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Recent updates on thiolated chitosan polymer in mucoadhesive drug delivery applications

Mohan Raj. V*, M. Komala

Department of Pharmaceutics, School of Pharmaceutical Sciences, Vels Institute of Science, Technology & Advanced Studies (VISTAS), Chennai, India

ABSTRACT

The concept of mucoadhesion has gained considerable interest in pharmaceutical industry and academic research due to this technology have potential to deliver highly efficient dosage forms especially for oral drug delivery. Thiolated chitosan polymer expected to strong cohesive properties with mucus layer, make them highly suitable excipients for controlled drug release dosage forms. The mechanism of enhancing mucoadhesion due to the high value of the thiol moieties on chitosan leading to a much higher concentration of thiolate anions, which are responsible for the reaction with thiol groups within the mucus gel layer that improves mucoadhesion based on the covalent attachment. Thiolated chitosan could have potential to prolong retention of the dosage form at the site of absorption, thereby improving its clinical efficacy of the encapsulated drugs. Within this Review, an overview of mucoadhesive system and properties of thiolated chitosan and its application toward oral mucoadhesive drug delivery is discussed.

Keywords: Thiolated chitosan, Mucoadhesive delivery system, Chitosan

INTRODUCTION

Chitosan has received considerable attention as a novel excipient in drug delivery systems because of its favourable properties, such as biodegradability, non-toxicity and biocompatibility. The primary amino group accounts for the possibility of relatively easy chemical modification of chitosan.[1] The inherent mucoadhesion properties of chitosan can be further enhanced by thiolation, more specifically by grafting thiol-containing side groups to chitosan. Recently, it has been shown that polymers with thiol groups provide much higher adhesive properties than polymers generally considered to be mucoadhesive. The new generation of mucoadhesive polymers capable of forming covalent bonds to the layer of mucus, unlike the first generation mucoadhesive polymers attached to the mucus gel layer through noncovalent bonding. Thiolated polymers mimic the natural mechanism of secreted mucus glycoprotein's, which are also covalently anchored in the mucus layer by the formation of disulfide bonds-the bridging structure most commonly encountered in biological systems. Due to the immobilization of thiol groups on mucoadhesive basis polymers, their mucoadhesive properties are 2- up to 140-fold improved.

In this review, the importance of chitosan, as a naturally occurring polysaccharide polymer, and its derivatives in drug delivery are illustrated. The usefulness of chitosan derivatives towards mucoadhesive drug delivery system is addressed. Finally, a very specific application of thiolated chitosan through Interpenetrating polymer network (IPN) also discussed.

Chemistry of Chitosan

Chitin is the second most abundant polysaccharide in nature, second only to cellulose; and is primarily present in the exoskeletons of crustaceans (such as crab, shrimp, lobster etc.).[2]Chemical structure of chitin consists of linear repeating units of 2-acetamido-2-deoxy-D-glucopyranose attached through β - (1→4) linkages shown in Figure 1.

Mohan Raj. V
Department of Pharmaceutics, School of Pharmaceutical Sciences, Vels Institute of Science, Technology & Advanced Studies (VISTAS), Chennai, India

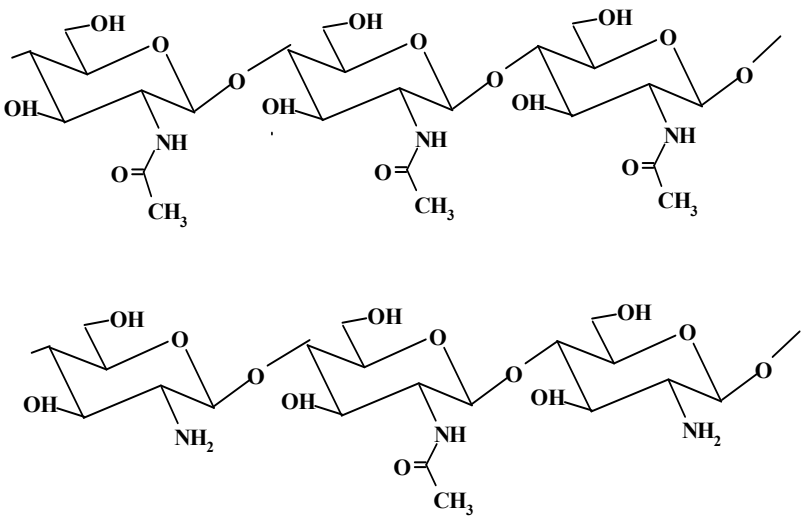


Figure 1 Chemical structure of a) Chitin b) Chitosan

Chitosan is deacetylated chitin; a structural modification of chitin often performed by alkaline hydrolysis.

Isolation of Chitin and Synthesis of Chitosan

Within its natural resources of commercial interest, chitin exists not as a stand-alone biopolymer, but rather in conglomeration with other biomaterials, mainly proteins, lipids, and inorganic salts. The isolation process of chitin starts at the sea-food industry and schematic representation is shown in Figure 02. One of the by-products of this industry, *viz.* shells from crab, shrimp, etc. are first crushed into a pulverous powder to help make a greater surface area available for the heterogeneous processes to follow. An initial treatment of the shell with 5% sodium hydroxide dissolves various proteins, leaving behind chitin, lipids and calcium salts (mainly as $CaCO_3$). Treatment with 30% hydrochloric acid hydrolyzes lipids; dissolves calcium salts (demineralization) and other minor inorganic constituents. Chitin thus obtained can be hydrolyzed using 50% sodium hydroxide at high temperature to provide chitosan.[3, 4] (Figure 2)

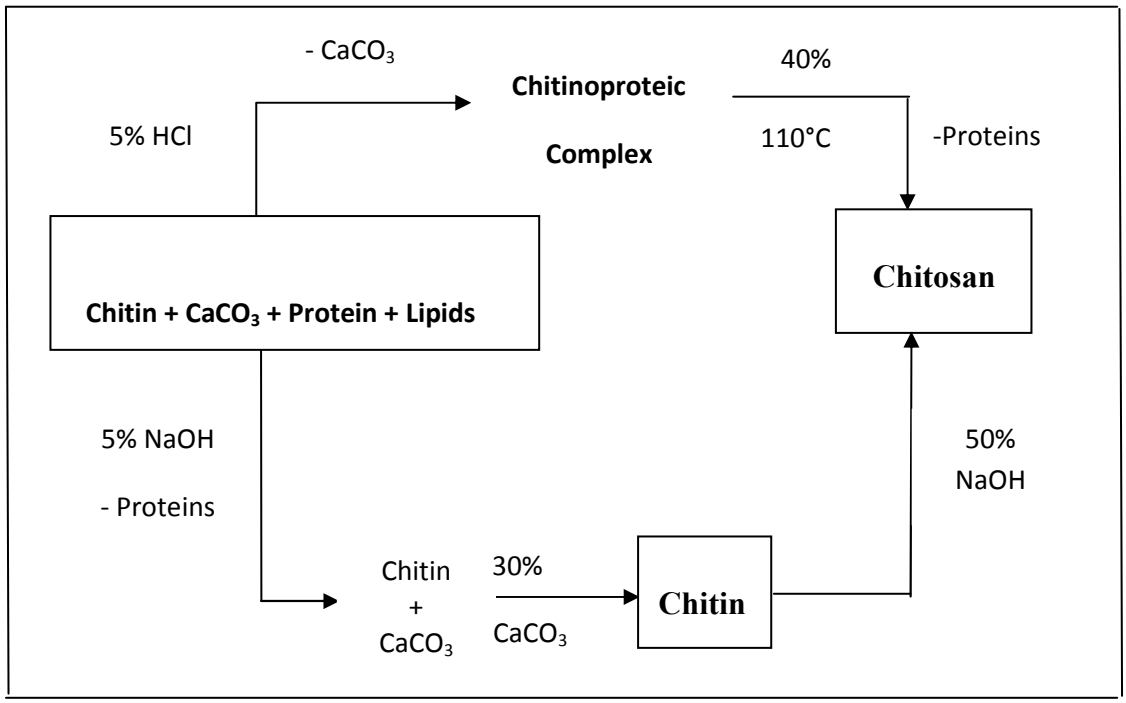


Figure 2: Schematic representation of synthesis of chitosan process

Alternatively, if isolation of chitin is not desired, the acid-base sequence may be reversed to directly produce chitosan. In this method, crushed shells are first treated with 5% hydrochloric acid to remove calcium salts. This is then followed by protein and lipids removal by the treatment with 40% sodium hydroxide at higher temperature. During the base treatment a concomitant hydrolysis of acetamido groups in chitin takes place, resulting in the formation of chitosan.[5]

In the United States, the production of chitin and chitosan is mainly carried out at the sea-food canning industry in the states of Oregon, Washington and Virginia. Other leading

countries producing these bio-polysaccharides from similar sources are China, Japan, Norway, Mexico and Chile. Current processes utilize 6.3 kg of HCl and 1.8 kg of NaOH in production of 1 kg of 70% deacetylated chitin from shrimp shells. Other factors controlling the cost are availability of water (for use in the process as well as a heat exchange medium), nitrogen gas (used to create inert atmosphere), transportation, energy costs and labor. In addition, recent advances in fermentation technology suggest that the cultivation of fungi *(Aspergillus Niger*) can provide an alternative source of chitosan.

Applications of Chitosan

Chitosan can be used as a carrier for sustained release systems for the anionic drug, the interactions between chitosan and the therapeutic agent are more pronounced, and based on an ionic cross-linking in addition, even stable complexes are formed from which the drug can be released even over a more prolonged time period. Chitosans can be homogenized with anionic polymeric excipients such as polyacrylates, hyaluronic acid, alginate, pectin, or carrageenan, resulting in comparatively stable complexes of high density. Mainly based on diffusion and erosion processes, incorporated drugs are released in a sustained manner from suchcomplexes.[6, 7] Chitosan nanoparticulate delivery systems, providing very stable complexes that led to a significantly improved drug uptake leads to enhancement of bioavailability. Chitosan used for developing various novel drug delivery systems and it's summarized in the given Table. 01.

Table 1: Chitosan used for various novel drug delivery systems

Delivery System	Examples
Gene delivery	Chitosan-TPP nanoparticles
Colonic controlled drug delivery	5-aminosalicylic acid (5-ASA) & diclofenac sodium (DS)
Oral immune delivery system	Eudragit-coated chitosan micro particles
Lung protein delivery	Microencapsulated chitosan nanoparticles
Vaccine delivery	Nasal influenza vaccine delivery
Mucosal delivery system	Chitosan-DNA micro particles
Intranasal drug delivery	Nasal delivery of insulin chitosan microspheres
Ocular Drug Delivery Systems	Insulin ocular solution
Intrathecal drug delivery	Baclofen-loaded microspheres in gel suspensions

Chitosan derivatives

Chitosan and its derivatives have been principally investigated as excipients in sedate details, and in medicate conveyance systems. The new methodology comprised of supplanting conceivably harmful mixes by common items, which quickly end up being promising. The pharmaceutical industries quickly comprehended the benefits of utilizing chitosan. The primary properties utilized in the pharmaceutical field are: controlled medication discharge, for example, mitigating naproxen, mucoadhesive properties, in situ gelling properties, transfection improving properties (deoxyribonucleic corrosive and little meddling ribonucleic corrosive ribonucleic corrosive based medications structure stable buildings with chitosan), and penetration enhancing properties.[8,9] Schematic representation of chitosan functional group involved in chemical reactions and to synthesis of various chitosan derivatives is shown in Figure 03.

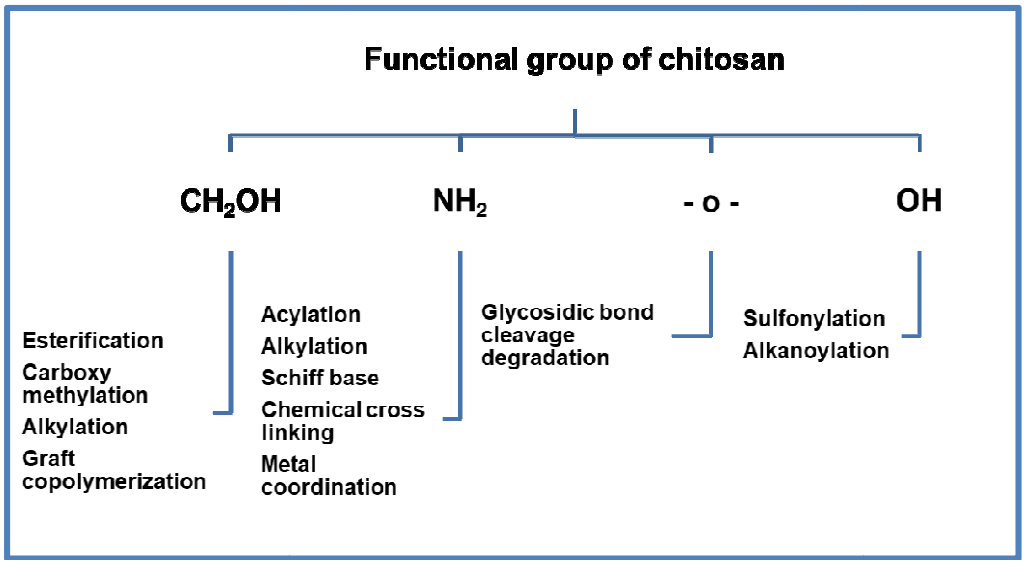


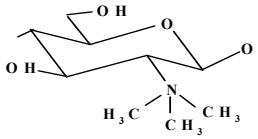
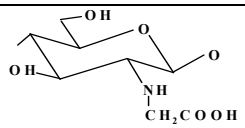
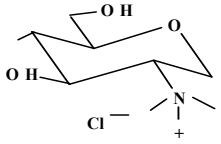
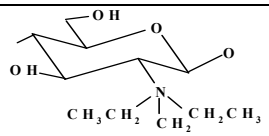
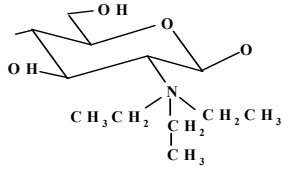
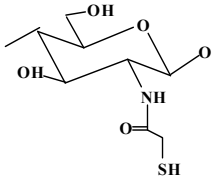
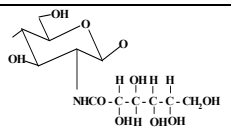
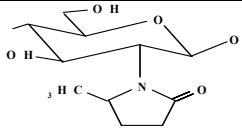
Figure 3Schematic representation of chitosan functional group involved in chemical reactions and to synthesis of chitosan derivatives

Chitosan and its derivatives can be easily processed into different forms such as solutions, gels/hydrogels, sponges, micro particles/nanoparticles, membranes and films (pure films or blends, adhesives), sponges, and fibers/nanofibers.[10,11,12]Chitosan and its derivatives based drug delivery systems is summarised in Table 02.Subsequently, they might be utilized in oral, ocular, nasal, vaginal, buccal, parenteral, intravesical, and transdermal administrations, and as inserts for medicate conveyance in both implantable and injectable forms. Drug delivery applications incorporate not just controlled medication discharge frameworks, for example, site-specific antibiotic conveyance in the stomach, and controlled arrival of proteins, yet in addition vaccine and gene conveyance.[13]

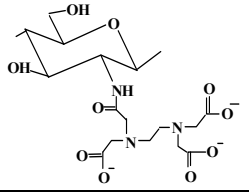
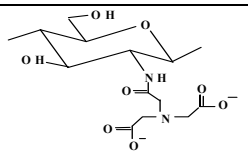
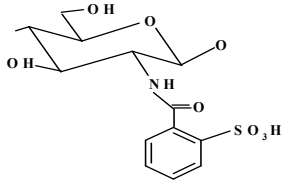
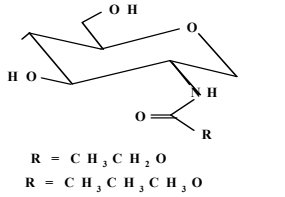
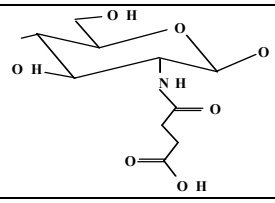
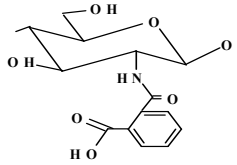
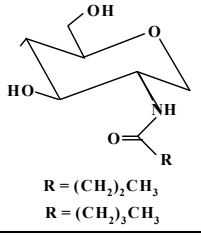
Chitosan is intriguing to be utilized for buccal conveyance because of its mucoadhesive bioactivity and assimilation enhancing property. Solid penetration enhancing properties are too referenced.[14]

The properties of chitosan as resulted in the development of vaccine delivery and injectable preparations. The transmucosal retention advertiser impact of chitosan is significant for nasal and oral conveyance of polar medications to administrate peptides and proteins, and for immunization conveyance. Flims and filaments prepared utilizing chitosan and chitin were produced for tissue engineering and wound dressing, as oral mucoadhesive and water-resisting adhesive by righteousness of their discharge qualities and adhesion.[15, 16]

Table 2: Recent developments of semi synthetic chitosan derivative polymers and its applications

Chitosan derivatives	Chemical structure	Applications
Trimethyl chitosan		Aqueous solubility oral absorption enhancer
Carboxymethylated chitosan		Aqueous solubility oral absorption enhancer Compatible with polyaions drugs
Trimethylammonium salt of chitosan		Improve water solubility at neutral Ph
Diethyl Methyl chitosan		Colonic absorption enhancing agent
Triethyl chitosan		Aqueous solubility
Thiolated chitosan		Strong mucoadhesive character Mucosal permeation enhancing agent
Galactosylated chitosan		Passive and active hepatic targeting carrier
Methyl pyrrolidinone chitosan		Penetration enhancement properties in both Buccal&Vaginal mucosa

Chitosan derivatives	Chemical structure	Applications

Chitosan-EDTA conjugates		Enzyme inhibitor
Chitosan-NTA conjugates		Enzyme inhibitor
N-Sulfobenzoyl Chitosan		Water soluble at neutral pH
Chitosan-polyethylene oxide & Chitosan-polypropylene oxide		Novel carriers for proteins and vaccines
Chitosan Succinate		Soluble at neutral pH Carrier for colon drug delivery system
Chitosan Phthalate		Soluble at neutral pH Carrier for colon drug delivery system
N-acylchitosan (Propionyl& Butyryl chitosan)		Increase hydrophobicity Controlled drug release

Mucoadhesive sites in the body

The various sites available for mucoadhesion in the body are ocular, oral – GIT, buccal, nasal, rectal and vaginal. Each site of mucoadhesion has its own advantages and disadvantages along with the basic property of prolonged residence of dosage form at that particular site. In buccal and sublingual sites, there is an advantage of fast onset along with bypassing the first-pass metabolism, but these sites suffer from inconvenience because of taste and intake of food. In GIT, there is a chance for improved amount of absorption because of microvilli, but it has a drawback of acid instability and first-pass effects.[17] Rectal and vaginal sites are the best ones for the local action of the drug but they suffer from inconvenience of administration. Nasal and ophthalmic routes have another drawback of mucociliary drainage and clearance by tears, respectively, that would clear the dosage form from the site.

Mucoadhesive drug delivery system

Mucoadhesive drug delivery system is nowadays a booming field for drug delivery research interest. These are delivery systems, which utilize the property of bio adhesion of certain biopolymers. Mucoadhesive buccal drug delivery systems offer many advantages over conventional systems such as ease of administration, be promptly terminated in case of toxicity by removing the dosage form from buccal cavity and it is also possible to administer drugs to patients who cannot be dosed orally via this route. Recently much attention has been focused on the design and evaluation of buccal drug delivery systems keeping in view their potential for future market. Therapeutic agents administered through buccal mucosa enters directly to the systemic circulations and thereby circumvent the first pass hepatic metabolism,

gastric irritation and other problems associated with conventional oral route.[18]

Mucoadhesive drug delivery system interact with the mucus layer covering the mucosal epithelial surface, & mucin molecules & increase the residence time of the dosage form at the site of the absorption. Mucoadhesive drug delivery system is a part of controlled delivery system.

Mechanism of mucoadhesion

Several theories have been put forward to explain the mechanism of polymer–mucus interactions that lead to mucoadhesion. To start with, the sequential events that occur during bio adhesion include an intimate contact between the bio adhesive polymer and the biological tissue due to proper wetting of the bio adhesive surface and swelling of the bio adhesive. Following this is the penetration of the bio adhesive into the tissue crevices, interpenetration between the mucoadhesive polymer chains and those of the mucus. Subsequently low chemical bonds can become operative.

Hydration of the polymer plays a very important role in bio adhesion to the mucosal site. There is a critical degree of hydration required for optimum bio adhesion. If there is incomplete hydration, the active adhesion sites are not completely liberated and available for interaction. On the other hand, an excessive amount of water weakens the adhesive bond as a result of an overextension of the hydrogen bonds. During hydration; there is a dissociation of hydrogen bonds of the polymer chains. The polymer–water interaction becomes greater than the polymer-polymer interaction, thereby making the polymer chains available for mucus penetration. Following polymer hydration intermingling between chain segments of the mucoadhesive polymer with the mucus occurs.

The factors critical for this model of mucoadhesion are the diffusion coefficient of the polymer, contact time and contact pressure. The polymer diffusion coefficient is influenced by the molecular mass between cross-links, and is inversely related to the cross-linking density.[19, 20]

Theories of mucoadhesion

Diffusion Theory: The essence of this theory is that chains of the adhesive and the substrate interpenetrate one another to a sufficient depth to create a semi-permanent adhesive bond. The penetration rate depends on the diffusion coefficient of both interacting polymers, and the diffusion co-efficient is known to depend on molecular weight and cross-linking density. In addition, segment mobility, flexibility of the bio adhesive polymer, mucus glycoprotein, and the expanded nature of both network are important parameters that need to be considered.[21, 22]

Electronic Theory: The adhesive polymer and mucus typically have different electronic characteristics. When these two surfaces come in contact, a double layer of electrical charge forms at the interface, and then adhesion develops due to the attractive force from electron transfer across the electrical double layer. Figure 04 shows theory of mucoadhesion. (Figure 04)

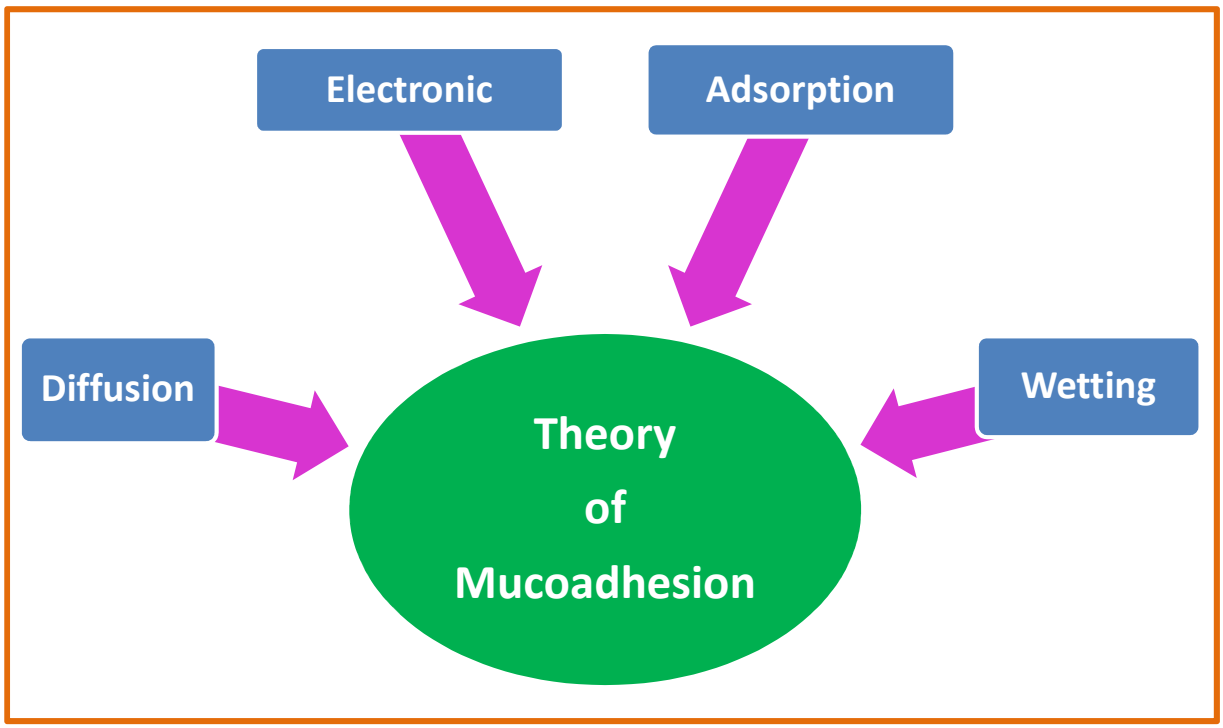


Figure 4: Theory of mucoadhesion

Adsorption Theory: The adsorption theory of bio adhesion proposes that adhesion of a polymer to a biological tissue results from the following two process; (i) Primary bonds that is somewhat permanent and therefore undesirable in bio adhesion; (ii) Vander Waals, hydrogen, hydrophobic and electrostatic forces, which form secondary chemical bonds.

Wetting Theory: Primary application to liquid bio adhesive system, the wetting theory emphasizes the intimate contact between the adhesive and mucus. Thus, a wetting surface is controlled by structural similarity, degree of cross linking of the adhesive polymer, or use of a surfactant. The work of adhesion; expressed in terms of surface and interfacial tension (Y) being defined as energy per cm^2 released when an interface is formed.

According to Dupres equation work of adhesion is given by:

$Wa = Y_A + Y_B - Y_{AB}$

Where, A & B refer to the biological membranes and the bio adhesive formulation respectively.

The work of cohesion is given by:

$Wc = 2Y_A$ or Y_B

For a bio adhesive material B spreading on a biological substrate, the spreading coefficient is given by:

$S_{B/A} = Y_A - (Y_B + Y_{AB})$

$S_{B/A}$ should be positive for a bio adhesive material to adhere to a biological membrane.

Fracture: Fracture theory of adhesion is related to separation of two surfaces after adhesion. The fracture strength is equivalent to adhesive strength as given by

$G = (E\varepsilon / L)$

Where: E=Young's modules of elasticity

ε =Fracture energy

L=Critical crack length when two surfaces are separated

Typical properties of thiolated chitosans

Thiolated chitosan have unique properties due to the covalent attachment of thiol groups to chitosan, various properties of this polysaccharide can be gained.[23] These properties are following,

1. Strong Adhesion to mucosal surfaces like mucins or keratins
2. Accelerated cross-linking process
3. Slow and stable swelling behaviour
4. Sustained release of encapsulated drugs
5. Enhance the permeation of the drug
6. Increase cellular uptake
7. Inhibition of efflux pumps
8. impede various enzymes
9. Complexes with different metal ions
10. Antioxidative and radical scavenging activity
11. Biodegradability and biocompatibility

Chitosan derivative for mucoadhesion (thioglycolated chitosan)

To improve the permeation effect, thiolation of polymers confers the attribute of strong mucoadhesivity. Thiolation is done by derivatization of the primary amino groups of chitosan with thioglycolic acid, 2-iminothiolane, cysteine, and thiobutylamidine.[24, 25] Chemical structure of thiolated chitosan represents in Figure 05. Thiolated chitosan is also known for its in situ gelling features due to pH-dependent formation of intermolecular and intramolecular disulfide bonds. The covalent attachment of TGA to the cationic polymer chitosan leads to conjugates exhibiting an up to 10 times improved mucoadhesion.[26] (Figure 05)

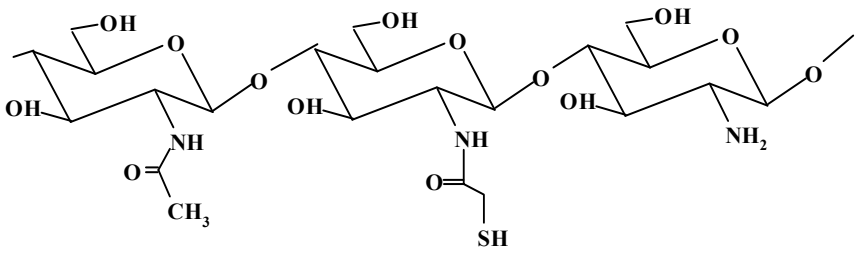


Figure 5: Chemical structure of thiolated chitosan

Synthesis thiolated chitosan polymer

Thioglycolated chitosan was synthesized by a carbodiimide, thioglycolic acid (TGA) was covalently attached to chitosan. This was achieved by the formation of amide bonds between the primary amino groups of the polymer and the carboxylic acid group of TGA. The synthesis reaction was carried out to prepare Chitosan-cysteine conjugates. 5 gram of chitosan was dissolved in 1% acetic acid solution. Add 5 gram of cysteine to the solution and then add 50 mM EDAC into the solution. The pH was adjusted to 5 with the addition of 1N NaOH .The mixture was continuously stirred for 3 hours. The solution was dialyzed in dialysis bag protected from light to eliminate EDAC and cysteine from the solution. The filtrate of the solution was dried in 40ºC for 12 hrs and stored in closed container until the use.[27]

Applications

The author also reported, from the drug delivery point of view these strongly enhanced mucoadhesive properties of chitosan might improve the efficacy of various dosage forms which should increase drug bioavailability by adhering to mucosal tissues. In particular for oral peptide drug administration thioglycolated chitosan seem to be an interesting tool. Consequently, a further improvement in the efficacy of such delivery systems might be achieved by using thiolated chitosan instead of the unmodified basis polymer. In order to avoid a degradation of peptide drugs by intestinal peptidases penetrating inside the delivery system itself, chitosan offers the ability of an easy covalent attachment of enzyme inhibitors to this carrier matrix.[28,29]These polymers can also provide a strong protective effect for the incorporated therapeutic peptide towards enzymatic degradation. Despite the chemical modification they are still biodegradable and show a good swelling behaviour. These properties might be useful in order to prolong the stability and the adhesion of different dosage forms on various mucosal tissues compared to well-

established polymers. Based on these properties thiolated chitosan derivatives represent a promising type of new mucoadhesive polymers.[30] Figure 6 shows mechanism of enhancing mucoadhesive properties of thiolated chitosan.

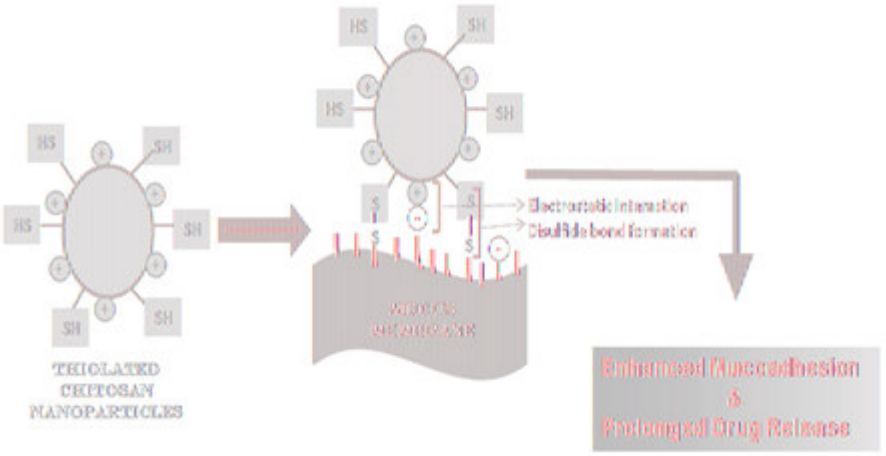


Figure 6.Mechanism of enhancing mucoadhesive properties of thiolated chitosan

Interpenetrating polymer network (ipn) between thiolated chitosan and other polymer

The chemical and physical combination methods and properties of multi-polymers have been of great practical and academic interest for the controlled release of drugs because they provide a convenient route for the modification of properties to meet specific needs. Among these methods, considerable interest has been given to the development of IPN based drug delivery systems. Interpenetrating polymer networks (IPNs) consists of two (or more) networks, at least one of them being synthesized and/or cross-linked within the immediate presence of the other, without any covalent bonds between them, which cannot be separated unless chemical bonds are broken. This would open up new avenues to use IPN in designing the novel controlled release drug release systems. A combination of judicially selected natural and synthetic polymers has been found to be useful in enhancing the release of short half□lived drugs under physiological conditions. In order achieve this; the properties of natural and synthetic polymers have been modified by grafting, blending and other means. Grafting of vinyl monomers onto natural polymers such as cellulose has been widely accepted.[31, 32, 33]

Currently several approaches are being pursued for the synthesis and characterization of IPN based nanoparticles like thiolated chitosan coated poly hydroxyethyl methacrylate nanoparticles. Poly hydroxyethyl methacrylate (pHEMA) nanoparticles coated by thiolated chitosan (chitosan-glutathione conjugate) nanoparticles were prepared using radical polymerization method and cerium (IV) ammonium nitrate as initiator.[34] The nanoparticles carried positive charge and a clear layer surrounded the poly (hydroxyethyl methacrylate) core of nanoparticles observed using TEM confirms the presence of thiolated chitosan as the coating layer. Core-shell isobutyl cyano acrylate/thiolated chitosan (IBCA/ChitoTBA) nanoparticles as a tool of combined system of polymers and colloidal particles for oral administration of poor absorption drugs was studied. Improved interpenetration ability with the mucus chain during the attachment process was suggested for the chitosan of high molecular weight, enhancing the bio adhesiveness of the system. The presence of thiol groups on the nanoparticle surface at high concentration increased the mucoadhesion capacity of nanoparticles by forming covalent bonds with the cysteine residues of the mucus glycoproteins.[35]

CONCLUSION

Natural polymers have been the prime choice of scientists across the world because of their biodegradable and biocompatible nature, along with their extensive applications in the fields of controlled drug delivery of the encapsulated drug molecules. Thiolated chitosan polymer has strong mucoadhesion, increase permeation, enhance cellular uptake of the drug, as well as many other properties might helpful to design new formulations which can enhance the efficacy of the drug. This review has provided a brief overview of the field of synthesis, properties and application of thiolated chitosan towards mucoadhesive drug delivery.

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