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Chitosan: A Promising Marine Polysaccharide for Biomedical Research

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Abstract

Biomaterials that were invented 50 years ago are still receiving considerable attention till to date to support advances in biomedical fields. The diversity of naturally obtained polysaccharides supplies a broad range of resources that are applicable in the biomedical field. Recently, chitosan marine polysaccharide derived from chitins, which are extracted from the exoskeleton of arthropods such as crab, shrimp and lobster, is becoming the most popular biopolymer in therapeutic interventions. This is a short review of chitosan, highlighting the history, properties, and chemical structure of chitosan together with the processing methods used to produce chitosan derivatives and the factors influencing their use in the biomedical field.

Keywords: Chitosan; History; Properties; Structure; Processing; Influenced-factors

Introduction

Biomedical research comprises basic, applied and translational research normally conducted to support the development of a growing body of new therapeutics in the medical field. Biomedical research is an evolutionary process that aids in the discovery of new medicines and therapies that demands scientific experimentation, evaluation and quantification by employing biotechnology techniques. The term biomaterial was initially coined 50 years ago. The study of biomaterials is known as biomaterial science. In the new biological era, biomaterial science embraces the elements of medicine, biology, chemistry, tissue engineering and materials science. According to the American National Institutes of Health, the term "biomaterial" refers to any substance or combination of substances, apart from drugs, obtained naturally or modified synthetically, which can be used entirely or partially for the replacement of any tissue, organ or function of the body. Biomaterials can be used as autograft, allograft or xenograft transplant materials. A successful biomaterial should possess several important characteristics, such as being biocompatible, anti-microbial, non-toxic, non-carcinogenic, and inexpensive and promoting better drug delivery. Chitosan-derived biomaterials are unique marine polysaccharides and have a variety of physiochemical and biological properties that allow their application in various biomedical fields [1]. Although recent discoveries of chitosan biomaterials have contributed to the application of chitosan in modern medicine, the mechanism underlying the benefits of chitosan is still unknown. This short review aims to highlight and comprises of the general discussion of chitosan's history, properties, and chemical structure of chitosan together with the processing methods used to produce chitosan derivatives and the factors that influence their use in the biomedical field.

Chitosan Properties

Chitin is a naturally derived biopolymer produced abundantly second to cellulose through biosynthesis. Chitins are characterized as white, non-elastic, hard, nitrogenous polysaccharides; an estimated one billion tons are synthesized annually [4,5]. Chitosan is derived from the *N*-deacetylated form of chitin. Chitosan is composed of β (1→4)-linked 2-acetamido-2-deoxy-β-D-glucose (*N*-acetylglucosamine). Chitin is structurally identical to cellulose, but it has acetamide groups (-NHCOCH$_3$) at the C-2 position. Additionally, chitosan is a linear polymer formed by α (1→4)-linked 2-amino-2-deoxy-β-D-glucopyranose and derived by *N*-deacetylation; it is characterized by the degree of deacetylation of the copolymer of *N*-acetylglucosamine and glucosamine. Chitosan biomaterials exclusively derived from the shells of arthropods such as crabs, shrimps, lobsters, and insects; they are also produced extracellularly by the cell walls of fungi and brown algae. Chitosan is rarely found in nature but is produced by dimorphic fungi such as *Mucor rouxii* by the action of the deacetylase enzyme on chitin [6-8].

Chitosan is an amino polysaccharide possesses strong positive electrical charge through which it strongly attracts and bonds to negatively charged molecules. Chitosan-derived biomaterials have received considerable attention as anti-microbial, functional, renewable, nontoxic, biocompatible, bioabsorbable and biodegradable biopolymer agents [9-11]. Chitosan is insoluble in water and organic solvents; it is soluble once mixed with acetic, nitric, hydrochloric, perchloric or phosphoric acids [12-14]. The solubility of chitosan-derivatives can be most easily observed in aqueous acidic solutions that have a pH below 6.5. The solubility range also can be altered upon depolymerization and chemical modification of the primary and secondary hydroxyl groups. Recently, carboxymethyl- and oligo-type chitosans have become widely studied forms due to their promising synthesis characteristics and wide range of applications in biomedical and biopharmaceutical areas of study [15-17].

The amine groups located on chitosan become protonated at acidic pH and transmit a positive charge to the chitosan chains. Most biological cell surfaces are anionic, and chitosan was thought to strongly adhere to the tissues at the site of a wound via electrostatic interactions due to its cationic characteristics. The solubilization of chitin to produce chitosan in acidic environments is found to occur via the protonation of the –NH_2 group at the C-2 position of the D-glucosamine repeat unit, whereby the polysaccharide is converted to a polyelectrolyte.

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Generally, chitosan has three types of reactive functional groups. Its amino groups have both primary and secondary hydroxyl groups at the C(2), C(3), and C(6) positions [18]. These are the groups that permit the modification of chitosan-like graft copolymerization for specific applications in tissue engineering. The degree of deacetylation and crystallinity and the molecular weight of chitosan are the main characteristics that can be modified to obtain different physio-mechanical properties. Chitosan consists of carbon (44.1%), hydrogen (6.84%) and nitrogen (7.97%) with an average molecular weight of 5.3 x 10^5 Daltons [19].

Chitosan components are insoluble in most solvents but slightly soluble in diluted organic acids such as acetic, lactic, malic, formic and succinic acids [20]. The uses and benefits of chitosan are limited due to its insolubility in water, high viscosity and aggregation of the protein molecules at higher pH levels. Pyrolysis gas chromatography, gel permeation chromatography, ultra-violet spectrophotometry, titration, separation spectrometry and near-infrared spectroscopy are the specific methods used to detect the degree of deacetylation of chitosan [21]. Commercialized chitosan biomaterials possess degrees of deacetylation that are greater than 70% and have molecular weights ranging from 1X10^5 to 1.2X10^6 Daltons [22]. Chitosan derivatives with higher molecular weights are potentially capable of providing better surface- and film-forming properties due to internal hydrogen bonding. It was also reported that chitosan with a higher molecular weight could slow the release of drugs [23]. Additionally, chitosan is believed to be more nitrogenous and effective in regulating metal chelation and polyoxy salt and film formulations compared to cellulose. However, chitosan derivatives also potentially chelate metal ions such as iron, magnesium and cadmium. The degree of deacetylation of a chitosan biomaterial is a function of the molarity of the glucosamine residues in the polymer chain, which determines the cationic charge on the molecule once diluted in acid solution. This clearly shows the proportion of free amino groups on the chitosan biopolymer (Figures 1 and 2) (Table 1) [24].

Factors Influencing the Use of Chitosan Derivatives in Biomedical Applications

Many factors and qualities have led to chitosan derivatives being

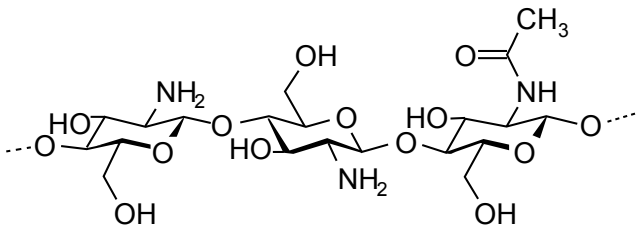

Figure 1: The chemical structure of chitosan [16,17].

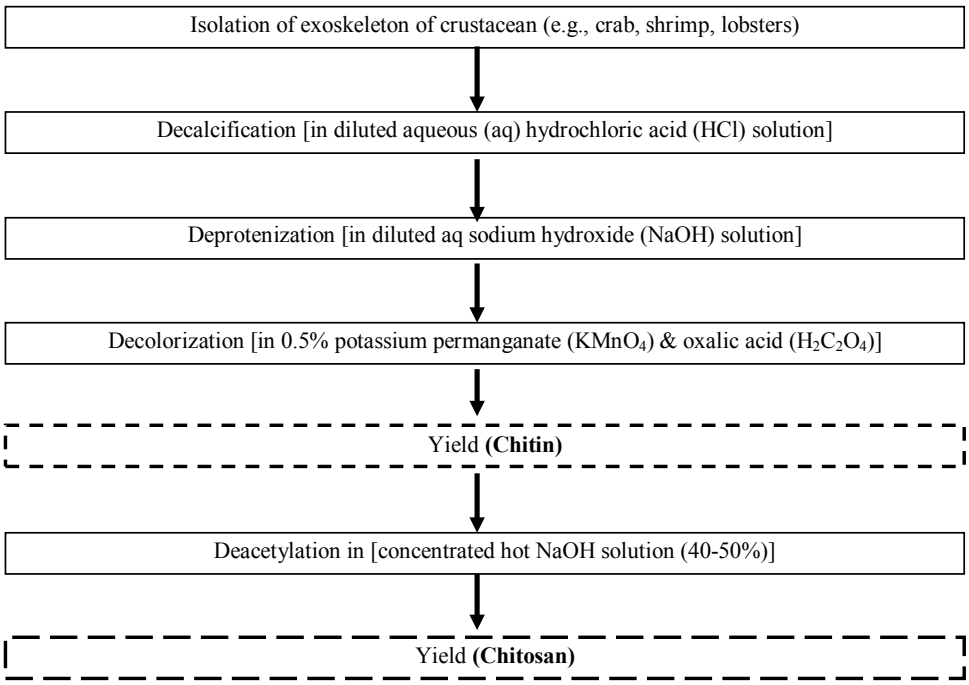

Figure 2: The main source of chitin derives from the shells of crabs and shrimp. Chitin is extracted by acid treatments to dissolve calcium carbonate followed by the extraction of alkaline to solubilize the proteins. The exoskeletons of arthropods must be (i) decalcified in HCl, (ii) deprotonated in NaOH, and (iii) decolorized in $KMnO_4$ and $H_2C_2O_4$ to yield chitin. Processed chitin needs to be deacetylated in hot concentrated NaOH to produce chitosan [25,26].

Year	Discovered by	Description
1811	Henri Bracannot (*Director of the botanical garden in Nancy, France; Professor of Natural History*)	▪ Conducted research on mushrooms and extracted chitin. ▪ Discovery-chitin did not dissolve in sulfuric acid.
1823	Ojer	▪ Coined the name 'chitin' which is derived from the Greek word 'khiton,' meaning 'envelope.'
1832	Opperman	▪ Chitin was extracted from insects–similar substances to chitin can also be found in insects
1843	Lassaigne	▪ Demonstrated the presence of nitrogen in chitin
1859	C. Rougeut	▪ Discovered chitosan ▪ Observed that substances containing chitin could be manipulated through chemical and temperature treatments that allow chitin to be solubilized. ▪ Treated chitin with concentrated potassium hydroxide at a high temperature.
1878	Ledderhose	▪ Identified chitin synthesized from glucosamine and acetic acid
1894 1930	Hoppe-Seyler German scientist and physiologist Rammelburg	▪ Proposed the name "chitosan." ▪ Identified additional sources of chitin other than insects and fungi ▪ Found that chitosan can be extracted from marine arthropods, e.g., crab, shrimp, lobster ▪ Hydrolyzed chitin in several ways ▪ Discovered that chitin is a polysaccharide of glucosamine
1950	Darmon and Rudall	▪ Discovered the structure of chitosan ▪ Advanced the study of chitin and chitosan through X-ray analysis ▪ Recorded the presence of chitin and cellulose in the cell wall through the use of X-ray analysis, which was the most advanced technology of the period. ▪ Recorded the absorption spectra of chitin, chitosan nitrate and wood cellulose in the region 3600 cm^{-1} to 750 cm^{-1} using polarized radiation
1951	▪ First book was published, 140 years after the initial observation by Bracannot, which was then confirmed by many researchers.	
1960-till present	▪ Many researchers have conducted studies using (modified and unmodified) chitosan-derivatives in the biomedical field	

Table 1: History of Chitosan [2,3].

recognized as significant marine polysaccharides in the biomedical field, such as their biocompatibility, biodegradability, renewability and bioadhesivity; their film-forming, non-allergenic, antifungal, antibacterial, immunoadjuvant and non-toxic properties; and the fact that they are polycationic, hydrating, antithrombogenic, anticholesterolemic and absorption promoting agents. *In vitro* models have been used to test for toxic effects of leachable materials or their derivatives, such as the effects of residual monomers, catalytic effects, and polymer erosion-related properties, in addition to their chemical composition, molecular weight, polydispersity, and degradation ability [27]. The effective alteration by different degrees of deacetylation and crosslinking; differences in molecular weight; polyethylene glycol treatment; wheat germ agglutinin treatment; graphene support; differences in viscosity, regularity, the nature of bonds, and the degree of crystallinity; rigorous heat intervention and plasma oxygenated treatments are observed to play a significant role in the use of chitosan as a biocompatible and biodegradable biomaterial. The ability to use a material or device for human treatment in a specific situation without causing toxic and injurious effects defines the material or device as biocompatible. Many studies revealed that chitosan scaffolds result in healthy cell morphology and proliferation, demonstrating their biocompatibility [17].

Biodegradation plays a significant role in the metabolic fate of chitosan in the body, and it is an essential process for all polymers that are utilized in drug delivery systems and as scaffolds in tissue engineering. Due to its systemic absorption and hydrophilic properties, chitosan is considered a biodegradable biomaterial. Chitosan biomaterials are capable of being degraded enzymatically by hydrolysis of the glucosamine-glucosamine and N-acetyl-glucosamine-N-acetylglucosamine linkages [28]. Depolymerization via oxidation-reduction reactions and free-radical degradation contribute to the *in vivo* degradation of chitosan [29,30]. All of these important properties make surface-modified chitosan biomaterial an excellent biopolymer that could be readily applied in a clinical setting.

Because chitosan is a well-known non-toxic biopolymer with antibacterial properties, many studies have been conducted with the aim of demonstrating the hemocompatibility of chitosan-derived biomaterials. As a result, these biomaterials have been shown to be good hemostatic agents, and chitosan-induced blood coagulation is generally well accepted. Although respective chitosan-based hemostatic agents have been fabricated by blending them with other improved substances under various preparation conditions, to the best of our knowledge, many research groups still have not completely elucidated the underlying pathway by which chitosan affects the coagulation cascade [31-33]. There are a number of important properties involved in determining the protein response at chitosan biomaterial interfaces, such as membrane surface topography, hydrophobicity and charge density. Strong chemical bonds formed between a protein and chitosan will increase the protein's affinity for the surface [34-37].

Conclusion and Future Recommendation

Chitosan derivatives were discovered in 1859 upon the chemical modification of chitin. Various types and forms of chitosan biomaterials are being used in diverse applications in the biomedical field, including as hydrogels, powders, pastes, sheets, porous scaffolds, solutions, sponges, beads, films, fibers and nanoparticles, using various methods of processing. Although lately attention has been paid to these naturally obtained chitosan biomaterials, the factors influencing the properties of these chitosans still remain to be determined. In the future, more advanced studies using animals and *in vitro* models are needed to establish and elucidate the properties of chitosan derivatives. Such research will provide a basis for the use of chitosan in human clinical trials.

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References

1. Keeling PJ, Burki F, Wilcox HM, Allam B, Allen EE, et al. (2014) The Marine Microbial Eukaryote Transcriptome Sequencing Project (MMETSP): illuminating the functional diversity of eukaryotic life in the oceans through transcriptome sequencing. See comment in PubMed Commons below PLoS Biol 12: e1001889.
2. What is chitosan: Origins of chitosan (2014)
3. Darmon SE, Rudall KM (1950) Infra-red and x-ray studies of chitin.
4. Muzzarelli RAA (1977) Chitin. Pergamon Press Oxford, U.K.
5. Muzzarelli RAA, Muzzarelli C (2005) Relevance to the biomedical sciences. Adv Polym Sci. 186: 151.
6. Aranaz I, Mengibar M, Harris R, Panos I, Miralles B, Acosta N, Galed G, Heres A (2009) Functional characterization of chitin and chitosan. Chem Bio 3: 203-230.
7. Koide SS (1998). Chitin-Chitosan: Properties, benefits and risks. Nutri Res 18: 6: 1091-1998.
8. Kumar MV, Hudson SM (2004) Chitosan in encyclopedia of biomaterials and biomedical engineering. Wnek GE, Bowlin GL, ed., Marcel D, New York. 1: 310-323.
9. Seda Tiğli R, Karakeçili A, Gümüşderelioğlu M (2007) In vitro characterization of chitosan scaffolds: influence of composition and deacetylation degree. See comment in PubMed Commons below J Mater Sci Mater Med 18: 1665-1674.
10. Biagini B, Muzzarelli RA, Giardino R, Castaldini C (1992) Biological materials for wound healing. In: Brine C.J, Sandford PA, Zikakis JP editors, Advances in Chitin and Chitosan, Elsevier Appl Sci, New York. 16–24.
11. Zhang J, Xia W, Liu P, Cheng Q, Tahirou T, et al. (2010) Chitosan modification and pharmaceutical/biomedical applications. See comment in PubMed Commons below Mar Drugs 8: 1962-1987.
12. Rinaudo M (2006) Chitin and chitosan: Properties and applications. Progress in Polym Sci 31: 603–632.
13. Sankararamakrishnan N, Sanghi R. (2006) Preparation and characterization of a novel xanthated chitosan. Carbohydr Polym 66: 160–167.
14. Kurita K (2006) Chitin and chitosan: functional biopolymers from marine crustaceans. See comment in PubMed Commons below Mar Biotechnol (NY) 8: 203-226.
15. Mourya VK, Nazma N. Inamdar, Ashutosh Tiwari (2010) Carboxymethyl chitosan and its applications. Adv. Mat. Lett. 1:1: 11-33.
16. Dash M, Chiellini F, Ottenbrite RM, Chiellini E (2011). Chitosan- A versatile semi-synthetic polymer in biomedical applications. Progress in Polym Sci 36: 981-1014.
17. Lakshmi SN, Cato TL (2007) Biodegradable polymers as biomaterials. Progress in Polymer Science (Polymers in Biomedical Applications) 32: 8–9, 762–798.
18. Xia WS (2003) Physiological activities of chitosan and its application in functional foods. J Chi Ins of Food Sci and Tech 3: 77-81.
19. Will Soutter. Chitosan Nanoparticles - Properties and Applications. (2014).
20. Sannan T, Kurita K, Iwakura Y (1977). Studies on Chitin. Kinetics of deacetylation reaction. Polym J 9:6: 649-651.
21. Kumar (2000). A review of chitin and chitosan applications. Reactive and functional Polym 46: 1-27.
22. Li Q, Lunn ET, Grandmason EW, Goosen MF (1997). In Applications and properties of chitosan, Goosen, MFA., Ed., Technomic Publishing Co., Inc. Lancaster, p3.
23. Cervera MF, Heinämäki J, Krogars K, Jörgensen AC, Karjalainen M, et al. (2004) Solid-state and mechanical properties of aqueous chitosan-amylose starch films plasticized with polyols. See comment in PubMed Commons below AAPS PharmSciTech 5: E15.
24. Shigemasa Y, Matsuura H, Sashiwa H, Saimoto H (1996) Evaluation of different absorbance ratios from infrared spectroscopy for analyzing the degree of deacetylation in chitin. See comment in PubMed Commons below Int J Biol Macromol 18: 237-242.
25. Rinaudo M (2006) Chitin and chitosan: Properties and applications. Progr in Polym Sci 31: 603–632.
26. Roberts GAF (1992) Chitin Chemistry, 1st ed. MacMillan, London.
27. Keong LC, Halim AS (2009) In vitro models in biocompatibility assessment for biomedical-grade chitosan derivatives in wound management. See comment in PubMed Commons below Int J Mol Sci 10: 1300-1313.
28. Kean T, Thanou M (2010) Biodegradation, biodistribution and toxicity of chitosan. See comment in PubMed Commons below Adv Drug Deliv Rev 62: 3-11.
29. Hsu SC, Don TM, Chiu WY (2002) Free radical degradation of chitosan with potassium persulfate. Polym Degrade Stabil 75: 73-83.
30. Zoldners J, Kiseleva T, Kaiminsh I (2005) Influence of ascorbic acid on the stability of chitosan. Carbohyd Polym 60: 215-218.
31. Okamoto Y, Yano R, Miyatake K, Tomohiro I, Shigemasa Y, et al. (2003) Carbohydra Polym 53: 337–342.
32. Megan SL, Bill C, McCarthy SJ, MoonSun J, John MW (2011) The modulation of platelet adhesion and activation by chitosan through plasma and extracellular matrix proteins.
33. Yamazaki M (2007) The chemical modification of chitosan films for improved hemostatic and bioadhesive properties. PhD dissertation. Raleigh, NC: North Carolina State University.
34. Corum LE, Eichinger CD, Hsiao TW, Hlady V (2011) Using microcontact printing of fibrinogen to control surface-induced platelet adhesion and activation. See comment in PubMed Commons below Langmuir 27: 8316-8322.
35. Gorbet MB, Sefton MV (2004) Biomaterial-associated thrombosis: roles of coagulation factors, complement, platelets and leukocytes. See comment in PubMed Commons below Biomaterials 25: 5681-5703.
36. Schmidt DR, Waldeck H, Kao WJ (2009) Protein adsorption to biomaterials, in Biological interactions on materials surfaces, New York, Springer, 1-18.
37. Andrade JD, Hlady V (1987) Plasma protein adsorption: the big twelve. See comment in PubMed Commons below Ann N Y Acad Sci 516: 158-172.

Citation: Periayah MH, Halim AS, Saad AZM (2014) Chitosan: A Promising Marine Polysaccharide for Biomedical Research. J Biotechnol Biomater 4: 168. doi:10.4172/2155-952X.1000168