REVIEW ARTICLE

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Applications and Perspectives of Chitosan as Functional Biopolymer; An Extended Review

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Abstract

Chitosan, a deacetylated derivative of chitin, has gained high importance for its nontoxicity, biocompatibility, biodegradability and antioxidant properties. The main objective of this review is to explore various applications of chitosan in different fields of life. It is used in food preservatives or coating material in natural origin due to its antimicrobial activity and film forming prpoerties. Chitosan-based coatings are made up by the combination of chitosan with organic, inorganic or with non-coating materials which includes gas fumigation, heat treatment and hypobaric treatment. It is used in various biomedical applications such as wound dressings, antibacterial coatings, tissue engineering scaffolds, drug delivery, stent coatings, biosensors and membrane seprations. Chitosan is a biopolymer which have different functional properties including enhacnced gelling properties, treatment of seafood industry effluent, drug compounds from aqua culture and sea food and nanocarrier abilities for bioactive compounds. Chitosan is also used for nasal formulations because of its efficient mucoadhesive properties including greater convenience, stability and long-term availability of drug in nasal cavity. Chitosan and its derivatives are used in nanocarriers for drug/ gene delivery or other healthcare purposes, due to their efficient hydrophilic properties.

Keywords: Chitosan, applications of chitosan, chitosan-based coatings, nano carriers, biomedical

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INTRODUCTION

Chitosan is the component of some fungi, shrimp and crab shell's cell wall. In nature chitin and chitosan are present as copolymer of each other. Chitin and chitosan are excellent prospects for biomaterials (i.e. interactive material). In nature chitin and chitosan are present as copolymer of each other. In 1859, Rought discovered the chitinan that was easily obtained by deacetylation of chitin. It's is an important artificial skin substitute. It forms a biocompatible, water absorbant film on the burn by keeping it in the chitosan acetate solution. They contain some specific properties i.e. environment friendly and degradable nature. Chitosan has a lot of applications due to its non-toxicity and high affinity (1).

The chemical structure of chition is like cellulose and it is insoluble in acidic solution presented in Figure 1. Chitosan is a linear polymer of a (1-4)-linked 2-amino-2-deoxy-b-D-glucopyranose and is easily derived from N deacetylation and is consequently a copolymer of N-acetyl glucosamine and glucosamine. It is derived from chitin (lies in exoskeleton of invertebrates) which is more important bioactive polymer and hence useful in chemical modifications. Chitosan is only positively charged polysaccharide which can be used in pharmaceutical, agricultural, industrial and cosmetic applications. It is also important in disease prevention, delay of aging, improvement of immunity and control of rythem (2).

Chitosan is nontoxic and degradable required for the manufacturing of immobilizing enzyme. Chitin and chitosan are the natural polyaminosaccharides. Chemically, chitin is composed of (1 → 4) linked 2-acetamido-2-deoxy-d-glucose subunits made a long chain of linner polymer. They dissolve in some solvents chitosan and chitin are analog of cellulose (2).

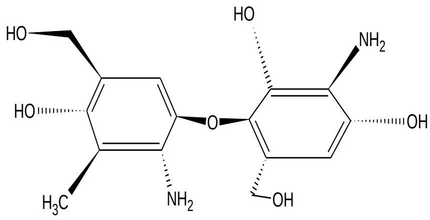

Figure 1: Strucure of Chitosan [2-amino-4-[2-amino-4-hydroxy-5-(hydroxymethyl)-3-methylphenoxy]-5-(hydroxymethyl) benzene-1,3-diol].

Chitin and chitosan are obtained from the shellfish of crab's shrimp labosters and wastes of seafood from the industry. The material can be passed through deproteinization in the solution of NaOH and released by HCl again, to purify the material NaOH can be used (3) for the chemical modification chitosan contain the hydroxal and amine group the presence of amino group can be formed chitosan a polyelectrolyte. Chitin is a hard material of white colour which is present in the internal as well as external structure of invertebrates. The production of chitosan is obtaine from crustacean shells which is waste of food industry. If it recovers the carotenoids and are feasible economically. chitosan contains the following properties biodegradability, bio-compatibility, non-toxicity, and adsorption (4).

These are natural polymers having great structural possibilities to create different applications and function in the biomedical area. In clothes of old aged people and babies, chitosan fibers are being used because it keeps skin from drying. It is also involved in the area of cartilage engineering (5). Chitin and chitosan have renewable origin, biodegradability, non allergenicity and biocompatibility in the body. Chitosan is a common copolymer with a molar fraction degree of acetylation (DA) of β-(1→4)-N-acetyl-D-glucosamine and a fraction (1-DA) of β-(1→4)-D-glucosamine (6, 7). Chitosan fibers are formed with poor moisture content persistency 2.0 g/d. Spinning conditions can change the fiber's properties such as spin stretch ratio, coagulation bath concentration and drying conditions. Incorporation of surfactants into the coagulation bath can result in better obstinacy of more than 4.4 g/d. These fibers are used in textiles. Chitosan fibers present great biomedical applications e.g. antimicrobial wound dressings affected by weight and pH (8, 9).

Applications of chitosan

Chitosan is used in various applications ranges from cosmetics, pharmaceuticls, plant defense and water treatment. For example, chitosan and derivatives are used in hair care (shampoos, rinses, hair sprays), skin care (creams, lotions, cleansing material etc) and oral care. It is widely used for osmosis, micro-filament, reverse osmosis and dialysis. These are also involved in production of paper, toilet paper, wrapping paper and cardboard. It is used in food industry for his non-toxicity for warm blooded animals. Chitosan gel in dyes is helpful in lasers and LEDs.

Applications in food industry

Polyethylene is used as the coating film during the packing of food material caused fermentation due to the oxygen and fluctuation of strong temperature due to water, which increases the growth of fungi (10). Chitin and chitosan are being used in food wrapping due to their film forming ability. It is also being used as a quality enhancer in different food stuffs due to its hypocholesterolemic effect, chitosan is used in the potato chips and noodles. It can be used in vinegar manufacturing due to the ability of cholesterol lowering. Ionic bonds can be formed at low pH, chitosan can be bind with the lipids and excrete out from the body cholesterol 'sterol and triacylglycerol inside the intestine chitosan combine with the cholesterol formed the miscalls which low the cholesterol level and the cholic acid in the liver on the other hand chitosan dissolved in the stomach and release in the intestine with oil droplet at pH 6-6.5 and excrete out from the body to control the acidity chitosan also used as a dehazing agent (11).

These biopolymers have a large range of applications which includes bioconversion which can be used for the production of useful food products. Chitosan films are long lasting, flexible, tough and difficuilt to degrade. Thus, these films are used as food wraps successfully e.g Japanese pears, kiwifruits, peaches, cucumber, tomamtos and straberries (12). Moreover, chitosan in fruit juices is a good clarifying agent. For animals and aquatic organisms, chitious material can be used for the production of seed supplement. Chitosan coating act as a protective barrier which transfer the moisture through the bread surface which helps in reducing the weight loss, retrogradation and retarding hardness. The effects of chitosan on the shelf life of wheat bread with different concentration and different molecular weight has also been investigated (13). Chitosan which have high molecular weight can extend the shelf life of bread than those which are of low molecular weight. Shelf life of eggs can be extended through chitosan coating which may act as the protective barrier which transfer the moisture and gas from albumin through the egg shell. Scott and silversides, (13) investigated that the albumin pH increases from 7.34 to 9.37 during 10-day storage of eggs at room temperature. This proves that chitosan film act as a barrier for the passage of both gas and moisture through egg shell.

Respiration rate and transpiration rate through plant surfaces is reduced, microbial growth can be retared, and texture quality of fruits can be improved by using the edible coatings which may serve as a protective barrier. Internal atmosphere can be modified by using the chitosan coating without triggering anaerobic respiration, while the chitosan-based films are permeable to CO_2 and O_2. This is the reason that it used to increase the shelflife of fruits and also control the decay of fruits. By the incorporation of calcium, vitamin E, or oleic acid into the chitosan film formulations, shelflife and nutritional values of fruits can be increased. Apples can be stored fresh for more than 6 months by coating them with N, O-carboxymethyl chitosan films and placing them in cold conditions (14). Chitosan also have the antimicrobial and antioxidant capacity (15) and the ability to reduce the oxidation of lipids and also reduced the bacterial growth during the preservation of meet products.

Composite coatings of chitosan

Essential oils and antimicrobial substances which are extracted from plants serve as a natural antioxidant. They are the mixtures of terpenoids, terpenes and other aliphatic and aromatic constituents (18). Anti fungal activity is enhanced by using the essential oils of lemon both *in vitro* tests and during the cold storage of strawberries which are inocubated with spore suspension botrytis cereal. When the chitosan is coated with phytic acid this can preserve the fresh cut lotus roots then the single chitosan coating (19), because the organice acids are dissociated easily in water and are biodegradeable that's why they are harmless for fruits coating. Chitosan coatings in fruit preservation can be increased by the use of organic matters such as ethanol and wax. When the chitosan is used in combination with ethanol, it can improve the control of grsy gold of table grapes when they are compared with the application of chitosan only and the effect was synergistic and atleast additive (20). Chitosan derivatives which have the high viscosities may be used as the binders or also used as food additive (21) improved their antioxidant, antibacterial and mechanical properties which are used for the application of green packaging.

Storage can cause the loss of commercial values and damage of fruits and vegetables. Chitosan control the fruit decay due to the antimicrobial and antifungal activities (22). By adjucting the permeability of oxygen and carbon dioxide, respiration rate of fruits and vegetables is reduced. To make the coating effective chitosan can be combined with other substance. Chitosan coating can be improved by two main methods, first, chitosan with other organic substances e.g., organic acids, essential oils and inorganic acids and the second, physical remedies including hypobaric and thermal treatment and gas fumigation is combined with the chitosan. Preservatives effects were increased after applying chitosan-based coating (23).

Antimicrobial activity

Kong *et al*. (24) described that chitosan and its derivative compounds present high antibacterial efficacy against the gram positive as well as gram negative bacteria. Chitosan is used as antibacterial additive in sea food because it can reduce the use of synthetic chemicals in the sea food preservation. It is showed that antibacterial activity of chitosan was expressed in aqueous system, however in smoked salmons the antibacterial activity was negligible because it is present in insoluble film forms. Due to its antimicrobial activity, it increases the shelflife or products (9). Chitosan present antimicrobial activity due to its positivly charged carbon of glucamine than the chitin (25). The positive charge on chitosan nd negative charge on microbes cause the leakage of intracellular material (26).

Waste water treatment

Water should be purified before releasing from the industries. Ion exchange chromatography is used to purify the industrial waste water due to the high adsorption quality of chitosan it can be used as purifying agent. Tonnes of the annual production of the textile dye from which more than 10% is discharged as a waste material which affects the environment due to the harmful impact on the ecosystem and the human beings (27, 28). Electrochemical techniques are used to remove the dyes which are very costly. Peels of different biological materials are also used such as banana and orange, but their adsorption capacity is very low towards the ionic dye (4). Chitosan-based nanofibers also have applications in filtration which include water purification media to air filter media. Chitosan, using the enzyme as effective tool, used to purify and clarify the waste from industries and effluent water from contaminated waste.

Anionic dyes are the major environmental pollutants in the industrial waste. Chitosan is cationic in nature so introduction of carboxyl group by using the process of enzymatic grafting of phenolic compound onto chitosan which increases the cacpacity for the absorbance of anionic dyes such as crystal violet and Bismarck brown C (28). Chitosan is used in the field of biotechnology due to its adsorption capicty for the metal and dyes. Chitoson obtain as a by-product of see-food during deacetylation of chitin. Fierro *et al.* (29) revealed that for the removal of phosphate and nitrate from waster chitosan-based algae system have better efficiency then the conventional cell system. It was showed that for cross-linked chitosan maximum adsorption occurred at pH 6.

Applications in enzyme technology

Enzyme isolation and purification is difficult, for convenience immobilization of enzyme can be used through which the enzyme stable their structure, sometime enzyme attach with the extra cellular membrane .it also increase the reusability of enzyme (30). Immobilized enzyme rather than industrial application also has application in the field of medical and organic synthesis. Chitosan can be used in the form of powder, flaks and gel in field of immobilizing enzyme (4). Characteristics for the material which is used for the process of immobilizing of enzyme should be same as functional groups for direct reaction and chemical modification, high affinity to proteins, mechanical stability and rigidity, hydrophilicity and regenerability. Chitosan-based materials are used in powder form, through flakes and gells of different geometrical configuration for the immobilization of enzyme. Covalent bonding and cross-linking are being used for the immobilized enzmyes on synthetic membranes. The polyelectrolytes which are used during this process are alginate, cerageenan, xanthan, various phosphates, organic sulphates and enzymes themselves.

Helathcare applications

The chitonic property of chitosan is due to the presence of amino group (31) for the release of the anionic drugs chitosan can be used which can be form complex with them and release for a long time (32). Trimethylation of the amino group can increase the muco-adhesive property of chitosan to about 3-4 folds. Chitosan self-branching can be studied without care of its safety profile the gene expiration level is 2 to 5 time higher as compared with lepofactamine and others (33). When cationic molecules form complexes with the drugs, positive zeta potential is formed due to the high amount of these catonic molecules, causing endolysis.

Hydrophobic character of chitosan is increased by making the enzymatic modifications of physiochemical and mechanical properties of chitiosan and soloubility is also increased at the physiological pH for the improvement of cell adhesion. Water soluble property of the chitosan derivatives was obtained at a physiological pH by using the hexyloxyphenols which uses tyrosinase enzyme as a catalyst (25). In the pharmaceutical fields, these chitosan derivatives are used for the production of drugs (34). When the collagen is grafted to chitosan by enzymatic grafting then it increases the antioxidant properties and also increases the growth of fibroblasts. Soluble hydrogels are produced by the chemoenzymatic method which have important role in pharmaceuticals and medical applications including tissue emgeneering, cartilage regeneration and drug targeting. Some hydrogels are following:

- Chitosan-polyethylene glycol tyramine act as a tissue engineering purpose (35).
- It can form taugh, water-absorbent, biocompatible films and hence applicable in burn treatment. It also allows oxygen permeability.
- Chitosan have all the abilities which is essential for ideal contact lenz, mechanical stability, optical clarity and gas permeability. It is also use in development of ocular bandage lense (10).

Due to mucoadhesive property chitosan works as auxillary agent in nasal system. The chitosan which is loaded by insulin increased the absorption of nasal drugs (36). Buccal site in more suitable for this type of system, the drug in the oral cavity stay for 1 hour and release in a controlled way. Chitosan as muco-adhesive work to stay the particle for long time (37). Nanoparticles mediated drugs can be stay for alog time in the gall bladder to make this work efficient used thiolated chitosan (38).

Drug/ gene delivery

For drug delivery applications, electrospun nano fibrils are used. Electrospining process aid in drug delivery. In the elcrospining process the effect on the drug activity is due to the high voltage which is applied during this process (39, 40) developed ibuprofen which is loaded with electrospun PEG-g-chitosan with poly-lactic co glycolic-acid (PLGA) which controls the drug delivery applications. The purpose of the presence of PEG-g-chitosan which causes the burst release of ibuprofen from the PGLA membrane (41). It is a challenging task in treatment of genetic disorders.for gene delivery the plasmid DNA has to be introduced into the target cells, which is firstly transcribed and then translated that all the genetic information goes to the new cell. Chitosan reacts with the negatively charged DNA and polyelectrolyte complex if formed and in this way DNA becomed protected against the nucleus degradation (46).

Wound dressing

The photo cross linked electrospunn which contains quarternary chitosan (QCS) are found efficient for the inhibition of growth of gramm negative and gram-positive bacteria (42). This shows that cross linked QCS/ Polyvinylpyrrolidone (PVP) elcrospun are used as the wound dressing applications. For the bacteriocidal activity against the gram-positive bacteria E. coli and gram-positive bacteria *S. auries* photocross linked nanofibrils QCS/PVA are used (43). Nanoparticales which are based on electrostatic interaction between chitosan and chondroitin sulphate is affected for the release of growth fector and protiens specifically platelets. Nanoparticles are absorbed by the adipoe tissues. It may be used as the bioactive agent for future. Vytokine and growth fector have an important role in the process of tissue repairing. They can regulate the mechanism which governs the mechanism of tissue regeneration and wound healing (44, 45).

Tissue engineering

Cartilage repair can be done with the help of catechol chitosan gel patches (46, 47). Initially chitosan catechol gell patches were in soft form, but then it converts into solid 3D form by containg the blood or media. It acts as a diffusion barrier which prevents the drug release to non-therapeutic direction. Subchondral drilling and microfracture are used for the betterment of healing in the damanged tissue. Polysaccharides are used in the growing mechanism biomaterial due to following reason; moieties which are present in the signalling scheme and in the area of cell recoginition in tissue engineering research and biodegradability.

Antioxidant capacity of chitosan

Oxidative stress level in normal persons by chitin and its derivatives have good correlation between oxidized albumin ratio and TPA. This shows the oxidative albumin ratio is a good marker for oxidative stress. However, in in vitro studies, in the presence of carbon albumin carbonyls and hydroperoxides was decreased in time depandant manners. Chitosan has a direct antioxidant activity which lowers the indices of oxidative stress in a systematic circulation. Chitosan also have the chelating ability when it is present in highy acylated from. Redical scavenging activity becomes less due to the high molecular weigh of the chitosan which have the compact structure, the stronger intramolecular hydrogen bonding weakens the activity of hydroxyl and amino groups. Duan *et al*. (45) showed that lipid stability of lignocod is enhanced by the 21 days of cold storage by the combination of chitosan with atmosphere packaging.

Chitosan-based drug delivery systems

Buccal drug delivery system

Buccal mucoadhesive drug delivery systems enable direct absorption of the drug through the mucous layer, which avoids the first pass metabolism and degradation in the presence of a gastric environment and higher bioavailability in comparison to the oral route (48). For blood pressure and cardiac disease treatment, chitosan and its co polymers are used, buccal drug delivery, using gelatin and chitosan microparticles is commonly being used for the delivery of several therapeutic drugs such as propranolol hydrochloride (49).

Nasal drug delivery system

Delivery through the nasal route helps in bypassing the first-pass effect and increases patient compliant with reducing dose frequency. The formulation with thiolated chitosan nanoparticles showed greater locomotor activity and reduced oxidative stress in rats compared to the one administered with unmodified chitosan nanoparticles (50), they developed chitosan derivatives nanoparticles and chitosan-pullulan composites for the nasal delivery of diphtheria toxoid (51).

Oral drug delivery system

Formulations with chitosan derivatives used for oral delivery increase the mean residence time in the absorption microenvironment because of their muco-adhesive and pH-responsive properties. Chitosan-dextran sulfate (CS-DS) matrix for the *in vitro* release of insulin using nano sized supramolecular gels have been investigated (52). The release of insulin from the nanogel is controlled by diffusion, disintegration and swelling of the matrix. Thus, such polymer-bonded drugs can be used for pH-triggered release of drugs. Hydrogels have many polymers which have the mucoadhasive and bioadhasive properties which are used in the hydrogel preparation. Chitosan hydrogels release their payloads under the influence of environmental stimulus (53).

CONCLUSION

Chitosan biopolymer is being used for a wide range of applications. This review provides in depth study of chitosan with its applications in modern world. Biomaterial applications of chitosan-based nanocomposite in wound dressing, tissue engineering, drug delivery and cancer chemotherapy. This review also summarizes the novel applications of chitosan in the production of natural-based biodegradable films and can be used in variety of sizes and forms especially in packaging industry, to reduce petroleum-based pollution from the environment. Nanostructured composite can be used to manufacture tissue engineering paradigms for wound healing. Multifunctional role of chitosan at different place is highlighted in this review including biomedical applications, as in drug delivery. Nanoparticle mediated drug delivery can prove to be an effective method for different diseases. We believe that this study will provide in depth knowledge related to the importance of chitosan nanomaterials and can prove to be useful for researchers working in nanobiotechnology.

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