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MODIFIED CHITOSAN AND ITS APPLICATION IN VARIOUS DRUG DELIVERY SYSTEM

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ABSTRACT

Chitosan is derived from chitin It is natural alkaline cationic polymer It is good biodegradability, biocompatibility, excellent biological activities and less toxic, so used in various biomedical fields Benefit of chitosan is that it can be processed into different forms like membranes, sponges, gels, scaffolds, microparticles, nanoparticles, nanofibers and 3D printed constructs Poor water solubility of chitosan is major issue, so its application is limited. Chemical modification of the chitosan, matrix structure can improve its solubility and biological activity, and increase its application area. In this review, many chemical modification methods of chitosan and its main activities and application research progress covered. Properties of modified chitosan are usually better than those of unmodified chitosan, so chitosan derivatives have been widely used. Progress in chitosan chemical modification, technologies and analyze the application of chitosan and its derivatives empliment in various fields. This review is presented to share insights into multiple modified Chitosan associated with their functional properties.

KEYWORDS: Alkaline cationic polymer; chemical modification; chitin chitosan derivatives.

1. INTRODUCTION

Chitosan is deacetylated chitin and soluble chitin, has the chemical name ((1-4)-2-amino-2-deoxy-D-glucose. The term “kitosan” (Kite-O-San) was firstly written by Hoppe-Seiler in 1894, to design deacetylated chitin.[3] 19 Chitin consists of units of β-(1–4)-N-acetyl-D-lucosamine.

Chitosan is unbranched binary polysaccharides composed of N-acetyl-D-glucosamine and D-glucosamine[4,5] Chitosan is obtained from chitin, a renewable resource that can be extracted from the exoskeleton of marine wastes (Annu et al.,

2018), marine arthropods, such as shrimps and crabs. Chitin has limited applications because of its acetyl groups, overcome by the deacetylation process, chitin is converted into chitosan.

There are three different polymeric forms of chitin and of chitosan are: α-, β- and γ-forms. Among them, α- chitosan is most stable and abundant form as, it has packed structure due to the antiparallel arrangement of the polymeric chains. Therefore, it is highly crystalline and has high intermolecular forces as compared to the others two. While β- form of chitosan has parallel and γ- chitosan has random arrangement of polymeric chains with low intermolecular forces (Kaur & Dhillon, 2015).[2] Molecular weight and degree of deacetylation play important role in determination of crystallinity and other physicochemical properties of chitosan.[2] Chitosan with a low molecular weight or high degree of deacetylation usually has stronger antitumor and antioxidant activities, whereas high molecular weight chitosan tends to have stronger antibacterial properties.[6]

Chitin and chitosan both have numerous applications only main difference between chitin and chitosan lies in their solubility and degree of deacetylation (DD) (Kaur & Dhillon, 2015). Chitosan is the only positively charged natural alkaline polysaccharide present in large quantities in nature.[7] Chitosan and chitin and cellulose are natural polysaccharide but their biological properties are different (Zargar et al., 2015). Chitosan and chitin structure almost resembles with cellulose, except which is that chitin has an acetamide group (–NHCOCH3) at C-2 position, while cellulose have –OH group at C-2 position. Chitosan contributes to antibacterial, hemostatic, antitumor, anti-Alzheimer's disease, immunity, wound healing, and other biological activities Mar.[8-14]

When chitosan act as biomedical research applications like promising material in preparation of sustained-release drug materials and drug carriers[15,16] Another use in textiles, beauty care, cosmetics, gene therapy, sutures, wound dressings, bioimaging, and antibacterial agents, etc.[17-21]

Application has limited because ,chitosan contain large number of hydroxyl and amino active groups in the molecular structure so easily forms hydrogen bonds, which results in a compact crystal structure that is insolubility in alkaline solutions and most organic solvents.

At same time, -NH2 and -OH in the chitosan molecule are chemically active, so other groups can be introduced at these sites for structural modification to improve performance.[22-23]

Modification of chitosan is necessary to increases biological activity of chitosan, improve its solubility, and prepare chitosan derivatives with required physicochemical and biological properties for specific applications. Chitosan modification by three different way, mainly chemical, physical, and compound modification.[1]

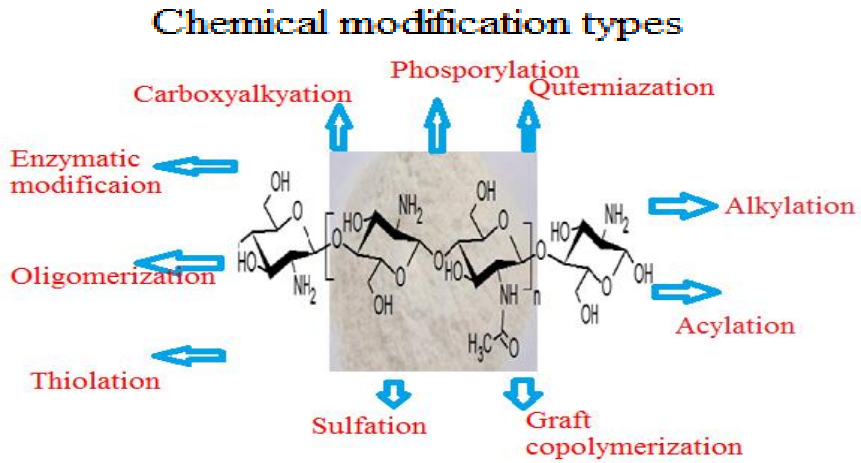
1. Physical modification generally only need adjustments in physical properties and in the mechanics of raw material
2. Compound modification involves preparing the composite material by combining chitosan and polymer materials, which can improve drug loading and embedding rates. In addition to improving the water solubility of chitosan,
3. Chemical modification can be compounded effectively increases the biological activity For example the advantages of antitumor, antioxidation, and antibacterial properties and application scope of chitosan.

We are discuss about chemical modification.

Chemical modification allows for the synthesis of derivatives with controllable solubility, ionic properties and hydrophilic and lipophilic properties which are more suitable as biomedicine carriers.[24]

Different Chemical modification is **Carboxylation Modification, Alkylation Modification, Acylation Esterification, Sulfonation Modification, Quaternary Ammonium Salt Modification, Graft copolymerization schiff Base**

However, chitosan modification is that -OH or -NH2 of chitosan will interfere with the reaction. So that unwanted groups are introduced into the product. This problem can be avoided by introducing protective groups. This is change by the reaction conditions and reagents. Chemical modification of chitosan can occur in the amino, hydroxyl, or amino and hydroxyl groups, thus forming N-modified, O-modified, or N, O-modified chitosan derivatives.[24]



1. Carboxylation Modification

At present, carboxymethyl chitosan is one of the most widely used chitosan derivatives. O-carboxymethyl chitosan has relatively good water solubility and pH sensitivity, which delivery carrier.[25] The reaction site of carboxylation of chitosan is mainly C6-OH on the molecular chain of chitosan[26] The order of carboxymethyl substitution in chitosan molecules is usually ranked as C6-OH > C2-NH2 > C3-OH, but the substitution position can be controlled by changing the reaction conditions and reagents.

Carboxylation The order of carboxymethyl substitution in chitosan molecules is usually ranked as C6-OH > C2-NH2 > C3-OH, but the substitution position can be controlled by changing the reaction conditions and reagents take place with the hydroxyl or amino group on the chitosan molecule alone, or with the two active groups at the same time. The commonly used reagents for carboxylation modification of chitosan is glyoxylic acid and chloroacetic acid. When the reaction reagent is glyoxylic acid, directly oxidize the hydroxyl groups on chitosan to carboxyl groups. When the reaction reagent is chloroacetic acid, chloroacetic acid can react with C2-NH2 and C6-NH2 on chitosan to generate N,O-carboxymethyl chitosan.[28] antibacterial properties of chitosan can be substantially improved.[27] In addition, carboxylated chitosan, which has better flocculation, thickening, and film-forming properties than chitosan, has been widely used in medical, agricultural, and hygiene fields.

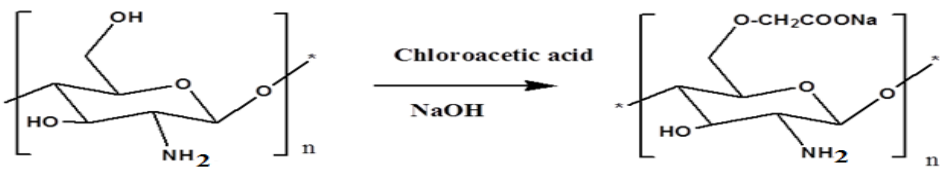


Fig no. 2

2. Alkylation Modification

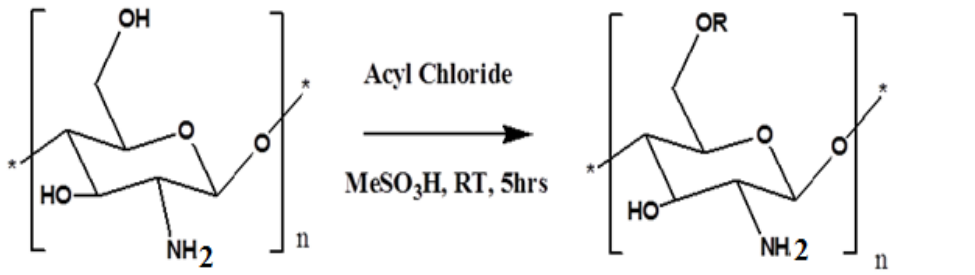
It is part of the hydroxyl or amino groups of chitosan undergoes an alkylation reaction with halogenated hydrocarbons or sulfates to generate alkylated derivatives under alkaline conditions. In addition to improving chitosan solubility, alkylated derivatives of chitosan demonstrate good biocompatibility, coagulability, and antibacterial and hemostatic properties (29) N-alkylated chitosan derivatives are usually synthesized in two ways, namely by the Schiff base method or via a reaction with halogenated alkanes.

Huang et al.[30] prepared alkylated chitosan via a Schiff base reaction between chitosan and lauric aldehyde under alkaline conditions and then characterized the grafted product. Later, the graft was prepared into a hydrophobic chitosan (HM-CHI) sponge. N-alkylated chitosan can also be prepared using halogenated alkanes.[31]

3. Acylation Modification

Organic acid derivatives (such as acid anhydrides, and acid halides) are used as acylating agents in a certain reaction medium, and then different aliphatic or aromatic acyl groups are introduced into the molecular chain of chitosan, which acylates chitosan. Acylated chitosan has good processing properties and slow-release effects.[32] The acylation reaction induce O-acylation on OH to generate ester, N-acylation on NH2, or a simultaneous amino and hydroxyl product.[1]

N-acylated chitosan, is simple, the degree of substitution is high[34] easier to synthesize and significantly improve the water solubility of chitosan, is usually used as a drug carrier or sustained-release agent in drug delivery. Modification of O-acylated chitosan is more difficult and complicated to accomplish[32] synthesized chitosan derivatives are fat-soluble and usually used for the preparation of polymer film materials to improve the hydrophobicity and stability of film materials. N,O-acylated chitosan is relatively easy to synthesize,[33] However, its structure is quite complex and less used.[32]

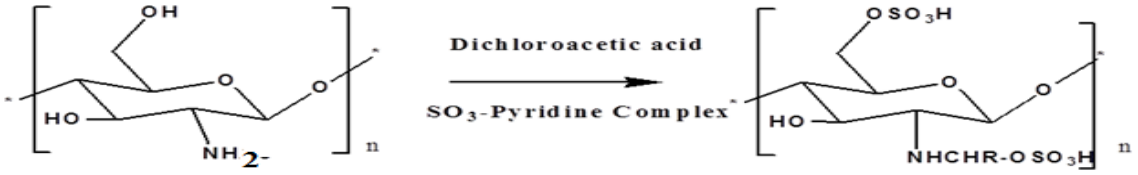


4. Esterification Modification

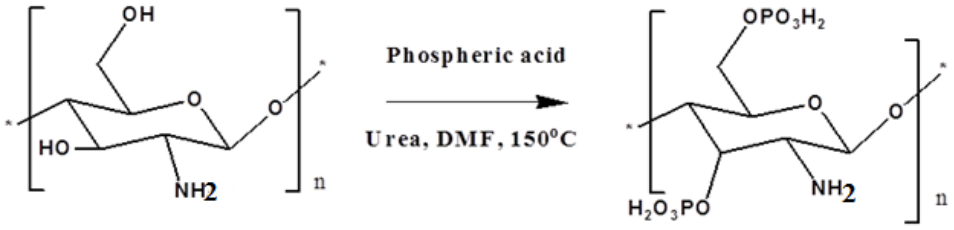
Hydroxyl or amino groups on chitosan undergo an esterification reaction with oxygen containing mineral acids or acid derivatives to produce esterified chitosan. Esterification modification enhances the adsorption and antibacterial abilities of chitosan to varying degrees.[35–37] Esterification reactions include sulfation and phosphorylation. Anticoagulant activity through a direct reaction of chitosan with sulfation reagents[37] (mainly including fuming sulfuric acid, sulfur dioxide, sulfur trioxide, and concentrated sulfuric acid.

Anticoagulant activity of sulfated chitosan is created via interactions between negatively charged sulfated groups and positively charged peptide sequences[37] and used as a carrier for antiviral drugs. BMP-2/S-NP/G can significantly

increase the formation of peripheral blood vessels and cardiovascular in rabbit radius and promote and accelerate bone regeneration.[38]



5 Phosphorylation of CS takes place with methanesulfonic acid with good water solubility Wu et al.[38] prepared a phosphorylated magnetic CS composite material (P-MCS) to adsorb the heavy metals lead and cadmium in an aqueous solution. The results showed that P-MCS had good adsorption against cadmium and lead, due to ion exchange and direct complexation between heavy metal ions and functional groups. The study show that P-MCS will eventually become an excellent source of material for treating wastewater containing heavy metal ions.[1] addition, phosphorylated CS has bactericidal and metal chelating properties.

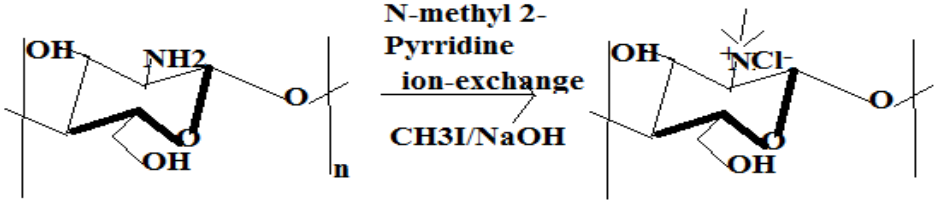


Quaternary Ammonium salt modification

Quaternization of CS is to introduce quaternary ammonium groups or small molecular Quaternary ammonium salts to the amino groups of CS, which can occur on hydroxyl groups. Quaternary ammonium salt groups feature large steric hindrances, such as strong hydrateability, which significantly weakens the hydrogen bond between CS molecules added to the quaternary ammonium salt group,so significantly improving its water solubility.And due to its permanent positive charge and large number of cations on the main chain, the CS derivatives exhibited excellent antibacterial activity and better antioxidant activity,[39] which promotes CS application as a food preservative,better biocompatibility, biodegradability, and good mucosal adhesion.[40]

There are two main synthetic methods for preparing N-quaternary ammonium CS excess halogenating reagents (such as alkyl iodide) directly react with CS to obtain halogenated CS quaternary ammonium salt.quaternary ammonium-salt-containing alkylene oxide react with CS to obtain a quaternized chitosan-containing hydroxyl group.

In addition, studies show that CS quaternary ammonium salt prepared via this method can be used as a carrier for hydrophilic drugs to achieve sustained and slow release[41] further explore a simpler and more efficient method to synthesize quaternary ammonium chitosan and antibacterial activity research.



N-N-N Trimethylchitosan chloride

7. Graft Copolymerization Modification

Common graft copolymerization methods include oxidative coupling copolymerization, free radical graft copolymerization, and condensation copolymerization. Li et al.[43] reagents used in free radical graft copolymerization are relatively safe and constitute commonly used graft copolymerization modification reaction systems. For example, Ja Dena-Aguilar et al.[44] used the synthesis method of chitosan graft copolymerization has diversity. It can introduce various groups, which is an important direction for the diversification of chitosan derivative materials and functions. In the future, we can focus on grafting drugs with some better therapeutic effects, which may give stronger and more efficacy to chitosan.

Graft copolymerization reactions, and graft copolymerization reactions can occur on C2-NH2, C3-OH, and C6-OH.[42]

Graft copolymerization is the most attractive method for improving Physicochemical and biological properties through physical and chemical modifications of CS. It is also an important method for introducing CS polyfunctional groups (such as hydroxyl, carboxyl, ester, and amide). Properties of the final graft copolymerization product are mainly controlled by the molecular structure, length, and number of side chains. Graft copolymerization of CS mainly involves graft copolymerization with alcohols, esters, acids, and amides.Graft copolymerization (1)

Chitooligosaccharides

Reducing the molecular weight of CS is a good way of decreasing viscosity issues and enhancing biological properties thanks to the production of chitooligosaccharides (COS)

Generally, oligosaccharides are defined as oligomers with a degree of polymerization ranging from 2 and 10.[47] The production of COS is mainly achieved by physical, chemical, and enzymatic methods.[47] has also been related to improving the solubilization of CS in water or acetic acid solutions[46,47] Depolymerization of CS is principally performed by acid chitosanolysis which is the most reported.[45]

Finally, enzymatic processes use specific enzymes like chitinase (48) and chitosanase (49), but also non-specific enzymes, such as pepsin,[50] cellulase,[51] lipase, pronase, protease,[52] lysozyme, papaïn, glucanase,hemicellulase, or pectinase. Main issues of enzymatic depolymerization are probably the cost of making it redhibitory for bulk use in commercial applications and the relative slowness of reactions. In contrast, the main drawbacks of chemical methods involve the use of non-green chemicals, the need of their removal, and the heterogeneity of final products.[4] New methods for reducing the molecular mass of CS have been described, e.g., high-pressure homogenization (HPH),[53] plasma,[54] or using zeolithes adsorbents[55] to purify acid hydrolysis COS.

Thiolated Chitosans

Using thiolating agents bearing thiol groups. These include cysteine 56, thioglycolic acid (TGA) (57)], 2-iminothiolane or 4-thiobutylamidine (TBA),[57] *N*-acetyl cysteine,[58] isopropyl-S-acetylthioacetimidate[59] and glutathione.[60] This technique has been pioneered by Bernkop-Schnürch and co-workers to enhance the mucoadhesion of polymers for pharmaceutical and biomedical applications. Thiolated chitosans are studied mucoadhesive materials. Despite their superior mucoadhesive properties, they also have some permeation enhancing effects, ability to inhibit efflux pumps and in situ gelling properties.[61]

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