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A Review: Chitosan as Natural Versatile Material for Biomedical and Diseases Treatment

RUNNING TITLE: APPLICATION OF CHITOSAN

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Abstract

Chitosan is a part of cellulose derived from polysaccharides obtained from as a chemically processed form of chitin. Chitosan has the cheapest sources is squid pens that are getting as waste in the squid processing industry. Chitosan has a unique structure, various properties, ubiquitous functionalities, and a broad range of applications in commercial as well as in the bio medicinal field. Chitosan contained a high amount of nitrogen (6.89%) and also a good chelating property. Chitosan can be converted by the involvement of numerous techniques into systems of drug delivery using techniques including spray drying, coacervation direct compression, and traditional granulation. Especially in such techniques, chitosan exhibits an important role in the release of a medicament to attain sustained and control release. Therefore, the demand of chitosan is increased worldwide due to the different applications. This review article condenses the recent use in various key areas related to micro and nanotechnology delivery systems of chitosan along with its application in the biomedical and pharmaceutical industry.

Keywords: *Chitosan, nanotechnology, carrier, drug-delivery, application*

1. Introduction

It is witnessed that chitosan being a polysaccharide in natural form is widely available on the earth obtained via de-acetylation of chitin. It is having unique properties of gel and film forming due to which it is used in pharmaceutical industries as potential carriers for development of various controlled drug delivery systems especially for protein and peptide drugs [1,2] . Chitosan-polyanions complexes are mostly used for the protein delivery, enzyme, drug and cell transplantation, immobilization. Along with these complexes, chitosan-alginate complex may be the most considerable drug delivery of hydrogel system[3]. Chitosan polyanions complexes have a number of applications in the pharmaceutical field, for instance, in case of gene delivery for rendering as non-viral vectors when combined with DNA along with the on-going research on chitosan polyanions complex which could be applied in the fields of applications of biosensors, treatment from waste-water, several drug delivery forms and also used as scaffolds in tissues engineering [4,5]. It has a bio polymer chain which is low solubility in aqueous and organic solvent. It is used in multitudinous applications. Chitosan is also used in cosmetics for use in a variety of pharmaceutical formulations and under investigation[6, 7]. Numerous studies have examined the suitability and efficacy of chitosan as a pharmaceutical formulation for drug delivery and cosmetic application. Those include managed applications for drug delivery, use as a part of mucoadhesive dosage type, rapid dosage form, enhanced distribution of peptides, colonic drug delivery system, and gene/protein delivery[8-10]. Chitosan has been manufactured in various pharmaceutical formulations including gels, films, beads, microsphere, tablets and liposome coating. In this review article condense the recent use in various key areas related to micro and nanotechnology delivery systems for the field of pharmaceutical and biomedical applications of the given form chitosan was analyzed.

2. Chitosan: structures and properties

It is very well known that chitosan being a natural polysaccharide is available on the earth obtained via de-acetylation of chitin. It stands to be a co-polymer comprising β-1,4-linked glucosamine (deacetylated units) along with N-acetyl-D-glucosamine (acetylated units) residues (Figure 1)[11].The repeating glucopyranose units of chitosan consist of cationic amino groups (-NH_2) on the C-2 position that can exhibit electrostatically interactions of anionic carboxylic acid (COO) groups having natural and synthetic polyions such as carrageenan and sodium alginate along with xanthan gum, CMSs, pectin, chondroitin sulphate, hyaluronic acid, poly acrylic acids, polyphosphoric acid, poly (L-lactide), urea formaldehyde, gutaraldehyde, TPP (tripolyphosphate) etc. to form polyelectrolyte complexes[12,13].Chitosan molecular weight is determined in market approx. 3800-20000 Daltons. It is soluble in dilute acids ex- acetic acid, formic acid. The chitosan is insoluble in water or organic solvents, and but when the free amino groups are protonated at acid pH (below pH 5), chitosan becomes a soluble cationic polymer with high charge density (Figure 2)[14, 15].

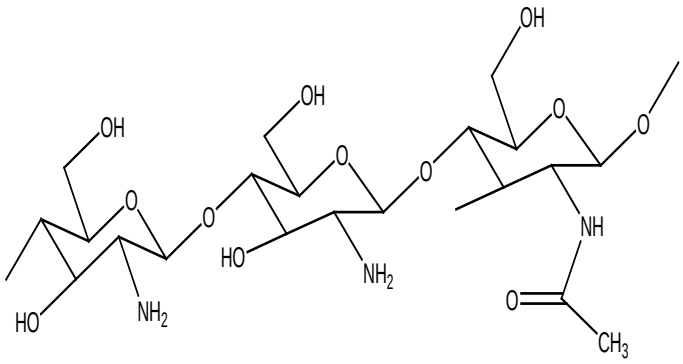

Fig 1: Molecular structure of chitosan

2.1 Chemical properties of chitosan

Naturally occurring polymers like Cellulose, Dextran, Pectin, Agar, and Agarose have an acidic or neutral nature while chitosan is highly basic in nature. Chitosan can also reduce the risk of cardiovascular diseases. The antimicrobial activity of chitosan along with its derivatives has been acknowledged[16-18].

- Linear amino polysaccharides with large nitrogen content.
- It is cationic biopolymer having high charge density
- Ability to form intermolecular hydrogen bonds leading to high viscosity
- In order to exhibit chemical activation and cross-linking, it has large number of reactive functional groups which shows an important factor.
- It is mostly soluble in dilute aqueous acidic solutions and insoluble in organic solvents and water.
- Salts with organic and inorganic acids are to be produced.
- It having the quality of formation of chelating and complex
- Ionic conductivity
- Poly-electrolytes (at acidic pH)
- Adsorbing properties used for filtration and separation

2.2 Biological biodegradability properties of chitosan[19-21]

- It is essential to see the metabolic experience in our body biodegradation, when polymer used as a drug delivery systems.
- When we look at the circumstance such as of hydrophilic polymers like chitosan, the systemic absorption exhibited must have possessed the right molecular weight. If the employee polymer dimensions are bigger, then there is chance for the polymer to endure degradation.
- The biodegradation rate is must for the usage chitosan in tissue engineering and drug-delivery systems.
- The amount of De-acetylation and molecular weight will be the factors managing the biodegradation rates of chitosan.
- Alterations in chitosan by the incorporation of chemicals are also influence the biodegradation rate of chitosan.

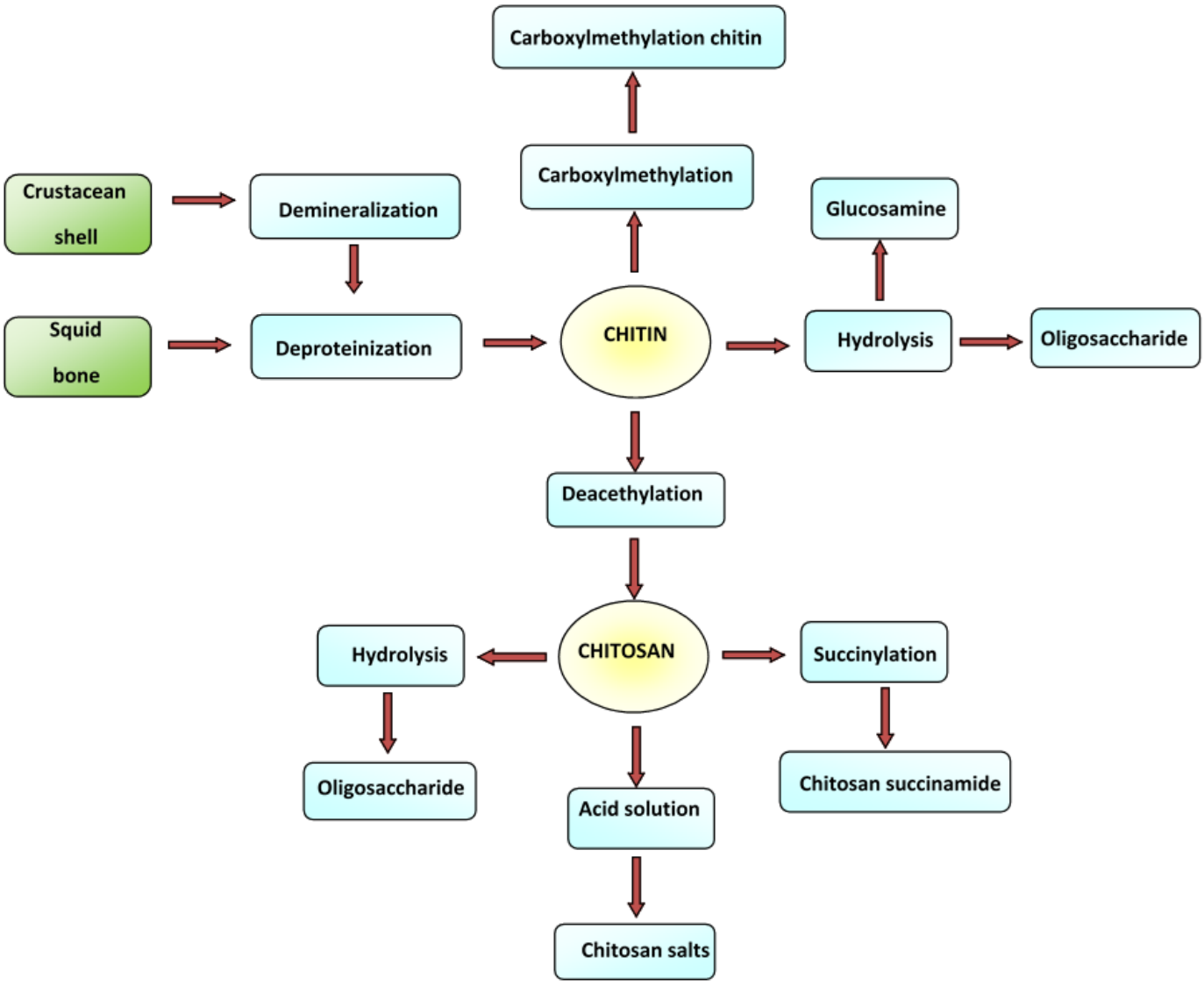

Fig 2: Process of formation of Chitin and Chitosan. Involvement of various chemical reaction in Chitin and Chitosan

2.4 Biological biocompatibility properties of chitosan

- Compatible along with living tissue or an income system through not being toxic, injurious, or physiologically reactive rather than leading to immunological rejection[22].
- The good news is times almost all recently produced biomaterials suggested for usage in humans are confronted with in vitro assessments that are then followed closely by in vivo assessments.
- Chitosan is actually polycationic in character at a pH<6.
- It is essential to test the biocompatibility of chitosan derivatives.
- Chitosan derivatives are contained in numerous kinds, for example, pastes and sheets along with tablets and fibers, porous structure scaffolds, solutions, films, hydrogels, microsphere and nanoparticles.
- Combination of lactic acid which is chitosan-LA along with acetic acid which is chitosan- AA to form the chitosan films. These on when comparison with commercially available Omniderm have been proved to work as wound healing materials.
- Chitosan microspheres with glutaraldehyde having cross-linking property display sluggish biodegradability suited for regulating delivery of several drugs.
- The biocompatibility reduces when we look at the order chitosan glutamate, hydrochloride, glycol, methylpyrrolidinone and lactate chitosan.

3. Biomedical and pharmaceutical application of chitosan

Biocompatibility, biodegradability, and low toxicity make chitosan a valuable polymer for biomedical applications. It has also been identified as a biodegradable and biocompatible along with certain specific applications have also been found, for instance, sponges and bandages to treat wounds and suture threads. Chitin is water insoluble and also exhibits lesser reactivity in nature[23].The enzymatic degradation of chitosan products has been non-toxic. The extent of acylation along with the pH and the molecular weight and different forms of chitosan preparation affects the overall biodegradation.

3.1 Chitosan as a biomaterial

Chitosan was basically clinically tested and approved for its utility in medical arena such as for contact lenses, adhesive tissue and bacterial adhesion for preventing it against sutures. It is to be seen that it has critical analysis in two areas of biomedicine. Initially, it was treated along with chitin for curing burns and ulcers, due to its haemostatic properties and hastening wound heal in effect. Secondly, it was used in tissue regeneration and reconstruction which was only due to its biodegradability and cell affinity, apparently its use in tissue engineering[24, 25].

3.2 Healing of wounds and burn

The diagnosis of chitin and chitosan wounds is definitely attributed to be the key factor in the medicine field and its application. Apart from showing anti-bacterial and anti-fungal properties along with oxygen permeability, the adhesive properties of chitosan are important properties associated with wound and burn treatment[26].

3.3 Tissue engineering

Tissue engineering techniques also involves 3-D mechanism for cell adhesion followed by tissue formation. The Chitosan have common structural features to glycosamino glycans (GAGs) present in several human tissues extracellular matrix[27].Henceforth, it has shown a wide use in tissue engineering, as it makes it easier to bind cells and retain differentiating functions.

3.4 Ophthalmology

Chitosan exhibits all important factors in order to make a good contact lens, higher optical clarity, and mechanical support and efficient gaseous permeability, especially toward oxygen, wettability and good compatibility of immunological system. Physical properties including modulus, tensile strength, tear strength, elongation, water content and permeability to oxygen. Chitosan antimicrobial property with its better wound healing effect and efficient film capacity turns it to be the best form suitable for ocular bandage lenses[45].

3.5 Chitosan as nanoparticles

For sustained release in oral formulation and as matrix in controlled release system, this chitosan has shown its prominent acceptance for beads and granules type. Chitosan films exhibit lesser water swelling capacity but in turn has membranes which thereby shows alternate hydrophilic abilities that can be formed by preparing a mixture or semi-interpenetrated and interpenetrated chitosan network along with efficient hydrophilic polymer like polyvinyl alcohol or gelatin[28,29]. Chitosan-CMC microcapsule of different compositions has been studied to play a defensive role to combat acidic pH of the stomach. Their application as drug carrier/nano carrier system has summarized in table 1.

Table 1: List of some chitosan-based nano-carrier drug delivery system and its outcome

Drug	Carriers	Outcome	Ref.
Rebamipide	Nanoparticles	Accelerate prostatic wound healing by inhibiting M1 macrophage-mediated inflammation	35
Chitosan-alginate	Nanodisks	Treatment of Prostate Cancer	36
Deferoxamine mesylate	Nanoparticles	Treatment of beta-thalassemia	37
Lovastatin	Nanoparticles	Treatment of obesity (due to cholesterol in the blood exceeding the recommended limit	38
Amiodarone	Nanoparticles	Antiarrhythmic treatment	39
Lomustine	Nanoparticles	Brain targeting and treatment	40
Esculin	Okra gum Nanoparticles	Brain targeting	41
Gatifloxacin	Nanoreservoir	Management of extraocular disorder	42
Essential Oil	Nanoparticles	Pulmonary Delivery of drug and treatment of respiratory disorder	43
Rosuvastatin	Nanoparticles	help lower "bad" cholesterol and fats	44
Fluconazole	Nanoparticles	Ocular Delivery	45
Curcumin	Nanoparticls	Cancer therapy and treatment	46
Naringenin	Nanoparticles	Targeted cancer therapy	47
Tacrine	Nanoparticles	Treatment and diagnosis of alzheimer's disease	48
Endostatin	Nanoparticles	Lung cancer treatment and management	49
Diclofenac	Nanoparticles	Pain relief treatment and sustained release formulation development	50
Ganciclovir	Nanoparticles	Viral treatment and curing by sustained release nanoparticles	51
Temoxifen citrate	Nanoparticles	Cancer therapy, treatment and targeting	52
Silibinin	Nanoparticles	Induced apoptosis in glioma cells	53

Chitosan nanoparticles have a large set of application in different filed of interests such as tissue engineering, bio imaging, cancer treatment, antimicrobial activity, drug delivery, hemostatic, fungi static, spermicidal, central nervous system depressant. The variety of quality found in chitosan nanoparticles such as

- Stability in Nano-scale
- Low toxicity
- Excellent biocompatibility
- Simple and mild preparation method
- Versatile routes of administration
- Sub-micron size for non-invasive route

It was investigated about chitosan that it also showed its use in case of protein immobilization which was said to appear because of coupling of enzyme β-glucosidase along with glutaraldehyde activated chitosan. The immobilized enzymes were more stable into chitosan beads than the free enzymes while effectively maintaining enzyme activities. Recently, it has also gained proper interest of the population for showcasing its potential in achieving colon specific delivery as it is susceptible to glycosidic hydrolysis found in the colon by involving microbial enzymes which is somewhat same with those of other enzymatically depolymerized polysaccharides[30, 48]. These polyions on arrival to colon undergoes degradation by microorganism's enzymes or break down leading towards subsequent reduction in molecular weight mechanical strength due to that no more able to hold the drug and thereafter released the drug abruptly. Various studies reported on the applications of chitosan for colon targeting[24].

3.6 Chitosan in green chemistry application[31-34]

- Ionic liquids happen to be attained so much more thought as green solvents due to the product regarding the advance of green chemistry.
- Additionally, it is a vital need for environmentally friendly protection.
- The reception of ILs has appeared as a rebel which has been thrilled both the academia in addition to chemical companies.
- The terms and conditions room temperature ionic liquid (RTIL), non-aqueous ionic liquid, molten salt, liquid organic salt and fused salt have got all already been utilized to describe ionic liquid.
- The ionic liquid has exceptional physicochemical characteristics which can be very helpful if traditional organic solvents are not really properly active or perhaps not appropriate.

3.7 Cosmetic application of chitosan

Chitosan finds its application ranging from plant protection to water treatment to different areas of pharmaceutical or cosmetic filed. This wide application is only possible due to its physical as well as chemical stability. With such wide variety of applications is attributed to the fact that it exhibits different properties for its utility. These properties show alterations also, for example, with change in molecular weight or degree of acetylation, the product may show some change. In cosmetic applications, use of organic acids is prevalent as good solvents. A natural developed chitosan can be used for the sub-type of hydrocolloids[38].

It has been clinically tested that chitosan is the only natural cationic gum that changes to viscous form when treated with acid as it becomes neutralized. It also shows that specific interaction is prevalent in case of hair or with skin covers. Fungi static and fungicidal nature has been found for chitosan and chitin. When a cosmetic product involves a number of biologically active components, the compatibility of chitosan goes hand in hand with it. The derivatives of chitosan along with its original form have basically two prominent advantages for better skin. Positive electrical charge being the initial one while another one hinders the penetration in skin due to its high molecular weight. [40-42].

For cosmetic preparation generally organic acids are the preferred ones, and chitin and chitosan have static fungicidal and fungal properties. The only known cationic gum is chitosan which turns to be viscous when neutralized with acid. These products find its utility in lotions, creams and permanent waving lotions. Even various

forms were identified as nail lacquers[6].Examples: make-up cream and powders nail polish, and moisturizers. Chitin and chitosan may be used in various sites of the body such as skin, hair, gums, and teeth.

Gums: gums are porous; mucous membrane covered connective tissue located in the oral cavity surrounding the teeth's neck and adjacent alveolar bone. The teeth are attached to the sockets of the tooth wall. Inflammation of the gum tissue, called gingivitis, causes the gum to partially detach from the tooth's neck. In order to cure gum disease, some studies reveal that application of chitosan acerbate directly on gums are the effective ones [51].

Dental cavities: Chewing gum or use of mouthwashes having chitosan may reduce the activity of bacteria in the mouth causing cavity but no significant data so far is present to support such norms.
Dental plaque: Formation of plague on the surface of teeth can be prevented when rinsed with chitosan mouthwashes for 2 weeks subsequently. .
Teeth: Dental caries and tooth degradation are major factors correlated with the mineral depletion and demineralization of enamel. Dental caries are characterized as a localized chemical dissolution of the tooth surface resulting from metabolic events in the dental plague[46].Any mineral lost due to dental caries or dental damage is tooth wear. Tooth wear can be formed due to contact of tooth with another tooth by physical means (attrition).

Hair- Keratin is basically the main protein in the hairs. Apart from it, the main constituents are lipids like ceramids. These lipids stops the interfere function with hair sensory perception.

3.8 Agriculture field

When seeds were treated with chitin, it was observed that it showed better growth effects. Fungal pathogens and root knot worm infestations were suppressed when incorporation of chitin was made on the soil surface. [32]. The use chitosan and chitin in the field of agriculture has basically four major directions. The are-

1. Pre and post-harvest plant defense against plagues and diseases.
2. Enhancing the action and biological control of antagonistic microorganisms,
3. Promoting symbiotic relationships between beneficial plant microorganisms,
4. Regulation and production of plant growth.

Fungicidal activity (that kills the fungus) of chitin and chitosan are seen against numerous phytopethogenic fungi. Chitosan and its derivatives have also been known for antiviral and antibacterial activity. There has also been evidence of chitinase and chitosanase development in seeds covered by chitin films and their derivatives. The chitosan showing anti-microbial effect and its effective film creating potential have been destroyed in the preservation of fruit and vegetables after harvest[34, 35]. Chitosan film covering on the fruits and vegetables provides them with antimicrobial protection and improves shelf life. Chitosan along its derivatives induce beneficial alterations in plant of fruit metabolism. The output is improved germination along with greater yield of crops. For example hydroponic seed or leaf coating or agrochemicals controlled fertilizer release.

3.9 Chromatographic separations

In case of chromatographic separations, chitin and chitosan exhibits a wide range of use. Chitosan is useful and advantageous in chromatographic support due to the presence of free –NH2 groups along with primary (-OH groups) and secondary (-OH) groups. Cases have also been witnessed for separation of nucleic acids in TLC.

4. Therapeutic Application

Cohn's disease (an intestinal disorder): Cohn's disease can be prevented by taking chitosan and ascorbic acid in combination by oral route that was under previous studies and researches.
High cholesterol: lowering of cholesterol levels cannot be said by use of chitosan. Some theories suggests that intake of chitosan does not lessen total cholesterol or say bad low density lipoprotein in patients already having high levels of cholesterol. But alternatively, some suggests that intake may decrease the levels of cholesterol in patients

having high levels of the same. Certain combinations also decrease the cholesterol level in obese people having high cholesterol[44].

High phosphorous levels (hypophosphatemia): It is totally unpredictable and unclear if chewing gum having chitosan in it can assist in lowering phosphorus levels in people on haemodialysis. Research results are conflicting, thus many such researches are to needed[44,45].

Kidney failure: Early research shows that taking chitosan by mouth may reduce high cholesterol, help to correct anaemia, and improve physical strength, appetite, and sleep in people with kidney failure that are on haemodialysis.

Plastic surgery: Early theories and reports reveal that application of chitosan on a surgery site helps the injury in healing and also decreases the formation of scar.

Weight loss: it is unclear that chitosan can assist in loosing weight. Some say that upon combination with low calorie diet can cause weight loss in small amounts. But intake of chitosan without cutting calories cannot help in doing so.

5. Toxicity of chitosan[52-54]

- Chitosan is thoroughly noticed to be a non-toxic, biologically suitable polymer.
- It is really approved for nutritional uses in Japan, Italy, and Finland and has now been authorized by the FDA, so, it can be used in injury dressings
- . The modification designed to chitosan will make it just about harmful and any residual reactants could be properly removed.
- It is very important to analyze in regards to the composition of chitosan along with a drug may possibly replace the pharmacokinetic and bio-distribution profiles.
- cellular uptake kinetics can be changed as a result of the charge interaction for e.g. in the case of DNA complexes
- This controlling, or reduction, regarding the positive charges from the chitosan molecule, has possessions on its interaction along with cells in addition to microenvironment, and it also frequently trusted to reduced uptake and a minimize in toxicity.
- A photo crosslinks chitosan, produced as a tissue glue similar to fibrin glue, azide-chitosan lactose had not been toxic over a 1 month time period after administration of just one ml at 30mg/ml this is not photo-cross-linked.
- Nevertheless, no histological evaluation, enzyme or any other pathological measures were reported; not enough toxicity is induced by survival of >1 month.
- Chitosan is taken from the outer skeleton of shellfish. There is a concern that people with allergies to shellfish might also be allergic to chitosan. However, people who are allergic to shellfish are allergic to the meat, not the shell. So some experts believe that chitosan may not be a problem for people with shellfish allergy.
- Warfarin is a blood thinner. There is some concern that taking chitosan might increase the blood thinning effects of warfarin (Coumadin). Taking chitosan with warfarin (Coumadin) could increase the chance of bruising or bleeding. If you take warfarin, avoid taking chitosan.

Conclusion

This review paper summarizes the extending the area of chitosan and its applications/ advancements that, utilize for the treatment of various diseases. The most valuable think of chitosan is to help in the transport of therapeutic molecules, and antibodies. It is utilized particularly for the diagnosis and treatment of infections, diabetes, cancer, antioxidants, inflammation, and arthritis. It is an impeccable natural substance used for stability, high flexibility, and enhancement of bioavailability, targeting, and half-life. Thus, due to its high profitable achievement of a product that can employ as a continuous clinical trial and it interests the attention of scientists. All things considered, in the field of biomedical, biotechnological, pharmaceutical, clinical utilization of chitosan will be examined in the coming decade.

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Authors' contribution

All authors have equal contribution.

Conflict of interest

The authors have no conflict of interest.

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