

# Chitosan – A Versatile Polymer for Targeted Drug Delivery

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**Abstract-** Chitosan has attracted attention of researchers working in the field of nanomedicine worldwide as effective drug delivery system. It is nontoxic, biocompatible, biodegradable, cationic polysaccharide. Being natural cationic polymer, it strongly interacts with anionic biomacromolecules and holds them tightly to deliver into systemic circulation without any toxicity to epithelium tissues. However, CS shows limited solubility at neutral or higher pH value. The main of the review is major advantage in choosing chitosan for drug delivery is mainly due to its biodegradable, biocompatible, nontoxic & mucoadhesive properties. However, the challenges involving the use of high cost materials, large amount of chemical agents, tedious as well as time-consuming process prevent the real world large scale applications of chitosan drug carriers. Presently, a variety of chitosan-based drug delivery materials in the forms of gels, tablets, films and particle have been developed and studied.

**Keywords-** Chitosan, Degree of N-acetylation, Cross linking, Nanocarrier, Micro emulsion.

## I. INTRODUCTION

Deacetylation from of chitin was derived as chitosan, is the second most abundant naturally occurring biopolymer and a major structural polysaccharide found in the exoskeleton of crustaceans such as crab and shrimp [1]. It consists of  $\beta$ -(1, 4)-2-acetamido-2-deoxy- $\beta$ -d-glucose and  $\beta$ -(1, 4)-2-amino-2-deoxy-d-glucose units. Thus, it comprises of copolymers of glucosamine and N-acetyl glucosamine [2]. It is considered to be the most widespread polycationic biopolymer having non-toxic, biocompatible and biodegradable characteristics [3]. It offers several advantages for mucosal delivery, such as low toxicity and excellent biodegradability [4] as well as immune stimulating [5], and high mucoadhesive properties [6]. Till date, chitosan has been extensively employed in food processing, agriculture, biomedicine, biochemistry and pharmaceutical applications [7]. Chitosan, due to its biodegradable behaviour has a strong potential for application as drug carrier. Presently, a variety of chitosan-based drug delivery materials in the forms of gels, tablets, films and particle have been developed and studied [8]. Micro-emulsion [9], chemical or ionic gelation, coacervation /precipitation and spray-drying are the commonly used methods to prepare

chitosan carriers. The amino and carboxyl groups in the chitosan molecule can be combined with glycoprotein in mucus to form a hydrogen bond leading to an adhesive effect which prolongs the retention time of drugs as well as improves drug bioavailability [10]. However, the challenges involving the use of high cost materials, large amount of chemical agents, tedious as well as time-consuming process prevent the real world large scale applications of chitosan drug carriers.

## II. ORIGIN OF CHITOSAN

Chitin, poly (N-acetyl- $\beta$ -D-glucosamine) is a natural polysaccharide of major importance, first identified in 1884. This biopolymer is synthesized by an enormous number of living organisms; and considering the amount of chitin produced annually in the world, it is the most abundant polymer after cellulose. It is extracted from the shells of crustaceans, such as shrimp, crab and other sea crustaceans, including *Pandalus borealis* and cell walls of fungi. Chitin molecular formula is  $(C_8H_{13}O_5N)_n$  and its deacetylated form Chitosan molecular formula is  $(C_6H_{11}O_4N)_n$ . Chitin and chitosan chemical structures are shown in figure 1.

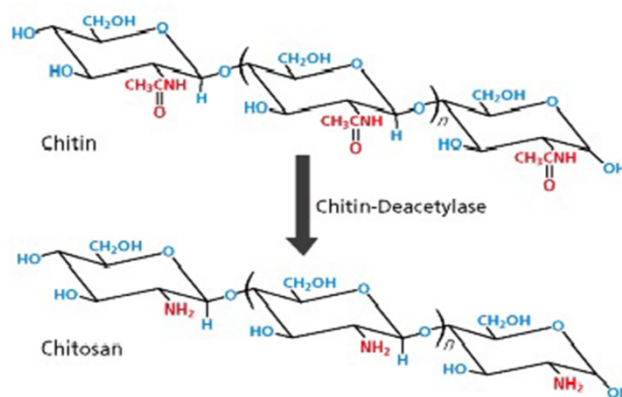


Figure 1: Chitin and chitosan chemical structure

## Degree of N-acetylation

An important parameter to examine closely is the degree of N-acetylation in chitin, i.e. the ratio of 2-acetamido-2-deoxy-D-glucopyranose to 2-amino-2-deoxy-D-glucopyranose structural units. This ratio has a striking effect

on chitin solubility and solution properties, the universally accepted non-toxic N-deacetylated derivative of chitin.

### Physical chemical properties of chitin and chitosan

Physical and chemical properties of chitosan depend mainly on its molecular weight and degree of Deacetylation [10]. Chitin and chitosan are of commercial interest due to their high percentage of nitrogen (6.89%) compared this makes chitin a useful chelating agent [11]. Chitin is highly hydrophobic and is insoluble in water and most organic solvents. It is soluble in hexafluoroisopropanol, hexafluoroacetone, and chloroalcohols in conjugation with aqueous solutions of mineral acids [12]. It is dissolved by selected acids such as: formic, acetic, lactic, malic and citric acids [13]. Recently gel forming ability of chitosan in N-methylmorpholine N-oxide and its application in controlled drug release formulations has been reported [14]. Chitosan

powder is a stable material at room temperature, although it is hygroscopic after drying. It should be stored in cool, dry place; preferably at a temperature of 2-8°C. Chitosan is incompatible with strong oxidizing agent [15].

### Chitosan production

It is estimated that approximately 10 billion tons of chitin can be synthesized in nature each year. The main sources of chitin (in% of dry matter) are crustaceans such as shrimp and crab (58–85%), insects (20–60%), molluscs(3–26%); cephalopods including squids, octopuses and annelids (20–28%), protozoans which contain a little chitin, coelenterates (3–30%), seaweed which can contain low quantities of chitin and fungi whose chitin contents are from trace to 45%. Chitosan productions from crustacean shell waste are shown in figure 2.

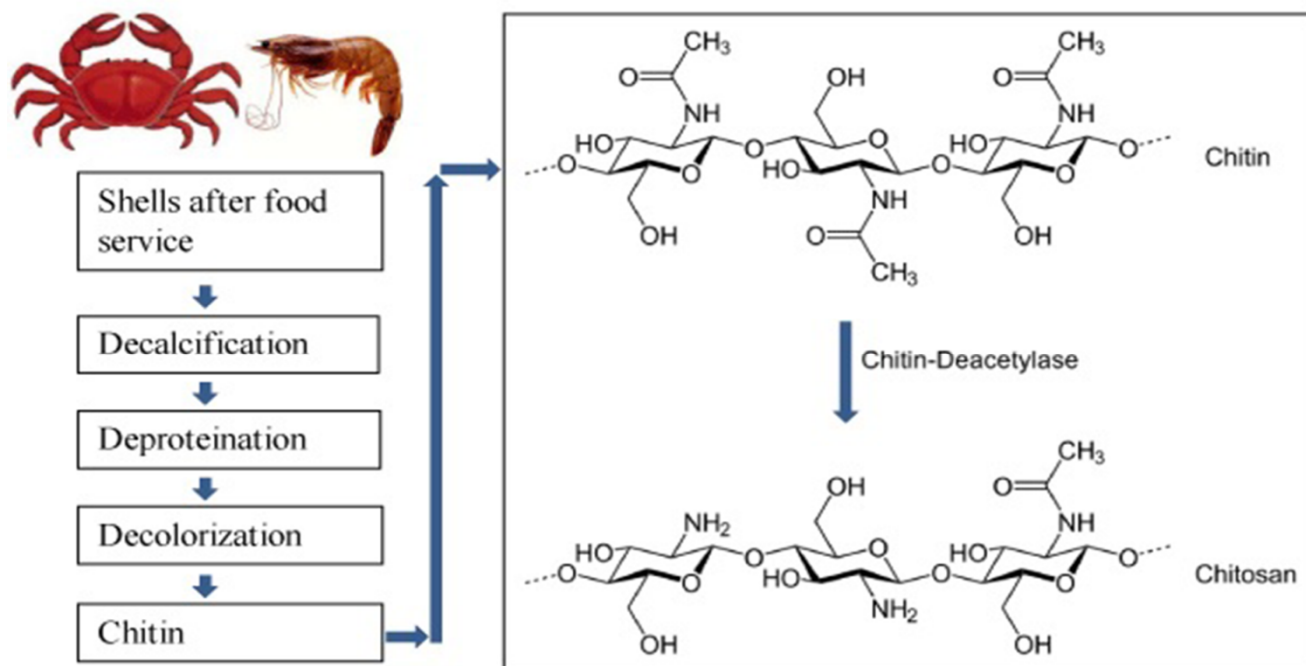


Figure 2: Chitosan productions from crustacean shell waste

### Purification of chitosan

Chitosan was purified by dissolving in 2% aqueous acetic acid solution and precipitating in 10 wt% NaOH solution. The precipitate was first washed with distilled water to neutrality and then rinsed with acetone. It was then vacuum dried at 70°C for about 8 h. Its degree of deacetylation, determined by IR method was found to be 64%.

### Water soluble derivative of chitosan at neutral pH

Chitosan and its derivatives soluble in pH values of lower than 6.0 may not be desirable for usage in medicine, cosmetics and food [16]. To improve its solubility at neutral pH, it is first derivatized with substituents containing Quaternary amino group, carboxymethylation and then sulfatation by adding strongly hydrophilic substituent [17].

### Action of Chitosan

Chitosan has a special feature of adhering to mucosal surfaces and is capable of penetrating the tight junctions

between epithelial cells, which make it ideal material for drug delivery. Therefore, chitosan and its derivatives have attracted significant interests as carriers for drug [18] or gene [19] delivery due to their excellent biocompatibility, biodegradability, biological activities, and adsorption properties [20, 21]. Various usage of chitosan nanoparticles are shown in figure 3. Since chitosan is the only natural positive polysaccharide, has several advantageous in forming stable complex with negative compounds, which makes chitosan a good candidate for the drug encapsulation and controlled release. In addition, chitosan has mucoadhesive as well as absorption-enhancing properties. It can interact with mucus and epithelial cells resulting in opening of cellular tight junctions [22, 23]. These properties make chitosan is an ideal and suitable candidate for the delivery of macromolecular therapeutics, like protein and peptides.

### III. PREPARATION METHOD

For the preparation of chitosan particles, several techniques are available such as mini-emulsion, chemical or ionic gelation, coacervation/ precipitation, and spray-drying methods. [24- 26]. Among them, ionotropic gelation with sodium tripolyphosphate (TPP) as the cross linker is the mostly adopted technique to fabricate CS NPs. Since this method is simple, mild, less toxic, aqueous environment and suitable for scaling up. Recently five more techniques are also available for preparation of chitosan nanoparticles. Different preparation methods for chitosan nanoparticles are shown in figure 4.

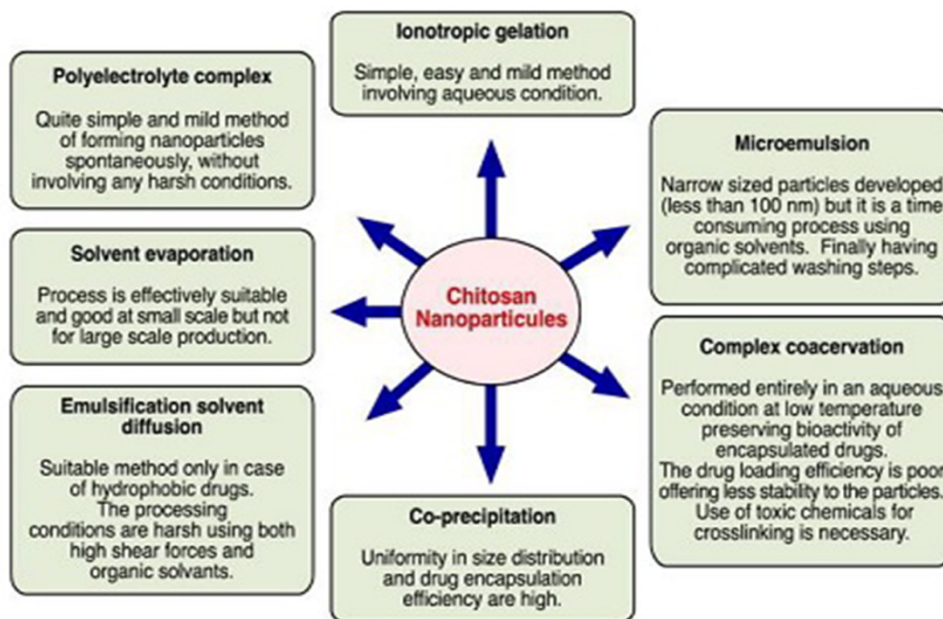


Figure 3: Different preparation methods for chitosan nanoparticles

### IV. IONOTROPIC GELATION METHOD.

The CS/TPP particles- formation can be divided into the two processes: 1.Mixing of the CS and TPP aqueous solution and dispersion of the TPP anions within the CS molecules and (2) cross linking (i.e. gelation) between the protonated amine groups and TPP anions [27]. Conventionally chitosan nanoparticles also prepared by ionotropic gelation technique by using sodium tripolyphosphate (TPP). The anionic phosphate group in TPP interacts with the positively charged amine group of chitosan thereby stabilizing the nanoparticles. Chitosan is dissolved in 0.1% acetic acid and stirred continuously to obtain a gel-like consistency. Sodium

tripolyphosphate (TPP)(1%,w/v)is added to the chitosan solution and the mixture are stirred for two hours without heating to obtain a uniform textured solution. The solutions are centrifuged at 18000 rpm for half an hour to pelletize chitosan nanoparticles. The size and surface charge of particles can be modified by varying the ratio of chitosan and stabilizer [25, 26]. Figure 3 shows different preparation methods for chitosan nanoparticles.

### V. COACERVATION METHOD

Chitosan particles are prepared using the precipitation-coacervation method developed by Berthold et

al. [28] with slight modifications. In brief, chitosan is dissolved in a 2% (v/v) acetic acid solution. Chitosan particles are formed by adding 50 mM precipitant salt solution drop wise to the chitosan solution using an infusion pump (Pump 11 Elite, Harvard Apparatus, Holliston, MA). Nonionic stabilizer Pluronic F-68 are added and allowed to stabilize for 2 h under constant stirring using a sonicator (S4000; Misonix Inc., Farmingdale, New York). Chitosan particles are collected after centrifugation at 25,000 g for 10 min at 4°C and freeze dried (FreeZone, Labconco, Kansas City, MO) before further use [28].

## VI. MICRO EMULSION METHOD

Chitosan NP prepared by microemulsion technique was first developed by Maitra et al [29]. This technique is based on formation of chitosan NP in the aqueous core of reverse micellar droplets and subsequently cross-linked through glutaraldehyde. In this method, a surfactant is dissolved in N-hexane. Then, chitosan in acetic solution and glutaraldehyde are then added to surfactant/hexane mixture under continuous stirring at room temperature. Chitosan nanoparticles are formed in the presence of surfactant. The systems are stirred overnight to complete the cross-linking process, which the free amine group of chitosan conjugates with glutaraldehyde. The organic solvent is then removed by evaporation under low pressure. The yields are obtained the cross-linked chitosan NP and excess surfactant, are then removed by precipitate with CaCl<sub>2</sub> finally the precipitate are removed by centrifugation. The final nanoparticles suspensions are then dialyzed before lyophilization. This technique offers a narrow size distribution of less than 100 nm and the particle size can be controlled by varying the amount of glutaraldehyde that alters the degree of cross-linking. Nevertheless, some disadvantages exist such as the use of organic solvent, time-consuming preparation process, and complexity in the washing step [30].

### Chitosan as a Nanocarrier

The idea of developing a drug that selectively destroy disease cells without damaging healthy cells was proposed by Paul Ehrlich, almost a century ago; he called his hypothetical drug the “magic bullet” [31]. Many drugs have problems of poor stability, water insolubility, low selectivity, high toxicity, side effects, and so on. Good drug carriers play a significant role in resolving these problems. Chitosan nanoparticles are a drug carrier with wide development potential and have the advantage of slow/controlled drug release, which improves drug solubility and stability, enhances efficacy, and reduces toxicity [32].

### Chitosan drug delivery systems

Chitosan approved by FDA for human administration, because they are biocompatible [33]. The use of controlled drug release systems has certain advantages compared to conventional form of dosages as they can minimize side effect, and also prolong the efficacy of the drug [34]. Drug delivery systems (DDS) based on chitosan have also been described, which are interesting with regard to adjust the drug release to physiological needs of body, as in the case of hormone release [35]. Since chitosan is only natural positive polysaccharide, has several advantageous in forming stable complex with negative compounds, which makes chitosan a good candidate for the drug encapsulation and controlled release. In addition, chitosan has mucoadhesive as well as absorption-enhancing properties. It can interact with mucus and epithelial cells resulting in opening of cellular tight junctions [22, 23]. These properties make chitosan is an ideal and suitable candidate for the delivery of macromolecular therapeutics, like protein and peptides. Therapeutic properties of chitosan nanoparticles The CS nanoparticles has attracted great attention in pharmaceutical applications including being targeted for colon or mucosal delivery, cancer therapy, or delivery of vaccines, genes, antioxidants, etc. because the primary amine groups render a positive charge and mucoadhesive properties that make CS very useful in drug delivery applications [36]. A CS nanoparticle is a very efficient and non-toxic absorption enhancer for both orally and nasally administered peptide drugs [37].

### Ophthalmic Drug Delivery

Due to their elastic properties, chitosan offer better acceptability, with respect to solid or semisolid formulation, for ophthalmic delivery, such as suspensions or ointments. Ophthalmic chitosan gels improve adhesion to the mucin, which coats the conjunctiva and the corneal surface of the eye, and increase precorneal drug residence times, showing down drug elimination by the lachrymal flow. In addition, its penetration enhancement has more targeted effect and allows lower doses of the drugs [38].

### Gene delivery

Gene delivery systems include viral vectors, cationic liposomes, polycation complexes, and microencapsulated systems [39, 40]. Viral vectors are advantageous for gene delivery because they are highly efficient and have a wide range of cell targets. However, when used in vivo they cause immune responses and oncogenic effects. To overcome the limitations of viral vectors, non-viral delivery systems are considered for gene therapy. Non-viral delivery system has

advantages such as ease of preparation, cell/tissue targeting, low immune response, unrestricted plasmid size, and large-scale reproducible production [41]. Chitosan has been used as a carrier of DNA for gene delivery applications, and it also, could be a useful as oral gene carrier because of its adhesive and transport properties in the GI tract [42].

### Buccal drug delivery

Chitosan is an excellent polymer to be used for buccal delivery because it has muco/bio adhesive properties and can act as an absorption enhancer [43]. Buccal tablets based on chitosan microspheres containing chlorhexidine diacetate gives prolonged release of the drug in the buccal cavity improving the antimicrobial activity of the drug [44].

### Chitosan applications

The biochemical properties of chitosan make it an excellent bio adhesive material, which excels at drug administration through subcutaneous, oral, ocular, and transdermal delivery [45]. Moreover chitosan is under investigation for a wide variety of biomedical applications including drug delivery, gene delivery, wound healing, antimicrobial applications, Antimutagenic, tissue engineering and vaccine delivery [46].

### Applications of Chitosan Nanoparticles

As chitosan is an effective antibacterial agent, gene delivery vectors and carriers for protein release and drugs, it is used too many ways also various usages of chitosan nanoparticles showed fig 4.

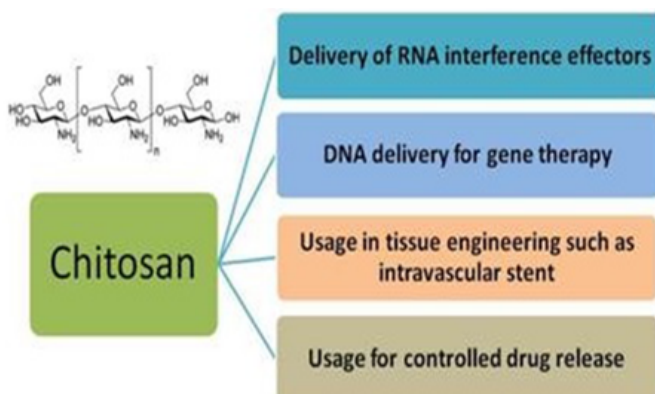


Figure 4: Various usages of chitosan nanoparticles

- It is a potential adjuvant for vaccines such as influenza, hepatitis B and piglet paratyphoid vaccine.
- It is a novel nasal delivery system for vaccines. These nanoparticles improve antigen uptake by mucosal

lymphoid tissues and induce strong immune responses against antigens.

- It has also been proved to prevent infection in wounds and quicken the wound-healing process by enhancing the growth of skin cells.
- Chitosan nanoparticles can be used for preservative purposes while packaging foods and in dentistry to eliminate caries.
- It can also be used as an additive in antimicrobial textiles for producing clothes for healthcare and other professionals.
- Chitosan nanoparticles show effective antimicrobial activity against *Staphylococcus saprophyticus* and *Escherichia coli*.
- These materials can also be used as a wound-healing material for the prevention of opportunistic infection and for enabling wound healing.
- The nanoparticles have also been proven to show skin regenerative properties when materials were tested on skin cell fibroblasts and keratinocytes in the laboratory, paving the way to anti-aging skin care products. (Chitosan for biomedical applications – University of Iowa)

## VII. CONCLUSION

Over the past several decades, many scientists have focused their attention on the development of ideal drugs that specifically target the site of action. Chitosan has attracted attention of researchers working in the field of Nanomedicine worldwide as effective drug delivery system. Chitosan nanoparticles have biodegradability, biocompatibility, low toxicity demonstrate great potential as carrier for controlled/sustained delivery of various therapeutic agents, and can be administered through various routes such as oral, nasal etc. These properties, together with the very safe toxicity profile, make chitosan an exciting and promising incipient for the pharmaceutical industry for present and future applications. To conclude that chitosan become a popular biopolymer in the medical fields because of its unique properties in the world of biopolymers, and there is no doubt that chitosan is a very promising carrier material for drug delivery.

### Conflict of Interest

The authors declare that there are no conflicts of interest.

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