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Review Article

Thiolated Biopolymers: Enhancing Mucoadhesive Properties for Advanced Drug Delivery Systems

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ABSTRACT

A class of modified polymers with promising potential for use in medicine administration and other biological applications is thiomers, often called thiolated biopolymers. This review examines the many biopolymers commonly used for thiolation, including hyaluronic acid, pectin, xanthan gum, gelatin, and moringa gum. The process of thiolation involves attaching free thiol groups to the polymer chain, which enhances their ability to form strong covalent bonds with mucosal surfaces and makes them more mucoadhesive. Thiolation procedures, including Traut's reagent, dithiothreitol (DTT) reduction, dithiol-aromatic compounds, thiol polyethylene glycolamine, and thioglycolic acid, are reviewed here. The importance of thiolation in improving drug delivery systems is emphasized, as it leads to increased mucoadhesion, bioavailability, and the possibility of regulated drug release. Several difficulties, including reduced mechanical strength, increased oxidation sensitivity, and specific toxicity, can be addressed with thiolated polymers. Enhanced drug delivery methods, regenerative medicine applications, and sustainable uses in various industries are some of the future viewpoints discussed in the analysis's concluding section.

Keywords: Thiolated biopolymers, Mucoadhesion, Drug Delivery System, Biomedical Application, Controlled Release.

INTRODUCTION

Biocompatible and biodegradable biopolymers are biologically derived. They are also called biomolecules, biopolymers, and biomaterials. Chemistry uses monomeric components connected by covalent bonds to form complex structures. They are structurally sustainable and renewable because they come from plants. Biopolymers have bacterial resistance, biological compatibility, and biodegradability [1,2]. Polynucleotides are long polymers; polypeptides are short polymers of amino acids; polysaccharides are linearly bound polymeric carbohydrate structures; and RNA and DNA are made of thirteen or more monomers. First, they are water-soluble and insoluble and easily acquired from our surroundings [3].

Thiolation makes polymers more mucoadhesive, making them useful in biological applications. Despite its difficulty, additional research and ingenuity in this field could lead to better pharmaceutical delivery systems and patient outcomes. Thiomers, thiolated polymers with mucoadhesive characteristics, were introduced in the 1990s. They are mucoadhesive because they form strong covalent bonds via disulfide-thiol exchange with cysteine-rich mucus glycoprotein subdomains. This interaction of thiolated polymers with mucosal tissues creates muco-adhesiveness employed to produce DDSs for dry eye and dry mouth illnesses. Thiomer polymers have better adhesion and retention periods than non-thiolated polymers, which improves localized drug delivery via various channels. This characteristic increases bioavailability, reducing dose frequency and patient non-compliance. Some thiomers also increase permeability, inhibit the efflux pump, and inhibit enzymes. They may shield peptide and protein drugs from digestive enzymes. Thiol oxidation at pH 5 or lower in solutions and gels may destabilize thiomers unless the environment is inert. Thiomers' effectiveness and mucoadhesion may decrease. Pre-activating thiol groups increases stability and mucoadhesion to overcome this putative oxidation barrie[4]. Polymers, which can be manufactured or natural, are made of macromolecules, multiples of monomers. They make minerals and artificial materials and contain live beings. Not all monomers with the same molecular weight, shape, and chemical makeup produce polymers. Most manmade and natural polymers are copolymers, which combine two or more monomers. Monomeric components linked by covalent bonds form biopolymers. They are renewable and used in numerous sectors. Biopolymers are promising due to their unique properties, biocompatibility, and abundance.

Protein, starch, cellulose, DNA, RNA, lipids, collagen, carbohydrates, and so forth are examples of biopolymers.

Biopolymers are natural polymers that are either biosynthesized by living things or chemically derived from biological components. They are a renewable resource since they are made of monomeric units joined by covalent bonds and come from living things like microorganisms and plants. Here are some of the key applications of biopolymers:

Biomedical Applications

- Biopolymers are widely used in the biomedical field due to their degradable, non-toxic, and biocompatible properties (Fig 1 and Table 1).
- They are utilized in tissue engineering, the pharmaceutical industry, medicines, drug delivery, and as materials for medical implants.

Food Industry

- In the food industry, biopolymers serve as edible films, emulsions, and packaging materials, offering an eco-friendly alternative to traditional packaging.

Environmental Benefits

- Biopolymers are biodegradable and obtained from renewable raw materials, posing a lesser risk to the environment compared to petrochemical products.

Electro-Active Biopolymers (EABP)

- Some biopolymers, such as starch, cellulose, chitosan, and pectin, have been identified to possess electronic and ionic conductivity, giving them potential in electronic applications.

Mucoadhesive Biopolymer

Mucoadhesive biopolymers are a type of bio-polymers that can adhere to the mucosal (mucus) surfaces. They are designed to stick to the wet surfaces of tissues for an extended period, which is beneficial for drug delivery applications. Drug distribution is enhanced and made more effective by the adhesion to the mucosal layer, which permits a longer residence time at the application site. These polymers can interact with the mucus layer through various interfacial forces, enhancing the bioavailability of the medication. We use mucoadhesive biopolymer for a controlled-release drug delivery system.

A mucoadhesive controlled-release drug delivery system is a type of pharmaceutical formulation that combines mucoadhesion with controlled-release mechanisms.

Mucoadhesion

This defines a substance's capacity to stick to the body's mucosal tissues. Mucoadhesive drug delivery methods work by interacting with the mucus layer that covers the mucosal epithelial surface, extending the dosage form's residence time at the absorption site.

Controlled Release

This aspect involves the delivery of medication at a predetermined rate, for a specified period, to maintain a therapeutic level of the drug without causing toxicity.

Together, these systems aim to:

- Provide an intimate contact between the dosage form and the absorptive mucosa, resulting in a high drug flux through the absorbing tissue.
- Enhance the bioavailability of the drug by bypassing first-pass metabolism.
- Improve therapeutic outcomes by releasing the drug at the action site, leading to better local and systemic effects (Table 1).

Gelatin

Gelatin, a combination of fractions composed entirely of amino acids joined by peptide bonds to form polymers with molecular weights ranging from 15,000 to 400,000 [5], has a relative density of 1.3 to 1.4 and contains 8 to 13% moisture [6]. The texture of gelatin is almost odorless and tasteless. Ether, methanol [7], 95% ethanol, acetone, and chloroform do not dissolve it. It is soluble in glycerin, acids, and alkalis, but precipitates in strong acids or alkalis. As it softens and swells over time, it absorbs five to ten times its weight in water. When cooled to 35 to 40°C, it turns into a gel or jelly. It dissolves in hot water. The system is present as a sol at 40°C. Gelatin is a multipurpose substance that shows characteristics such as gel formation. Thickening, water binding, emulsifying, film formation, foaming, and whipping. Because of its multiple uses, particularly in water binding (gelation), gelatin is now used on a macro and micro level as a component in many goods [8]. The resulting gel is known as hydrogel. The size of the gelatin generated by controlled hydrolysis further determines the strength of this hydrogel, which is expressed as Bloom. The gelatin is categorized as Type-A and Type-B [9] based on hydrolysis. Pork skin is hydrolyzed acidically to produce type-A gelatin, which gives the mixture its elasticity and flexibility. Animal skin and bones are hydrolyzed to produce type B gelatin, which gives the mixture a high gel strength. Type A gelatin's isoelectric range is between pH 7 and 9, while type B's range is between pH 4.7 and 5.4 [10-14]. Gelatin's high water-binding capacity and water solubility are due to the presence of functional groups, mainly OH, COOH, and NH2, which aid in the formation of hydrogels. Covalent bonds are formed between gelatin chains by the reaction of functional groups with complementary reactivity, such as an amine-carboxylic acid or an isocyanate-OH/NH2 reaction. Since gelatin is a protein, it has the chemical properties of such materials, including amino acids with the functional groups -COOH and -NH2 (most proteolytic systems, for instance, break down gelatin to produce its amino components). Acids, bases, aldehydes, aldehydic sugars, anionic and cationic polymers, metal ions, plasticizers, preservatives, and surfactants are among the substances that gelatin reacts with. Acylation, esterification, deamination, cross-linking, polymerization, and basic reactions with acids and bases are examples of common reactions. [15,16]

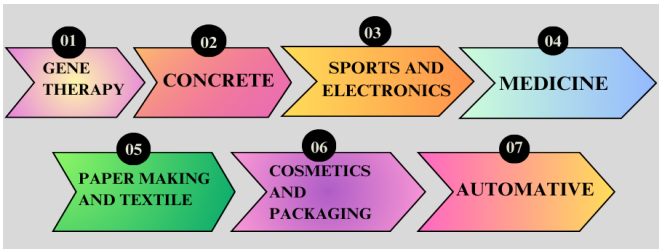

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Fig 1: Application of biopolymers

Hyaluronic Acid

Hyaluronic acid (HA) is a member of the polysaccharide family and is a glycosaminoglycan molecule[17]. The units of glucuronic acid and N-acetyl-D-glucosamine alternate to form the HA molecule. HA is found in nearly all vertebrate tissues[18-20]. HA has an extremely big molecular weight of many millions. HA produces very viscous solutions and is very soluble in water. These solutions have unique viscoelastic

Table 1: Illustrating various polymers, their sources, solubility, and charges

Polymer	*Source*	*Solubility*	*Charge*
Gelatin	Animal collagen of bones, skin, and white connective tissue tissue, tendons, ligaments	Soluble in hot water or alcohol	Positive or negative (The extraction process from collagen determines the isoelectric point.)
Hyaluronic Acid	• Fermentation of certain bacteria • Rooster combs • Bone broth Foods such as soy products, oranges, almonds, kale, and sweet potatoes	Soluble in water, slightly soluble in organic solvents	Negative charge
Chitin	Shrimp and crab shells, a plentiful byproduct of the food processing industry, contain chitin, a biopolymer that can be employed in biomedical applications in massive amounts.	Dilute in an acidic medium	Positive charge
Pectin	The richest sources of pectin are found in the peels of citrus fruits such as oranges, lemons, limes, grapefruit, and passionfruit	Soluble in hot water	Negative charge
Xanthan gum	It is produced by a strain of bacteria known as Xanthomonas campestris. These bacteria are found on the leaf surfaces of various Green vegetables	Soluble in both hot and cold water	Negative charge
Moringa gum	Extracted from the stem or bark of Moringa Oleifera.	Soluble in water	Negative charge

properties[21]. HA can form intramolecular hydrogen bonds, which can result in three-dimensional structures. Because hyaluronic acid retains water in its structure, it can form gels. The weight of trapped water is over a thousand times that of HA. Tissues containing HA include the cervix, skin, articular cartilage, nucleus pulposus, and glycocalyx of endothelial cells. HA gels and solutions are commonly used as a dermal filler.

Because hyaluronic acid retains water in its structure, it can form gels; the weight of trapped water is more than a thousand times that of HA. Tissues containing HA include the cervix, skin, articular cartilage, nucleus pulposus, and glycocalyx of endothelial cells. HA generates very viscous solutions and is highly soluble in water, giving these solutions unique viscoelastic properties. HA gels and solutions are frequently used as a dermal filler. It can support the proliferation of epithelial tissue cells, macrophages, eosinophils, and some animal tissue cells. The molecular weight of HA often determines its function. For example, low molecular weight HA is essential for healing and scar formation, whereas high molecular weight HA may preserve tissue integrity. Because HA absorbs water, it gives animal tissue flexibility and lubrication in the connective tissues of muscles. Hyaluronic acid is frequently used as a component in biomaterials. The potential of HA as a wound dressing, for example, has been extensively researched. Because HA contains many functional groups, it can be cross-linked utilizing a variety of physical and chemical methods. The ability of HA to stimulate mesenchymal and epithelial cell migration and differentiation makes it suitable for use in tissue healing. HA is an excellent material for tissue engineering due to its biological characteristics. An aqueous solution of HA can be used to create 3D porous materials. The properties of HA hydrogels and 3D HA materials can be changed by the cross-linking method and the HA concentration. Cross-linking increases a material's resistance to enzymatic breakdown. Because HA hydrogels can hydrate the skin, they are frequently utilized for skin rejuvenation. Additionally, as a dermal filler, HA has been administered intradermally. Additionally, HA is a component of cosmetic gels and creams that address a range of medical conditions[22,23]. One substance that promotes collagen is hydrogel HA. HA's ability to create films is advantageous for hair care as well. There are several applications for hyaluronic acid outside of cosmetics. Due to its capacity to alter cellular activity, HA is also utilized for several therapeutic applications, including medication administration, organ implantation, and coatings. Physical and chemical cross-linking techniques are not the only ways to alter the characteristics of hyaluronic acid. It is possible to combine hyaluronic acid with a biopolymer or another polymer. Combining less expensive synthetic polymers with polysaccharides is one way to reduce the cost of materials. Polymer scaffolds for biomedical applications can be made by combining hyaluronic acid with synthetic or another natural polymer. This review aims to present the most recent research on hyaluronic acid mixed with collagen and chitosan. However, it should be mentioned that hyaluronic acid can also be combined with biopolymers and other polymers.

Chitin

One of the most significant natural polysaccharides is chitin, also known as poly (β-(1–4)-N-acetyl-D-glucosamine). The Greek word "chiton," which means a coat of mail, is the source of the name "chitin." Henri Braconnot, a French chemist, was the first to describe the use of chitin in 1811. Chitin ($C_8H_{13}O_5N$) shares a structure with cellulose, but it contains 2-acetamido-2-deoxy-β-D-glucose (NAG) monomer units that are joined by β(1→4) bonds.[24-26] Chitosan is the deacetylated form of chitin, which can have different levels of deacetylation. It dissolves in an acidic solution; however, it can be problematic at times. Chemical hydrolysis or enzymatic preparations can be used to convert chitin to chitosan. It has been predicted that 1011 tons of chitin are produced each year naturally worldwide. Chitin's material form is often an inelastic, white, rigid

nitrogenous polymer. It has additionally been found to be the main source of beach contamination in coastal regions. Chitin is present in nature as crystalline microfibrils that serve as structural elements in the exoskeletons of arthropods and the cell walls of fungi[27,28]. Because of its better defense and reinforcing properties, chitin is also produced by a wide variety of other living organisms in the lower plant and animal kingdoms. Cellular processing and chitin production are extremely intricate, multifaceted, and interrelated processes that begin intracellularly and culminate in the incorporation of chitin into external supra-macromolecular structures like fungal cell walls and arthropod cuticles.

Since no examples of a quantitatively significant long-term accumulation of chitin have been found in nature, its production, breakdown, and turnover must be well balanced. Apart from the availability and abundance of chitin, it has been revealed that many species include enzymes that break down chitin. The biodegradability of chitin is due to the wide distribution of chitinase enzymes in nature.

Pectin

Pectins are non-starchy linear polysaccharides found in plant cell walls. They were first extracted and isolated in 1820 and were commercially produced in Germany in 1908. Pectin's versatility and numerous advantages make it a rapidly growing material in pharmaceutical and biotechnology. It serves as a thickening agent, gelling agent, and colloidal stabilizer in the food and beverage sector. It can create a gel-like consistency in aqueous solutions when calcium ions, sugar and acid are present. Pectin can also absorb and clear biogenic toxins, xenobiotics, anabolic steroids, metabolites, and harmful products[29]. The physicochemical parameters of pectin are significantly influenced by the degree of esterification of galacturonic acid units within its structure. Factors such as processing, harvesting conditions, plant source origin, isolation, purification, and storage also influence the degree of esterification [30].

Pectin is a crucial component in the food industry due to its gelling and stabilizing properties. It is predominantly present in plant cell walls, especially in apple pomace, citrus peels, and sugar beet pulps. Pectin is most abundant in the middle lamella of the cell wall. Commercial pectins are mostly derived from citrus fruit peels and apple pomace, which are leftovers from the juice-making process. Pectin can also be found in carrots, cabbage, bananas, sugar beets, mango waste, and pomelo peel. Once the extract has been refined by filtration and concentrated under vacuum, the pectin is precipitated by adding ethanol or isopropanol. After drying and milling, pectin is typically standardized with sugar, calcium salts, or organic acids to improve its performance. Low-esterified pectins are created by treating the initial pectin with dilute acids, whereas amidated pectins are created by adding ammonium hydroxide [31].

Pectin is a promising biopolymer in the pharmaceutical industry, known for its natural preventive properties, reducing blood cholesterol levels, and treating gastrointestinal and respiratory disorders. It has been effective in regulating local bleeding and hemorrhage, treating diarrheal conditions in children and infants, and showing antimicrobial action against Escherichia coli. Pectin also immobilizes food constituents in the intestine, reducing digestion rates and resulting in lower food absorption [44]. Its wide water-binding capacity reduces food consumption. Pectin has promising pharmaceutical uses, including controlled-release dosage forms, carrier, and ionotropic gelation and gel coating. Its safe toxicity profile makes it an interesting and promising excipient for the pharmaceutical industry. Pectin hydrogels act as binding agents in controlled-release matrix tablet formulations and as encapsulating agents in sustained-release dosage forms alone or in combination with gelatin [32]. Low methoxy pectin in combination with aluminum hydroxide and magnesium oxide has been effective in treating duodenal and gastric ulcers. HM pectin during administration acts as a demulcent, reducing gastric irritation and improving the sustained release action of aspirin.

Xanthan gum

The gram-negative, small, rod-shaped aerobes in the genus *Xanthomonas* belong to the Pseudomonadaceae family. Although the majority of the species in this genus are phytopathogens, many of them also generate xanthan gum. At the commercial level, aerobic fermentation utilizing organic acids as stimulants at 27 to 30°C can turn 70% of the substrate into gum.

A hetero-polysaccharide, xanthan gum, is produced by *Xanthomonas* species. It is a naturally occurring, high molecular weight polysaccharide molecule that is mostly produced by different fermentation methods. For water-based systems, its exceptional rheological qualities make it a highly helpful stabilizing agent. It has a wide range of uses, from oil drilling to the food industry. In the food sector, it is commonly utilized in low-calorie items in general as well as salad dressings, sauces, milk products, gravies, and sweets. Additionally, xanthan gum is utilized to make agricultural flowables, polishes, varnishes, and cleansers. This chapter explains how xanthan gum is extracted from microorganisms, what influences production, and how it is used in various industries.

Recent studies have focused on xanthan gum (XG), an extracellular microbial polysaccharide generated by *Xanthomonas campestris*, due to its outstanding characteristics and commercial viability. The structure includes a 1-4-linked β-D glucose backbone and a trisaccharide side chain with one glucuronic acid group and two mannoses. The carboxyl groups of the side chain cause a stretched and disordered conformation in the aqueous state due to electrostatic repulsion between the side chain and the backbone. XG has been widely utilized in a variety of sectors, including food, cosmetics, medicine, and petroleum, as a thickening, stabilizer, emulsifier, gelling, and suspending agent (flocculant) for rheological modification due to its shear-thinning capacity throughout a wide pH and temperature range. Furthermore, recent investigations have shown that XG BPST has the potential to stabilize and reinforce soil from a geotechnical engineering standpoint. XG has shown the ability to boost clay's undrained shear strength by creating viscous hydrogels that connect with charged clay surfaces. It can also boost the shear strength of sand-clay mixtures via the aggregation effect. XG-based materials have been employed in a range of technical areas, including petroleum and medical, to inject fluids at various concentrations. Prior geotechnical engineering research has demonstrated that, depending on the injection pressure, soil parameters, and rheological properties of the XG hydrogel, highly concentrated XG hydrogels can limit permeability by entering sandy soils and joint apertures.

Moringa gum

A member of the Moringaceae family, *Moringa oleifera Lam*, also called *M. pterygosperma* Gaertn., is the plant that yields moringa gum. Common and regional names for the plant include "drumstick tree," "horse plant radish tree," and "kelor tree" (Anwar & Bhanger, 2003). The plant grows between 5 and 10 meters tall and is found on the plains in both wild and cultivated conditions (Morton, 1991). Commonly found near riverbanks, this plant thrives in tropical climes [33].

According to Bhattacharya *et al*. (1982), the gum derived from the *Moringa oleifera* plant contains L-arabinose, D-galactose, D-glucuronic acid, L-rhamnose, D-mannose, and D-xylose in a mole ratio of 14.5: 11.3: 3: 2: 1: 1. Singh (2016) used periodate oxidation tests to identify the gum's structure. It verified that gum polysaccharide is substantially branched and that (1→3)-β-type connections are present. The methylation of pure gum provided additional confirmation of the gum polysaccharide's molecular structure. There have been reports of MOG modifications to improve its morphological and physicochemical characteristics. Numerous methods, including grafting, carboxymethylation, cross-linking, acid hydrolysis, thiolation, and acryloylation, have been used to derivatize MOG [34].

MOG and its derivatives have prospective uses in a variety of industries, such as wastewater treatment, pharmaceutical excipients, and drug delivery.

A patent for the MOG, which was used to create the bio-nanoparticles, is available. In short, the gum powder was cleaned using diethyl ether, chloroform, and methanol (50% methanol and 100% ethanol) before being dried. After adding HCl to the purified MOG aqueous extract in a Soxhlet device to reach a final concentration of 0.5 N, the mixture was extracted for 60 minutes at 100°C. After cooling to 25°C, the acid-hydrolyzed polysaccharide was extracted and 1 M NaHCO3 [35].

Numerous illnesses and conditions, including fever, headache, dysentery, asthma, and digestive problems, have been discovered to be treated pharmacologically by MOG. Additionally, it is used to treat syphilis and rheumatism and as an astringent, rubefacient, abortifacient, and antioxidant. MOG is regarded as safe for use in food and pharmaceuticals because of its special qualities, which include biodegradability, biocompatibility, non-toxicity, cost-effectiveness, secure storage, and handling.

Medicinal Uses

Topically applied (on the skin), Moringa gum and roots can heal wounds, abscesses, warts, gingivitis, and even snakebites. Its potent anti-inflammatory, antifungal, and antibacterial properties contribute to its effectiveness. Moringa gum has been traditionally used to treat syphilis, gastrointestinal issues, and rheumatism.

Other Applications:

- Fabric Printing: Moringa gum (Sohjana gum) finds use in fabric printing.
- Water Purification: It has been explored for water purification purposes.
- Culinary Uses: While not as common, Moringa gum has culinary applications.
- Cosmetics: It can be incorporated into cosmetic formulations.

Thiolation of mucoadhesive polymers is a chemical modification process that involves introducing free thiol groups (-SH) onto the polymer chain. This modification enhances the polymer's mucoadhesive properties, which means it can adhere more effectively to mucosal surfaces, such as those found in the gastrointestinal tract, the eye, or the nasal cavity. The presence of thiol groups allows for the formation of strong disulfide bonds with the mucin layer on mucosal surfaces. These bonds increase the duration that the polymer can remain attached to the mucosal surface, which is particularly beneficial for controlled drug delivery systems.

Thiolated polymers, also known as thiomers, exhibit improved mechanical properties and a more cohesive matrix, which can lead to a slower and more controlled release of the drug. In summary, thiolation is a valuable technique for enhancing the effectiveness of biopolymers used in drug delivery by improving their adhesion to mucosal surfaces and their overall mechanical strength.

Methods of Thiolation

Thiolation by Traut's Reagent

According to the literature, for the thiolation procedure, the biopolymer was dissolved in a non-amine buffer (pH 7.4), and Traut's reagent and EDTA were added in amounts based on the protein size and concentration of the biopolymer (Fig 2). The reaction mixture was then incubated at room temperature for one hour. After filtering the unreacted reagent, Ellman's reagent was used to identify sulfhydryl groups [37,38].

Thiolation by Dithiothreitol (DTT) Reduction

The chemical 2,3-dihydroxy-1,4-dithiolbutane has a trans isomer known as DTT. It can maintain free thiol groups even when oxygen is present and reduce all biological sulfhydryl groups. The biopolymer was dissolved in a 7.4 pH phosphate buffer. The amount of biopolymer and its concentration dictate how much DTT and EDTA are required (Fig 3) [37,39,40].

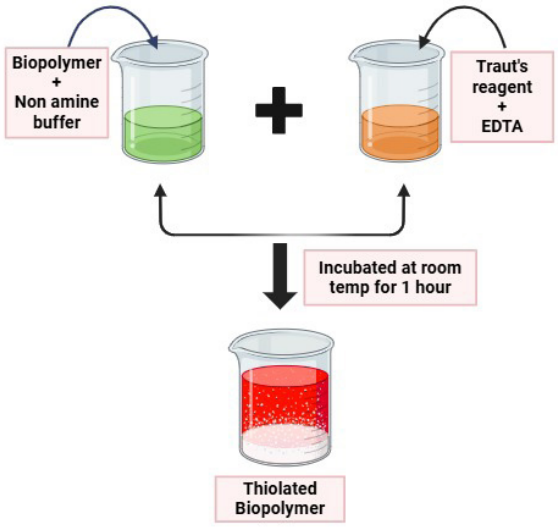

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Fig 2: Thiolation by Traut's Reagent

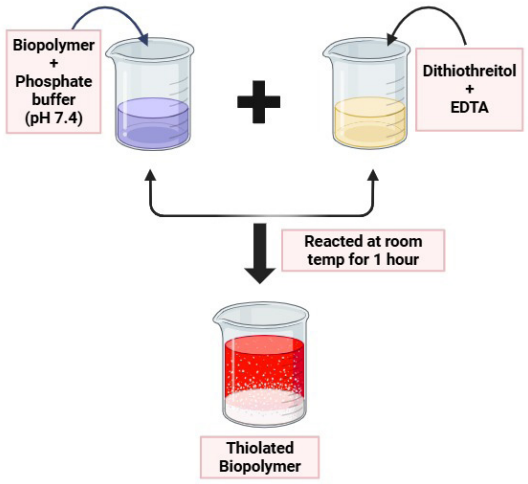

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Fig 3: Thiolation by DTT Reduction

Thiolation by Dithiolaromatic (PEG6-CONHNH2)

Non-native disulfide linkages are formed when a substance known as dithiol aromatic displaces and increases the amount of cysteine residues. The biopolymer was combined with sodium hydrogen phosphate and sodium periodate to experiment, and it was then left in the dark for half an hour. To the previously produced solution, mixtures of ethanol, dithiol aromatic, and phosphate buffer solution were added. The preparation underwent a one-hour reaction at room temperature. Lastly, the unreacted reagent was filtered, and the presence of sulfhydryl groups on the thiolated biopolymer was assessed using Ellman's technique (Fig 4) [37,41].

Thiolation by Thiol Polyethylene Glycolamine (SH-PEG-NH2)

After adding biopolymer to 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide-hydrochloride, phosphate buffer pH 7.4, thiol polyethylene glycol amine, or EDAC, to the mixture. After that, the mixture was incubated for around two hours on a rotator. Sulfhydryl groups (-SH) were discovered to be present in the thiolated biopolymer by employing Ellman's reagent and unreacted chemical filtration (Fig 5) [37,42].

Thiolation by Thioglycolic Acid

After the biopolymer's ethanolic extract had been dissolved in thioglycolic acid (TGA), EDAC, or 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide-hydrochloride was progressively added to the mixture while being constantly stirred for about three steps. The unreacted molecule was filtered, and the sulfhydryl groups (-SH) were detected with Ellman's reagent (Fig 6) [37,43].

Importance of thiolation of mucoadhesive polymer

Thiolated polymers, also known as thiomers, are a type of polymers that have special mucoadhesive qualities that enable them to create robust covalent connections with mucus glycoprotein subdomains that are rich in cysteines. They are therefore perfect for creating drug delivery systems (DDSs) for a variety of disorders affecting the dry mucosal surface. The better adhesion and retention time that thiomers provide over their non-thiolated counterparts results in greater bioavailability and decreased patient non-compliance. Along with increasing permeability and protecting protein and peptide medications from digestive enzymes, they can also block specific enzymes. Different polymers have been thiolated utilizing various thiolation moieties, and thiomers have been studied for application in a variety of administration methods. Thiolated polymers have a wide range of uses, such as controlled drug release, mucoadhesion, and tissue engineering. Thiolated polymers, commonly known as thiomers, have special mucoadhesive qualities that allow them to establish robust covalent connections with subdomains of cysteine-rich mucus glycoproteins. They are therefore perfect for the development of drug delivery systems (DDSs) for several disorders that affect the

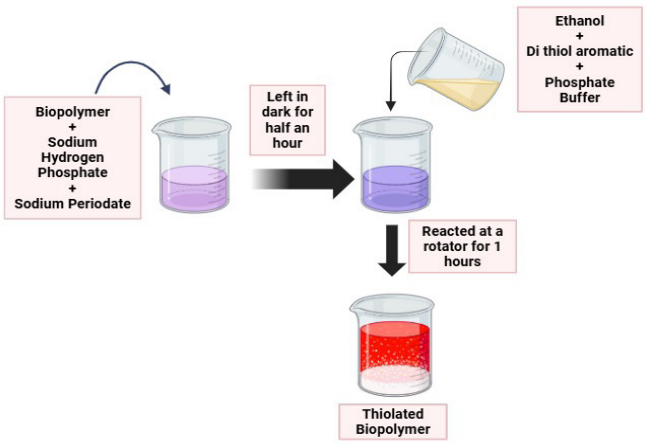

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Fig 4: Thiolation by Dithiolaromatic (PEG6-CONHNH2) BioRender.com

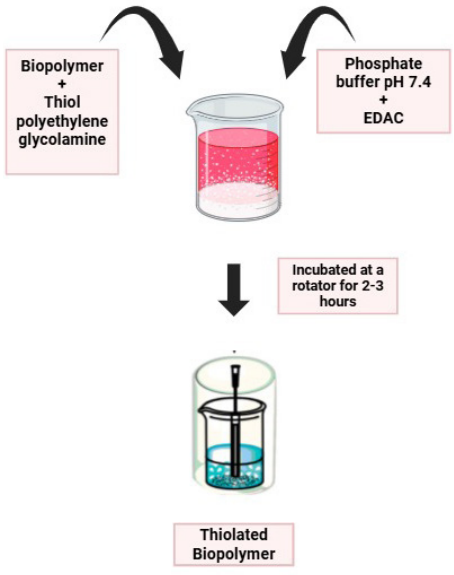

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Fig 5: Thiolation by Thiol Polyethylene Glycolamine (SH-PEG-NH2)

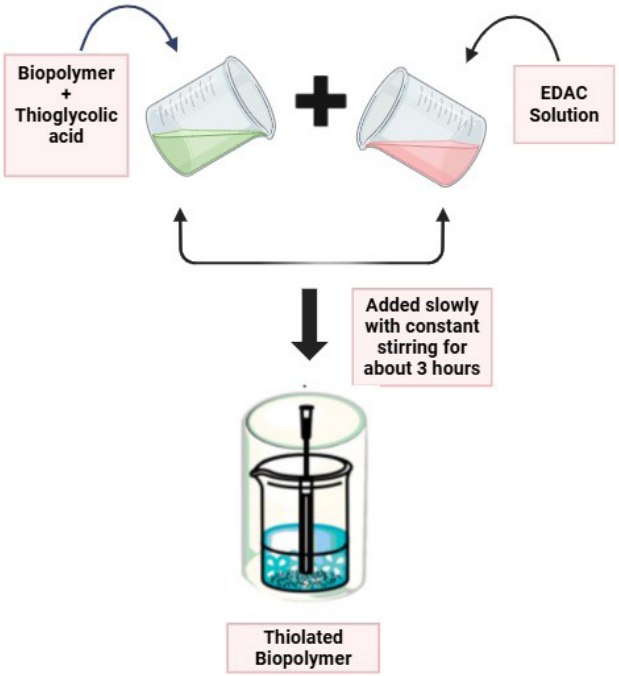

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Fig 6: Thiolation by Thioglycolic Acid

dry mucosal surface. Thiomers' superior adhesion and retention duration over their non-thiolated counterparts leads to increased bioavailability, and a reduction in patient non-compliance can increase permeability, prevent certain enzymes from working, and protect medications made of proteins and peptides from enzyme digestion. Various polymers have been thiolated utilizing various thiolation moieties, and thiomers have been studied for application in a variety of administration strategies (Table 2).

Challenges and Limitations of Thiolated Polymers

Thiolated polymers, while offering several advantages for various applications, also present several drawbacks that need to be carefully considered. This detailed document will explore the key challenges associated with the use of thiolated polymers, providing a comprehensive understanding of their limitations and the potential obstacles that need to be addressed.

Reduced Mechanical Strength

One of the primary drawbacks of thiolated polymers is their reduced mechanical strength compared to their non-thiolated counterparts. The introduction of thiol groups can disrupt the polymer's backbone structure, leading to a decrease in overall tensile strength, elasticity, and resistance to deformation. This can be a significant limitation in applications where the material needs to withstand high mechanical stresses or loads, such as in the development of medical devices or structural components.

Increased Susceptibility to Oxidation

Thiolated polymers are more susceptible to oxidation due to the presence of reactive thiol groups. These groups can readily undergo oxidation reactions, leading to the formation of disulfide bridges or other oxidized species. This increased susceptibility to oxidation can result in a deterioration of the polymer's physical and chemical properties over time, potentially compromising its performance and stability in various applications. Proper storage and handling conditions are crucial to mitigate this issue and maintain the integrity of thiolated polymers.

Limited Thermal Stability

Thiolated polymers often exhibit limited thermal stability compared to their non-thiolated counterparts. The presence of the thiol groups can make the polymer more susceptible to thermal degradation, leading to a reduction in the material's ability to withstand high temperatures or prolonged exposure to heat. This can be a significant drawback in applications where the polymer is subjected to elevated temperatures, such as in certain manufacturing processes or high-temperature environments.

Potential Toxicity Concerns

Thiolated polymers may raise toxicity concerns due to the potential release of thiol-containing compounds or their metabolites. These compounds can be reactive and potentially harmful to biological systems, particularly in biomedical applications where the polymer is intended for direct contact with living tissues or the human body. Extensive toxicological evaluation and careful risk assessment are necessary to ensure the safe use of thiolated polymers in such applications.

Reduced Drug Loading Capacity

In drug delivery applications, the incorporation of thiol groups into polymers can sometimes reduce the overall drug-loading capacity of the material. This is because the thiol groups may occupy space within the polymer structure, leaving less available volume for the encapsulation or attachment of therapeutic agents. This limitation can impact the efficiency and performance of thiolated polymer-based drug delivery systems, potentially requiring the optimization of formulation parameters or the exploration of alternative polymer designs to overcome this challenge.

Difficulties in Achieving Consistent Drug Release

The presence of thiol groups in polymers can introduce additional complexity in achieving consistent and predictable drug release profiles. The reactivity of the thiol groups and their potential interactions with the drug or the surrounding environment can lead to variations in the drug release kinetics, making it challenging to maintain a reliable and reproducible drug delivery performance. Careful design and extensive characterization of thiolated polymer-based drug delivery systems are often necessary to overcome this limitation and ensure the desired therapeutic outcomes.

Future Perspectives

Because of their improved mucoadhesive qualities, possibility for controlled drug release, and potential for use in biomedicine, thiolated polymers, or thiomers, have drawn a lot of interest. Thiolated polymers' hopes for the future center on growing their utilization in sustainable applications, nanotechnology, regenerative medicine, and sophisticated drug delivery systems.

Table 2: Illustrating various biopolymers, thiolation moiety, and formulation

Sr. No.	*Biopolymer*	*Thiolation moiety*	*Thiolation formulation*
1.	Gelatin	Traut'sreagent	Hydrogel
2.	Gelatin	L-cysteine	Hydrogel
3.	Hyaluronic Acid	Dithiobis (propanoic dihydozide) and Dithiobis (butyric dihydrozide)	Hydrogel
4.	Hyaluronic Acid	L-cysteine	Tablets
5.	Chitosan	3-mercaptopropionic acid	Nanoparticles
6.	Chitosan	Traut's reagent (2 Iminothiolane)	Microparticles
7.	Pectin	Thioglycolic acid	Beads
8.	Pectin	4-Aminothiophenol	Hydrogels
9.	Xanthum Gum	Thioglycolic acid and mercaptopropionic acid	Buccal Pellets
10.	Moringa Gum	Thioglycolic acid	Tablets

Cutting-Edge Drug Delivery Methods

The creation of medication carriers based on thiolated polymers that are customized for each patient, increasing therapeutic effectiveness and lowering side effects, is known as personalized medicine.

Targeted Drug Delivery

By lowering systemic toxicity, thiolated nanoparticles can be designed to release drugs at targeted sites, as in cancer treatment.

Controlled-Release Formulations

Advances in hydrogels and nanoparticles based on thiolated polymers will result in extended medication release, improving patient adherence. Oral Peptide and Protein Drug Delivery: By shielding oral protein medications (such as insulin and growth hormones) from enzymatic breakdown, this method improves their stability and absorption.

Regenerative medicine and tissue engineering

Scaffolds that biodegrade

Thiolated biopolymers can be utilized to create scaffolds that promote tissue regeneration, especially in applications involving wound healing, bone, and cartilage.

Self-Healing Hydrogels

Studies on thiolated hydrogels with self-healing qualities may enhance their use in organ regeneration and wound repair.

Smart Biomaterials

Combining stimuli-responsive materials with thiolated polymers can result in novel uses for drug release and controlled tissue healing.

Transdermal and Mucoadhesive Drug Administration

Formulations for Long-Acting Mucoadhesives

Enhanced adherence and retention on nasal, vaginal, ocular, and oral mucosal surfaces for extended medication effectiveness.Transdermal Patches: Creation of patches based on thiolated polymers for hormone treatment, nicotine replacement therapy, and pain relief.

Ophthalmic Drug Delivery

Adding thiolated polymers to eye drop formulations to improve retention and cure long-term eye conditions.

Utilizing Nanotechnology

Nanocarrier Systems

Creation of nanoparticles based on thiolated polymers for targeted drug delivery in neurological and cancer treatments.

Gene Delivery Systems

By shielding genetic material from deterioration, thiolated polymers can enhance the delivery of DNA/RNA-based therapies.

Biosensors

Thiolated biopolymers in biosensors can enhance the diagnosis of diseases, particularly when it comes to real-time biomolecule detection.

Overcoming Present Issues

The goal of the research is to stabilize thiolated polymers against oxidation to increase their shelf life.

Safety and Biocompatibility

To reduce toxicity and guarantee compatibility with human tissues, advanced formulations will be created.

Scalability and Cost-Reduction

Cheaper thiolated polymers for extensive pharmaceutical and biological uses will be possible thanks to effective manufacturing techniques.

DISCUSSION

Thiolated biopolymers and their improved mucoadhesive characteristics for advanced drug delivery systems are thoroughly reviewed in this work. It covers several biopolymers gelatin, hyaluronic acid, chitin, pectin, xanthan gum, and moringa gum as well as several techniques for introducing thiol groups onto their structures. By enhancing the mucoadhesive properties of these biopolymers, the thiolation process helps them to generate stronger covalent connections with the cysteine-rich subdomains of mucus glycoproteins. Improved bioavailability and lower patient non-compliance in medication delivery systems can follow from this enhanced adhesion and retention time on mucosal surfaces. Along with their exciting future possibilities in fields such as personalized medicine, regenerative engineering, and sustainable industrial processes, the paper also emphasizes the possible difficulties and restrictions of thiolated polymers.

CONCLUSION

Thiolation can change biopolymer properties, making it useful in tissue engineering, medicine delivery, and other applications. As long as research addresses the challenges, thiolated biopolymers can be developed and used in many fields. Many research institutions have studied thiolated polymers for 20 years. The covalent bond between thiol groups and polymeric backbones enhances several features.

Immobilizing thiol groups on polymeric excipients that bind with cysteine-rich keratin and mucus glycoprotein subdomains increases stickiness. Utilizing thiol groups' strong reactivity, thiomers have been widely researched for their in situ gelling properties using several chemical cross-linking methods. We tested different thiolated polymers as matrices. Thiolated polymer hydrogels are intriguing because of their biocompatibility and cross-linkability.

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