chains are created by the oxidation of the thiolated polymer at physiological pH levels, which results in the creation of both intramolecular and intermolecular disulfide bonds. In the pH range of 5–6, it creates an intramolecular and intermolecular disulfide bond, forming a three-dimensional network structure. This arrangement allows for extended regulated release of the medicine while also ensuring greater stability of the carrier vector. This property allows thiolated chitosans to be applied to the mucosa of the nose, mouth, eyes, and vagina [69, 98–100].

• Inhibition of enzyme activity: Thiomers inhibit zinc-dependent proteases, including carboxypeptidases and aminopeptidases. The ability of thiomers to bind zinc ions is the basis of the inhibitory mechanism. Its application in the oral delivery of peptide- and protein-based medications is made possible by this inhibitory effect [69].

Table 2. Thiolated Chitosan

Product	Drug	Results	Reference
Chitosan-Cys conjugate	α-Mangostin	▪ Thiolated chitosan NPs cross-linked with genipin and surface modified with Eudragit exhibited stronger mucoadhesion than uncoated NPs and cysteine-based NPs. ▪ NPs exhibited anti-tumor activity. ▪ It was concluded that muadhesive thiolated chitosan NPs are a suitable carrier for the controlled release of α-mangostin into the colon-targeted delivery.	[101]
Preactivated Chitosan-thioglycolic acid and mercaptonicotinic conjugate (PTCS)	Octreotide	▪ Because the -SH groups were preactivated, PTCS-NPs' mucoadhesion and penetration enhancement were significantly greater than those of thiolated nanoformulations. ▪ The oral bioavailability of PTCS-NPs was 7.2 times higher than that of octreotide. ▪ By using preactivated thiolated chitosan, confirmed the idea of the improved bioavailability of octreotide.	[102]
Functionalized Chi with a series of thio-acids	No specific drug reported	▪ This is directly related to the presence of thiol-containing substituents, as the acquired results are consistent with the structure-activity relationship previously established for other chitosan derivatives. ▪ It demonstrates that N-acyl thiolated chitosans are a promising option for the synthesis of high-yield, biocompatible, and reasonably priced antibacterial compounds.	[103]
Lipid carrier coated with chitosan-N-acetylcysteine conjugate nanostructure	Curcumin	▪ The amount of curcumin in albino rabbit tears increased 2.4 times when ocular drug release was evaluated.	[104]
pH-responsive Chitosan-thioglycolic acid (TGA) conjugate	Heparin	▪ A basic ionic gelation technique was used to successfully create a pH-responsive nanoparticle system made of TCS and HP-55 (a cross-linking agent). ▪ TCS/HP-55 NPs' mucoadhesive and intestinal penetrative qualities were greatly enhanced both in vivo and in vitro.	[105]
Chitosan -3-mercaptopropanoic acid (3-MPA) conjugate	No specific drug reported	▪ At high TPP concentrations, chitosan treated with thiol groups demonstrated a stable nanoparticle structure. ▪ The hydrodynamic diameter and surface charge values of chitosan nanoparticles were found to significantly interact with the molar ratio (Ch-SH/TPP). This demonstrates that the size and charge ranges at which new nanoparticles can be produced are 100 nm and 200 nm, and 30 mV and 40 mV, respectively.	[106]

Chitosan-N-acetyl cysteine conjugate	Lysozyme	▪ Chitosan-N-acetyl csteine conjugate tablets showed an 8.3-fold increase in mucoadhesive properties. ▪ It has been evaluated as a potentially useful novel vector for the creation of biodegradable and mucoadhesive compositions.	[107]
Chitosan-thioamidine conjugate	Fluorescence labeled dextrane (FD4)	▪ The mucoadhesive properties of chitosan-thioethylamide (TEA) conjugate tablet formulations are found to increase by three to nine times, respectively. The composition may find application as a vector for controlled drug release.	[98]
Chitosan–TGA conjugates	Clotrimazole	▪ Its strong mucoadhesive property allowed it to exhibit regulated medication release behavior. ▪ It has been reported that vaginal infections can be treated using chitosan-TGA conjugates.	[108]
Chitosan–TGA conjugates	Lysozyme	▪ Results of tensile experiments and the rotating cylinder method show that the mucoadhesive behaviors of tablets made from chitosan-TGA conjugate increase by 6.3 and 10.3, respectively, and consequently, the retention time rises.	[109]
Thiolated chitosan Nanoparticles with pentaerythritol tetrakis (3-mercaptopropionate)	Insulin	▪ With *in vivo* trials, insulin provided extended release to ensure biodistribution and bioavailability due to its interaction with intestinal mucus.	[110]
Nanoformulation of thiolated chitosan coated with hyaluronic acid	Vincristine	▪ In vitro studies demonstrated vincristine's fast release during 12 hours, whereas the modified nanoformulation demonstrated prolonged constant release for up to 72 hours at pH 7.4 and 6.8.	[111]
Nanoparticles of thiolated chitosan-eudragit RS100	Moxifloxacin	▪ Thiolated versions of both polymers were synthesized by providing disulfide bond formation, and in vivo studies showed that the nanoformulation provided controlled release and consequently improved bioavailability.	[112]
Nanoparticles of thiolated chitosan with 3MPA	Tobramycin	▪ Thiolated chitosan-loaded nanoparticles have enhanced precorneal retention, sustained drug release, and high ocular bioavailability at low doses due to their strong surface charge	[113]

CONCLUDING REMARKS

Mucoadhesive polymer-based drug delivery systems have a remarkable importance in many applications in pharmaceutical technologies. Chitosan and its modified derivatives, which have excellent biocompatibility, low toxicity and good mucoadhesion, have been used safe as mucoadhesive biopolymers with various form such as tablet, gel, wound dressing, scaffold and nanoparticulate formulation etc. The

studies reported in the literature clearly reveal the reasons why these versatile biopolymers is extensively used in many fields of the pharmaceutical technology and nanobiotechnology.

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