

NEXT GENERATION NANOCHITOSAN

Applications in Animal Husbandry, Aquaculture and Food Conservation

Edited by
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ACADEMIC PRESS

An imprint of Elsevier

elsevier.com/books-and-journals

Academic Press is an imprint of Elsevier
125 London Wall, London EC2Y 5AS, United Kingdom
525 B Street, Suite 1650, San Diego, CA 92101, United States
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, United Kingdom

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ISBN: 978-0-323-85593-8

Publisher: Nikki Levy
Acquisitions Editor: Kelsey Connors
Editorial Project Manager: Kyle Gravel
Production Project Manager: Sruthi Satheesh
Cover Designer: Miles Hitchen

Typeset by Aptara, New Delhi, India

CHAPTER 6

Nanochitosan derived from marine annelids

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Introduction

The phylum Annelida consists of segmented worms which are identified with the presence of coelom which is a body cavity (or coelom), bristles that are moveable (or Setae/Chaetae), and a segmented body through annulations that goes transversely. They are made up of a complex group containing up to 22,000 well-known species (Aguado et al., 2014). Annelids are coelomated organisms which are triploblastic, bilaterally symmetrical and coelomate organisms, usually have a circulatory system that is closed and a nephridia which plays a vital role in osmoregulation. Their sizes vary from millimeters to meters long and also possess feeding structures of varying complexities, different morphology of chaetal and sensory organs. They ubiquitous and distributed all over the world right from the deepest sediments of marine habitants to moderate altitudes of fresh water habitants as well as from the temperate to the tropic region (Donald and Bruno, 2009).

This phylum of invertebrate animals is divided into three groups: hirudinea, polychaeta, and oligochaeta. The marine annelids which are members of the class polychaeta have been found to display the more primitive features of the phylum (Susan et al., 2015). There are 6000 known species of the polychaetes and most of them are found floating ocean, wandering at the bottom or found living in the tube built by them. They have varying color ranging from dull to brilliant while of the species are known to be bioluminescent, such as *Chaetopterus*, *Terebella*, and *Cirratulus* (Hastings, 2011). The earthworms belong to the class Oligochaetae, which are known to live primarily in damp soils; few members live in fresh water and estuarine habitat. The leeches are the major member of the class Hirudinea (Bleidorn, 2009).

The body of the annelids is usually multiple arrangement of segments that are organized in a similar way with coelomic segments. This pattern of arrangement of the small repeating units is termed metamerism. There are considerable differences in

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DOI: https://doi.org/10.1016/B978-0-323-85593-8.00012-6

metamerism in annelids, this is because the segments are commonly joined and could also be noticed to disappear secondarily. Metameric subdivisions of the coelom also serve as a hydrostatic skeleton (Agaudo et al., 2014). Annelids are said to be the most highly organized animals with the power of regeneration of lost body segments. The potentials for regeneration of lost segments are higher in the polychaetes and lower oligochaetes and lesser in the higher oligochaetes. Leeches, however, do not have this ability. Most polychaetes and oligochaetes can regenerate lost segments in the tail region (Zoran, 2010).

The body of many marine annelids is separated into two or three regions. Depending on whether the annelid is free-moving, sedentary, or pelagic, their body form is known to differ. The prostomium which is the first segment lies in front of the mouth and succeeded by another segment called the peristome and then, a series of segments bearing fleshy outgrowths called the parapodia. The parapodia contain bundles of setae or chaetae which are hairs that are secreted epidermally made up of β-chitin (Piet, 2014). Examples of marine annelids are Chaetopterus, *Perinereis cultrifera*, Sea mouse (Aphrodita), *Neanthes arenaceodentata*, *Capitella capitata*, Cirriformia, *Nereis diversicolor*, etc. (Bartolomaeus et al., 2005).

The popularity of some annelids is due to their economic advantage and significance. The use of medicinal leeches has been documented in the removal of blood from sick persons as a means of reducing inflammation. Documentations have also revealed their usage for other medicinal applications for a period more than two thousand years for sciatica, skin infection, and musculoskeletal pains. Also, the knowledge of the anticoagulant characteristics of the blood feeding leeches brought about the identification of various proteins which have the potential to inhibit some steps of the process of coagulation in some vertebrates. Presently, they are also applied in the area of microsurgery, for the reduction of blood pressure and reducing the risk for coagulation process. There are some other annelids that have medical applications such as *Bonellia viridis* which has the ability to produce Bornellin; a substance known to possess antimicrobial properties (Beesley et al., 2000; Rouse and Pleijel, 2001; Aguado et al., 2014).

The burrowing activities of annelids such as earthworms in the terrestrial environment and lugworms in the coastal sediments, has been documented to stimulate microbial activities and proper soil aeration. Thus, helping to improve soil fertility and better agricultural yield. Earthworms and lugworms are commonly used as bait in fishing and also as food in aquaculture. Some annelids found in the marine environment are also useful as engineers in the ecosystem for example the Sabellariidae which are good reef-building agents. Annelids are important in ecotoxicological assessment and monitoring of the environment, in which some of the species as vital as useful indicators of some peculiar environmental conditions and as useful agents in the remediation of some contaminants that are present in soil (Rouse and Pleijel, 2001; Aguado et al., 2014).

Therefore, this chapter intends to provide a detailed information on the comprehensive application of nanochitosan derived from marine annelids.

The uniqueness of nanochitosan derived from marine annelids

Chitin is well known as the next natural polymer with the highest natural abundance after cellulose, it is a naturally occurring polysaccharide (Aam et al., 2010). It is mostly found in some organisms such as cnidarians, fungi and algae, round worms, echiruda, bryozoa, and entoprocta (Merzendorfer and Zimoch, 2003; Kaur and Dhillon, 2014; João et al., 2015). About 10^{12}–10^{14} tons of chitin is found in the ocean yearly, produced from living organisms within the ocean (Dhillon et al., 2013), out of this, 2.8×10^{10} kg is obtained from the arthropods found in fresh water while 1.3×10^{12} kg from the marine ecosystem (Cauchie, 2002). Consequently, there is a need for the development of commercial procedures for the extraction of chitin from these huge deposits because of its economic importance. Additionally, this will help in eradication of seafood wastage and pollution of the aquatic environment (Xu et al., 2009).

Basically, three major forms of chitins have been documented which entails, alpha α, beta β, and gamma γ chitin. The most abundant of them all is the α-chitin which is found in the cell wall of fungal, yeast cells, shrimps shells, crabs, and in the cuticle of insects (Yadav et al., 2019). The arrangement of the polysaccharide chains in alpha chitin is in antiparallel thus allowing effective maximum bonding. This is responsible for the higher stability of the alpha chitin amongst the other types known in nature hence bringing about chitin fibrils having high level of crystallinity index, up to 80% (Yadav et al., 2015). The beta chitin is rarer when compared to the alpha and is found in connection with proteins that are found in pens of squids (Rudall, 1969; Rudall and Kenchington, 1973) also in the tubes that are produced by vestimetiferan worms and pogonophoran (Blackwell et al., 1965). It is also found in lorica and chaetae of Aphrodite where they are produced by seaweeds and protozoa (Gaill et al., 1992).

Recent studies have reported the secretion of a relatively purer form of beta chitin by *Theodoxus fluviatilis*, which is a diatom. The beta chitin is in monocrystalline spine. The orientation of the polysaccharide chains in beta chitins are in parallel while the crystallinity index is 70%. This arrangement is responsible for a greater distance that exist between the polymer chains that are in adjacent positions which is responsible for the higher reactivity of the beta chitin as well as it higher solubility in organic solvent (João et al., 2015). There is presence of gamma chitin in fungi such as *Lactarius vellereus*, *Mucor rouxii*, *Penicillium crysogenum*, and *Aspergillus niger*. The orientation of the polymer chain in the gamma chitin is a combination of the alpha and beta like orientation which involves the arrangement of two parallel chains which are alternatively with another chain that is antiparallel in orientation (Susana and Eva, 2012; Yadav et al., 2015).

Chitosan is formed from chitin through a partial deacetylation process. It is a polysaccharide that is linear in nature and made of acetylated and deacetylated units of D-glucosamine that are held together by bonds of β (1,4) glycosidic groups. This procedure is the chemical means of producing chitosan starting from chitin as raw material (Kurita et al., 1977; No and Meyers, 1995) and this is employed in large scale for

the production of chitosan due to its economy for mass production and ease (No and Meyers, 1995). The extent of deacetuylation in the production of chitosan is determined usually by the ratio N-acetyl glucosamine and glucosamine present. In chitin, the percentage of glucosamine is less than N-acetyl glucosamine, while in chitosan the reverse is the case (Viarsagh et al., 2010; Ramirez et al., 2010). Chitin to chitosan conversion process can also be induced through the activities of enzymes (Kafetzopoulos et al., 1993; Aiba, 1994; Ilyina et al., 1999; Tokuyasu et al., 2000). It is worth noting that the properties of the chitosan prepared are depended significantly on the type of organism from which the raw material is sourced and the method of production employed (Rege and Block, 1999; Berger et al., 2005).

Chitosan and chitin are biopolymers having a vast economic importance. Chitosan possess a wide range of uses in food production, medicine, cosmetics, water processing, detergent, paper, textile, antimicrobial agent, antioxidant, edible film industry, and other biotechnological application. However, the effectiveness of chitosan is reduced by its larger molecular size, hence, a need for reduction into chitosan nanofibers, nanowhiskers, and nanoparticles (Liu et al.,2011a,b; Zhou and Wu, 2011; Iqbal et al., 2012).

Nanochitosan is known to possess special physicochemical properties which include mini size impact, quantum size impact, macro quantum tunnel impact, and surface effect (Ramezani et al., 2015). The nanoparticles of chitosan can be produced through different techniques such as successive disintegration (Iqbal et al., 2012), disassembling technique (Liu et al., 2011; Zhou and Wu, 2011), formation of micelles from the self-assembling of chitosan that is amphiphilic in nature (Li et al., 2014), ionotrophic between sodium tripolyphosphate and chitosan (Shu and Zhu, 2000).

Owing to its improved physiochemical properties, nanochitosan can be utilized for enhancing moderated drug delivery, enhancement of therapeutic effects as well as delivery of drugs to targeted organs (Prabaharan and Mano, 2005), inhibition of the growth of bacteria in food materials due to its antibacterial potency, thereby bringing about an improvement in the shelf life of the products (Du et al., 2009; Ramezani et al., 2015).

Methods utilized by different authors with respect to chemical approaches in production of chitosan from chitin of Polychaeta species

Deacetylation is the process associated with the chemical-based preparation of chitosan from chitin extracted from different species of organisms. The extent of deacetylation and molecular weights of the chitosan produced is generally determined in characterizing the produced chitosan. Optimum conditions and parameters for the chemical and enzymatic production of chitosan from the squid species; *Illex argentines* were determined by Vázquez et al. (2017). Chitin was produced by alkaline deproteinization and chitosan was produced through the deacetylation of chitin. Optimum values to maximize the degree of deacetylation were determined with the independent variables; NaOH concentration and processing time. The degree of deacetylation of the chitosan

was assessed by nuclear magnetic resonance (NMR) and the molecular weights of chitosan obtained were ascertained. The results obtained revealed optimum conditions for chitosan production varying between 14.9–16.4 hours and 61–63.7% of NaOH (15.3–15.9 M). The antibacterial properties of chitosan were shown to increase with the degree of deacetylation. Boarin-Alcalde and Graciano-Fonseca (2016) conducted a study aimed at developing a procedure for the extraction and deacetylation of chitin obtained from scales of Nile tilapia; *Oreochromis niloticus*. Demineralization, deproteinization, depigmentation, and deodorizing procedures were conducted on the samples to extract chitin from it. For the production of chitosan from the chitin, deacetylation was carried out using a 40% NaOH aqueous solution. The chitosan obtained was purified and characterized. Proximate analysis of the chitosan revealed a lower yield of chitosan from *Oreochromis niloticus* compared to crustaceans from which chitosan was produced in other studies. It was concluded that the chitosan produced could be improved in terms of higher yields with even better deacetylation.

Knidri et al. (2019) determined the optimum conditions (concentration, time, irradiation power) for the use of chitin in the production of chitosan. They assessed the application of microwave technology in the extraction and production of chitosan and chitin using microwave technology. Several parameters, such as concentration of the alkali used for deacetylation, irradiation power and reaction time, which influence the qualitative properties of the chitin and chitosan produced, were also studied. Chitin was extracted from the shrimp, *Parapenaeus longirostris* via the demineralization and deproteinization process, after which deacetylation was carried out by treatment with varying concentrations of NaOH (20%, 30%, 40% and 50% (w/w)), over varying reaction times (4, 8, 10, 12 and 14 min) and irradiation power (90 W, 160 W, 350 W, 500 W and 650 W). The deacetylation degree and molecular mass of the chitosan produced was determined. The results showed that the deacetylation degree rise with a rise in irradiation power, with the highest DD of 82.8% observed at 650 W power. A similar result was observed in the other experiments where the degree of deacetylation was revealed to increase with an increase in the reaction time and concentration of NaOH. It was concluded that while the usual industrial-scale process of deacetylation of chitin was very dangerous (due to the use of high molarities of NaOH), microwave irradiation (500–650 W) could remedy the problem by allowing for treatments with lower concentration of NaOH for a relatively longer duration for the production of high molecular weight chitosan.

A process of depolymerization conducted after chitin deacetylation, leading to the preparation of low molecular mass chitosan was demonstrated by Farias et al. (2019). The preparation of chitin and low molecular weight chitosan using shrimp waste and assessment of the effects of two pathways (the acid and oxidative pathways) on physicochemical parameters of the chitosan was conducted. Chitin was extracted by the process of demineralization, deproteinization and deodorization. Deacetylation of chitin

extracted was done by treatment with 45% (w/w) NaOH for 90 minutes, after which it was purified and dried. Depolymerization was carried out on the chitosan by treatments with different chemicals. The results revealed a reduction in the molecular weight of the chitosan from 200.3 kDa to >50 kDa after 300 minutes of reaction. It was also observed that the depolymerization process led to an increase in the extent of acetylation of the chitosan. It was concluded that low molecular mass chitosan, produced by depolymerization, had an even wider range of applications as a result of improved characteristics (such as an increase in solubility in water).

Chitin and chitosan have also been extracted and characterized from mushroom species. Erdogan et al. (2017) detailed the procedures involved in the extraction of chitin from two mushroom species; *L. vellereus* and *Phyllophora ribis* and production of chitosan from the chitin. They analyzed the physicochemical properties of the chitin and chitosan produced from the two species of mushrooms. The method for the extraction of chitin from the mushroom was carried out in three steps: demineralization by treatment with a 2M HCl solution, deproteinization by treatment with a 2M NaOH solution and decolorization by a 1:2:4 mixture of distilled water, chloroform and methanol. Production of chitosan from the chitin extracted was done by treatment with 60% NaOH at 130°C for 4 hours. The chitosan produced from the two mushrooms were dried in an oven at 50°C for one day. The results showed a chitosan output of 73.1% for *L. vellereus* and 75.3% for *P. ribis.* It was also observed that *P. ribis* had a lower chitin content than *L. vellereus*, though both had higher chitin content in comparison to other insects and mushrooms.

Elieh-Ali-Komi and Hamblin (2016) discussed the procedure for the preparation of chitosan and chitin from the grounded shells of the barnacle; *Chelonibia patulais*, and their applications as biomedical nanomaterials. Firstly, the process of demineralization (by the addition of 1M HCl for 10 minutes) and deproteinization (by the addition of 2M NaOH for 20 minutes) was carried out to produce chitin which was eventually converted to chitosan by deacetylation by the addition of 40% NaOH at 120°C for 1–3 hours. The results showed a yield of 70% deacetylated chitosan.

Ahing and Wid et al. (2016), indicated that the both soaking frequency and temperature were observed to have a role in chitin production with certain degrees of deacetylation. The chitin from which chitosan was produced was obtained from shrimp shell waste and was treated with HCl and NaOH to demineralize and deproteinize respectively. The first soaking to achieve deacetylation was carried out by soaking the chitin obtained from the procedures stated above in 48% NaOH for 48 hours at 25°C. After this, the chitosan was rinsed in running water and soaked the second time. Then, chitosan obtained from the first and second soaking was characterized in terms of degree of deacetylation and solubility in acid solutions. The results showed that chitosan produced from soaking twice had a higher solubility (98.32%) compared to chitosan produced by soaking once (97.78 %) at room temperature, and a solubility of up to 99.48% at a higher temperature of 60°C. From the results, the degree of acetylation of the chitosan

produced after one soaking was 75.24 % compared to the degree of acetylation after two soakings (88.57%). It was concluded that by soaking twice (with the application of heat treatment) in NaOH for deacetylation, a better quality of chitosan with higher solubility could be produced.

Al Hoqani et al. (2020) conducted an investigation on the chemical extraction of chitin and production of chitosan from shrimp wastes collected from different areas in Oman. Optimum conditions for demineralization, deproteinization and decolorization of chitin were determined by treating the different samples with varying concentrations HCl, NaOH, and H_2O_2, respectively, over different time periods. After this, deacetylation was carried out at different NaOH concentrations and time periods to ascertain the optimum conditions for the process. FTNIR spectroscopy of the resulting chitin and chitosan revealed that the optimum conditions for demineralization, deproteinization, decolorization and deacetylation were 3% HCL at 25°C for 1 hour, 50% NaOH at 110°C for 3 hours, 30% H_2O_2 with continuous stirring for 3 hours and 50% NaOH, respectively. It was concluded that the method and conditions, which led to the extraction of chitin of about 53.13%, could be applied in the commercial preparation of chitosan and chitin. Tolesa et al. (2019) studied the process of extracting chitin from shells of shrimp using ammonium-based ionic liquids including diisopropyl ethyl ammonium acetate ([DIPEA][Ac]), diisopropylethyl ammonium propanoate ([DIPEA][P]) and di methylbutyl ammonium acetate ([DMBA][Ac]). The shrimp shells were collected, washed, ground, and ionic liquids were synthesized. The ionic liquids were mixed with the ground shells and chitin was extracted from the shrimp shells by mixing with aqueous citric acid, stirred for 5 hours. Chitin obtained from this process was subjected to treatment by 40% NaOH (10% w/v) and highly deacetylated chitosan was obtained by heating the mixture for a 12-hour period at 100°C. The results showed a 93% degree of deacetylation of chitosan produced from the chitin extracted from shrimp shells. Analysis by XRD, HNMR, FTIR, TGA, and SEM further confirmed the production of chitosan from chitin. A Techno-Economic Analysis (TEA) was carried out by Gómez-Ríos et al. (2017) for two different methods utilized for the production of chitosan from shell waste of the shrimp; *Penaeus Vannamei*. In the first method (physical-chemical deacetylation), cleaned, dried and ground shell wastes were depigmented (discolored) by suspending in an 80% w/w ethanol–water solution, deproteinized by treatment with 3.7 w/w NaOH at 71°C under constant stirring and demineralized using 5.2% w/w HCl solution at room temperature. The second method was a combination of fermentative-physical-chemical deacetylation, which mainly involved the fermentation of shell waste of shrimp using lactic acid bacteria. Deacetylation of the chitin extracted was carried out by treatment with 50% w/w NaOH solution while being constantly stirred at 90°C and atmospheric pressure. The temperature and pressure was adjusted to 120°C and 1.2barg respectively after 75% of the deacetylation process was completed. The results, as revealed by characterization of the chitosan produced, showed a mean

deacetylation of 89%. It was concluded that while both processes were profitable, they could be further improved to ensure even higher profitability and sustainability.

Furthermore, Tokatli and Demirdöven (2018) carried out a study to optimize and evaluate extraction parameters of chitin starting from shrimp waste and production of chitosan. The first stage of demineralization was carried using different concentrations of 10% w/v HCl (0.5–1.5 $moldm^{-3}$) at room temperature for a period of time ranging from 30 to 1440 minutes. The deproteinization step was performed by treatment with 10% w/v NaOH at temperatures ranging from 60 to 100°C for 30–1440 minutes. The final stage of decolorization was carried out by treatment with 35% H_2O_2 overnight at room temperature. Chitin obtained from these processes was deacetylated using 40–50% NaOH at a temperature range of 100–120°C over a time period of 60–720 minutes. The extent of deacetylation and the molecular mass of the chitosan produced was determined. The results, as detailed by a model, revealed that the optimum conditions for chitin production in the demineralization and deproteinization steps were 0.73 $moldm^{-3}$ HCl for 132.61 minutes at room temperature and 0.95 $moldm^{-3}$ NaOH for 75.65 minutes at 60.49°C. The chitin yield under these conditions was observed to be 10.13%. These optimum conditions for the production of chitin were used in optimizing conditions for chitosan production. A maximum of 77.1% of chitosan with a DDA of 78.2% was produced when deacetylation was performed using 40% NaOH at 120°C for 300 min.

Extraction of chitosan and chitin from pupa shells of *Musca domestica* (housefly) was conducted by Kim et al. (2016) using chemical processes. The procedure involved treatment of the shells (ground and unground) with 500 mL of 2N HCl for 3 hours decalcification (demineralization) and another treatment with 500 mL of 1.25N sodium hydroxide solution at 95°C for 3 hours for deproteinization to take place. Preparation of chitosan from the chitin was done by boiling the chitin isolated from pupa shells of *M. domestica* in 500 mL of 50% (w/v) NaOH solution at 95°C for 3 hours and a 50% (w/w) sodium hydroxide solution at 105°C for 5 hours. The degree of deacetylation and the viscosity of the chitosan produced were determined as a measure of the molecular weight. It was documented that the degree of deacetylation of chitosan (produced by treatments and concentrations of NaOH, and at different temperatures) ranged between 7.04% and 92.39% with maximal yield produced at the highest concentration of NaOH, highest temperature and for the longest period of time.

Different authors have demonstrated various means employed in the chemical production of chitosan, with varying extent of deacetylation and molecular masses. Optimum conditions for the processes were also determined to allow for maximal chitosan yield.

Application of nanochitosan from annelids in water treatment

Tabriz et al. (2019) developed an antifungal polyethersulfone (PES) membrane produced from quaternized N-trimethyl chitosan (TMC) and was utilized in water

treatment. Membranes with 5% concentration TMC, relatively had large pore size than PES membranes without chitosan. A 15% TMC and chitosan, increased surface wettability and enhanced antifungal activity by 72% and 63% on *A. niger* and *Fusarium solani*, respectively. Kwok et al. (2018), compared the sorption abilities of nanochitosan and chitosan to arsenite (As(III)) and arsenate (As(V)). Asenate was found to be more absorbed than asenite while nanochitosan was established to be more better absorbent than chitosan. Das et al. (2020) designed a hybrid composite of graphene oxide/chitosan/PVA by FTIR and SEM aiming to remove Congo red dyes in water treatment. Porosity and thermal stability were improved in GO/chitosan/PVA hybrid. This showed a more promising asorption in aqueous solution than chitosan/PVA composite.

Applications of nanochitosan from annelids in cosmetology

Application of nanochitosan in cosmetology is known to cut across several areas including skin care, teeth, lips, mucous membrane, and genital organ (Aranaz et al., 2018). A major focus of many studies involving the applications of nanochitosan in cosmetology is antiaging and its effects on the skin. Chen et al. (2017) conducted a study which examined the effect of chemically modified chitosan on skin aging. Chitosan with 85% degree of deacetylation was procured, modified to quaternized carboxymethyl chitosan and further modified by grafting with organic montmorillonite nanocomposite via the solution-induced intercalation method to produce a polymer/layered silicate nanocomposite. This chemically modified chitosan nanocomposite was then used to prepare a cosmetic cream which was characterized and tested for its efficacy in preventing skin aging. Moisture absorption and retention properties, as well as UV-protection properties of the formulated cream was evaluated and compared with hyaluronic acid, reported to be one of the natural substances with the highest moisturizing properties. From the results, it was observed that the nanocomposite-containing cream had an even higher moisture-retention and UV-protection activity (blocking 90% of UV radiation) than hyaluronic acid. Furthermore, in determining the dermal irritation prevention ability of the cream, it was observed that the fecal coliforms, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, aerobic bacteria, mold, and yeast count was much less than the index level. Also, the lead, mercury, and arsenic concentrations were less than the evaluation criterion.

Afonso et al. (2019) studied the impact of the addition of antiaging compounds, including vitamin C and annatto seeds powder, on the characteristics of chitosan films for use as cosmetic masks. Chemical reacetylation process was performed by reacting chitosan with acetic acid up to the desired degree of acetylation and characterization of the chitosan films was conducted. An evaluation of the mechanical parameters of the film revealed a rise in flexibility during application of creams containing these compounds. The results revealed an increase in antioxidant activity as a result of a synergistic action between the bioactive compounds and the chitosan film. This antioxidant activity was of particular significance due to their reported widespread use in skin restoration

and prevention of aging. It was concluded that the addition of bioactive compounds (vitamin C and annatto seeds powder) to chitosan films for use in cosmetology led to a better performance in the prevention of skin aging by improving its flexibility and antioxidant activity.

The incorporation of nanochitosan and its complexes in cosmetic formulations has also been widely studied. Liping et al. (2020) investigated the physical and chemical parameters of chitosan/vitamin C complex (CSVC) and its application in the manufacturing of cosmetic products. Chitosan with 85–95% degree of deacetylation was purchased and vitamin C was incorporated into it. The moisture retention, radical scavenging, and antibacterial activity of the resulting complex were assessed. The moisture retention properties of CSVC complex (with glycerol as control) were observed to be better than just chitosan, with the vitamin C molecules seen to improve the hygroscopicity of the complex. The antifree radical and antibacterial properties of the complex were observed to act in a concentration-dependent manner, with an MIC of 5 mg/mL on a 24-hour *Escherichia coli* culture observed. It was summarized that the CSVC complex would be useful as an upgrade to just chitosan as a cosmetic product.

Jimtaisong and Saewan (2014) documented the use of the chitosan derivative, carboxymethyl chitosan in cosmetics. Moisture absorption and retention, antimicrobial and antioxidant potential of carboxymethyl chitosan was also discussed. On the moisturizing potential of carboxymethyl chitosan, it was reported that its positive charge and relative high molecular weight allowed them to be retained on the surface of the skin, thus making for a good moisturizer. The antibacterial effect of carboxymethyl chitosan was reported to increase with a rise in concentration of the compound. In addition, the action of chitosan and its derivatives against common fungal species including *Candida krusei, Candida glabrata*, and *Candida albicans*, and was also evaluated with the organisms showing sensitivity of varying degrees to the agents. Furthermore, the in vitro and in vivo antioxidant activity of carboxymethyl chitosan was reviewed. Lower weight chitosans were observed to have a higher antioxidant ability than higher weight chitosans. These properties are known to be essential in cosmetic products and hence the incorporation of carboxymethyl chitosan would ensure an improvement in their quality.

Shariatinia (2018) reported the various applications of chitosan derivatives in areas which included; cosmetics, tissue restructuring and drug delivery. On its applications in cosmetics, it was pointed out that chitosan and its derivatives were particularly useful due to its antibacterial properties and biocompatibility. Other properties of chitosan and its derivatives that allowed for its use in cosmetics include moisture absorption–retention agents and emulsion stabilizing materials, skin adhesion. It was also noted that while the results obtained from different procedures revealed that chitosan and its derivatives had good cosmetic properties, most of the materials were still in their testing stage and not yet completely ready for industrial-scale production and incorporation into cosmetic products for use by the general public, hence requiring further investigation.

Casadidio et al. (2019) highlighted the general properties of chitosan and its diverse applications in cosmetics, agriculture, food and nutrition, waste treatment, paper industry, textile industry and many other areas. On its application in skin care cosmetics, its antiaging, moisturizing, ultraviolet-protective, skin-cleansing properties were discussed. Applications of chitosan and other compounds derived from it in nail, hair and oral care were also detailed.

The biocompatibility of chitosan-containing films was assessed by Libio et al. (2016). They carried out a study to prepare neutralized chitosan citrate and acetate films with the aim of evaluating their biocompatibility and physical integrity. Chitosan (with an approximate degree of acetylation of 25%) was obtained and neutralized in citric acid and sodium citrate buffer and acetic acid and sodium acetate buffer solutions. Films obtained from these treatments were tested on skin from pig ears for their biocompatibility, bioadhesion, hydration degree and exfoliation. It was observed that the citrate buffer neutralized films was significantly biocompatible with the skin as evidenced by a better structural integrity and lower degree of swelling. Analysis by scanning electron microscopy revealed that the citrate-neutralized films had a significant hydration level within 10 minutes compared to the control (untreated skin). A better bioadhesive and exfoliating activity was observed in skins with neutralized chitosan films compared to the controls.

Sionkowska et al. (2017) produced films from a mix of collagen, hyaluronic acids and chitosan and studied their mechanical, surface and film-forming properties. Each of the components were dissolved in a 0.1 M solution of acetic acid and mixed in varying proportions (chitosan and collagen in ratios of 25:75, 50:50, and 75:25 with 1, 2, and 3% of hyaluronic acid). Scanning electron microscopy was used to evaluate the hair protection potential of the collagen/chitosan/hyaluronic blend. From the results obtained from evaluating its surface properties, it was noted that a rise in the amount of chitosan in the mix led to a corresponding increase in the surface free energy. Analysis of the film-forming properties revealed the highest increase in Young's modulus of hairs treated with a collagen/chitosan/hyaluronic acid mix in a percentage ratio of 75:25:1. It was further pointed out that the mix was observed to be more stable in aqueous solutions which indicated a nonreadiness of the blends to dissolve after getting wet with water. It was summarized that treatment of hair with chitosan-collagen-hyaluronic acid blend would lead to an improvement in the properties of the hair.

The properties and safety of carboxymethyl hexanoyl chitosan, a chemically modified chitosan derivative used in cosmetic products was investigated by Lee et al. (2013). Several important characteristics such as molecular weight, solubility, hydrophilic-lipophilic balance, antioxidant, antimicrobial, and hydration activities were evaluated. To investigate its safety in use, its cytotoxicity to mouse fibroblast was assayed. The results revealed a significant inhibition (from 87.3% to >99%) of all forms of microorganisms by 2% Chitosonic® acid after a period of 18 hours with gram negative organisms

observed to be more susceptible. The scavenging effect of Chitosonic® acid on free radicals was determined as a measure of its antioxidant activity with 1% and 4% Chitosonic® acid having scavenging rates of 66% and 89%, respectively. The hydration activity of Chitosonic® acid was also analyzed by evaluation of its water absorption and retention rates (85% in 48 hours at 90% relative humidity and 93% in 24 hours at 23% relative humidity, respectively). Cytotoxicity testing of up to 0.5% Chitosonic® acid revealed no damage of L-929 fibroblasts. As a matter of fact, a 20% increase in L-929 cells viability was observed with 0.1% Chitosonic® acid. The results generally showed carboxymethyl hexanoyl chitosan could be incorporated into cosmetic formulations as an active ingredient without any safety risks.

Morganti et al. (2014) defined nanocosmetology as "the cosmetic intervention at the molecular scale to repair and control human biological systems of skin, aged or affected by minor disorders, such as acne and xerosis". Morganti et al. (2014) illustrated the procedures involved in the production of chitin nanofibril-hyaluronan (CN-HA) nanoparticles. Their capacity to entrap and deliver active groups, enhance entry through layers of skin and efficiency as antiaging agents in cosmetic formulations was evaluated. CN-HA micro/nanoparticles were prepared using a modification of the gelation method and analyzed using scanning electron microscopy (SEM). In vivo and in vitro studies on the antiaging, antioxidant and antiinflammatory potencies of CN-HA nanoparticles were conducted. Also, possible cytotoxicity of CN-HA nanoparticles against fibroblasts and keratinocytes was determined using the methylthiazol assay. On the entry of CN-HA nanoparticles through skin layers, the results showed that positive surface charges on their surface allowed for better penetration through stratum corneum layers. It was reported that this facilitated penetration into skin would allow for an inside-out re-balance of skin hydration and elasticity in skins of aged individuals. It was also discovered that the CN-HA nanoparticles, when applied topically, was able to remove free radicals and hence inhibit release of inflammatory cytokines and metallo proteinases. Cytotoxicity assays revealed that the CN-HA nanoparticles had an insignificant effect on fibroblasts and keratinocytes. The role of chitosan in enabling retention of active ingredients of cosmetic products in superficial layers of the skin was evaluated by Siqueira et al. (2011). They prepared benzophenone-3-loaded chitosan-coated polymeric nanocapsules and incorporated it in hydrogels, which were used in determining its effect in sunscreen formulations when applied on the skin. The results demonstrated a much higher concentration of the sunscreen in the skin's stratum corneum after application of benzophenone-3-loaded chitosan-coated polymeric nanocapsules compared to nonchitosan coated nanocapsules. It was discussed that the cationic and bioadhesive nature of the chitosan coating was responsible for the prolonged presence of benzophenone-3 in the horny layer of the skin and much less in the receptor compartments, indicating a lower likelihood of its permeation into the blood. The results generally indicated an

improvement in the retention of sunscreen in the more surface layers of the skin by coating benzophenone-3 with chitosan.

On the usage of nanochitosan in controlled delivery of drug, Ushirobira et al. (2020) conducted a study to produce dutasteride-loaded nanocapsules and evaluated the effect of coating with chitosan on permeation of the drug when a topically by an in vitro set up, using Franz-type diffusion cells. The results revealed a significant control of drug release in the first 6 hours of the study. The authors observed that chitosan coating maintained its ability to control drug release even when physical stimulation, which could lead to an increase in the drug accumulation by about 5 times, was applied. It was concluded that this ability could help in curbing adverse effects of drugs.

Application of nanochitosan from annelids in pharmaceutical industry

Chitosan is used in antithrombogenic substances for encapsulation of drugs, immobilization of cells, moderated release of drugs and as carrier. It is typical example of a polycationic substance that is pseudo natural in occurrence (Younes et al., 2009; Quemeneur et al., 2010; Rinuado, 2014). Chitosan based materials are broadly applied due to certain unique properties such as hydrophilic nature, biodegradability, presence of polar groups that easily interact with the polymers such as amino and hydroxyl groups which are associated with hydrogen bondings and the N-acetyl groups involved in hydrophobic interactions (Rinuado et al., 2009; Younes and Rinaudo, 2014).

Chitosan are basic, cationic polysaccharide and mucoadhesive. Chitosan has the ability to enhance penetration, intracellular transfer of drugs and opening of the tight junction of epithelium (Mohammed et al., 2017). Nanochitosan is a derivative of chitosan which has unique physicochemical features. It is highly bioactive and friendly with the environment. There are different methods available for the preparation of nanochitosan. One of them involve the cross linking physically through ionic gelation between the specific negatively charged macromolecules like pentasodiumtripolyphosphate and chitosan (Calvo et al., 1997). The nanoparticles from chitosan were observed to be stable at 37°C inside different buffer systems, where their ability to resist effect of pH and temperature were tested in media which stimulates the intestine and stomach (Oliveira et al., 2012). Nanochitosans have been employed in various areas including a pharmaceutical industry which includes:

Drug delivery carriers

It has been documented that after drug delivery, a good drug delivery carrier is expected to be removed. It should not be toxic neither should it accumulate in the body (Dev et al., 2010). Nanoparticles fabricated using chitosan meet these requirements in its potentials to control the release of drug while it could also help in the avoidance of hazardous solvent of organic nature. The colloidal form of chitosan is capable of entrapping macromolecules and has been found to pass through epithelia and mucosa more effectively (Janes et al., 2001).

Chitosan being a polysaccharide source of nanoparticles has been used in the area of drug delivery since they are nontoxic, biodegradable, hydrophyillic and stable. Also the interaction between the chitosan that are cationic in nature and the mucin which are anionic makes chitosans to be more muco adhesive (Waleed et al., 2019). Also, the burst effect and gradual discharge of drugs which were shown in in vitro studies are responsible for their pressing necessity to be use in in vivo (Bilia et al., 2014). The technology of nanoparticles is therefore an indispensable tool in novel release of drugs to target areas in organisms, have properties of moderated discharge, compatible levels of serum of the active agents from environmental degradation and enzymatic internal retention (Waleed et al., 2019). Methods for the production of nanoparticles are selective to a broad range of drugs (Nagpal et al., 2010a).

The effectiveness of encapsulation of drugs through layer by layer has been reported to be enhanced by natural polymers when incorporated into cationic chitosan (Haidar et al., 2008; Alishahi and Aider, 2012). The close association of polyethylene oxide and chitosan nanoparticle has been utilized in the area of protein transport (Calvo et al., 1997). The combination of tripolyphosphate and chitosan has also been used in the formulation an oral system of delivering drugs. In this mechanism, the bead produced from chitosan in solution form with tripolyphosphate is used for the entrapping of nano and microparticles (Bodmeier et al., 1989; Honarkar and Barikani, 2009). Nanoparticles based on chitosan are also used in the area of treating gastrointestinal infections, as antitumor agents and in the treatment of pulmonary diseases. They are also used for the delivery of drugs into the brain in the cases of people suffering from ocular infections (Mohammed et al., 2017).

Recent studies have shown that nanoparticles based on chitosan have been utilized in the encapsulation of levofloxacin employed in the treatment of ocular disease and these were noticed not to pose irritation for the ocular administration (Ameeduzzafar et al., 2018). In a related study, polyelectrolyte complex produced through the combination of carboxylic curdlan and chitosan was employed for the delivery of 5-fuorouracil (Yan et al., 2018). More recently, chitosan has gained popularity in the delivery of peptide related vaccines through the viginal and also in the application of microbicides for the treatment of diseases that are transmitted through sexual intercourse (Marciello et al., 2017; Shariatinia, 2019).

The blending of chitosan with polylactic acid can also be done as well as with alginate, collagen in the delivery of antibiotics, chemotherapeutics, vaccines, DNA, immunosuppressant, and antiinflammatory (Yang et al., 2021; Yadav et al., 2019). In a related study, Ding et al. (2015) employed iron oxide nanomaterial in the coating of chitosan and used this in the delivery of 5-fuorouracil which is a drug used in the treatment of cancer disease. The potential of chitosan nanoparticles in concentrating around the targeted site thereby bringing about a decrease in the levels of the unused drugs as well as the connected side effects has further boosted it's in the delivery of drugs (Grenha et al.,

2010). The introduction of *Nigella sativa* into nanoparticles in solid form as a novel system of drug delivery reveals their efficiency as carrier in the pharmaceutical industries with their remarkable physical stability (Al-Haj et al., 2010).

Waleed et al. (2019) documented the inhibitory effectiveness of nanochitosan on the *Schistosom mansoni* infection using nanochitosan together with *N. sativa* (black seeds) in the mice studied. The findings from the study reveal that all the worms together with the eggs were killed by the combination of *N. sativa* chitosan in comparison with only reduction brought about by *N. sativa* alone, *Nigella* alone as well as the chitosan nanoparticles.

Numerous scientists have also documented the application of nanochitosan in the area of delivery of drugs (Liang et al., 2019; de Oliveira Pedro et al., 2018; Li et al., 2019; Hyun et al., 2019; Jaiswal and Madhav, 2019).

Vaccine production

Moreover, numerous scientists have reported the utilization of chitosan nanoparticles fabrication of vaccines (Mohamed et al., 2018; Li et al., 2016; van der Maaden et al., 2015; Pawar and Jaganathan, 2016; Hu et al., 2017)

Control of blood cholesterol

Chitosan can be used to battle obesity and hypercholesterolemia. It does this by binding to lipids (cholesterol) micelles and inhibits their absorption. It also increases the excretion of bile acid by which the amount of fecal fat increases (Gallaher et al., 2000; Muzzarelli and Muzzarelli, 2005). In humans, the hypocholesterolemic effect of chitosan is achieved by its combination with bile acids in the digestive tract and excretes them into feces, thereby reducing the resorption of bile acids, so that the cholesterol pool in the body is decreased and consequently, the serum cholesterol level is decreased (Maezaki et al., 1993).

Hemostasis and wound healing

An important step in wound healing is hemostasis through blood coagulation. Platelets in the blood are responsible for blood coagulation. Research has also shown that chitosan has a hemostatic effect (Klokkevold et al., 1999). The ability of chitosan to cause hemostasis is due to both its physical and chemical properties especially that of its amino group (Okamoto et al., 2003). Well known chitosan based hemostatic dressings include the Syvek patch, Chito-Seal (Abbot), the M-Patch, Trauma DEX (Medafor), RDH (Marine Polymer Technologies) and Clo-Sur PAD (Medtronic-scion) (Castro and Paulin, 2012).

Application of nanochitosan derived from annelids in medicine

Chitin is a naturally-occurring linear polysaccharide deacetylated in solid-state alkalinity or enzymatic hydrolysis. In terms of distribution and utilization, it is the second-largest

renewable biomaterial after cellulose (Elgadir et al., 2015). Chitosan is the most important chitin derivative with unique biochemical properties such as bactericidal, biodegradability, compatibility, nontoxicity, immunoenhancing, antitumoral, and antimicrobial potential (Kravanja et al., 2019) and easy functionality. These chitosan properties make it highly desirable in medicine and pharmacy. Chitosan nanoparticles (CS-NP), also referred to as nanochitosan, in the range of 10–1000 nm, can be prepared as biocompatible polymeric nanoparticles (Adhikari and Yadav, 2018) and are easily internalized by the cells (Malatesta et al., 2015). Due to chitosan's hydrophilic nature, CS-NP can prolong blood circulation with more extravasation and passive targeting (Gaur et al., 2000); thus, CS-NP is a suitable candidate for drug delivery (Lee et al., 2008; Zhang et al., 2009).

Nano-chitosan and its derivative have positive surface charges, enabling their use as nonviral vectors for gene therapy and mucoadhesive properties, facilitating their attachment to mucous membranes (Mohammed et al., 2017). Furthermore, thiolated nanochitosan, like chitosan-thiolated acid, chitosan-glutathione, chitosan-thioethylamidine, and chitosan-cysteine, increases its mucoadhesiveness (Bernkop-Schnürch et al., 2003; Yin et al., 2009). However, *N*-trimethyl chitosan chloride (TMC)-cysteine based nanoparticles have remarkably greater permeation and adhesion to muco than TMC nanoparticles (Bernkop-Schnürch et al., 2003). Nanochitosans are generally designed for nonparenteral administration (Houshmand et al., 2020; Mohammed et al., 2017). Nonetheless, they are also used in targeted parenteral drug delivery (Ahmed and Aljaeid, 2016; Key and Park, 2017; Swierczewska et al., 2016; Zhang et al., 2016a). Chitosan chemical liability permits using relatively simple technological processes to acquire homologues and analogues with different physicochemical and biological properties, which allows for compatibility with biosystems and biodegradability in the body, forming nontoxic, low molecular weight compounds. Due to their large surface area, the development and utilization of nanochitosan and other groups derived from it are widely needed in pharmacy and medicine, especially as carriers of drug substances, which will be widely reviewed in this chapter. Some medical and pharmaceutical applications of nanochitosan are discussed below:

Nanochitosan application in drug delivery

The significant advantages of nanocarriers such as nanochitosans in drug delivery include their increased treatment selectiveness in targeting the affected cells, reduced side effects and toxicity, and enhancing blood circulation half-life and bioavailability. The mechanisms involved in nanochitosan drug delivery are polymer swelling, the adsorbed drug diffusion through pores, diffusion of drugs through the polymer erosion, polymeric matrix, polymer degradation or erosion, and a combination of erosion and degradation (Liu et al, 2018; Singh and Lillard, 2009). Likewise, due to chitosan solubility, nanochitosan drug release is pH-dependent (Manca et al., 2008; Miladi et al., 2015). Different factors like particle size, the stability of the active agent (chemical or thermal) and final product, duplication of the profiles of kinetic release, and the last outcome of

residual toxicity (Rajan, et al., 2017) affect diverse technique employed in the production of nanochitosan in the delivery of drugs. These methods include:

Polyelectrolyte complex formation: This involves electrostatic interactions between the positive cation group such as the chitosan amine group and the negative anion group like the dextran sulfate group (Erbacher et al., 1998).

The diffusion approach: This depended on the incomplete mixing of water and the organic solvent (El-Shabouri, 2002; Niwa et al., 1994). The preparation of the emulsion is done through the injection of an organic layer unto the solution of the chitosan which contains the agent of stabilization. The mixability of the organic solvent with water is overcome through the dilution of the emulsion with a large quantity of water. This comes immediately after high-pressure homogenization and mechanical stirring is done. The nanoparticles are then formed through the precipitation of polymer from the diffusion of the organic solvent through water (Nagpal et al., 2010b; Rajan et al., 2017).

Complex coacervation technique: This is associated with the coacervation between the negatively charged phosphate group of the DNA and the positively charged amine groups (Bowman and Leong, 2006; Chen et al., 2007; Leong et al., 1998). The entrapment effectiveness, size of particles, release properties, and charge on the surface is controlled by the weight proportion of the polymers that are present (Chen et al., 2003; Roy et al., 1999).

Co-precipitation: This entails remarkably high encapsulation efficiency and size uniformity. In this approach, the nanoparticle having a great uniform size is produced through the grafting of D,L–lactic acid on the chitosan so as to act as a carrier of the drug for a long time drug release (Nagpal et al., 2010b).

Emulsification-cross linking: Here, new surfactant-polymer nanoparticles are prepared for effective and efficient water-soluble drug encapsulation and sustainable release (Chavanpatil et al., 2007).

Ionotropic gelation: This is a mild and simple method performed in an aqueous surrounding. It is based on electrostatic interaction between the positively charged chitosan amine group and negatively charged polyanion group like tripolyphosphate (Calvo et al., 1997).

Microemulsion: In this technique, nanochitosan is formed in the aqueous core of reverse micellar droplets and subsequently cross-linked through glutaraldehyde (Rajan et al., 2017). The free chitosan amino group conjugates with glutaraldehyde, and the particle size can be controlled by varying glutaraldehyde amount, changing the degree of crosslinking.

Solvent evaporation method: This technique involves emulsifying the polymer solution into an aqueous phase preceding the polymer-solvent evaporation, inducing the polymer precipitation as nanospheres (Nagpal et al., 2010b).

Sieving method: Here, a nonsticky glassy hydrogel was obtained by crosslinking chitosan with glutaraldehyde followed by sieving with a suitable mesh size to get nanoparticles (Agnihotri et al., 2004).

Routes of nanochitosan administration in drug delivery

Oral drug delivery: Due to its mucoadhesiveness, permeability enhancement, biocompatibility, biodegradability, and efflux pump inhibition, chitosan is one of the most suitable polymers for oral drug delivery (Kumar et al., 2016). Moreover, positively charged chitosan and negatively charge mucin interaction allows for prolonged contact between the drug and the absorptive surface; thus, promoting absorption (Aspden et al., 1997). Hence, drug bioavailability can be improved by utilizing nanochitosan as a coating material for liposomes and nanocapsules to enhance their residence time (Lueßen et al., 1996; Vila et al., 2002).

Some examples of nanochitosan application in oral drug delivery include the following:

Improving the absorption of epigallocatechin gallate and catchin, flavonoids and strong antioxidant that are found in green tea through encapsulating them within nanochitosan because they are not efficiently retained across the membrane of the intestine as a result of degradation (Dube et al., 2010).

Increasing tamoxifen permeation across the intestinal epithelium through the paracellular pathway by exploiting nanochitosan mucoadhesiveness (Barbieri et al., 2013, 2015), which improves treatment by increasing drug concentration in tumor sites. Also, nanochitosan can be used as a potential drug delivery system for mifepristone, an anticancer drug with poor water solubility and low oral bioavailability. It has been shown to improve its anticancer activity and bioavailability in vivo by ensuring controlled drug delivery in a sustained release mechanism of action (Zhang et al., 2016b).

Nanochitosans are also suitable carriers for oral vaccine delivery of extracellular *Vibrio anguillarum* (pathogenic bacteria) products. They were found to be stable in the gastric pH, having sustained release and preventing entry of the antigenic protein into the spleen and kidney (Gao et al., 2016; Van Der Lubben et al., 2001a). Nanochitosan carrying vaccines are prepared without organic solvents, altering the antigenic immunogenicity if the peptide's secondary structure is disturbed (Van Der Lubben et al., 2001b).

Gastrointestinal tract drug delivery: Nanochitosan has also been shown to be the most suitable nanoparticle for drug delivery in colonic diseases because of biocompatibility, colon enzymes biodegradability, and chelating ability (Cerchiara et al., 2015; Coco et al., 2013; Giovino et al., 2013; Wang et al., 2016).

Mucosal and pulmonary drug delivery: This refers to a noninvasive drug delivery method to the respiratory system, systemic circulation and the brain. The properties of nanochitosan, including low toxicity and transient opening of the mucosal membrane tight junctions, make it desirable in drug delivery through the nasal cavity by para- and trans-cellular pathway as well as the trigeminal nerves (Casettari and Illum, 2014; Illum, 2003). The para- and trans-cellular pathway permeability increases in a reversible, dose-dependent manner depending on the chitosan molecular weight and deacetylation level (Schipper et al., 1996).

Examples of nasal drug delivery include the following:

Treatment of diseases such as prostate cancer, epilepsy, Alzheimer's disease and other hormone-dependent diseases (Illum, 2003; Shahnaz et al., 2012).

Carboxymethyl nanochitosan of carbamazepine, used in treating epilepsy, improves bioavailability and brain targeting intranasally (Liu et al., 2018). Also, the bioavailability of leuprolide, prostate cancer, and hormone-dependent diseases therapy increased when formulated with/as nanochitosan (Illum, 2003; Shahnaz et al., 2012).

In Insulin delivery, nanochitosan–dextran sulfate and Alg have been used as promising insulin carriers and other polypeptides (Sarmento et al., 2007). The systemic absorption of insulin has been shown to improve following nasal instillation with nanochitosan (Fernández-Urrusuno et al., 1999), reduced blood glucose level (Lin et al., 2007), and enhanced insulin absorption nasally than aqueous chitosan (Nagpal et al., 2010b).

Intestinal absorption of salmon calcitonin can be enhanced and prolonged by nanochitosan mainly by their mucoadhesiveness and close interaction with the intestinal barrier (Prego et al., 2006). The mechanism of action is mediated by the positively charges chitosan through interactions with the tight junction proteins occludin and ZO-1, redistribution of F-actin, and slight destabilization of the plasma membrane. The environmental pH also affects the ability of chitosan to enhance permeation (Nagpal et al., 2010b).

Likewise, in pulmonary drug delivery, the positive charge on the chitosan surface presents the CS-NP mucoadhesive properties to the lung mucosa, increasing potential drug absorption (Islam and Ferro, 2016). Additionally, itraconazole (an antifungal drug) aerosolization properties, including high drug concentration at the site of action, passive targeting and reduced systemic toxicity, can be improved significantly by formulating it with CS-NP (Jafarinejad et al., 2012).

Other mucosal and pulmonary CS-NP drug delivery use include vaccine delivery, in which nanochitosan has shown improved antigenic uptake by the mucosal lymphoid tissues, inducing strong systemic and mucosal immune responses (Van der Lubben et al., 2001c), baclofen and siRNA, heparin (LMWH), estradiol, tetanus toxoid, theophylline and rifampicin (Mohammed et al., 2017).

Moreover, chitosan encapsulating *Bacillus* Calmette-Guerin (BCG)-polysaccharide nucleic acid (PSN) (BCG-PSN) can protect the nucleic acid components from in vivo nuclease destruction and form polysaccharide NPs, which could significantly enhance the bioavailability and have sustained-release effect (Yang et al., 2021).

Other medical and pharmaceutical applications of nanochitosan

Tissue engineering: Being a natural polymer, chitosan is a suitable biomaterial in tissue engineering for fabrication of extracellular tissue matrixes (Ahsan et al., 2018; Mohebbi et al., 2018; Rodríguez-Vázquez, et al., 2015; Roy et al., 2021; Sultankulov et al., 2019; Tao et al., 2020).

In controlled drug delivery and stability improvement: Chitosan NPs are suitable carrier in delivering active agents and drug via chemical and ionic crosslinking and

ionic complexation. Due to high chitosan affinity for cell membranes, it has been used as a coating agent for liposome formulations (Prabaharan and Mano, 2004). Nanochitosan containing drugs, genes, or proteins, have been successfully used as a drug delivery system in human fluids and ophthalmology with visual system diseases and has shown better stability (Nagpal et al., 2010a).

In brain drug delivery: Chitosan NPs have also been used as carriers for brain drug delivery to improve brain targeting efficiency, especially for central nervous system disorders therapies (Nagpal et al., 2010a). Tumor-targeting peptides like chlorotoxin and transferrin could be used to modify CS-NP to improve the capacity for targeting a brain tumor (Yu, et al., 2019). Different strategies have been developed to reach the brain tissue to meet the current demand for effective therapeutic interventions. Several of these mechanisms depend on the transient disruption of the blood-brain barrier through osmotic pressure, ultrasound or pharmacological entities, intra-cerebroventricular infusion, convection-enhanced delivery, intra-cerebral injection or implants (Santander-Ortega et al., 2017).

Besides, CS-NPs can be used in renal failure and hemodialysis (Misgav et al., 2017), biosensor monitoring and bio imaging (Lee, et al., 2017; Sengiz et al., 2015), as antiplaque agents in dentistry by its antibacterial activity (Rodrigues et al., 2018), and as an antimicrobial and antifungal agent in wound dressing due to its excellent tissue-adhesive properties (Bano, et al., 2017). Finally, nanochitosan specifically targets cancer cells because of their preferential accumulation in tumor cells due to enhanced permeation and retention, lowering the p-glycoprotein induced multidrug resistance. Other anticancer nanochitosan mechanism includes antiangiogenic mechanism (Adhikari and Yadav, 2018; Xu, et al., 2009), immunoenhancement mechanism (Kuppusamy and Karuppaiah, 2013), anticellular apoptotic mechanism (Kuppusamy and Karuppaiah, 2013; Wimardhani et al., 2014), anticellular proliferation (Qi et al., 2007; Wimardhani et al., 2014).

Limitations and recommendations

Chitosan is marked by structural and chemical heterogeneity because it has some mineral and protein admixtures after processing under narrow chemical conditions. It is also characterized by a broad molecular weight distribution resulting in the formation of insoluble gel particles when dissolving and thus significantly limiting its usefulness. Since purification is needed to obtain CS-NPs, nanoparticle formulator must carefully match the desired chemical and physical chitosan properties and the anticipated biological environment with the chitosan processing method (Mohammed et al., 2017). Formulation of experimental techniques for the production of chitosan nanoparticles and their derivatives that are of nanostructural origin is vital, together with the determination of their potential physicochemical modification and supramolecular and molecular characteristics. Though chitosan has been shown to possess a remarkable potential in

drug delivery, toxicity studies in cases involving humans are very vital and need to be considered (Saboktakin et al., 2011). There is a need to demonstrate the level of superiority to other nanoparticles so as to highlight the importance of examining the degree of CS-NPs surface coverage and carrying out dissolution studies in bio relevant media during formulation development.

Conclusion

This chapter has provided a detailed information on the pharmaceutical and bio-medical applications of CS-NPs is huge and more applications are being proposed and developed with respect to the bio-medical usages of CS-NPs. Moreover, it was also established that the bioconversion of agricultural solid waste management perspective as well as application of chitosan derived from these agoinduatroal wastes for the synthesis of CS-NPs from discarded harvested shellfish and shrimps is a viable waste reduction strategy. There is a need for researches to intensify effort for the application chitosan for the production of the drug delivery application of CS-NPs with respect to medical burden such as malaria and tuberculosis which is known to currently afflict large sections of population such as women and children in developing countries, especially Sub-Saharan African countries.

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NEXT GENERATION NANOCHITOSAN

Applications in Animal Husbandry, Aquaculture and Food Conservation

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A practical reference of novel applications of nanochitosan to improve the production of a healthy and abundant food supply

Next Generation Nanochitosan: Applications in Animal Husbandry, Aquaculture and Food Conservation provides a comprehensive and state-of-the-art information on the application of nanochitosan for improving products, especially for the evaluation of biological active molecules, disease therapeutics, transport vehicles for DNA, targeted drug delivery, gene therapy, developing towards high performance fish yields, preservation of foods, tissue engineering, and improving the taste of aquatic and animal feeds as **fish growth promoter**.

The reference is for postgraduate and graduate students for industry professionals in the agri-food sector, dairy sector, and the aquaculture sector. It is especially useful for industrial fisheries that deal with wild capture fishing and aquafarming, and scientists and engineers working on post-capture processing stages. Additionally, environmentalists may find this as an essential reference because it reveals challenges around farming techniques in a world facing climate change, escalating population growth, and an ever-increasing scarcity of water. Details on the application of nanochitosan as an effective additive for the delivery of vaccines, hormones, vitamins, nutrients and antioxidants, biological active constituents and their wider application for the protection and management of farm animals and fishes against disease-causing pathogens are provided.

Key Features

- Provides applications for the protection and management of farmed animals and fish against disease-causing pathogens
- Includes relevant information, commercialized products, and innovative technologies on nanochitosan with industrial perspectives
- Highlights the application potentials of nanochitosan across the entire value chain of food production.

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ISBN 978-0-323-85593-8