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The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.23
TPI 2021; SP-10(7): 150-155

www.thepharmajournal.com
Received: 16-05-2021
Accepted: 18-06-2021

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Application of chitosan and chitosan derivatives: A review

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Abstract
Chitosan is a chitin-derived biopolymer, one of the most abundant and renewable materials on earth. Chitin is a primary component of fungal cell walls, arthropod exoskeletons such as crustaceans, e.g. crabs, lobsters and shrimp and insects, molluscan radulae, cephalopod beaks, fish and lissamphibian scales. Due to its unique macromolecular structure, biocompatibility, biodegradability and other intrinsic functional properties, chitosan has attracted significant scientific and industrial interests since the late 1970s. The practical applications of chitosan and derivatives are in the food, agriculture, aquaculture, pharmacy, medicine, cosmetology, textile, and paper industries. In reality, nutraceuticals and cosmeceuticals are growing markets, and the next markets in the production of chitosan should be therapeutic and biomedical products. The goal of numerous fundamental studies is also chitosan. A number of works on chitosan applications published over the past two decades are highlighted in this study.

Keywords: chitosan, biopolymer, applications

Introduction
The main commercial polymers are derived from raw products based on petroleum using processing chemistry that is not always safe or environmentally friendly. Over the past decades, there has been a growing interest in exploring natural alternatives to synthetic polymers mostly the biopolymers. Biopolymers are polymers derived from or synthesized from natural materials from living organisms. Because of their biological roots, and also because of their non-toxicity and biodegradable nature, they have spread considerably. The biopolymer chitosan has received a lot of attention in fundamental science, applied research, and industrial biotechnology because of its remarkable macromolecular structure, physical and chemical properties, bioactivity, and flexibility, very different from those of synthetic polymers (Crini 2019; Crini *et al*. 2009) [2]. Chitosan and its derivatives, in the form of solutions, suspensions and particles, have functional applications. As an eco-friendly biopolymer, chitosan serve an environmental purpose and extended to clarification and purification of water, treatment of waste water, remediation, dewatering of sludge and membrane filtration. In the fields of electrochemical sensors, biocatalysis, adhesives, bioimaging, ionic liquids, green solvents, and detergents (Crini and Badot 2008; Bhatnagar and Sillanpää 2009; Sudha 2011) [1, 63, 5]. Japan, the USA, Korea, China, Canada, Norway, Australia, France, the UK, Poland, and Germany are the markets for chitin and chitosan, Ferraro *et al*. 2010 [6]; Japan dominated the sector in 2015, accounting for 35 percent of the industry. Indeed, Japan has been substantially advanced in the technology, marketing and use of these biopolymers since the 1980s (Badawy and Rabea 2017; Bonecco *et al*. 2017) [7, 8]. About 700-800 tons of chitosan is consumed annually by the market in this region. This review highlights the application of chitosan in different areas.

Food industry
As a widely recognized food additive, dietary fibre (hypocholesterolemic effect), and functional ingredients for the market, chitosan was approved by the US Food and Drug Administration. Since the 1990s, Chitosan has also been approved as a food additive in Japan and Korea. Chitosan is used as a dietary ingredient (food additives, functional foods), anticholesterolemic dietary products, neutraceuticals, antimicrobial and antioxidant (food protection) for antimicrobial coatings in fruits and vegetables because of its bioactive nature and cationic nature (Shahidi *et al*. 1999; Gutiérrez 2017; Han *et al*. 2018) [9, 10, 59, 11]. Kardas *et al*. (2012) [12] showed that chitosan and its derivatives have a wide range of specific food

industry applications, including food preservation from microbial degradation, shelf-life extension, biodegradable film formation, and food packaging. Fibers, films, gels, beads, or nanoparticles can form the products used as a packaging or coating material. A similar conclusion has also been stated by Van den Broek *et al*. (2015) [13], examining the growth of chitosan films and blends as packaging content. Due to its antimicrobial and film-forming activities, chitosan has been considered an effective alternative to substitute non-biodegradable and non-renewable polymers as a source of food preservative or coating material, as well as to minimize the widespread use of harmful pesticides in food safety Nadia Morin-Crini *et al*, (2019) [2]. Chitosan films have shown superior results and strong mechanical properties and have the benefit of being able to combine functional substances such as vitamins and as antimicrobial agent releasing carriers. Chitosan films, however are extremely permeable in the application of packaging. They also appear to exhibit resistance to fat diffusion and selective gas permeability due to their hydrophilic character and water vapor. In the reviews by Kardas *et al*. (2012) [12], Elsabee and Abdou (2013) [14], Van den Broek *et al*. (2015) [13], and Wang *et al*. (2018) [45, 15], a review of the various methods to address these disadvantages can be found. As films in food packaging fields, blends, composites, and multilayer systems containing chitosan have been suggested and seem promising. Nutraceuticals, especially in Japan, emerged as an industry in Asia in the early 1990s. Functional foods, nutritional supplements, and herbal/natural products are included in the nutraceutical market. The nutraceutical properties of chitosan, along with its dietary fiber use, include its antibacterial, anti-infammatory, antioxidant, anti-carcinogenic and anti-ulcer bioactivity. Chitosan has poor viscosity, high water binding properties, and non-digestibility in the upper gastrointestinal tract (Muzzarelli and de Vincenzi 1997; Roller and Valley 2003; Badawy and Rabea 2017) [16, 17, 7]. As a dietary fibre, by preventing the absorption of dietary fat and cholesterols, it has the capacity to reduce cholesterol. Chitosan and its derivatives have been shown to help the human body lose weight and body fat, thus reducing systolic and diastolic blood pressure (Philibert *et al*. 2017) [18]. Compared to other fibres, it also greatly enhances the excretion of strongly atherogenic saturated fatty acids. Chitosan, as a valuable prebiotic, can also encourage colonic conditions.

Beverage industry

It can be used for clarification, deacidification, stabilization, removal of ochratoxin A, enzymes and other unwanted substances, such as metals and pesticides, in the processing of wine (Bornet and Teissedre 2011) [19]. Chitosan is also used as an environmentally friendly coagulant for clarification of passion fruit (Domingues *et al*. 2012) [20] and as a natural focusing agent for clarification of beer (Gassara *et al*. 2015) [21]. Rocha *et al*. (2017) [22] provided an overview of the recent matrices based on chitosan used for the clarification, storage, encapsulation, and active and intelligent packaging of different types of beverages, including fruit juices, nectars, condensed fruit juices, tea, coffee, and tisanes, including alcoholic, dairy-based drinks, and non-alcoholic.

Pharmacy

Pharmaceutical applications for chitosan began to appear in the late 1980s (Nagai *et al*. 1984; Felt *et al*. 1998; Kumar 2000) [23, 24, 25]. Chitosan and its derivatives have mainly been explored as excipients in drug formulations and drug delivery systems in this area (Badwan *et al*. 2015) [26]. The latest method was to substitute natural products with potentially harmful chemicals, which soon proved to be promising. The key properties used in the pharmaceutical field are: controlled release of drugs, e.g. anti-infammatory naproxen, mucoadhesive properties, in situ gelling properties, transfection enhancing properties (deoxyribonucleic acid and ribonucleic acid small interfering ribonucleic acid). Chitosan can be used as solutions, gels, tablets, capsules, fibres, films, and sponges and its derivatives (Ali and Ahmed 2018) [27, 37]. Consequently, they can be used in dental, ocular, nasal, vaginal, buccal, parenteral, intravesical, and transdermal administration, and in both implantable and injectable forms, as implants for drug delivery. Applications for drug delivery include not only controlled drug release systems, such as site-specific delivery of antibiotics in the stomach and controlled protein release, but also vaccine and gene delivery systems (Singh *et al*. 2018) [28]. Over the past two decades, chitosan has been used as stable excipients in oral dosage form (Felt *et al*. 1998; Kumar 2000; Kumar *et al*. 2004) [24, 25, 29]. Compared to commercial products, Chitosan tablets may exhibit a sustained release of drugs. Chitosan is interesting because of its mucoadhesive bioactivity and absorption enhancement property to be used for oral delivery also, stated as strong permeation enhancing properties. For tissue engineering and wound care dressing, films and fibers prepared using chitosan and chitin were formed as an oral mucoadhesive and water-resistant adhesive due to their release characteristics and adhesion (Kato *et al*. 2003; Illum and Davis 2004). Chitosan-containing and derivative pharmaceutical formulations are reported for slimming use, body weight control and for example, as cosmetics to increase skincare effectiveness. The use of nanocomposites in drug delivery also appears promising, as Ali and Ahmed have recently reported.

Medicine

Chitooligosaccharides, the derivatives of chitosan can be formulated into different forms for the application in medical. For instance, gels and hydrogels, solution, nanoparticles and microparticles, membranes, films and fibres, drug formulation and delivery, antimicrobial, gene therapy, would healing, tissue engineering include possible medical and biomedical applications of chitosan (Allan *et al*. 1984; Riva *et al*. 2011; Ali and Ahmed 2018; Hamedi *et al*. 2018) [32, 33, 27, 37, 34]. Especially useful for wound care are their bacteriostatic and fungistatic properties. Two of the most interesting properties of chitosan are combined in this application: antimicrobial activity and biocompatibility. There is also a stimulatory effect of chitosan and its oligosaccharides on cells. The goal of tissue engineering is to repair or substitute damaged body parts or missing organs by transplanting supportive scaffolds with suitable cells that produce new tissue in combination with biomolecules (Dash *et al*. 2011; Saravanan *et al*. 2013; Ahmed *et al*. 2018) [35, 36, 27, 37]. Dash *et al*. (2011) [35] stated that in wound healing applications, chitosan is an ideal dressing because it not only protects the wound from bacterial infection, but also facilitates healing and causes less scarring. Chitosan derivatives have been described as novel scaffolds to address these issues, tissue engineering materials. A discussion of the use of several derivatives as new products in bone tissue engineering can be found in the reviews by Logith Kumar *et al*. (2016) [38] and Ahmed *et al* (2018) [27, 37]. The use of chitosan-based membranes and scaffolds was investigated not only for tissue engineering and wound healing, but also as an anticancer drug delivery, osteogenic drug delivery, and delivery of growth factor by Anitha *et al*. (2014) [39]. Biodegradability, cytocompatibility, multifunctionality, and unique mechanical properties are the main characteristics of these biomaterials. Chitosan films are air-permeable flame. It encourages the regeneration of cells while shielding tissues from microbial attacks. Chitosan has a calming effect on tissue regeneration as well. It is used for high-grade burns and surgical applications in the manufacture of artificial skin for skin grafts (suture threads). Chitosan in the digestive tract can trap lipids at their pH of insolubilisation. This decreases the amount of cholesterol in the blood considerably. Chitosan has bioadhesive properties that make it possible for adhesive sustained release formulations to be of interest. Mucoadhesivity allows drug adsorption to be increased especially at neutral pH (Dash *et al*. 2011; Vunain *et al*. 2017) [35, 40]. Due to its ability to form complexes, biodegradability, and biocompatibility, Chitosan is a prominent system-based gene delivery vector, although its transfection efficiency and cell specificity are poor. Its role in gene transmission is assisted by its capacity to protonate through electrostatic interactions in acidic media, forming a complex with deoxyribonucleic acids (Choi *et al*. 2016) [41]. Compared to widely used systems, the chitosan-deoxyribonucleic acid complexes are simple to prepare and are more successful. Chitosan sulfate has the potential to interfere with the mechanism of blood clotting. This is a subject for systematic medical applications. This derivative has been shown to possess high anticoagulant potency compared with heparin. Sulfated chitosan, unlike heparin, does not show anti-platelet activity, causing severe bleeding in patients (Badawy and Rabea 2017) [7].

Dentistry

The important properties of chitosan that have been cited for dentistry are: Bioactivity, anti-infammatory, wound healing, haemostatic and bone repair practices (Queiroz *et al*. 2015; Kmiec *et al*. 2017; Navarro-Suarez *et al*. 2018; Zheng *et al*. 2018) [42, 46, 43, 44, 45]. Chitosan is used in solution form by dissolving in acetic or methanesulfonic acid, microspheres, hydrogel and toothpastes, and its combination with additives such as amorphous calcium phosphate, amelogenin and quinic acid has enhanced the ability of these chitosan preparations to prevent tooth decay and enamel degradation. The gel/hydrogel form of chitosan refers to the treatment of chronic periodontitis and cancer sores. Queiroz *et al*. 2015 [42, 46] stated that chitosan can play an important role in preventive dentistry because of its inherent flexibility, efficacy, and ability to act as a protective barrier to the penetration of acids into enamel and its mineral loss. In addition, chitosan preparations are able to repair early lesions of the caries when combined with remineralizing agents. Chitosan and herbal fullness-based toothpastes, mouthwashes, and chewing gums have antimicrobial effect on oral biofilm and a decrease in the amount of Streptococcus mutans in the oral cavity (Kmiec *et al*. 2017) [43]. The use of nanotechnology in dentistry and the new developments in nano-biomaterial products have recently been addressed by Navarro-Suarez *et al*. (2018) [44]. The use of biomaterials in dentistry was also reviewed by Zheng *et al*. (2018) [45], focusing on new techniques using a combination of scaffolds, cells, and biologically active molecules to assemble functional structures for dental purposes that repair, preserve, or enhance damaged tissues. Underwood and van Eps (2012) [47] identified the use of nanoparticles for drug delivery, diagnostics, and vaccine formulations. A promising area appears to be nanomedicine utilizing revolutionary nanosystems.

Cosmetics

In the formulation of cosmetics, Jimtaisong and Saewan (2014) [48] extensively explored the use of carboxymethyl chitosans as multifunctional ingredients. In cosmetology, chitin is also interesting because the skin tolerates it well. It is an effective hydrating agent and a film-forming tensor that has two frequently cited advantages: it provides water and prevents dehydration. Chitosan and chitin also have metal chelating properties that are responsible for a very large number of contact allergies. Carboxymethyl chitosan products are used as an antioxidant agent, retain moisture absorption, antimicrobial agent and stabilization of the emulsions products in cosmetics. The use of carboxymethyl chitosans as multifunctional ingredients in cosmetics formulation was comprehensively addressed by Jimtaisong and Saewan (2014) [48].

Agriculture

In plant protection since the 1990s, chitosan products have been used against plant pathogenic bacteria that cause decay and harmful effects of agricultural crops during the growing season and post-harvest period (Yin and Du 2011) [49]. They behave as bactericidal and/or bacteriostatic (killing bacteria) (hindering the growth of bacteria). The exact mechanism is still not fully known, however. A debate can be found in the study by Muñoz-Bonilla *et al*. (2014) [50], on models suggested for antibacterial behavior of chitosan. The polycationic character of chitosan that makes contact with negatively charged organisms is the most accepted mechanism (bacterium cell membrane). It is also an excellent antifungal agent because of the chelating properties of chitosan (Divya and Jisha 2018; Badawy and Rabea 2016; Rabea *et al*. 2003) [52, 51]. Many defensive responses in plants are triggered by the presence of chitosan. It is typically employed as an effective elicitor in plant disease control. As devices for controlling the release of agrochemicals, chitosan products were suggested (fertilizers, pesticides). They are used either alone or blended with other plant disease products (plant bacteria and fungi control), pests and insects, plant growth promotion, seed coating and post-harvesting products as biocides (Divya and Jisha 2018; Grande-Tovar *et al*. 2018; Sharif *et al*. 2018) [52, 53]. Chitosan also has inhibitory effects on plant viruses and viroids. As a biopesticide, it has excellent potential. Chitosan products have been proposed as devices for controlling the release of agrochemicals and can function as a seed-soaking agent (fertilizers, pesticides). They are used either alone or blended with other plant disease products (plant bacteria and fungi control), pests and insects, plant growth promotion, seed coating and post-harvesting products as biocides (Divya and Jisha 2018; Grande-Tovar *et al*. 2018; Sharif *et al*. 2018) [52, 53].

Aquaculture

The crustacean shells contain large amounts of carotenoids which have not been synthesized to date and which are marketed in aquaculture as a fish food additive, especially for salmon. Alishahi and Aïder (2012) [55], have outlined the use of chitosan and its derivatives in aquaculture. It can be used as a functional food, as dietary supplements (synbiotics), as a carrier for bioactive compounds, for the release of drugs, for the encapsulation of toxins or nucleic acids, and for the removal of contaminants from water and waste water. In addition to reducing degradation of water quality, the removal of organic compounds and inorganic nutrients from aquaculture wastewater prior to discharge may also be further reused for prawn, fish and shellfish cultivation. It has been used to enhance the quality of aquaculture waste water as it could eliminate suspended solids (SS), organic compounds, NH3, PO43, and pathogens. Chitosan can be used as a coagulant, adsorbent, or bactericide Chung YC (2006) [56]. Lian *et al*., 2016 [57], the antibacterial analysis of shrimp culture in natural seawater, chitosan microcapsules were added. Seawater was found to be relatively clear in the NCCM (Norfloxacin chitosan/chitosan oligosaccharide microcapsules) added groups and Vibrio's biomass steadily increased compared to the control and norfloxacin groups. In the norfloxacin groups, the inhibition rate of Vibrio obviously decreased after day 5, while it remained high and stable in the NCCM groups throughout the experiment period. The results showed that in the farming of *Penaeus vannamei* Boone, the chitosan microcapsules as release materials have excellent antibacterial effects on Vibrio.

Textile industry

The use of chitosan is among the potential approaches introduced by the textile industry. Chitosan provides an innovative avenue for the production of bioactive textiles on a wide scale. Chitosan could act in textiles as active compounds, e.g. as antimicrobial textile finishing, and as cosmetotextiles. Cost-effectiveness, non-toxic, biocompatible, biodegradable, antimicrobial activity, antistatic activity, chelating property, deodorizing property, film-forming power, chemical reactivity, dyeing capacity for improvement, thickening property, and wound healing activity are among the characteristics of chitosan used in the textile industry (Giri Dev *et al*. 2005; Gutiérrez 2017; Roy *et al*. 2017; Islam *et al*. 2013) [58, 10, 59, 60, 61].

Pulp and paper industry

The first use of chitosan was documented in the papermaking industry in 1936 (Struszczyk 2002) [62]. The key use of paper was to increase wet strength. As a functional material, chitosan can also interact with cellulose pulp during paper formation and be film-forming to give coherent rupture resistance during paper formation (Song *et al*. 2018). In order to encourage compliance with environmental legislation, this biopolymer is also non-toxic, biodegradable, and eco-friendly. In the decontamination of pulp and paper waste water, chitosan is often used as a chelating and complexing agent to eliminate lignin, pigment, and undesired pollutants, and to reduce the overall demand for organic carbon and chemical oxygen (Crini *et al*. 2009; Cheba 2011) [1, 63].

Conclusion

The objective of this review was to provide an overview of chitosan applications, based on a large number of valid references that have been published in the last two decades. This is an ambitious project, of course, and the examples given in this article are not exhaustive but show the interest of chitosan in many areas clearly. The food, pharmaceutical, and cosmetic industries are the major markets for chitosan. Due to increased consumption, the demand for chitosan is expected to rise rapidly, not only in cosmetics, but also in the treatment of water, the beverage industry, and diet. Rising markets are nutraceuticals and cosmeceuticals. In developing countries, there is also an increased demand for chitosan. It is also expected that medicinal and biomedical products will have a positive market effect. It is important to note that while several papers and patents have been published over the past two decades, there are still restricted applications of chitosan in the biomedical field, mainly due to the severe difficulty of accessing the biopolymer at its source with adequate purity and reliability. Furthermore the production of new materials is very limited, mainly because of their cost, which remains higher than that of polymers with similar properties based on petroleum. In the near future, more industrial advances in the following fields are expected: anticancer drugs, gene delivery, catalysis, sensor applications, wrapping and packaging materials, cosmetotextiles, and bioimaging.

Acknowledgement

I would like to acknowledge the co-authors for their support and contribution in writing this review paper.

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