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Fundamentals and Applications of Chitosan

Nadia Morin-Crini, Eric Lichtfouse, Giangiacomo Torri, and Grégorio Crini

Abstract Chitosan is a biopolymer obtained from chitin, one of the most abundant and renewable material on Earth. Chitin is a primary component of cell walls in fungi, the exoskeletons of arthropods, such as crustaceans, e.g. crabs, lobsters and shrimps, and insects, the radulae of molluscs, cephalopod beaks, and the scales of fish and lissamphibians. The discovery of chitin in 1811 is attributed to Henri Braconnot while the history of chitosan dates back to 1859 with the work of Charles Rouget. The name of chitosan was, however, introduced in 1894 by Felix Hoppe-Seyler. Because of its particular macromolecular structure, biocompatibility, biodegradability and other intrinsic functional properties, chitosan has attracted major scientific and industrial interests from the late 1970s. Chitosan and its derivatives have practical applications in food industry, agriculture, pharmacy, medicine, cosmetology, textile and paper industries, and chemistry. In the last two decades, chitosan has also received much attention in numerous other fields such as dentistry, ophthalmology, biomedicine and bio-imaging, hygiene and personal care, veterinary medicine, packaging industry, agrochemistry, aquaculture, functional textiles and cosmetotextiles, catalysis, chromatography, beverage industry, photography, wastewater treatment and sludge dewatering, and biotechnology. Nutraceuticals and cosmeceuticals are actually growing markets, and therapeutic and biomedical products should be the next markets in the development of chitosan. Chitosan is also the

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object of numerous fundamental studies. An indication of the widespread exploitation and constantly growing importance of this biopolymer is the total of over 58,625 scientific articles published between 2000 and 2017. In this chapter, after a description of chitosan fundamentals, we highlight selected works on chitosan applications published over the last two decades.

Keywords Chitosan · Chitin · Biopolymer · Fundamentals · Properties · Applications

2.1 Introduction

Main commercial polymers are derived from petroleum-based raw products using processing chemistry that is not always safe or environmental friendly. Over the past three decades, there has been a growing interest in developing natural alternatives to synthetic polymers, namely biopolymers. Biopolymers are polymers derived from living organisms or synthetized from renewable resources. They have expanded significantly due to their biological origin and mostly to their non-toxicity and biodegradable nature. Biopolymers include polysaccharides such as cellulose, starch, chitin/chitosan, and alginates.

Because of its remarkable macromolecular structure, physical and chemical properties, bioactivities, and versatility, quite different from those of synthetic polymers, the biopolymer chitosan has received much attention in fundamental science, applied research and industrial biotechnology (Crini et al. 2009; Kim 2011, 2014; Miranda Castro and Lizárraga Paulín 2012; Teng 2012; Sashiwa and Harding 2015; Dima et al. 2017; Philibert et al. 2017). Chitosan and its derivatives have practical applications in numerous fields: food industry and nutrition, agriculture and agrochemistry, aquaculture, pharmacy, medicine and biomedicine, dentistry, ophthalmology, cosmetology, hygiene and personal care, bio-imaging, veterinary medicine, textile and fiber industries, paper industry, chemistry, catalysis, chromatography, beverage industry, photography, wastewater treatment and sludge dewatering, biotechnology, and nanotechnology (Davis 2011; Ferguson and O'Neill 2011; Sarmento and das Neves 2012; Yao et al. 2012; Bautista-Baños et al. 2016; Dutta 2016; Ahmed and Ikram 2017; Amber Jennings and Bumgardner 2017a, b; Han et al. 2018; Pakdel and Peighambardoust 2018; Pellá et al. 2018; Sharif et al. 2018; Song et al. 2018; Wei et al. 2018; Zhao et al. 2018).

Chitosan is a semi-synthetic commercial aminopolysaccharide derived by deacetylation of the naturally occurring biopolymer chitin. Chitin is the most abundant of the renewable polysaccharides in the marine environment and one of the most abundant on Earth after cellulose (Muzzarelli 1977; Roberts 1992a; Kurita 2006; Rinaudo 2006; Souza et al. 2011). Chitin is an important source of carbon and nitrogen for marine organisms and its ecological importance in the marine environment is nowadays recognized. The main sources exploited for chitin and chitosan

production at industrial scale are marine crustaceans, the shells of shrimps and crabs and the bone plate of squids (Kean and Thanou 2011; Nwe et al. 2011a, b; Kim 2014; Younes and Rinaudo 2015; Elieh-Ali-Komi and Hamblin 2016; Dima et al. 2017; Philibert et al. 2017; El Knidri et al. 2018).

Chitosan extraction from crustaceans in food industry wastes is economically feasible (Truong et al. 2007; Crini et al. 2009). In addition, its commercial production allows the recovery of pigments, proteins, fish meal additive in aquaculture, and also nutraceuticals which are beneficial in human health promotion (Philibert et al. 2017; Dave and Routray 2018). Chitosan can be marketed as a green product. Chitosan is also of great commercial interest due to its high percentage of nitrogen, of 6–7%, compared to synthetically substituted cellulose, of 1.25%, that makes it an effective chelating and complexing agent. Other reasons are undoubtedly its appealing polyelectrolyte properties at acidic pH, and biological properties. Indeed, most of the applications can be related to its cationic nature, which is unique among abundant polysaccharides and natural polymers. Chitosan has unique characteristics such as biocompatibility and biodegradability, and possess reactive functional groups that make is useful in different areas of applications in the form of solutions, suspensions, gels/hydrogels, powders, microparticles/nanoparticles, beads, sponges, foams, membranes and films, or fibers/nanofibers (Muzzarelli 1977; Roberts 1992a; Crini 2005; Kurita 2006; Rinaudo 2006; Crini et al. 2009; Younes and Rinaudo 2015).

The literature on chitosan is vast and spread across different disciplines including chemistry, biochemistry, health science, agriculture and ecology. The past two decades have shown a fast increase in the number of studies on chitosan. Between 2000 and 2017, 58,625 chitosan-related publications have been published including 18,097 on applications (ISI Web of Science database). It is interesting to note that a majority of these works come from Asian nations including Japan (the undisputed leader), Korea, China, Singapore, Taiwan and Thailand (Khor and Lim 2003). A large number of generalist reviews and book chapters has been also published on practically all the aspects of chitosan biopolymer, so many that it would not be feasible to cite them all. Table 2.1 lists selected comprehensive reviews and book chapters on the history, production, characterization, structure, chemistry, derivatives, and toxicology of chitosan. Table 2.2 shows the top ten most cited reviews in the ISI Web of Science database for 2000–2017 with "Chitosan" and "Review" in the topic.

This chapter summarizes some of the developments related to the applications of this biopolymer, based on a substantial number of relevant references, and provides useful information about its most important features. After a brief description of chitosan fundamentals, we present an overview of the applications of chitosan. We include an extensive bibliography of recent studies on chitosan, both basic and applied. Nevertheless, the examples presented are not exhaustive due to the very large number of papers published.

Table 2.1 Selected reviews published during the last two decades on the history, production, characterization, structure, chemistry, derivatives and toxicology of chitosan

General topic	References
Characterization Degree of deacetylation Molecular weight Distribution of N-acetyl groups Spectroscopy: IR, NMR, Raman, X-Ray Elemental analysis Acid-base titration Conductometric/ Potentiometric titration Colloid titration Chemical/Enzymatic hydrolysis	Heux et al. (2000), No and Meyers (2000), Jiang et al. (2003), Shahidi and Abuzaytoun (2005), Wang et al. (2006), Kasaai (2008, 2009, 2011), Crini et al. (2009), Dos Santos et al. (2009), Maniukiewicz (2011), de Alvarenga (2011), Czechowska-Biskup et al. (2012), Zając et al. (2015), Sivashankari and Prabaharan (2017), and Tsai and Chen (2017)
Chemistry Solubility Solution state/Gel state Chain conformation Polyelectrolyte complexes, macromolecular complexes, electrostatic properties Aggregation Self-assembly/Self-assembled systems	Hudson and Smith (1998), Ravi Kumar (2000), Hejazi and Amiji (2001), Kubota and Shimoda (2004), Bodnar et al. (2005), Muzzarelli and Muzzarelli (2005), Shahidi and Abuzaytoun (2005), Crini et al. (2009), Pillai et al. (2009), Hamman (2010), Uragami and Tokura (2010), Jayakumar et al. (2010a), Lakshmanan et al. (2011), Ujang et al. (2011), Rinaudo (2012), Teng (2012), Zambito (2013), Kim and Venkatesan (2014), Mateescu et al. (2015a, b), Younes and Rinaudo (2015), Lizardi-Mendoza et al. (2016), and Salehi et al. (2016)
Derivatives Physical modifications Chemical modifications: derivatization, cross-linking, grafting reactions, hydrolysis Gels/Hydrogels Glucosamines/ Oligosaccharides Chitooligosaccharides/ Chitosan oligomers/ Chitooligomers Technology/Nanotechnology/ Electrospinning Films/Membranes Fibers/Nanofibers	Synowiecki and Al-Khateeb (2003), Canh et al. (2004), Jalal Zohuriaan-Mehr (2005), Wang et al. (2006), Kurita (1986, 1998, 2006), Crini et al. (2009), Muzzarelli and Muzzarelli (2009), Dutta and Dutta (2011), Kim (2011, 2014), Kim and Je (2011), Kim and Kim (2011), Vidanarachchi et al. (2011), Xiao et al. (2012), Yao et al. (2012), Ahmadi et al. (2015), Ahmed and Ikram (2017), Aminabhavi and Dharupaneedi (2017), Ruiz and Corrales (2017), Argüelles-Monal et al. (2018), Divya and Jisha (2018), Liang et al. (2018), and Liaqat and Eltem (2018)
History	Jeuniaux (1966), Muzzarelli (1977), Roberts (1992a), Winterowd and Sandford (1995), Labrude (1997), Labrude and Becq (2003), Shahidi and Abuzaytoun (2005), Rauh and Dornish (2006), Wisniak (2007), Crini et al. (2009), Khoushab and Yamabhai (2010), Nwe et al. (2011b), Muzzarelli et al. (2012), Berezina (2016), Annu et al. (2017), and Karthik et al. (2017)

(continued)

Table 2.1 (continued)

General topic	References
Production Sources Industrial production Extraction: chemical, biological, enzymatic Microorganisms Chitin deacetylases	Viney and Harish (2002), Synowiecki and Al-Khateeb (2003), Sen (2005), Kurita (2006), Abdou et al. (2008), Peniche et al. (2008), Crini et al. (2009), Brück et al. (2011), Davis (2011), Jo et al. (2011), Knezevic-Jugovic et al. (2011), Nwe et al. (2011a, b, 2013, 2014), Arbia et al. (2013), Gortari and Hours (2013), Setyahadi (2013), Kaur and Dhillon (2014, 2015), Aljawish et al. (2015), Younes and Rinaudo (2015), Majekodunmi (2016), Sivashankari and Prabaharan (2017), Dave and Routray (2018), de Lima Batista et al. (2018), El Knidri et al. (2018), and Grifoll-Romero et al. (2018)
Structure Structural aspects/ Morphology/Crystallinity Crystallography Structure-property relationship	Vårum and Smidsrød (2004a), Dutta et al. (2004), Kurita (2006), Rinaudo (2006), Dash et al. (2011), Younes and Rinaudo (2015), and Sahariah and Másson (2017)
Toxicology Toxicity Cytotoxicity Biodegradation	Kurita (1998), Pillai et al. (2009), Kean and Thanou (2010), Dash et al. (2011), Jimtaisong and Saewan (2014), Sahariah and Másson (2017), and Sadler and Funnell (2018)

Table 2.2 The top ten most cited reviews in the ISI Web of Science database for 2000–2017 with "Chitosan" AND "Review" in the topic; out of a total of 2702 reviews appearing, October 01, 2018

1. Rinaudo M (**2006**) Chitin and chitosan: Properties and applications. Progress in Polymer Science 31:603–632. Times cited: 3092.
2. Kumar MNVR (**2000**) A review of chitin and chitosan applications. Reactive and Functional Polymers 46:1–27. Times cited: 2297.
3. Crini G (**2006**) Non-conventional low-cost adsorbents for dye removal. Bioresource Technology 97:1061–1085. Times cited: 2229.
4. Rabea EI, Badawy MET, Stevens CV, Smagghe G, Steurbaut W (**2003**) Chitosan as antimicrobial agent: Applications and mode of action. Biomacromolecules 4:1457–1465. Times cited: 1401.
5. Agnihotri SA, Malikarjuna NN, Aminabhavi TM (**2004**) Recent advances on chitosan-based micro- and nanoparticles in drug delivery. Journal of Controlled Release 100:5–28. Times cited: 1388.
6. Suh JKF, Matthew HWT (**2000**) Application of chitosan-based polysaccharide biomaterials in cartilage tissue engineering: A review. Biomaterials 21:2589–2598. Times cited: 1221.
7. Berger J, Reist M, Mayer JM, Felt O, Peppas NA, Gurny R (**2004**) Structure and interactions in covalently and ionically crosslinked chitosan hydrogels for biomedical applications. European Journal of Pharmaceutics and Biopharmaceutics. 57:19–34. Times cited: 1120.
8. Dash M, Chiellini F, Ottenbrite RM, Chiellini E (**2011**) Chitosan – A versatile semi-synthetic polymer in biomedical applications. Progress in Polymer Science 36:981–1014. Times cited: 1110.
9. Shahidi F, Arachchi JKV, Jeon YJ (**1999**) Food applications of chitin and chitosans. Trends in Food Science Technology. 10:37–51. Times cited: 1066.
10. Khor E, Lim LY (**2003**) Implantable applications of chitin and chitosan. Biomaterials 24:2339–2349. Times cited: 1053.

2.2 Chitosan Production and Properties

2.2.1 History

In 1811, Braconnot, Director of the *Jardin Botanique* of Nancy, France, discovered an alkaline-insoluble fraction from mushrooms by treatment with dilute warm alkali (Simonin 1856, 1870, 2013; Prévost and D'Amat 1956; Tracey 1957; Jeuniaux 1966; Muzzarelli 1977; Roberts 1992a; Winterowd and Sandford 1995; Labrude 1997; Labrude and Becq 2003; Wisniak 2007). Braconnot described this new product containing a substantial percent of nitrogen and found that the liquid contained acetate of ammonia contaminated with oil (Braconnot 1811, 1813). This fraction also produced acetic acid by degradation with concentrated sulfuric acid (Braconnot 1811; Tracey 1957; Rudall and Kenchington 1973). Braconnot gave the name alkaline-insoluble fraction as *fongine*/fungine, a substance "*d'une nature particulière*".

In 1823, Odier isolated a similar alkaline-insoluble fraction from the elytra of insects by repeated treatments with hot hydroxide solutions (Odier 1823). He gave it the name of *chitine*/chitin, from Greek word chitos, meaning tunic or envelope (Odier 1823; Rudall and Kenchington 1973; Souza et al. 2011). However, Odier tested for nitrogen in this residue and found none. Odier's paper was promptly published in an English translation by Children in 1824 (Children 1824). Children, repeating the same experiments, also extracted an alkaline-insoluble fraction from may bug elytra and found the presence of nitrogen by elemental analysis (Children 1824; Tracey 1957; Nwe et al. 2011b).

In 1843, Lassaigne isolated a chitinous material from treatment of exoskeleton of silkworm butterfly and confirmed the presence of nitrogen in chitin (Lassaigne 1843). He proved that chitin was not a cellulose but a new product containing nitrogen (Tracey 1957). The same year, the Lassaigne's finding were corroborated by Payen (1843), although initially he had convinced himself in 1840 that Braconnot's fungine was cellulose (Tracey 1957).

In the 1870s, Ledderhose hydrolyzed arthropod chitin with the aim to identify the structure of the products (Ledderhose 1876, 1878). In 1875, Ledderhose, treating lobster shells with hot concentrated hydrochloric, found that the shells dissolved in this solution and that on evaporation the solution yielded characteristic crystals. He identified the crystalline compound as a new amino-containing sugar, which he named *glykosamin*/glucosamine (Ledderhose 1876). Later, Ledderhose showed that acetic acid was also a product of hydrolysis of arthropod chitin (Ledderhose 1878). The presence of glucosamine as the repeated unit of chitin was confirmed a few years later by the works of Winterstein (Winterstein 1893, 1894) and Gilson (Gilson 1894, 1895). At the ends of the 1890s, it was established that chitin occurs in both animals and plants and that there was no detectable chemical differences between products from the two sources. However, the controversy of the structure of chitin has continued.

The history of chitosan dates back to 1859 with the work of Rouget (Rouget 1859; Brimacombe and Webber 1964; Muzzarelli 1977; Sharon 1980; Roberts 1992a; Winterowd and Sandford 1995). Rouget treated chitin with strong alkali, which resulted in a new substance that could, unlike chitin itself, be dissolved in acidic aqueous solutions (Rouget 1859). He named the product "*chitine modifiée*", modified chitin. In 1894, Hoppe-Seyler treated the shells of crabs, scorpions and spiders with potassium hydroxide at 180 °C and found a "new" product (Hoppe-Seyler 1894). He gave it the name of chitosan. This product was a partially deacetylated, acid-soluble derivative of chitin. This was also prepared from fungal material by both Winterstein (1894) and Gilson (1894).

In the middle of the 1930s, the structure of chitin and chitosan was characterized using data from X-ray diffraction (Meyer and Pankow 1935; Clark and Smith 1936) and later by enzymatic analysis and infrared spectroscopy (Muzzarelli 1977; Roberts 1992a). In 1936, there was the first use in papermaking industry. In the same year, two patents, one for producing chitosan from chitin and the other for making films and fibers from chitosan, were obtained by Rigby. However, lack of adequate manufacturing facilities and mostly cutthroat competition from synthetic polymers restricted their commercial development. "Re-discovery" and revived interest in the 1970s encouraged the need to better utilize biowastes from marine crustaceans (Muzzarelli 1977; Roberts 1992a, 1998; Winterowd and Sandford 1995; Rauh and Dornish 2006; Wisniak 2007; Crini et al. 2009; Khoushab and Yamabhai 2010; Nwe et al. 2011b). Several manufacturers started to produce and to market chitin and chitosan products. Numerous patents have been filed since the 1970s, and an abundant scientific literature has built up (Muzzarelli et al. 2012; Berezina 2016; Annu et al. 2017; Karthik et al. 2017). Today, there are more than 2000 applications of chitin, chitosan and their numerous derivatives (Philibert et al. 2017).

2.2.2 Chitin

Among numerous biopolymers, chitin is produced in the largest amounts, and after cellulose, it is the most abundant organic compound from living organisms on Earth. This polysaccharide is widely distributed in the animal and vegetal kingdom, constituting an important renewable resource. Chitin is found in the exoskeleton of crustaceans, the cuticles of insects, and the cell walls of fungi (Rudall and Kenchington 1973; Muzzarelli 1977; Muzzarelli et al. 1986a; Roberts 1992a; Kurita 1986, 1998, 2006; Rinaudo 2006; Nwe et al. 2011b). Other examples are given in Table 2.3. The content of chitin is 30–40% in shrimps, 15–30% in crabs, 20–30% in krills, 20–40% in squids, 3–6% in clams, 3–6% in oysters, 5–25% in insects and 10–25% in fungi (Muzzarelli et al. 1986a; Skjåk-Braek et al. 1989; Roberts 1992a; Horst et al. 1993; Felt et al. 1998; Kurita 2006; Rinaudo 2006; Nwe et al. 2011b). A discussion on chitin content can be found in the recent review by Hamed et al. (2016).

From a structural point of view, both chitin and cellulose are polymers of monosaccharide made up of β-(1 → 4)-2-acetamido-2-deoxy-β-D-glucopyranose and

Table 2.3 Sources of chitin and chitosan in aquatic organisms, terrestrial organisms and microorganisms

Aquatic crustaceans	Other sea animals	Insects	Mushrooms and Fungi	Other microorganisms	Other terrestrial crustaceans
Shrimps Crabs Lobsters Crayfishes Krill	Squids Cuttlefishes Annelida Mollusca Coelenterata	Scorpions Spiders Brachiopods Cockroaches Beetles Silkworms Ants Mosquitoes Honey bees	*Agaricus bisporus* *Auricularia auriculajudae* *Lentinula edodes* *Trametes versicolor* Blastocladiaceae Ascomydes *Aspergillus niger* *Mucor rouxii*	Green algae Brown algae Yeast Spores	Nematode *Porcellio scaber* *Armadillidium vulgare*

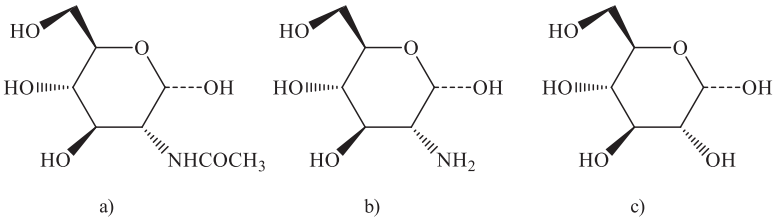

Fig. 2.1 Structure of (**a**) N-acetyl-glucosamine, monomer of chitin, (**b**) glucosamine, monomer of chitosan and (**c**) glucose, monomer of cellulose

β-(1 → 4)-2-deoxy-β-D-glucopyranose units, respectively (Fig. 2.1). Chitin is generally represented as a linear long-chain homo-polymer composed of N-acetyl glucosamine units, [poly(N-acetyl-β-D-glucosamine)] (Fig. 2.2). Depending on its source, chitin exists in three different polymorphic forms, namely α-, β- and γ-chitin (Bouligand 1965; Neville and Luke 1969a, b; Neville 1975; Neville et al. 1976; Muzzarelli 1977; Roberts 1992a; Horst et al. 1993; Berezina 2016), which can be differentiated by X-ray diffraction, and infrared and NMR spectroscopy (Muzzarelli 1977; Roberts 1992a; Maniukiewicz 2011). α-Chitin isomorph is by far the most abundant. The sources for α-, β- and γ-chitin are crabs (e.g. *Callinectes sapidus*, *Chionoecetes opilio*) and shrimps (*Pandalus borealis*, *Crangon crangon*), squids and loligo (*Ommastrephes bartrami*, *Loligo formosana* Sasaki), respectively. These forms differ in their arrangement of macromolecular chain. In α-chitin, the chains are arranged antiparallel to each other while in β-chitin they are parallel. In γ-chitin, the chains are arranged randomly in which two parallel chains and one antiparallel chain form the structure. An update discussion on this topic can be found in the references by Maniukiewicz (2011), Anitha et al. (2014), and Younes and Rinaudo (2015).

Chitin is structurally similar to cellulose: it shares many structural similarities as, for example, the conformation of the monomers and the diequatorial glycosidic

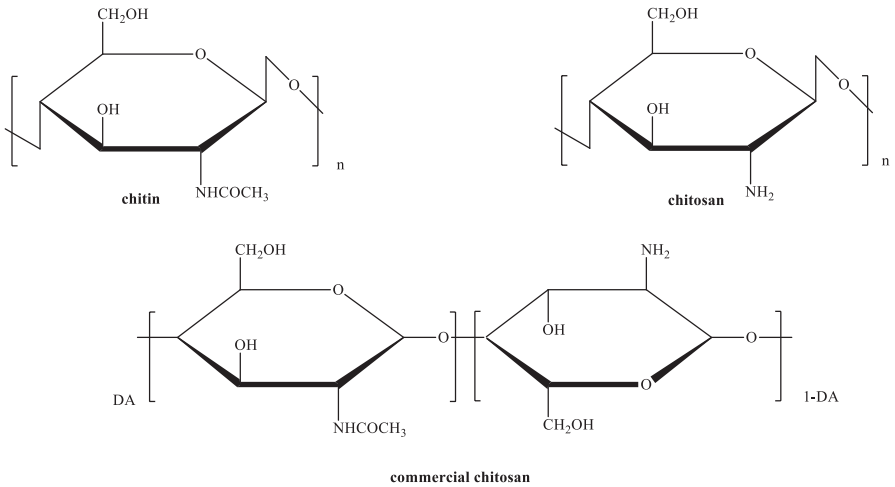

Fig. 2.2 Schematic representation of completely acetylated chitin [poly(*N*-acetyl-ß-D-glucosamine], completely deacetylated chitosan [poly(D-glucosamine] and commercial chitosan, a copolymer characterized by its average degree of acetylation (DA) per cent

linkages. Both biopolymers play similar roles since they both act as structural support and defense materials in living organisms. However, chitin is an aminopolymer and has acetamide groups at the C-2 positions in place of the hydroxyl groups in the repeating unit of macromolecular chains (Figs. 2.1 and 2.2). Chitin is also an extremely insoluble material (Austin 1984; Kienzle-Sterzer et al. 1984; Muzzarelli 1977; Muzzarelli et al. 1986b; Skjåk-Braek et al. 1989; Roberts 1992b, c; Hudson and Smith 1998). Despite its huge availability, its insolubility is a major problem that confronts the development of processes and uses of this chitin, and so far, few large-scale industrial uses have been found. For instance, chitin is an effective material for sutures because of its biocompatibility, non-toxicity, biodegradability, antimicrobial activity and low immunogenicity. Chitin also accelerates wound-healing in spray, gel and gauze and it can be used to control drug release (Pillai et al. 2009; Younes and Rinaudo 2015).

More important that chitin is its main derivative, chitosan. Indeed, partial deacetylation of chitin results in the commercial production of chitosan which is a polysaccharide composed by macromolecules of D-glucosamine and N-acetyl glucosamine (Hudson and Smith 1998). The fully deacetylated product is rarely obtained due to the risks of side reactions and chain depolymerization. Chitosans may be considered as a family of linear binary copolymers of β-(1 → 4)-linked N-acetyl glucosamine units and 2-amino-2-deoxy-β-D-glucose, and do not refer to a uniquely defined polysaccharide, but to products having different proportions of D-glucosamine and N-acetyl glucosamine units and of varying chain lengths. In fact, the "chitosan label" generally corresponds to polymers with less than 25–40% acetyl content. So, each commercial chitosan is a copolymer characterized by its average degree of acetylation (DA) per cent (Fig. 2.2). This degree of acetylation is

defined as the percentage DA or fraction F_A of N-acetylated glycosidic units in chitosan or chitin biopolymer. It is also customary to express this parameter as degree of deacetylation DD (= 1-F_A or = 100-DA per cent). In chitin samples, the degree of acetylation is typically 90% indicating the presence of some amino groups, as some amount of deacetylation might take place during chitin extraction. Depending on the source, a variable and small proportion of these units are also deacetylated in natural chitin (Peniche et al. 2008). However, this remains always a subject of debate (Peniche et al. 2008; Pillai et al. 2009; Younes and Rinaudo 2015).

2.2.3 Production

Although chitin is found in many aquatic organisms, in many insects, in terrestrial crustaceans, in mushrooms, and in some fungi, from a production point of view, the raw biopolymer chitin is only commercially extracted from marine crustaceans primarily because a large amount of wastes/biowastes is available as low-cost by-products of seafood processing industry (Truong et al. 2007; Nwe et al. 2011b, 2014; Dave and Routray 2018). Shrimps, crabs, lobsters, krill, and squid biowastes from marine industry are the major resources used for the large-scale production of chitin and chitosan. The shells of these marine crustaceans contain 15–40% chitin, proteins (20–40%) and calcium carbonate (20–50%) being two other major components. Pigments, lipids and other minerals including metals and salts are minor components. Of course, the percentages vary considerably with the species used (quality and freshness of shell) and the season (Peniche et al. 2008; Nwe et al. 2014). Other possible sources from marine organisms of chitin production include clams and oysters. Figure 2.3 shows a simplified representation of preparation of chitin, chitosan and their derivatives from aquatic crustacean biowastes. The shells are first ground to the appropriate size and washed profusely with water to remove any organic material adhered to their surface (Acosta et al. 1993). To isolate chitin from the shells of shrimps and crabs, and bone plates of squids, three main steps are then required, namely deproteinization, demineralization, and decolorization. The order of the first two steps is considered irrelevant if protein or pigment recovery is not an objective (Peniche et al. 2008; Nwe et al. 2011b).

The conventional protocol for chitin production is performed through chemical processes using inorganic strong alkali for protein extraction at a given temperature, usually 50–60 °C, and acids for removal of inorganic components, and oxidants for decolorization. These processes permit to dissolve inorganic salts, mainly calcium carbonate and calcium phosphate, using hydrochloric acid and proteins using sodium hydroxide, to eliminate lipids and pigments (melanins, carotenoids), and to obtain a colorless commercial product. The considerable quantities of carotenoids can be used as fish food additives. Calcium carbonate can be converted to calcium oxide and sodium carbonate. The proteins extracted can be recovered by lowering the pH of the solution to its isoelectric point for precipitation. The recovered proteins can be also used as a high-grade additive for livestock starter feeds. This

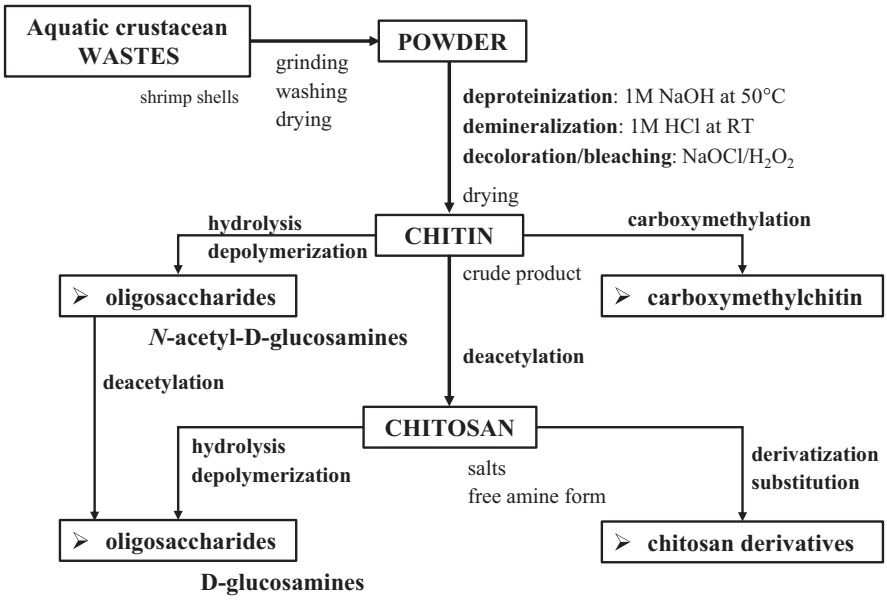

Fig. 2.3 Simplified representation of preparation of chitin, chitosan and their derivatives from aquatic crustacean biowastes

decreases the manufacturing costs of chitin. Calcium carbonate is usually eliminated with dilute HCl solutions at room temperature although other acids have been also studied with success. The acid concentration, reaction time and temperature must be carefully controlled in order to minimize the hydrolytic depolymerization and deacetylation of chitin and/or to prevent thermal degradation (No and Meyers 1995; Percot et al. 2003; Peniche et al. 2008). The color of crustacean shells is due to the presence of pigments such as astaxanthin, cantaxanthin, astacene, lutein and β-carotene (Acosta et al. 1993; No and Meyers 1995; Kurita 1998). Decolorization/bleaching is achieved through the use of potassium permanganate or sodium hypochlorite (Kurita 1998, 2006) or by solvent extraction (Acosta et al. 1993; Peniche et al. 2008). Oxidation may attack the free amino groups and introduce modifications in the macromolecules (Acosta et al. 1993). Pigments may be also recovered as high value side products.

Purified chitin is then converted to chitosan by hydrolysis of acetamide groups of chitin using sodium hydroxide solutions 40%–60% v/v (No and Meyers 1995; Kurita 1998). The deacetylation process de-esterifies the N-acetyl linkages. Generally, the reaction is carried out under N_2 atmosphere or in the presence of a scavenger of oxygen to avoid depolymerization and to prevent chain degradation. The specific reaction conditions depend on several factors such as the origin of the raw material, the previous treatment and the desired degree of acetylation. Deacetylation of chitin is undertaken using homogeneous or heterogeneous processes (Fig. 2.4). Homogeneous deacetylation is achieved with more moderate

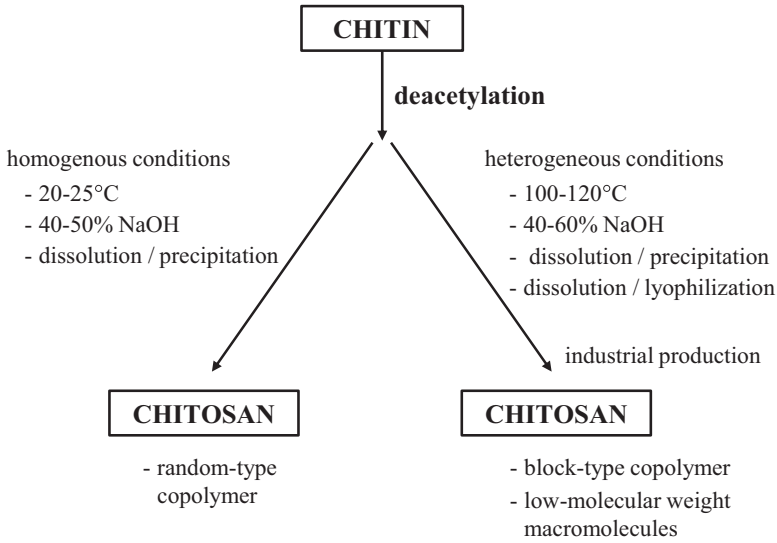

Fig. 2.4 Deacetylation of chitin using homogeneous and heterogeneous processes

alkali concentrations at room temperature and chitosans obtained do not exhibit chain compositional dispersion while chitosans obtained by the heterogeneous process are polydispersed in terms of degree of acetylation of their chains and distribution. High temperatures are preferred for industrial chitosan production (Kurita 1986, 1998, 2006). The chitosan obtained is finally dried into flakes, and then dissolved in acetic acid and filtered to remove extraneous materials resulting in a water-soluble salt. To purify it, the product is dissolved in excess acid and filtered using porous membranes. Adjusting the pH of the solution to ca. 7.5 by NaOH causes flocculation due to the deprotonation and the insolubility of the macromolecule chains at neutral pH. The sample is then washed with water and dried. Data published on worldwide chitosan market is estimated to be over 40,000 metric tons in 2018 (Philibert et al. 2017).

The chemical methods for chitin/chitosan production from biowastes are widely used for industrial purposes due to their low cost and suitability to mass production (Nwe et al. 2014; Younes and Rinaudo 2015). However, their production leads to inconsistent physicochemical characteristics of products, e.g. different grades of quality, protein contamination, different levels of degree of acetylation and inconsistent molecular weight, because of seasonal, climate and variable supply of raw materials, e.g. quality of the shell, species nature, as well as macromolecular variability and difficulties of process conditions: long processing times, toxicity of reactants, as previously reported by No and Meyers (1995). This results in a wide unpredictable range of properties and this is a major concern for the use of crustacean chitosan in the medical and pharmaceutical fields.

Another often cited issue is the fact that the extraction processes are not ecological. The industrial methods consume high amounts of water and energy, use large

amounts of alkali, and generate large quantities of hazardous chemical wastes. To overcome these problems, alternatives to the chemical production of chitin and chitosan are the biological treatments such as microbial production and enzymatic hydrolysis (Kurita 1998, 2006; Kim 2011; Jo et al. 2011; Philibert et al. 2017). Actually, the biotechnology fermentation process of chitin from crustacean wastes is proposed on an industrial scale. However, the proteins and minerals are not completely removed by the biological treatment. Other drawbacks are a lower quality and a higher cost compared with the industrial, chemical process. The fermentation processes offer, however, new perspectives for the production of chitosan. Microorganisms and terrestrial organisms like insects, terrestrial crustaceans, and mushrooms were also considered as alternative sources for the large-scale production of chitin and chitosan. In particular, the biotechnological production of chitin/chitosan from microbial sources appears promising because the products obtained are pure with specific characteristics. However, the yield of purified chitin and chitosan from these sources is lower than that of aquatic crustacean sources. Different preparation methods often result in differences in the degree of acetylation, distribution of acetyl groups, chain length (molecular weight) and conformational structure of chitin and chitosan. In addition, although significant efforts have been made to optimize the fermentation process for the production of these two biopolymers, the technology may still be significantly improved. For more details on the chitin/chitosan production, the following reviews can be consulted: Muzzarelli et al. 1986a; Skjåk-Braek et al. 1989; Horst et al. 1993; Kurita 1998; Rinaudo 2006; Nwe et al. 2011a, b, 2013, 2014; Younes and Rinaudo 2015; Philibert et al. 2017.

2.2.4 Nomenclature of Chitin and Chitosan

Nowadays, chitosan and chitin are known as copolymers of D-glucosamine and N-acetyl-D-glucosamine units, characterized by their average degree of acetylation or degree of deacetylation. However, the nomenclature of chitin and chitosan remains always a subject of debate. Until the end of 1990s, it was agreed to define chitin and chitosan as polymers with degree of acetylation more than 40% and less than 40%, respectively (Peters 1995). In the 2000s, Eugene Khor (National University of Singapore) defined that "when the number of N-acetyl glucosamine units is higher than 50%, the biopolymer is termed chitin; conversely, when the number of D-glucosamine units is higher, the term chitosan is used" (Khor 2001; Khor and Lim 2003). In 2008, George AF. Roberts (Nottingham University, UK) proposed to develop a nomenclature system and to characterize chitin and chitosan with their mole fraction of D-glucosamine or N-acetyl glucosamine (source: European Chitin Society). In 2011, Nitar Nwe (Kansai University, Japan) also proposed to develop a systematic nomenclature system for chitin and chitosan products (Nwe et al. 2011a, b).

Chitin and chitosan can be also defined on the basis of their differences in solubility in water. Chitosan is soluble in aqueous acetic acid while chitin is insoluble

and also in the vast majority of common solvents. This is the reason why chitin was considered an intractable polymer and for many years, it remained mainly a laboratory curiosity (Peniche et al. 2008). Based on the solubility properties of products in acid and alkaline solutions, the name of chitin and chitosan was previously given by Odier in 1823 and Hoppe-Seiler in 1894, respectively. Because of its high cohesive energy related to strong intra- and intermolecular interactions through hydrogen bonds, commercial chitin like cellulose is difficult to dissolve.

Chitin also possesses a low content of amino groups, and therefore, its macromolecules are not soluble in water and do not swell in common solvents, except β-chitin. Chitosan has a rigid crystalline structure through intra- and inter-molecular hydrogen bonding. However, it is soluble in acidic media, except in benzoic acid and in oxalic acid. Indeed, in contrast to chitin, the presence of free amino groups on the C-2 position of the D-glucosamine unit along the macromolecule chains allows chitosan to dissolve in dilute aqueous acidic solvents through the protonation of these groups and the formation of the corresponding polymer salt. The biopolymer is then converted to a polyelectrolyte in acidic media. Nowadays, the nomenclature described in Table 2.4 is accepted. However, as discussed by Nwe and collaborators, "Do all type of chitosans with 45-50% degree of acetylation dissolve in water?" The answer to this question is not yet clear (Nwe et al. 2011b).

2.2.5 Characterization

Each commercial batch of chitosan is characterized by its degree of acetylation or degree of deacetylation, molecular weight, and others specific characteristics such as appearance of product, purity, crystallinity, solubility, turbidity of polymer solution, ash content, etc. (Nwe et al. 2014; Younes and Rinaudo 2015). These characteristics are of major importance on applications of these products. Several reviews can be consulted on these different aspects of chitosan characterization (Table 2.1). Commercial industrial or technical chitosans are usually offered as flakes or powders with prices ranging from 15 to 100 US$/kg, depending mainly on degree of

Table 2.4 Nomenclature of chitin and chitosan

Product	Characteristics	Degree of deacetylation	Molecular weight
Chitin	Insoluble in alkaline solution Insoluble in dilute organic acids	>50%	>5 kDa
Chitosan	Insoluble in alkaline solution Soluble in dilute organic acids Precipitation in solution with alkaline pH	<50%	>5 kDa
Chito-oligosaccharide Oligochitosan	Soluble in alkaline solution Soluble in acid solution Soluble in neutral media	All	<5KDa

acetylation/degree of deacetylation and purity parameters and specifications of products, e.g. appearance, viscosity, ash content, and metal content lower than 10 mg/kg. An ultrapure grade chitosan, e.g. with low levels of heavy metals, total metals, bacteria, ash, and of protein, and with no bleaching step during extraction and purification processes, for biomedical applications can cost upward of US$ 20,000/kg (Fig. 2.5). Several companies also offer chitosan as bead forms.

The main characteristic of a commercial sample is its average degree of acetylation. The most convenient method for the determination of the degree of acetylation for soluble samples is ^{1}H-NMR spectroscopy (Hirai et al. 1991; Vårum et al. 1991, 1992; Rinaudo 2006; Kasaai 2008, 2009, 2011). The value is calculated from the integral ration between proton of acetyl group of N-acetyl glucosamine and the protons of D-glucosamine. Other methods include solid state NMR, FT-IR, Raman spectroscopy, UV spectroscopy, circular dichroism, potentiometry, conductimetry, hydrolytic and enzymatic techniques (Focher et al. 1992; Raymond et al. 1993; Rinaudo et al. 1997; Peniche et al. 2008; de Alvarenga 2011). The degree of acetylation of a sample is an important factor influencing its physical and chemical properties: solubility, flexibility and polymer conformation, viscosity, crystallinity, conductivity, tensile strength and photoluminescence. It also influences the biological properties of chitosan: biodegradability, biocompatibility, mucoadhesion, hemostatic, analgesic, adsorption enhancer, antimicrobial, anticholesterolemic, and antioxidant.

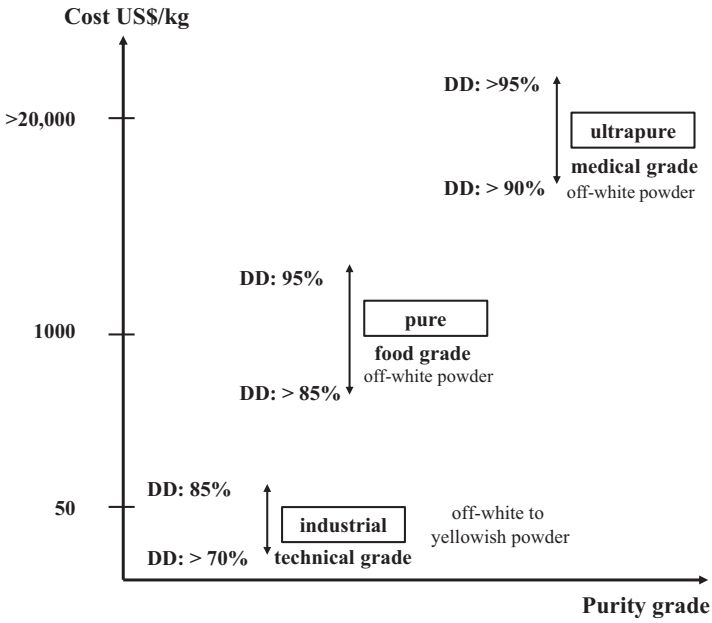

Fig. 2.5 Cost-purity relationship of chitosans (DD: degree of deacetylation)

Another important characteristic to consider is the molecular weight of each sample, after dissolution, and its distribution. This parameter influences on the viscosity of aqueous solution of chitosan and has also a significant role not only on the chitosan properties but also in the industrial applications in many fields. For example, in medical and agricultural domains, low-molecular weight chitosans are preferred (Nwe et al. 2011b). The most relevant technique used for molecular weight determination is viscosimetry. Other techniques such as gel permeation chromatography, light scattering and osmometry (Rinaudo et al. 1997; Peniche et al. 2008; Kasaai 2011) can be used. Polysaccharides are in general polydisperse with respect to molecular weight, and chitosan products are no exception. The molecular weight of a sample is thus an average over the whole distribution of molecular weights. Each sample can be characterized by a polydispersity index (Rinaudo 2006; Peniche et al. 2008). An important step in chitosan characterization is also the distribution of acetyl groups along the macromolecular chain. Indeed, this may influence the solubility of the sample and the inter-chain interactions (Younes and Rinaudo 2015). This distribution can be evaluated using ^{13}C-NMR spectroscopy (Vårum et al. 1991, 1992; Kasaai 2011).

The degree of acetylation and molecular weight are undoubtedly the most important parameters to establish the physical and chemical identity of chitin and chitosan products. These parameters have an important effect of the physical, chemical and biological properties of products. However, both parameters vary with the source of the raw material and the preparation method. In addition, they dictate the functional and technological properties of these biopolymers. Other properties such as solubility, viscosity, and gelling capacity are also dependent on these two parameters (Gunjal et al. 2004; Rinaudo 2006; Nwe et al. 2011a, b, 2014).

2.2.6 Properties

Chitosan presents multiple physical-chemical, biological and technological properties as reported in Table 2.5. The main property of chitosan is its cationic nature and its particular behavior in solution. Indeed, this biopolymer is the only natural cationic polymer in the nature (Muzzarelli and Muzzarelli 2005; Rinaudo 2006). Figure 2.6 illustrates chitosan's versatility in aqueous solution. At low pH, usually less than about 6.3, chitosan's amine groups are protonated conferring polycationic behavior to polymer while at higher pH (above 6.3), chitosan's amine groups are deprotonated and reactive. Usually, chitosan becomes soluble in all aqueous acidic media when the average degree of acetylation is lower than 50%. Chitosan is soluble in dilute inorganic acids such as HCl, HBr, HNO_3 and $HCLO_4$, in concentrated H_2SO_4, in organic acids, e.g. acetic, citric, formic, lactic, and in organic solvents: tetrahydrofuran, ethyl-acetate, 1,2-dichlorethane. Acetic and formic acids are the most commonly used for solubilization of chitosan. However, the solubility is a difficult parameter to control because it is related to the degree of acetylation, the ionic concentration, the pH of the solution used, the nature of the acid used for

Table 2.5 Intrinsic physical-chemical, biological and technological properties of chitosan

Physical-chemical properties	**Selected references**
Biopolymer with rigid D-glucosamine structure containing numerous amino/hydroxyl groups Linear amino-polysaccharide with high nitrogen content, hydrophilicity and high crystallinity Two grades of high and low molecular weight Three main grades of purity: technical, pure and ultra-pure Reactive amino/hydroxyl groups for physical modification, chemical activation or enzymatic modification: high reactivity Weak base, powerful nucleophile: $pK_a \sim 6.3$ Soluble in dilute acidic aqueous solutions Insoluble in water and organic solvents Forms salts with organic and inorganic salts Water retention Capacity to form hydrogen bonds and chemical interactions Aggregation behavior Electrostatic, chelating and complexing properties Surface active properties Ionic conductivity Rheological behavior	Muzzarelli et al. (1986a, b), Roberts (1992a), Winterowd and Sandford (1995), No and Meyers (1995), Kim et al. (1999), Viney and Harish (2002), Vårum and Smidsrød (2004b), Yilmaz (2004), Shahidi and Abuzaytoun (2005), Rinaudo (2006), Rauh and Dornish (2006), Peniche et al. (2008), Elsabee et al. (2009), Sahoo and Nayak (2011), Teng (2012), Sashiwa and Harding (2015), Annu et al. (2017), and Tripathi and Singh (2018)
Biological properties	**Selected references**
Non-toxicity Biocompatibility; not digestible by humans: dietary fiber Biodegradability Hydrating agent Encapsulating material, microencapsulation Delivery systems and drug releasing activity; carriers and immunoadjuvants in vaccine delivery Bioactivities: analgesic effect, antimicrobial (antibacterial, antifungal), antioxidant, anti-inflammatory, anti-acid, antiulcer, anticoagulant, antihypertensive, hypolipidemic, antidiabetic, anticancer, antitumor, anti-HIV, bioadhesivity Abilities: healing, self-healing, wound healing; mucoadhesion, bone regeneration, immuno-adjuvant	Peniche et al. (2003), Rabea et al. (2003), Vårum and Smidsrød (2004b), Shahidi and Abuzaytoun (2005), Rinaudo (2006), Goy et al. (2009), Friedman and Juneaj (2010), Dash et al. (2011), Kim and Kim (2011), Vyas et al. (2011), Ta et al. (2011), Dutta and Dutta (2011), Je and Ahn (2011), Yamazaki and Hudson (2012), Fernandez-Saiz (2012), Estevinho et al. (2013), Karadeniz and Kim (2014a, b), Moratti and Cabral (2017), Tachaboonyakiat (2017), Verlee et al. (2017), Vunain et al. (2017), Jardine and Sayed (2018), Perinelli et al. (2018), Sharif et al. (2018), Singh et al. (2018), Tripathi and Singh (2018), and Vasconcelos and Pomin (2018)

(continued)

Table 2.5 (continued)

Technological properties	Selected references
Polyelectrolyte at acidic pH; cationic biopolymer with high charge density at pH < 6.3: one positive charge per glucosamine residue Interaction with negatively charged molecules; adheres to negatively charged surfaces Adhesivity/Bioadhesivity Film-forming ability Versatility: solutions, biosorbent, fibers, films Gelation ability; viscosity: high to low Coagulating agent / Flocculating agent Entrapment and adsorption properties Filtration and separation Materials for isolation of biomolecules	Muzzarelli et al. (1986b), Sandford (1989), No and Meyers (1995), Kim et al. (1999), Vårum and Smidsrød (2004b), Shahidi and Abuzaytoun (2005), Hamman (2010), Mati-Baouche et al. (2014), and Younes and Rinaudo (2015)

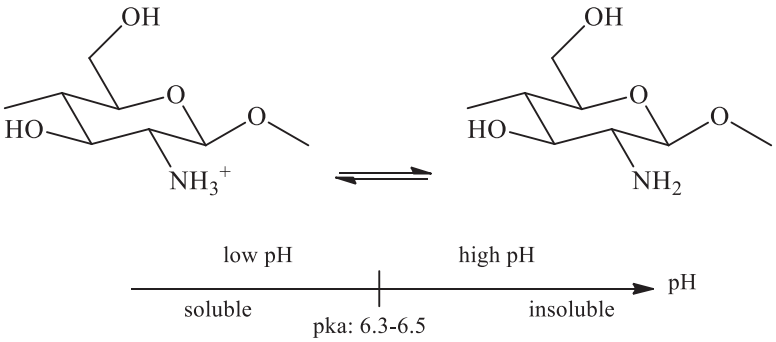

Fig. 2.6 Schematic illustration of chitosan's versatility in aqueous solution: at low pH, less than pK_a, chitosan's amines are protonated conferring polycationic behavior to macromolecules; at higher pH, above pK_a, chitosan's amines are deprotonated and also reactive (useful for derivatization, substitution, etc.); in the latter case, chitosan can undergo associations that can lead to networks such as gels and films to fibers

protonation, and also the distribution of acetyl groups along the macromolecular chain, the latter depending on the conditions of production of chitosan.

The protonation reaction is interesting because, after dissolution, chitosan can be precipitated into beads, cast into films and membranes, spun into fibers or nano-fibers, and also crosslinked to produce fibers or sponges. The processing of chitosan is easier than that of chitin. However, the stability of the products is lower due to the larger hydrophilic character and the pH sensitivity. For better stability, chitosan may be crosslinked using epoxides or glutaraldehyde. Composites and blends are also produced taking advantage of the polycationic properties of chitosan in acidic conditions.

The polyelectrolyte character of chitosan greatly influences its solution properties. There is an interesting structure-property relationship in chitosan. The excellent previous reviews of Vårum and Smidsrød (2004a), Dash et al. (2011), Younes and Rinaudo (2015), and Sahariah and Másson (2017) can be referred to on these

subjects. As a polyelectrolyte, chitosan is able to form electrostatic interactions useful for example in wastewater treatment and presents film-forming capacity and bioadhesivity, properties used in packaging and edible films. These electrostatic interactions are also applied for preparation of layer-by-layer polyelectrolyte capsules or films. The behavior of chitosan in solution is also important for medical applications. Its characteristic features such as being cationic, hemostatic and insoluble at high pH can be reversed by sulfating the amine groups which makes the macromolecule anionic and water-soluble, with the introduction of anticoagulant properties. The presence of the amino groups allows to explain most of chitosan biological properties (Domard and Domard 2001; Vårum and Smidsrød 2004a; Kumirska et al. 2011). Its mucoadhesion can be explained by the interaction between the negatively charged residues in the mucin – the glycoprotein that composes the mucus – and the amino groups positively charged. The hemostatic activity of chitosan can also be related to its cationic character. Red blood cell membranes charged negatively can interact with the positively charged chitosan chains. Besides, chitin shows less effective haemostatic activity than chitosan, confirming this explanation. The polycationic nature of chitosan also allows explaining chitosan analgesic effects. Other examples can be found in the reviews by Croisier and Jérôme (2013), Younes and Rinaudo (2015), and Sahariah and Másson (2017). The facile derivatization also makes chitosan an ideal candidate for the synthesis of biomaterials with specific functionality.

2.2.7 Biodegradation and Toxicity of Chitosan

Chitosan (CAS No. 9012-76-4) is widely regarded as being a non-toxic, biologically compatible, and eco-friendly product (Roberts 1992b; Illum 1998; Thanou et al. 2001; Kean and Thanou 2010). It is approved for excipients, food and dietary applications, and in weight-loss products in Japan, Korea, Italy and Finland. It has been approved by the US Food Drug Administration for use in wound dressing, bandages and hemostatic agents (Illum 1998; Felt et al. 1998; Singla and Chawla 2001; Kato et al. 2003; Illum and Davis 2004; Kean and Thanou 2010; Badwan et al. 2015).

Enzymatically, chitosan can be degraded by enzymes able to hydrolyze glucosamine linkages (Dash et al. 2011). Chitosan is known to be degraded in vertebrates predominantly by lysozyme and by certain bacterial enzymes in the colon. Given adequate time and appropriate conditions, chitosans, in most cases would degrades sufficiently to be excreted. However, as already discussed, the term chitosan represents a large group of structurally different chemical entities that may show different specific characteristics (degree of acetylation, molecular weight, ash content), and biodegradation and toxicological profiles. In addition, chitosan modifications, e.g. by derivatization or cross-linking reactions, could make it more or less toxic and any residual reactants should be carefully removed.

An interesting discussion on these topics can be found in the comprehensive review by Kean and Thanou (2010). These authors concluded that regulatory

agencies encounter many difficulties in approving all existing chitosan-based products as generally regarded as safe (GRAS) materials. Younes and Rinaudo (2015) pointed out that, for biomedical applications, chitin and chitosan need to be highly purified since residual proteins and pigments can cause side effects. Sadler and Funnell (2018) recently discussed the authorized EU health claim for chitosan in relation to its role in the maintenance of normal blood cholesterol levels. Due to the associated risk of elevated blood cholesterol levels with cardiovascular disease, the development of food and beverage products that can help to maintain healthy blood cholesterol concentrations was potentially beneficial to public health. Their review discusses the approved health claim for chitosan, describes the scientific evidence that substantiates the claim, considers how this claim could be used in practice and the consumer perception of health claims.

2.2.8 Derivatives

As already mentioned, chitin is water-insoluble and chitosan exhibits a limitation in its solubility in water and reactivity. The poor solubility of unmodified chitosan in organic solvents also make its utilization limited. Therefore, many studies have paid attention to modify their chemical structure (Austin 1984; Kienzle-Sterzer et al. 1984; Muzzarelli et al. 1986b; Skjåk-Braek et al. 1989; Roberts 1992b, c; Zhang et al. 1993; Hudson and Smith 1998). Often, the methods of modification are adapted from the cellulose world (Muzzarelli et al. 1986c; Kurita 2001, 2006; Rinaudo 2006; Harish Prashanth and Tharanathan 2007; Mourya and Inamdar 2008; Kim and Venkatesan 2014). Chitosan has three types of reactive functional groups: two hydroxyl groups on C-3 and C-6 in each repeating unit and one amino group on C-2 in each deacetylated unit (Fig. 2.1). These groups allow the conjugation of many substituents resulting in new modified derivatives (Fig. 2.7). The main reactions are quaternization (useful to increase the solubility of chitosan in neutral water), acetylation, reductive amination, acylation, phosphorylation, Schiff's bases, and cross-linking modifications (Austin 1984; Kienzle-Sterzer et al. 1984; Kurita 1986, 1998, 2006; Muzzarelli et al. 1986b, c; Skjåk-Braek et al. 1989; Roberts 1992b, c; Hudson and Smith 1998; Kurita 2001, 2006; Harish Prashanth and Tharanathan 2007; Thakur and Thakur 2014; Wang et al. 2016). The main derivatives are quaternary ammonium chitosan salts, carboxymethyl-chitosans, carboxyalkyl-chitosans, aryl-chitosans, hydroxyalkyl-chitosans, sulfated derivatives, phosphorylated chitosan, succinyl-chitosan, and thiolated chitosans (Sashiwa and Aiba 2004; Jayakumar et al. 2006, 2007; Alves and Mano 2008; Mourya and Inamdar 2008). Two update reviews have been compiled by Argüelles-Monal et al. (2018) and Yu et al. (2018). Argüelles-Monal et al. (2018) discussed the latest advances in methods and strategies of chitosan functionalization such as the click chemistry approach. Table 2.6 shows some chitosan derivatives and their potential applications. Carboxymethyl-chitosans are the most fully explored derivatives of chitosan. Under controlled reaction conditions, many products can be obtained with different selectivity (Fig. 2.8) and degree

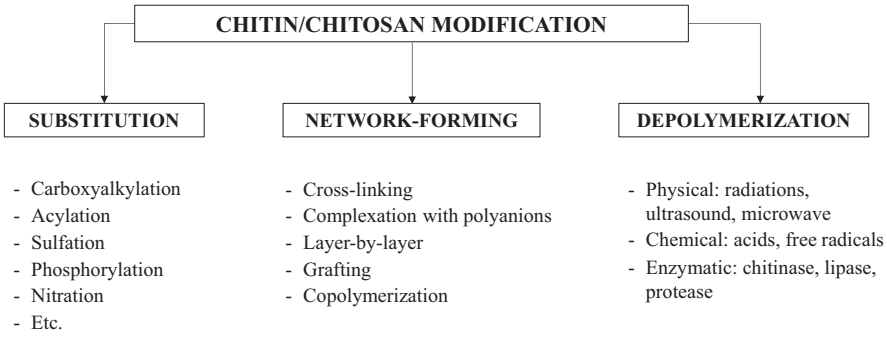

Fig. 2.7 Multifaceted modification potential of chitin and chitosan biopolymers

of substitution. The graft copolymerization of chitosan with particular emphasis on atom transfer radical polymerization as a new strategy to prepare new materials has been discussed by Thakur and Thakur (2014). The authors described the synthesis, characterization, and multifunctional applications of many types of chitosan-based copolymers. They concluded that the technique is promising to incorporate the desired functionalities in chitosan for targeted applications. However, future research needs to look into a better understanding of the structure and chemistry of different polymerization reactions. Wang et al. (2012) also reported that graft copolymerization of chitosan is an alternative route to prepare derivatives for target applications.

Numerous studies have been also conducted to transform the biopolymers chitin and chitosan into low molecular weight chitosans or oligosaccharides using physical, chemical, electrochemical and/or biotechnological processes (Liang et al. 2018; Mourya and Inamdar 2008). Cleavage of glycosidic bonds leads to production of oligomers with important variations in the degree of polymerization (chain lengths). These low molecular weight oligosaccharides, known as chitooligosaccharides, abbreviated COS, or oligochitosans (chitosan oligomers, chitooligomers) present low viscosity and relatively small molecular sizes which in turn make them water soluble and having versatile biological activities such as readily adsorbed *in vivo*, cholesterol lowering, antibacterial and antitumor effects (Hamed et al. 2016; Liaqat and Eltem 2018). They are also soluble in solutions at acid and alkaline pH. Indeed, these products have a remarkably widespread range of biological activities and own an important potential for numerous industrial applications. In target applications such as biomedicine, cosmetics and agriculture, e.g. as antibacterial agent or for plant growth stimulator, low molecular weight chitosans and oligomers are more effective than high-molecular weight chitosans (Peniche et al. 2008; Nwe et al. 2014). Low molecular weight chitosans or oligosaccharides can be obtained from high-molecular weight chitosans by physical, e.g. gamma-ray irradiation, microwave treatment or ultrasonic method, mechanical method (sonication), chemical treatment (oxidation, hydrolysis) using acids or free radicals (HCl, H_2O_2, HNO_2) or enzymatic method using specific or non-specific enzymes, e.g. chitinase, chitosanase, cellulases, lipases, lysozyme, and protease (Liaqat and Eltem 2018; Liang

Table 2.6 Chitosan derivatives and examples of applications

Some chitosan derivatives	Important properties and comment	Application	References
Carboxymethyl-chitosans			
O-carboxymethyl-chitosan N-carboxymethyl-chitosan O,N-carboxymethyl-chitosan N,N-carboxymethyl-chitosan n-Lauryl-carboxymethyl-chitosan	The most fully explored derivatives of chitosan Amphoteric products Water soluble in a wide range of pH The solubility depends on pH Film- and gel-abilities Clarifying agent	Fruit preservation Plant protection Excipients Drug delivery systems Dental care Carriers for hydrophobic cancer drugs Cosmetics Surfactants Beverage industry (clarification) Cotton fabric	Mourya and Inamdar (2008), Elsabee et al. (2009), Jimtaisong and Saewan (2014), Tastan and Baysal (2015), Rocha et al. (2017), Sahariah and Másson (2017), Verlee et al. (2017), and Farion et al. (2018)
Chitosan 6-O-sulfate			
O-sulfated chitosan N-sulfated chitosan 2-N,6-O- sulfated chitosan N-butyl-O-sulfate chitosan N-octyl-O-sulfate chitosan N-palmitoyl-O-sulfate chitosan	Structural analogy to heparin: 2-N,6-O- sulfated chitosan Anticoagulant activity Antimicrobial agent Hemostatic agent Anti HIV-1 activity	Drug delivery Blood anticoagulant Hemagglutination inhibition activity Hemo-compatibility Antitumor activity Antioxidant property Tissue engineering Lipoprotein lipase-releasing activity Treatment of neurological diseases neural repair Superplasticizer	Jayakumar et al. (2007), Elieh-Ali-Komi and Hamblin (2016), Verlee et al. (2017), and Yu et al. (2018)
Quaternized derivatives			
N-substituted quaternary ammonium N,N,N-trimethyl-chitosan chloride N-(2-hydroxyl) propyl-3-trimethylammonium chitosan chloride	Cationic derivatives Water soluble in a wide range of pH Interactions with negatively species Mucoadhesion Better moisture retention and absorption compared to chitosan	Flocculating agent Use in papermaking, paper packaging Antistatic agent Antifungal agent Dental care Drug delivery, gene delivery Gene transfection Interactions with cell membranes	Mourya and Inamdar (2008), Kedjarune-Leggat and Leggat (2011), Huang et al. (2014), Muñoz-Bonilla et al. (2014), LogithKumar et al. (2016), Pardeshi and Belgamwar (2016), and Sahariah and Másson (2017)

(continued)

Table 2.6 (continued)

Some chitosan derivatives	Important properties and comment	Application	References
Alkylated derivatives			
Hydroxyethyl chitosan Hydroxypropyl chitosan Hydroxybutyl chitosan Alkyl-glycosides branched chitosan N-acyl derivatives N-carboxyacyl chitosan N-lauryl derivatives	Amphiphilic products Hydrophobic properties Highly substituted derivatives Modifications require multiple protection and deprotection steps Ability to form physical gels, sponges Rapid gelation kinetics Micelle formation High moisture absorption rate Compatible with neutral and cationic surfactants Rheological modifiers	Surfactant agents Papermaking, hydrophobization of cellulose fibers Hemostatic agent Gene transfection Paints Oil recovery	Macquarie and Hardy (2005), Prabaharan and Mano (2005), Mourya and Inamdar (2008), Prabaharan and Tiwari (2011), Canh et al. (2004), Muñoz-Bonilla et al. (2014), Verlee et al. (2017), and Yu et al. (2018)
N-methylene phosphonic chitosans			
Grafted with alkyl chains Bifunctional derivatives	Anionic products with possible amphoteric character Soluble products Complexing properties Film-forming	Chelating agent Ability for metal removal Cosmetology Anti-corrosion protection	Ramos et al. (2003), Canh et al. (2004), Prabaharan and Tiwari (2011), and Yu et al. (2018)
Target derivatives/reactions			
Schiff's base formation Reductive amination Amide formation Michael addition EDTA-chitosan Thiolated chitosan Thiourea derivatives Phosphorylated chitosan Azidated derivatives Folate-based derivatives Imidazole chitosan Phthaloylated chitosan Conjugated with lipids	Highly porous structure High solubility over a wide range of pH pH-sensitive High transfection efficiency High cellular uptake Mucoadhesive materials	Gene carrier Anticancer agent Drug delivery Ocular drug delivery Delivery of contrast agents Metal chelation	Canh et al. (2004), Macquarie and Hardy (2005), Prabaharan and Mano (2005), Jayakumar et al. (2006, 2008), Mourya and Inamdar (2008), Muñoz-Bonilla et al. (2014), Ahmed and Ikram (2016), Choi et al. (2016), Osman and Arof (2017), and Yu et al. (2018)

(continued)

Table 2.6 (continued)

Some chitosan derivatives	Important properties and comment	Application	References
Carbohydrate-branched chitosans			
Sugar derivatives Glycol-based chitosan Glucosamine chitosan Galactosylated chitosan Mannose or lactose derivatives Cyclodextrin-linked chitosan Cyclic-host bound chitosan	Water-soluble derivatives at wide range of pH Ability to form physical or chemical gels Faster biodegradability Enhanced antimicrobial properties	Drug delivery Self-assembled systems Bone healing Coagulating/ Flocculating agents Adsorbents	Sashiwa and Aiba (2004), Jalal Zohuriaan-Mehr (2005), Prabaharan and Mano (2006), Alves and Mano (2008), Mourya and Inamdar (2008), Prabaharan and Tiwari (2011), Wang et al. (2012), and Muñoz-Bonilla et al. (2014)
Chitosan-grafted copolymers			
Polyethylene glycol-grafted chitosan Polypeptide-grafted chitosans Polyethyleneimine-grafted chitosan Chitosan functionalized poly(vinyl alcohol) Amino acid modification Caproic acid grafted chitosan Stearic acid grafted oligosaccharides Copolymer with acrylamide Copolymer with methylmethacrylate Chitosan-dendrimer hybrid	Water-soluble derivatives The solubility depends on the degree of grafting Induced hydrophilicity or hydrophobicity Biodegradability and non-toxicity: poly(γ-glutamic acid)-chitosan complexes Enhance cell penetrating Improved intracellular release Thermos-responsive gels	Drug delivery Self-assembled systems Oral delivery of insulin Protein vaccine delivery Gene carriers Wastewater treatment	Canh et al. (2004), Sashiwa and Aiba (2004), Harish Prashanth and Tharanathan (2007), Mourya and Inamdar (2008), Wang et al. (2012), Thakur and Thakur (2014), Choi et al. (2016), Rafique et al. (2016), Sahariah and Másson (2017), Farion et al. (2018), Rahangdale and Kumar (2018), and Yu et al. (2018)

(continued)

Table 2.6 (continued)

Some chitosan derivatives	Important properties and comment	Application	References
Cross-linked chitosans			
Gels/Hydrogels Glutaraldehyde chitosan Self-assembled systems Ionic modification Tripolyphosphate as cross-linker Genipin-cross-linked products Modification by aldehydes Glycosaminoglycan-based systems	Biocompatible and cationic products Thermosensitive properties pH-dependent Biosorbents Scaffolds Injectable hydrogels	Wastewater treatment Enzyme immobilization Drug delivery Tissue engineering Veterinary applications Drug eluting stents	Crini (2005), Crini and Badot (2008), Dash et al. (2011), Luna-Bárcenas et al. (2011), Van Vlierberghe et al. (2011), Yao et al. (2012), Xiao et al. (2012), Zhao (2012), Croisier and Jérôme (2013), Zambito (2013), Ahmadi et al. (2015), Tonda-Turo et al. (2016), Ahmed and Ikram (2017), Aminabhavi and Dharupaneedi (2017), and Ali and Ahmed (2018)
Composites/Miscellaneous			
Chitosan complexes Metal ion chelates Chitosan/gelatin microspheres Glycol chitosan Cyanoethyl chitosan Linoleic acid chitosan complex Imidazole chitosan Chitosan-coated materials Hyaluronic acid-chitosan nanoparticles Alginate-chitosan systems Blending with starch Calcium phosphate-based systems Hydroxypropyl-chitosan/gelatin systems Cellulose-chitosan blends Hydroxyapatite composites Modified ceramic nanoparticles Chitosan and clays	Microcapsules Bioactive nanoparticles Nanoemulsions Membranes Delivery vehicles Hybrid scaffolds, multifunctional scaffolds Nanofibers Biosensors	Insulating papers and special papers Dialysis Drug delivery Wound dressing Bone repair Bone tissue engineering Surgical dressing Gene transfection ability Gene therapy Anticancer agent Glucose sensor Antimicrobial textiles Veterinary vaccines Bioimaging agents Wastewater treatment	Mourya and Inamdar (2008), Van Vlierberghe et al. (2011), Dash et al. (2011), Gerdts et al. (2013), Elsabee and Abdou (2013), Islam et al. (2013), Muñoz-Bonilla et al. (2014), van den Broek et al. (2015), Abdul Khalil et al. (2016), Ahmed and Ikram (2016), and Elieh-Ali-Komi and Hamblin (2016)

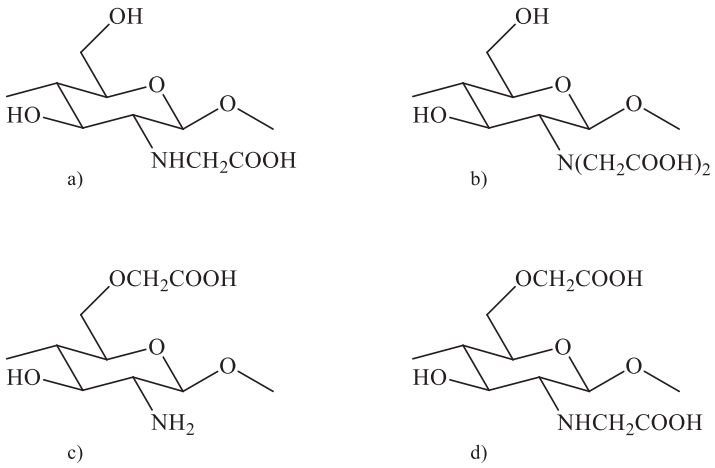

Fig. 2.8 Different chemical structures of carboxymethyl chitosans: (**a**) N-carboxymethyl chitosan; (**b**) N,N-carboxymethyl chitosan; (**c**) O-carboxymethyl chitosan; and (**d**) N,O-carboxymethyl chitosan

et al. 2018). The biotechnological processes have also been gained interest because they permit the production of high-value commercial by-products such as chitinases, lactic acid, antioxidants, valuable protein hydrolysates, carotenoids, and solubilized calcium ions (Philibert et al. 2017).

2.3 Chitosan Applications

Currently, chitosan and its derivatives have practical applications in the form of solutions, suspensions, particles, e.g. beads, resins, spheres, nanoparticles and sponges, gels/hydrogels, foams, membranes and films, fibers, microscopic threads, and scaffolds in many fields: medicine and biomedicine, pharmacy, cosmetology, hygiene and personal care, food industry and nutrition, agriculture and agrochemistry, textile and paper industries, edible film industry and packaging, biotechnology, chemistry, and catalysis, chromatography, beverage industry and enology, photography and other emerging fields such as nutraceuticals, functional textiles and cosmeto-textiles, cosmeceuticals, nanotechnology, and aquaculture (Sandford 1989; Onsoyen and Skaugrud 1990; No and Meyers 1995; Li et al. 1997; Ravi Kumar 2000; Khor 2001; Struszczyk 2002; Honarkar and Barikani 2009; Crini et al. 2009; Ferguson and O'Neill 2011; Kardas et al. 2012; Khor and Wan 2014; Hamed et al. 2016; Amber Jennings and Bumgardner 2017a; Arfin 2017; Badawy and Rabea 2017; Dima et al. 2017; Philibert et al. 2017). Chitosan as biopolymer is also proposed for environmental purposes and applied in clarification and water

purification, wastewater treatment, remediation, sludge dewatering and membrane filtration (Crini and Badot 2008; Bhatnagar and Sillanpää 2009; Sudha 2011; Ravichandran and Rajesh 2013; Yong et al. 2015; Barbusinski et al. 2016; Kos 2016; Nechita 2017; Desbrières and Guibal 2018; Pakdel and Peighambardoust 2018).

Research on chitosan is also very active in electrochemical sensors, bio-imaging, bio-catalysis, ionic liquids, green solvents, adhesives, and detergents. However, the main markets are the food industry and nutrition, and the pharmaceutical, cosmetic, and medicine industries. It is interesting to note that the vast majority of these biological and chemical applications are based on the cationic nature of chitosan and on its versatility as biomaterial. The markets for chitin and chitosan are Japan, USA, Korea, China, Canada, Norway, Australia, France, UK, Poland, and Germany (Ferraro et al. 2010; Nwe et al. 2011b; Badawy and Rabea 2017; Bonecco et al. 2017). Japan dominated the industry accounting for 35% of the market in 2015. Indeed, since the 1980s, Japan is considerably advanced in the technology, commercialization and use of these biopolymers (Badawy and Rabea 2017; Bonecco et al. 2017). The market in this country absorbs about 700–800 tons chitosan per year.

2.3.1 Food Industry

Table 2.7 describes applications of chitosan and its oligosaccharides in food industry. Chitosan has been approved by the US Food and Drug Administration as a generally recognized as sage food additive, dietary fibre (hypocholesterolemic effect), and functional ingredients for the consumer. Chitosan is also approved as a food additive in Japan and in Korea since the 1990s (Vidanarachchi et al. 2011; Gutiérrez 2017). Due to its bioactive nature and cationic character, chitosan is used as nutritional ingredient (food additives, functional food), antimicrobial and antioxidant agent (food protection), for antimicrobial coatings for fruits and vegetables, in anticholesterolemic dietary products, and as nutraceuticals (Shahidi et al. 1999; Agulló et al. 2003; Synowiecki and Al-Khateeb 2003; Vidanarachchi et al. 2011; Kardas et al. 2012; Je and Kim 2012, 2013; van den Broek et al. 2015; Gutiérrez 2017; Han et al. 2018).

Friedman and Juneja (2010) pointed out the outstanding antimicrobial activities of chitosan in solution, powders, and edible films and coating against microorganisms. The better results were obtained with low molecular weight chitosan. Actually, research is directed to new chitosan derivatives and oligomers that can be applied as antimicrobial agent against food microorganisms. These derivatives seem promising, in particular for nutraceutical applications. Kardas et al. (2012) demonstrated that chitosan and its derivatives offer a wide range of unique applications in the food industry including preservation of foods from microbial deterioration, shelf-life extension, formation of biodegradable films and food packaging. The products used as a packaging or coating material can be formed into fibers, films, gels, beads, or nanoparticles. Van den Broek et al. (2015), reviewing the development of chitosan

Table 2.7 Applications of chitosan and its oligosaccharides in food industry (selected reviews)

Topic	Form	Applications
Food technology Nutrition Functional foods Food additives Food mimetic Food protection Food preservation Seafood quality preservation Industrial bio-products Nutraceutical ingredients Dietary food additives Dietary fiber Prebiotic ingredient Flavors/Aromas Essential oils Feed additives Immobilization of enzymes Edible film industry Packaging Coating material Food processing wastes Removal of substances	Solution Film Blend Coating Bead	Additives: fining agent, texture controlling agent, natural flavor extender, emulsifying agent, gelling agent, color stabilizer, dye-binding properties, thickener and stabilizer for sauces, flavor extender Improve nutritional quality Bioactivities: antibacterial, antifungal, antioxidants Preservation of foods from microbial deterioration: protective for fruits Filmogenic properties; microbial films (bactericidal, fungicidal); food wrapping Edible films: controlled release of antioxidants, flavors or nutrients; antimicrobial substances controlled release; reduction of oxygen partial pressure; moisture transfer control; temperature control; controlled rate of respiration Diet foods and dietary fibers: not digestible by humans; glucose dialysis; water holding capacity Hypolipidemic and hypocholesterolemic activities: reduction of lipid absorption, bind fats/lipids, reduce cholesterol Astringency: able to precipitate saliva proteins Non-digestible feed ingredients: prebiotics Production of single cell protein Enhancement of the calcium absorption Encapsulation of nutraceuticals Fractionation of agar Biotechnology: immobilization matrix Bioconversion for the production of value-added food products Recovery of waste material from food-processing discards Infant feed ingredient Animal feed additive Undesired substances removal: dyes, suspended solids Water purification
References		
Goosen (1997), Muzzarelli and de Vincenzi (1997), Shahidi et al. (1999), Domard and Domard (2001), Struszczyk (2002), Agulló et al. (2003), Peniche et al. (2003), Roller and Valley (2003), Begin et al. (2004), Cagri et al. (2004), Shahidi (2004), Krajewska (2005), No et al. (2007), Fernandez-Saiz et al. (2010), Rodrigues et al. (2012), Je and Kim (2012, 2013), Alishahi (2012), Coma (2012), Elsabee and Abdou (2013), Muñoz-Bonilla et al. (2014), van den Broek et al. (2015), Zivanovic et al. (2015), Gallo et al. (2016), Hamed et al. (2016), Gutiérrez (2017), Han et al. (2018), Perinelli et al. (2018), and Wang et al. (2018)		

films and blends as packaging material, also reported a similar conclusion. Due to its antimicrobial and film-forming activities, chitosan has been considered as an appropriate alternative as source of food preservative or coating material for replacing the non-biodegradable and non-renewable polymers, and also reducing the extensive application of harmful pesticides in food protection. Indeed, its films have a selective permeability to gasses (Friedman and Juneja 2010; Fernandez-Saiz et al.

2010; Kardas et al. 2012; Elsabee and Abdou 2013; Muñoz-Bonilla et al. 2014; van den Broek et al. 2015). In addition, the chitosan films have shown superior results, good mechanical properties and they have the advantage of being able to incorporate functional substances such as vitamins and as carriers releasing of antimicrobial agents. However, chitosan films in packaging application are highly permeable to water vapor, and due to their hydrophilic character, they also tend to exhibit resistance to fat diffusion and selective gas permeability. A discussion on the different strategies to overcome these drawbacks can be found in the reviews by Kardas et al. (2012), Elsabee and Abdou (2013), van den Broek et al. (2015), and Wang et al. (2018). Blends, composites and multilayer systems containing chitosan have been proposed as films in food packaging fields and seem promising.

The field of food industry and nutrition is the most important user of chitosan (Gutiérrez 2017; Philibert et al. 2017) and the main markets are localized in Asia (Japan, Korea, China), North America, and in Europe. In the USA, the market in food and beverages is estimated to be 2288 metric tons in 2018. The demand for chitosan is growing rapidly, in particular for potential applications in nutraceutical ingredients and feed stocks. Nutraceuticals as an industry emerged in the early 1990's in Asia, in particular in Japan. The nutraceutical industry includes functional foods, dietary supplements and herbal/natural products. Actually, the US market represents the largest nutraceutical market in the world and the Europe (Germany, France, Netherlands, Sweden) the second. China is expected to be the world's largest consumer of nutraceuticals by 2030. Many products available (ChitoClear®, Chitoseen™-F, MicroChitosan NutriCology®, etc.) are marketed as fat reducers and cholesterol-lowering agents, and also as antioxidant agents. For instance, ChitoClear® is noted as a natural, safe and effective weight loss supplement when used in conjunction with a healthy life style (PRIMEX, Iceland). It seems to have a potential in weight management and obesity treatment. However, there is a debate surrounding the effectiveness of chitosan at blocking fat absorption. The nutraceutical properties of chitosan include its antibacterial, anti-inflammatory, antioxidant, anti-carcinogenic, and antiulcer bioactivities, along with its application as a dietary fiber. Chitosan has non-digestibility in the upper gastrointestinal tract, high viscosity, and high water binding properties (Muzzarelli and de Vincenzi 1997; Roller and Valley 2003; Badawy and Rabea 2017). As a dietary fiber, it has ability to lower cholesterol by blocking the absorption of dietary fat and cholesterols. Chitosan and its derivatives have been shown to facilitate weight and body fat loss in the human body thus decreased systolic and diastolic blood pressure (Philibert et al. 2017). Additionally, it significantly increases the excretion of highly atherogenic saturated fatty acids compared with other fibers. As a valuable prebiotic, chitosan can also promote colonic conditions. Gutiérrez (2017) recently reported that chitosan and its derivatives also exert strong antioxidant activity and their effects are similar to those of phenolic antioxidants. Chitosan products also offer benefits as components of animal feeds and this is also a growing market. They permit food processors to recycle protein from biowastes into animal feed. They have beneficial nutritional properties and they can control the release of feed additives in animals.

2.3.2 *Beverage Industry*

Table 2.8 summarizes the potential uses of chitosan in beverage industry. In wine production, it can be used for clarification, de-acidification, stabilization, elimination of ochratoxin A, enzymes and other undesired substances, e.g. metals and pesticides (Bornet and Teissedre 2011). Chitosan is also used as eco-friendly coagulant for passion fruit clarification (Domingues et al. 2012) and natural flocculant for beer clarification (Gassara et al. 2015). Recently, Rocha et al. (2017) presented an overview of the recent chitosan-based matrices used for clarification, preservation, encapsulation, and active and intelligent packaging of different beverage types, such as alcoholic, dairy-based drinks, and non-alcoholic, including fruit juices, nectars, concentrated fruit juices, tea, coffee, and tisanes. Only the clarification using chitosan of fungal origin (Oneobrett®, Bactiless™) seems to be well implemented in the market.

Table 2.8 Applications of chitosan and its derivatives and oligosaccharides in beverage industry

Topic	Form	Applications
Beverages Functional beverages Enology Beer industry Packaging	Solution Particle Bead	Filtration and clarification of fruit juices and beverages (wines, beer, tea) Natural flocculant: turbidity removal, removal of suspended solids and colloids (polyphenols, proteins, polysaccharides, minerals) Acidity-adjusting agent: de-acidification of fruit juices and beverages Stabilization of beverages (white wines) Preservative in fruit juices, wines and milk Color stabilizer Prevention of oxidation of the wine color Antimicrobial agent: preservation of drinks from microbial deterioration (bacteria, yeasts, moulds) Natural flavor extender Bioactive compounds encapsulation: protection to oxidation, to improve the bioavaibility of probiotics, making of undesirable taste Preservatives and active packaging Complexing agents in wine industry: metal removal Removal of dead yeast, excess tannin, particulates Water purification
References		
Shahidi et al. (1999), Struszczyk (2002), Chatterjee et al. (2004), Bornet and Teissedre (2005, 2011), Rungsardthong et al. (2006), Domingues et al. (2012), Gassara et al. (2015), Tastan and Baysal (2015), and Rocha et al. (2017)		

2.3.3 Pharmacy

For chitosan, pharmaceutical applications started to appear in the late 1980s (Nagai et al. 1984; Felt et al. 1998; Ravi Kumar 2000). In this field, chitosan and its derivatives have been mainly explored as excipients in drug formulations and in drug delivery systems (Badwan et al. 2015). The new approach consisted of replacing potentially toxic compounds by natural products, which rapidly proved to be promising. The pharmaceutical industry rapidly understood the advantages of using chitosan. Although hundreds of papers and patents related to chitosan-based pharmacy have been published since the late 1980s, this sector continues to interest both the scientific community and the industry, mainly in terms of bioactivities. The most important features and advantages of chitosan can be found in the review by Bernkop-Schnürch and Dünnhaupt (2012). Its derivatization also contributed to expansion of application and decrease toxicity.

The main properties used in the pharmaceutical field are: controlled drug release, e.g. anti-inflammatory naproxen, mucoadhesive properties, *in situ* gelling properties, transfection enhancing properties (deoxyribonucleic acid- and small interfering ribonucleic acid ribonucleic acid-based drugs form stable complexes with chitosan), and permeation enhancing properties (Bernkop-Schnürch and Dünnhaupt 2012). Chitosan also exhibits efflux pump inhibitory properties like other polysaccharides. Chitosan and its derivatives may be used as solutions, gels, tablets, capsules, fibers, films and sponges (Ali and Ahmed 2018). Consequently, they may be used in oral, ocular, nasal, vaginal, buccal, parenteral, intravesical, and transdermal administration, and as implants for drug delivery in both implantable and injectable forms. Table 2.9 reports different methods for the preparation of chitosan-based drug delivery systems (Felt et al. 1998; Ravi Kumar 2000; Peniche et al. 2003; Ravi Kumar et al. 2004; Dash et al. 2011; Ali and Ahmed 2018). Akbar and Shakeel (2018) recently discussed the various forms of chitosan materials as drug delivery device and attempted to report the vast literature available on chitosan based systems in drug delivery applications. Hamedi et al. (2018) also summarized the potential applications of chitosan-based hydrogels for pharmaceutical and biomedical uses, particularly with regard to drug delivery in wound dressings.

Drug delivery applications include not only controlled drug release systems, e.g. site-specific antibiotics delivery in the stomach and controlled release of proteins, but also vaccine and gene delivery (Singh et al. 2018). Chitosan is used as safe excipients in oral dosage form over the last two decades (Felt et al. 1998; Ravi Kumar 2000; Ravi Kumar et al. 2004). Chitosan tablet can exhibit a sustained drug release compared to commercial products. Bernkop-Schnürch and Dünnhaupt (2012) reported that tablets are the likely most favorable dosage form since they provide an accurate dosage, are easy to manufacture and handle, and are favored by patients. The buccal route is an alternative choice to deliver drugs. Chitosan is interesting to be used for buccal delivery due to its mucoadhesive bioactivity and absorption enhancement property. Strong permeation enhancing properties are also mentioned.

Table 2.9 Chitosan-based drug delivery systems prepared by different methods

Form	Applications	Drug(s)
Microspheres	Water-in-oil emulsion cross-linking Coacervation/precipitation Spray-drying Ionic gelation Sieving method	Diclofenac, aspirin, 5-fluorouracil
Beads	Coacervation/precipitation	Bovine serum albumin, salbutamol
Nanoparticles	Emulsion-droplet coalescence Coacervation/precipitation Ionic gelation Reverse micellar method	Insulin, cyclosporin A
Gels/Hydrogels	Cross-linking reactions	Caffeine, lidocaine
Tablets	Matrix coating	Diclofenac, salicylic acid
Capsules/Microcapsules	Capsule shell	Insulin
Films	Wet casting from salt solutions	Testosterone, trypsin
Sponges/Foams	Freeze drying Reactions in supercritical fluids	Triamcinolone acetonide

Injectable preparations containing chitosan have received considerable attention within the last years. The properties of chitosan also resulted in the development of vaccine delivery (Bernkop-Schnürch and Dünnhaupt 2012). The transmucosal administration of drugs has been described in detail by Illum and Davis (2004). The transmucosal absorption promoter effect of chitosan is important for nasal and oral delivery of polar drugs to administrate peptides and proteins, and for vaccine delivery. Films and fibers prepared using chitosan and chitin were developed for tissue engineering and wound care dressing, as oral mucoadhesive and water-resisting adhesive by virtue of their release characteristics and adhesion (Kato et al. 2003; Illum and Davis 2004). The chitosan-based fiber production was discussed in detail by Pillai et al. (2009). Promising developments were under way not only in biomedicine but also in emerging domains such as nutraceuticals and cosmeceuticals. Indeed, pharmaceutical formulations containing chitosan and derivatives are also proposed for slimming application, body weight management and as cosmetics to enhance skincare efficacy for example. The use of nanocomposites in drug delivery also seems promising as recently reported by Ali and Ahmed (2018). Other applications of chitosan and its derivatives are described in Table 2.10.

2.3.4 Medicine

The medical and biomedical potential applications of chitosan include pharmaceutical formulation and drug delivery (antibiotics, anti-inflammatory substances, vaccines, proteins, peptides, growth of factors), antimicrobial applications, gene delivery, gene therapy, wounds healing and burns, regenerative medicine, tissue

Table 2.10 Applications of chitosan and its derivatives including oligosaccharides in pharmacy (selected reviews)

Topic	Form	Applications
Excipients Drug delivery Drug release Vaccines Biopharmaceutics Nutraceuticals Body weight management Cosmeceuticals Dermatology Ophthalmology Oral drug delivery Imaging agents	Solution Powder Microsphere Bead Tablet Capsule, microcapsule Nanoparticle Nanocomposite Sponge	Excipients Encapsulation of sensitive drugs: to increase and to modulate drug release rate Controlled drug delivery carriers Controlled release of proteins and peptides Gene delivery (nucleic acid) Dermatological products: to treat acne Hydrating agent Hemostatic and anticoagulant Bacteriostatic agent Mucoadhesion Biological adhesive: water-resisting adhesive *In situ* gelation Transfection Permeation enhancement Healing: wound healing, self-healing Efflux pump inhibitory properties Products for radio-pharmaceutical domains Nutraceutical ingredients
References		
Goosen (1997), Illum (1998), Dodane and Vilivalam (1998), Felt et al. (1998), Ravi Kumar (2000), Hejazi and Amiji (2001), Agnihotri et al. (2004), Canh et al. (2004), Ravi Kumar et al. (2004), Prabaharan and Mano (2005), Varshosaz (2007), Dash et al. (2009), Kang et al. (2009), Hamman (2010), Riva et al. (2011), Bernkop-Schnürch and Dünnhaupt (2012), Xiao et al. (2012), Zhao (2012), Yong and Wong (2013), Badwan et al. (2015), Mateescu et al. (2015b), Majekodunmi (2016), Lucio and Martínez-Ohárriz (2017), Parhi (2017), Ahsan et al. (2018), Akbar and Shakeel (2018), Ali and Ahmed (2018), Krishnaswami et al. (2018), Naskar et al. (2018), and Tripathi and Singh (2018)		

engineering (bone, ligament, cartilage, tendon, liver, neural and skin regeneration), applications in cancer (treatment, therapy, diagnostic strategy), dermatology, ophthalmology, dentistry, biosensors, and many other applications such as bio-imaging (magnetic resonance imaging), support for immobilized enzymes and veterinary medicine (Table 2.11). For medical applications, chitosan and its derivatives as chitooligosaccharides can be easily processed into different forms such as solutions, gels/hydrogels, sponges, microparticles/nanoparticles, membranes and films (pure films or blends, adhesives), and fibers/nanofibers (Allan et al. 1984; Hon 1996; Dumitriu 2001; Yilmaz 2004; Jayakumar et al. 2010b, 2011b; Riva et al. 2011; Elieh-Ali-Komi and Hamblin 2016; Amber Jennings and Bumgardner 2017a, b; Rijal et al. 2017; Ali and Ahmed 2018; Hamedi et al. 2018; Liaqat and Eltem 2018). The use of chitosan-based materials in 2D-scaffolds such as films and fibers and 3D-scaffolds such as gels and sponges is discussed in the reviews by Croisier and

Table 2.11 Applications of chitosan and its oligosaccharides in medicine and biomedicine (selected reviews)

Topic	Forms	Applications
Drug delivery Biomedicine Biomedical engineering Biofabrication Tissue engineering Regenerative medicine Wound dressing Growth factor Biomedical adhesives Medical materials Medical devices Implants Orthopedics Therapeutic domains Microbiology Immunization Immunology Gene therapy Cell biology Cell therapy Cell adhesion and proliferation Cell-biomaterials interactions Protein adsorption onto biomaterials Cancer diagnosis Cancer therapy Carriers of anticancer drugs Ophthalmology Bio-sensing Bio-imaging Bio-printing 3D-printing	Solution Gel/hydrogel Powder Microsphere Microcapsule Bead Nanoparticle Film Fiber, nanofiber Nonwoven bioactive fiber Sponge 2D- and 3D-scaffolds Shaped object Adhesive	Drug delivery: delivery of antibiotics, peptides, proteins, vaccines Growth factor delivery Biological response modifier Gene delivery, targeted delivery, deoxyribonucleic acids therapy, gene therapeutics, small interfering ribonucleic acid delivery Antifungal, antimicrobial, anti-infectious Hemostatic effects; enhances blood coagulation Anticoagulant hydrogel containing heparin Blood cholesterol control Adjuvant properties Bioadhesive Artificial skin; skin burn Promotes tissue growth; tissue repair and regeneration Cartilage tissue engineering Scaffolds for cell culture; stimulates cell proliferation Material supporting nerve repair Wound healing properties Scaffolds for bone regeneration: bone substitutes and cements; rebuilding of bone Biocompatible and biodegradable materials for use as implants, blood substitutes, blood vessels or wound dressing material Antitumor agent, tumor inhibition Treatment of leukemia, diabetes Sutures, surgical threads, bandages, sponges Dental implants Contact lenses Magnetic resonance imaging
References		

(continued)

Table 2.11 (continued)

Topic	Forms	Applications
Francis Suh and Matthew (2000), Khor and Lim (2003), Elder et al. (2004), Berger et al. (2004a, b), Illum and Davis (2004), Sashiwa and Aiba (2004), Barbosa et al. (2005), Yi et al. (2005), Shi et al. (2006), Jayakumar et al. (2007), Lee (2007), Alves and Mano (2008), Kang et al. (2009), Muzzarelli (2009, 2011), Venkatesan and Kim (2010), Khor (2011), Sahoo and Nayak (2011), Dash et al. (2011), Dutta et al. (2011), Jayakumar et al. (2011a), Lakshmanan et al. (2011), Liu et al. (2011), Luna-Bárcenas et al. (2011), Sarmento and das Neves (2012), Wang et al. (2012), Croisier and Jérôme (2013), Kim and Pangestuti (2013), Anitha et al. (2014), Jana et al. (2014), Junginer and Sadeghi (2014), Muñoz-Bonilla et al. (2014), Balan and Verestiuc (2014), Azuma et al. (2015), Pokhrel et al. (2015), Dutta (2016), Ahmed and Ikram (2016), Elieh-Ali-Komi and Hamblin (2016), Choi et al. (2016), LogithKumar et al. (2016), Ahmad et al. (2017a, b), Amber Jennings and Bumgardner (2017b), Balagangadharan et al. (2017), Bano et al. (2017), Ellis and Korbutt (2017), Harris et al. (2017), Layek and Singh (2017), Vunain et al. (2017), Aljohani et al. (2018), Ahsan et al. (2018), Ahmed et al. (2018), Ahsan et al. (2018), Ali and Ahmed (2018), Anraku et al. (2018), Baranwal et al. (2018), De Mori et al. (2018), Dimassi et al. (2018), Ding et al. (2018), Hamedi et al. (2018), Hu et al. (2018), Li et al. (2018), Komi et al. (2018), Krishnaswami et al. (2018), Liaqat and Eltem (2018), Mohandas et al. (2018), Nezakati et al. (2018), Oryan et al. (2018), Pellá et al. (2018), Qasim et al. (2018), Shariatinia and Jalali (2018), Singh et al. (2018), Tripathi and Singh (2018), Xing et al. (2018), Vasconcelos and Pomin (2018), Xu et al. (2018), and Zhao et al. (2018)		

Jérôme (2013), Anitha et al. (2014), Ahmed and Ikram (2016), and LogithKumar et al. (2016), with a special focus on tissue engineering and wound healing applications. Their bacteriostatic and fungistatic properties are particularly useful for wound treatment. This application combines two of the most interesting properties of chitosan: antimicrobial activity and biocompatibility. Chitosan and its oligosaccharides have also a stimulatory effect on cells. Materials in the forms of nonwovens, nanofibers, composites, films and sponges can accelerate wound healing and dermal regeneration. These products have been on the market since the early 1990s, mainly in North America and Asia, and more recently in Europe (Germany, France). Actually, the main biomedical commercial applications of chitosan are in wound healing.

Various forms of wound dressing chitosan-based materials are commercially available in the market: HemCon® Bandage, ChitoGauze® PRO, ChitoFlex® PRO, ChitoSam™,Syvek-Patch®, Chitopack C® and Chitopack S®, Chitodine®, ChitosanSkin®, TraumaStat®, TraumaDEX®, Celox™, etc. For example, HemCon® Bandage is an engineered chitosan acetate preparation designed as a high-performance hemostatic dressing (HemCon Medical Technologies, Inc., USA). Other biomedical products are in the market. Reaxon® (Medovent, Germany) is a chitosan-based nerve conduit which is resistant to collapse and helps to avoid the undesired drawbacks of autografts. This hydrogel is bioactive (supports nerve regeneration equivalent to the autograft), biocompatible (prevents irritation and inflammation), antiadhesive (inhibits scar tissue and neuroma formation), and antibacterial (prevents infection). Its particular structure also facilitates the transport of

nutrients and oxygen. ChitoSeat™ is a family of chitosan based hemostatic sealants that are suitable for surgical hemorrhage of hard and soft tissue (LUNA, USA).

In tissue engineering, the aim is to restore or replace damaged body parts or lost organs by transplanting supportive scaffolds with appropriate cells that in combination with biomolecules generate new tissue (Dash et al. 2011; Saravanan et al. 2013; Ahmed et al. 2018). Dash et al. (2011) reported that chitosan is an ideal dressing in wound-healing applications due to the fact that not only it protects the wound from bacterial infection but also it promotes healing and it produces less scarring. In addition to the reparative nature of the material, it can also deliver a therapeutic payload to the local wound, for example, fibroblast growth factor-2 which stimulates angiogenesis by activating capillary endothelial cells and fibroblasts. The potential use of chitosan in this topic is, however, limited due to is poor solubility in water, faster *in vivo* depolymerization/degradation, hemo-incompatibility, and also weak antimicrobial property. To overcome these problems, chitosan derivatives have been proposed as novel scaffold materials for tissue engineering. A discussion on the use of many derivatives in bone tissue engineering as emerging products can be found in the recent reviews by LogithKumar et al. (2016) and by Ahmed et al. (2018).

For bone regeneration, several injectable materials were used. Chitosan-calcium phosphate composites appear to have a promising clinical application. Chemically modified hyaluronic acid-chitin and chitosan-hyaluronic acid material were reported to be osteoinductive and exhibited rapid degradation and neovascularization in vivo. Chitosan scaffolds are potentially a useful alternative to synthetic cell scaffolds also for cartilage tissue engineering. Anitha et al. (2014) reviewed the use of chitosan-based membranes and scaffolds not only for tissue engineering and wound healing but also as anticancer drug delivery, osteogenic drug delivery, and growth factor delivery. The key features of these biomaterials are their biodegradability, cytocompatibility, multi-functionality and specific mechanical properties. n-Lauryl-carboxymethylcellulose has been proposed as carrier for hydrophobic cancer drugs. This amphiphilic substance is safe in terms of membrane toxicity. Materials for cancer chemotherapy are important but still under development (Saneja et al. 2016). Chitosan-based biomaterials were proposed against diabetes and related complications (Kim and Karadeniz 2013; Kim and Pangestuti 2013; Karadeniz and Kim 2014a, b) and also as new adhesives (Mati-Baouche et al. 2014).

Chitosan is a biocompatible substance with no antigenic properties, and thus it is perfectly compatible with living tissues. Its hemostatic and antithrombogenic bioactivities make it suitable in all fields of medicine: for controlled drug release, drugs encapsulation, enzymes and cells immobilization, and also as gene carriers. Chitosan is biodegradable and enzymes break it down into oligo-products that are then dealt with by the metabolism. Many chitosan derivatives are also biocompatible and non-toxic with living tissues. Other advantages of chitosan-based materials often cited are related to their hydrophilic property, biodegradability, antibacterial activity, bioadhesivity, mucoadhesivity, and complexing property. Like alginate polysaccharide, chitosan has the characteristic of forming gels in addition to possessing viscosity-related properties, complete biodegradability, and even anti-tumor influence. Chitosan forms films that are permeable to air. It facilitates cellular regeneration

while protecting tissues from microbial attacks. Chitosan has also a stimulating effect on the regeneration of tissues. It is used in making an artificial skin for skin grafts on high degree burns and in surgical applications (suture threads). Chitosan can trap lipids at their insolubilisation pH in the digestive tract. It considerably reduces the level of cholesterol in the blood. Chitosan possesses bioadhesive properties which make it of interest in adhesive sustained release formulation required. Mucoadhesivity permit to enhance the adsorption of drugs especially at neutral pH (Dash et al. 2011; Liu et al. 2011; Dutta 2016; Amber Jennings and Bumgardner 2017a, b; Vunain et al. 2017).

Genetic materials such as deoxyribonucleic acids and ribonucleic acid are used in gene therapy as pharmaceutical agents to treat various diseases (Lee 2007; Dash et al. 2011; Kedjarune-Leggat and Leggat 2011; Choi et al. 2016; Badawy and Rabea 2017). However, the use of genetic materials is limited due to rapid degradation by nuclease, large size, poor cellular uptake, high anionic charge density, and also non-specificity. To overcome these problems, non-viral vectors as cationic chitosan were proposed as promising delivery biomaterials in gene therapy (Kedjarune-Leggat and Leggat 2011). Chitosan is a prominent system-based gene delivery vector due to its facility to form complexes, biodegradability and biocompatibility, although its transfection efficiency and cell specificity are low. Its role in gene delivery is supported by its ability to protonate in acidic media forming a complex with deoxyribonucleic acids through electrostatic interactions (Choi et al. 2016). The chitosan-deoxyribonucleic acids complexes are easy to prepare and are more effective compared to the commonly used systems. Chitosan/deoxyribonucleic acids complexes were reported to transfect into various cell types: human embryonic kidney cells, cervical cancer cells, primary chondrocytes, and fibroblast cells. As recently reviewed by Badawy and Rabea (2017), the transfection efficiency of chitosan depends on the degree of acetylation, molecular weight, pH of the transfecting media, cell type, and the charge ratio between the luciferase plasmid to chitosan. Limitations in the use of chitosan for non-viral gene therapy were previously reported by Kedjarune-Leggat and Leggat (2011). Most of the results on gene therapy using chitosan were obtained from experiments in vitro and further research is needed in vivo. In addition, studies still need to understand the effects of the characteristics of the carriers on cellular entry and intracellular trafficking processes (Choi et al. 2016).

Sulfated chitosan has the ability to interfere with blood clotting process. This is a subject of extensive medical applications. Compared to heparin, this derivative has been shown to possess high anticoagulant potency. Unlike heparin, sulfated chitosan does not show anti-platelet activity, which causes excessive bleeding in patients (Badawy and Rabea 2017). Another example of extensive medical studies concern the production of chitosan-based vaginal tablets used as drug delivery systems due to their adequate release properties and good adhesive properties (El-Kamel et al. 2002; Raafat and Sahl 2009; Bernkop-Schnürch and Dünnhaupt 2012). However, as claimed by Raafat and Sahl (2009), the antimicrobial properties of chitosan might have a negative impact on the vaginal microflora. Its vaginal use for treatment of chronic diseases has therefore to be seen with caution. Another application related

to chitosan is based on the fact its modified particles provide an excellent template for bio-imaging. Chitosan-based nanoparticles containing imaging agents were studied for radiopharmaceutical applications and magnetic resonance imaging (Kumar et al. 2004; Dash et al. 2011).

The medical and biomedical potential applications of chitosan also include ophthalmology, dentistry, and veterinary medicine. In ophthalmology, due to their non-toxic character and permeation enhancing properties, chitosan-based formulations are used as drug delivery systems including coated colloidal systems, hydrogels, and nanoparticles (Bernkop-Schnürch and Dünnhaupt 2012; Elieh-Ali-Komi and Hamblin 2016; Krishnaswami et al. 2018). Chitosan possesses all the characteristics required for making an ideal contact lens: optical clarity, mechanical stability, optical correction, gas (oxygen) permeability, wettability and immunological compatibility (Elieh-Ali-Komi and Hamblin 2016; Badawy and Rabea 2017). The antimicrobial activity, film-forming ability, and wound-healing properties also make chitosan suitable for development of ocular bandage-lenses for traumatic injuries (Elieh-Ali-Komi and Hamblin 2016).

2.3.5 Dentistry

The relevant properties of chitosan cited for dentistry are: bioactivity, anti-inflammatory, wound healing, hemostatic activities and bone repair (Queiroz et al. 2015; Kmiec et al. 2017; Navarro-Suarez et al. 2018; Zheng et al. 2018). Chitosan is used in the form of solution (acetic or methanesulfonic acid used as solvents), microspheres, hydrogel and toothpastes, and its association with additives such as amorphous calcium phosphate, amelogenin and quinic acid improved the ability of these chitosan preparations in preventing dental caries and enamel erosion. Its applications in dentistry are described in Table 2.12. Chitosan in gel/hydrogel form applies to the treatment of chronic periodontitis and canker sores. Due to its inherent versatility, efficiency and ability to act as a protective barrier to the penetration of acids into enamel and its mineral loss, chitosan can play an important role in preventive dentistry. In addition, when associated with remineralizing agents, chitosan preparations are able to repair early caries lesions (Queiroz et al. 2015). Toothpastes, mouthwashes and chewing gums based on chitosan and herbs fullness functions antimicrobial effect on oral bio film and reduction of the number of *Streptococcus mutans* in the oral cavity (Kmiec et al. 2017). They freshen the breath and prevent the formulation of plaque and tooth decay. Salts of chitosan added to tooth paste mask the unpleasant taste of silicon oxide and bind powders, so that they maintain their granular shapes. Chitosan complex and fluoride microparticles increase fluoride absorption and protection cavities. Endodontic cements based on chitosan reduces inflammation and support bone regeneration. Navarro-Suarez et al. (2018) recently discussed the use of nanotechnology in dentistry and the latest innovations in nanobiomaterials products. Zheng et al. (2018) also reviewed the application of biomaterials in dentistry, with a focus on new techniques using a

Table 2.12 Applications of chitosan and its oligosaccharides in dentistry

Topic	Form	Applications
Dental surgery	Solution	Agent to prevent diseases: dental caries,
Dental therapy	Hydrogel	periodontitis, erosive lesion, dental plaque inhibitor
Dental materials	Toothpastes	Ingredient in dentifrices
Implants	Bioadhesive	Oral care, dental care: toothpaste, chewing gum
Drug delivery systems	Powder	Chitosan-containing chewing gum having
Oral hygiene	Granule	antibacterial effects or to increase salivary secretion
Antibacterial effect	Nanoparticle	Delivery of fluoride
Restorative dentistry	Sponge	Dental adhesives
Dental composites	Composites	Nanobiomaterials
Wound healing		Agent to promote wound healing in bone tissue
Nanodentistry		Scaffolds and carriers for molecular therapy
		Cell protective activity
References		
Sapelli et al. (1986), Khor and Lim (2003), Stamford Arnaud et al. (2010), Hayashi (2011), Keegan et al. (2012), Hayashi et al. (2013), Farea et al. (2014), Queiroz et al. (2015), Kmiec et al. (2017), Wieckiewic et al. (2017), Elkassas and Arafa (2017), Ahsan et al. (2018), Navarro-Suarez et al. (2018), and Zheng et al. (2018)		

combination of scaffolds, cells and biologically active molecules to assemble functional constructs that restore, maintain or improve damaged tissues for dental purposes.

2.3.6 Veterinary Medicine

Senel and McClure (2004) previously reviewed the applications of chitosan in veterinary medicine including wound healing, bone regeneration, analgesic and antimicrobial effects. They also discussed the potential application of chitosan to drug and vaccine delivery in veterinary species, and as nutritional ingredient. Given the restrictions imposed by financial and animal restraint considerations, especially in fanning applications, the veterinary drug delivery areas most likely to benefit from chitosan are the delivery of chemotherapeutics such as antibiotics, antiparasitics, anaesthetics, painkillers and growth promotants to mucosal epithelium for absorption for local or systemic activity, and the delivery of immunomodulatory agents to the mucosal associated lymphoid tissue for induction or modulation of local immune responses. Other applications in veterinary medicine are showed in Table 2.13. The use of nanoparticles for drug delivery, diagnostics and vaccine formulation has described by Underwood and van Eps (2012). Nanomedicine using innovative nanosystems seems to be a promising domain. Products have already reached the market. For instance, chitosan-based nutritional supplements (Epakitin™, Nutri+Gen®) are commercially available for use as essential nutrients supplement or in chronic kidney disease in dogs and cats. The Epakitin formulation containing both chitosan and calcium carbonate is a safe and highly palatable kidney-protective

Table 2.13 Applications of chitosan and its oligosaccharides in veterinary medicine

Topic	Forms	Applications
Delivery systems	Solution	Time release drugs for animals
Vaccine delivery	Powder	Mucosal formulations
Adjuvant	Microsphere	Mucosal delivery of antigens
Biological properties	Microcapsule	Improve the immune response
Mucosal immunization	Nanoparticle	Hemostatic
Wound healing	Gel, hydrogel	Wound-healing activity
Tissue regeneration	Sponge	Regenerative medicine: tissue engineering
Nutritional supplement	Film	Vaccines
Nanomedicine	Filament	Surgical threads
		Food for dogs
		Reduce urea levels
		Body-care products: shampoo, sprays
References		
Şenel and McClure (2004), Şenel (2011), Underwood and van Eps (2012), Drewnowska et al. (2013), Gerdts et al. (2013), Tonda-Turo et al. (2016)		

phosphate binder. Many body care are also available (ChitoCure®, ChitoClear®): shampoo, ear-cleaner, conditioner, sprays for companion animals, etc.

2.3.7 Cosmetics

It is possible to produce chitosans as well as chitosan derivatives with varying chain lengths and differentiated properties for applications in cosmetics, hygiene and personal care. The molecular weight of most chitosan products are so high that they cannot penetrate the skin and this is an important advantage that make it suitable for skin care. These materials include chitosan hydrochloride, chitosan acetate, chitosan lactate, carboxymethyl-chitosan, quaternized-derivatives, oligosaccharides, and also chitin sulphate and carboxymethyl-chitin. They can be dissolved in aqueous solutions or used in solid form. In cosmetics, the specific properties employed are: cationic (chitosan and hair carry opposite electrical charges), bacteriostatic, fungistatic, antistatic, film-forming, moisture-retaining (chitosan retain moisture in low humidity and maintain hair's style in high humidity), and controlled release of bioactive agents. Chitosan is also of great interest in cosmetic formulations because it is compatible with other ingredients such as starch, glucose, saccharose, polyols, oils, fats, waxes, acids, non-ionic emulsifiers and non-ionic water-soluble gums. However, chitosan is incompatible with ionic gums, sulphonated surface-active agents, alkalis, and sulphuric acids. Chitosan and its derivatives can be combined with other hydrating agents, solar filters and other bioactive products used in the formulations. They facilitate their effects. Some derivatives of chitosan can form foam and create emulsifying actions.

Some of the chitosan applications (Table 2.14) are: hair care, e.g. shampoos, coloring products, hairspray, and setting lotion, creams and lotions (face, hand and

Table 2.14 Applications of chitosan and its oligosaccharides in cosmetics

Topic	Form	Applications
Toiletry Hygiene Personal care Skin care Oral care Dental care Hair care Cosmeceuticals Fragrances Essential oils	Solution Powder Film	Functional additives Moisturizers: maintain skin moisture, tone skin Thickening agent Hydrating and film-forming agent Role in surfactant stability; stabilize emulsion Antistatic effect Bacteriostatic Encapsulating agent Delivery systems Products: shampoos, creams, skin creams, creams for acne treatment, lotions, bath lotions, nail polish, fixtures, make-up powder, lacquers, nail lacquers, nail enamel, varnishes, hair sprays, hair colorants, wave agents Cleaning products: cleansing milk, face peel, facial toner, soap, bath agent Hair care: elastic film on hair, increase its softness and mechanical strength, improve suppleness of hair, remove oils and sebum from hairs; reduce static electricity in hair, retain moisture and maintain hair's style Oral care, dental care: toothpaste, chewing gum
References		
Goosen (1997), Struszczyk (2002), Rinaudo (2006), Crini et al. (2009), Muñoz et al. (2012), Lima et al. (2012), Senevirathne et al. (2012), Chalongsuk and Sribundit (2013), Jimtaisong and Saewan (2014), Costa and Santos (2017), and Rahangdale and Kumar (2018)		

body products), color cosmetics (make-up, nail polish, eye shadow, and lipstick), deodorizing products, micro-encapsulation of active agents, and dental care, e.g. toothpaste, tooth-gel, and mouth wash. Chitin is also interesting in cosmetology because it is well tolerated by the skin. It is an effective hydrating agent and a film-forming tensor having two advantages often cited: it supplies water and it avoids dehydration. Chitosan and chitin also present chelating properties towards metals that are responsible for very many contact allergies. Carboxymethyl-chitosans products are mainly used in cosmetics as antioxidant agent, moisture absorption-retention agent, antimicrobial agent, delivery system and emulsion stabilization. Jimtaisong and Saewan (2014) comprehensively discussed the utilization of carboxymethyl-chitosans as multifunctional ingredients in the formulation of cosmetics. They also included in their review information on cytotoxicity of these products to ensure their safety.

Numerous chitosan-based products for cosmetic use are commercially available: Curasan™, Hydamer™, Zenvivo™, Ritachitosan®, Chitosan MM222, etc. Cosmetic industry is a strongly growing market. The cosmeceutical market has also been growing particularly rapidly of late. Cosmeceuticals (Chitoseen™-K) are cosmetics with pharmaceutical/medicinal benefits. These products seem to provide not only a health benefit but also cosmetic qualities. They contain essential oils and active ingredients such as vitamins, enzymes, antioxidants, and phytochemicals. They can be applied as creams, lotions and ointments (Lima et al. 2012; Muñoz

et al. 2012; Senevirathne et al. 2012). Since the last decade, they continue to revolutionize the world of hair, lip, tooth and skin care by offering safe and natural ingredients for consumer's personal use.

2.3.8 Agriculture

Applications of chitosan in agriculture are summarized in Table 2.15. Chitosan products are used in plant protection from the 1990s against plant pathogenic bacteria that induce decay and harmful effects of agricultural crops during the growing season and postharvest phase (Yin and Du 2011). They behave as bactericidal (killing the bacteria) and/or bacteriostatic (hindering the growth of bacteria). However, the exact mechanism is still not fully understood. A discussion on models proposed for antibacterial actions of chitosan can be found in the review by Muñoz-Bonilla et al. (2014). The most accepted mechanism involves the polycationic character of chitosan which permits to interact with negatively charged species (bacterium cell membrane). The chelating properties of chitosan also make it an excellent antifungal agent (Rabea et al. 2003; Muñoz-Bonilla et al. 2014; Badawy and Rabea 2016; Divya and Jisha 2018). The presence of chitosan activates many defense responses in plants. Usually, it is employed in plant disease control as a powerful elicitor.

Table 2.15 Applications of chitosan and its oligosaccharides in agriculture

Topic	Form	Applications
Plant protection Antimicrobial agent Antioxidant Horticulture Agrochemistry Soil enrichment Postharvest Edible films	Solution Spray Coating Powder Gel Powder Nanoparticle	Protection of plants Coating material: seeds, fruits, vegetables Stimulation of plant growth and plant production Increase of crop yields Reduce the growth of phytopathogenic fungi Effects on gene expression Pest control Soil treatment (nutrients) Modify plant-microbial interactions Elicitor to stimulate the accumulation of secondary metabolites and to induce plant defenses Frost protection Controlled agrochemical release Fertilizers and biocontrol agent (time release of products) Bio-fertilizer, fertilizer protectant Spray for pesticide removal (fruits) Pesticide formulations; biopesticides; biofungicides
References		
Goosen (1997), El Hadrami et al. (2010), Yin and Du (2011), Sharp (2013), Muñoz-Bonilla et al. (2014), Katiyar et al. (2014), Xing et al. (2015), Badawy and Rabea (2016, 2017), Bautista-Baños et al. (2016), Hadwiger (2017), Ippólito et al. (2017), Orzali et al. (2017), Divya and Jisha (2018), Grande-Tovar et al. (2018), and Sharif et al. (2018)		

Chitosan products were proposed as devices for controlling the release of agrochemicals (fertilizers, pesticides).They are used as biocides either alone or blended with other products against plant diseases (control of plant bacteria and fungi), pests and insects, plant growth promotion, seed-coating, and postharvest (Divya and Jisha 2018; Grande-Tovar et al. 2018; Sharif et al. 2018). Chitosan has also inhibitory effect on viruses and viroid of plants. It has a great potential as biopesticide. It can function as a seed-soaking agent, a root-applying agent, and a spray agent. These activities play an important role on plant disease control and stress resistance. Blending of chitosan with other products, such as gum, starch, and alginate, is a convenient method to improve its properties for slow release of pesticides. The use of chitosan products can elicit defense to more than 60 diseases on several plants. Their potent effect on plant disease control is from their antimicrobial and plant innate immunity elicited activity. The inhibition activity was observed on different stages of fungal growth such as mycelia, sporulation, spore viability and germination, and production of fungal virulence factors. Chitosan products can be used in various ways: coating seed (soybean, cotton, cucumber, wheat, rice), soil enrichment (for potato, soybean lettuce, spinach), foliar spraying (for peanut, soybean, cabbage, rice, maize, cotton), supplement in hydroponic (rice, wheat, peanut), and supplement in plant tissue culture medium (*Chrysanthemum*, *Limonium*, carrot). As seed coating agent, they protect plants, e.g. cotton, tomato, wheat, and have a positive effect on germination rate, seedling growth parameters, and the yield of different cultivars, e.g. soybean sprouts, ornamental plants, maize, wheat, lentil, rice, and peanut. Their bioactivities as antifungal activity, enhancement crop yield, induction of defensive system of plants and plant-growth promotion play key roles in their application for agriculture.

The two main problems of chitosan in agriculture applications are commercial chitosan standardization and solubility. Indeed, chitosan bioactivities are dependent on several parameters including degree of acetylation, molecular weight, concentration of chitosan, pH of the solution, its viscosity, and the target of microorganism. The antimicrobial activity of non-modified chitosan against various microorganisms such as bacteria, yeasts, fungi and viruses has received much attention in the last two decades. The literature data showed that this bioactivity property depends on various factors such as molecular weight, which is probably the main factor affecting the efficacy, although literature is sometimes contradictory. Generally, the antibacterial activity increase as the molecular weight decreases. However, it is difficult to find a clear correlation between the molecular weight and this bioactivity (Badawy and Rabea 2017). In spite of its unique biological aspects, the water-insoluble property is another major limiting factor for its wide application in agriculture. Recently, to overcome these problems, chitosan derivatives and oligomers produced by enzymatic and chemical modifications have been proposed. It is expected that these biopolymers would be promising candidates in agriculture. Research are also in progress on the mechanisms of chitosan-induced defense and on the signal perception of chitosan. Nanotechnology using innovative chitosan nanoparticles seems to be a promising domain. The methods of preparation of

chitosan nanoparticles and their potential applications as antimicrobial agent, plant growth-promoting agent and plant protector have been discussed in the recent review by Divya and Jisha (2018).

2.3.9 Aquaculture

A prerequisite for the greater use of chitin in industry is cheap manufacturing processes and/or the development of profitable processes to recover chitin and byproducts such as proteins and pigments. It is well-known that the recovery of chitinous products from wastes is an additional source of revenue. Crustacean shells contain considerable quantities of carotenoids which so far have not been synthesized, and which are marketed as a fish food additive in aquaculture, mainly for salmon. The use of chitosan and its derivatives in the aquaculture was described by Alishahi and Aïder (2012). It can be used as functional food, nutritional supplements (synbiotics), carrier abilities for bioactive compounds, drug release, encapsulation of pathogens or nucleic acids, and for pollutant removal from water and wastewaters (Table 2.16). There is also a constant need for the development of efficient vaccines and delivery systems to prevent and control the emerging and re-emerging infectious diseases in aquaculture. There are innumerable infectious diseases for which the development of efficient vaccines has been difficult to achieve. The failure is mainly due to the inability to design vaccines evoking appropriate immune responses. The use of chitosan-based nanoparticles has provided a tremendous opportunity to design vaccine delivery systems that are efficient in targeted delivery, providing stability to antigens, and act as efficient adjuvants. Many of the

Table 2.16 Applications of chitosan in aquaculture

Topic	Form	Applications
Quality water	Powder	Removal of organic compounds and inorganic nutrients; removal of bacteria, of ammonia
Nutrition	Microsphere	Functional food; to enhance gelling properties
Functional foods	Bead	Micro-carrier abilities for bioactive compounds: proteins, pigments
Nutritional supplements		Probiotics to improve feed conversion, growth rates, weight gain, immune system and disease resistance of fish
Probiotics/Prebiotics		Microencapsulation of drugs and drug delivery; oral delivery (vaccination)
Controlled release of compounds		Immuno-stimulant against bacterial diseases
Treatment of seafood effluents		Antimicrobial, antioxidant and antioxidative stress
References		
Chung et al. (2005), Chung (2006), Borgogna et al. (2011), Cerezuela et al. (2011), Alishahi and Aïder (2012), Harikrishnan et al. (2012), Niu et al. (2013), Zaki et al. (2015), Lian et al. (2016), and Bernardi et al. (2018)		

nanoparticles are able to enter the antigen presenting cells by different pathways and induce appropriate immune responses to the antigen. Vinay et al. (2018) reviewed the use of chitosan for the delivery of fish vaccines and compared the potential of these delivery systems for the development of new vaccines against different fish pathogens.

2.3.10 Textile Industry

Applications of chitosan and its derivatives in textile industry are described in Table 2.17. Among the possible approaches initiated by the textile industry, the use of chitosan presents an innovative possible avenue for large scale development of bioactive textiles (Giri Dev et al. 2005; Enescu 2008; Sahan and Demir 2014; Gutiérrez 2017; Roy et al. 2017). Indeed, more research and practical use results indicate that chitosan might act as active compounds in textiles, e.g. as antimicrobial finishing of textiles, and cosmetotextiles. The characteristics of chitosan used in textile industry include cost-effectiveness, non-toxic, biocompatible, biodegradable, antimicrobial activity, antistatic activity, chelating property, deodorizing property, film-forming ability, chemical reactivity, dyeing improvement ability, thickening property, and also wound healing activity. Although the antimicrobial activity of chitosan is well document in the literature, its mode of action is yet not fully understood (Islam et al. 2013). There are many possibilities for the development of new textile and cosmetic products containing chitosan-based nanoparticles with advanced properties (UV-blocking, water repellence, self-cleaning). Their applications seem promising.

Table 2.17 Applications of chitosan and its derivatives in textile industry

Topic	Forms	Applications
Textiles Functional textiles Cosmeto-textiles Medical textiles	Microcapsule Gel Gelatinous dispersion Coating Fiber	Dye-binder for textiles Impregnated textile materials Binding agent for non-woven Surface modification of textiles Textiles with anti-bacterial properties Textile printing and antimicrobial finishing Textile preservative and deodorant agent Non-allergenic fibers Sanitary fibrous products Surgical threads
References		
Giri Dev et al. (2005), Enescu (2008), Ummu Habeeba et al. (2007), Crini et al. (2009), Francesko et al. (2010), Islam et al. (2013), Şahan and Demir (2014), Hamed et al. (2016), Voncina et al. (2016), Gutiérrez (2017), and Roy et al. (2017)		

Table 2.18 Applications of chitosan and its derivatives in pulp and paper industry

Topic	Form	Applications
Papermaking industry Pulp and paper Water treatment Papermaking-related industries	Coating Powder Nanoparticle	Wet strength agent; strengthening additive Retention and drainage agents Paper sizing and finishing Surface coating application: coated papers with antibacterial and antimicrobial properties Confer strength to paper against moisture Biodegradable packaging for food wrapping Wrapping and toilet paper Chromatography paper Card board Carbonless copy paper Modification of cellulose fibers Photochromic paper Papermaking wastewater treatment
References		
Muzzarelli (1983), Struszczyk (2002), Crini et al. (2009), Cheba (2011), Samyn et al. (2018), and Song et al. (2018)		

2.3.11 Pulp and Paper Industry

Applications of chitosan in pulp and paper industry are described in Table 2.18. The first use of chitosan in the papermaking industry was reported in 1936 (Struszczyk 2002). The main use was to improve wet-strength of paper. Chitosan as functional material is also able to interact with cellulose pulp during the formation of paper and to be film-forming to offer cohesive resistance to rupture (Song et al. 2018). This biopolymer is also non-toxic, biodegradable and eco-friendly in order to facilitate compliance with environmental regulations. Chitosan as chelating and complexing agent is also used in the decontamination of pulp and paper wastewaters for removal of lignin, color and undesired contaminants, and for the decrease in total organic carbon and chemical oxygen demand. Samyn et al. (2018) recently reviewed the use of nanoparticles and nanostructured materials in papermaking.

2.3.12 Biotechnology

Some applications of chitosan in biotechnology are described in Table 2.19. Numerous enzymes (lysozyme, urease, *Escherichia coli* cells, amylases) were immobilized with chitosan. They are entrapped and absorbed in the macromolecule chains. In biochemistry, chitosan is used as a support for enzymes, mainly by cross-linking reactions. Chitosan and its derivatives have also shown biotechnology applications as biosensors and biodevices. Depolymerization and de-N-acetylation of chitin by chitinases and deacetylases generates a series of derivatives such as

Table 2.19 Applications of chitosan and its derivatives in biotechnology

Topic	Form	Applications
Enzymology Enzyme technology Separation Bioseparation Biomembranes Electrodes Biosensors	Powder Bead Microsphere Nanoparticle Sponge Membrane	Enzyme and cell immobilization Cell recovery Cell-stimulating materials Protein separation Matrix for affinity and gel permeation chromatography Electronic devices, biosensor construction Metabolic analysis of biological fluids
References		
Zikakis (1984), Struszczyk (2002), Krajewska (2005), Wang (2012), Suginta et al. (2013), Philibert et al. (2017), and Grifoll-Romero et al. (2018)		

chitooligosaccharides which find numerous applications in biotechnology as recently reviewed by Grifoll-Romero et al. (2018).

2.3.13 Chemistry

Table 2.20 describes some applications of chitosan in chemistry. Chitosan is the object of numerous studies concerning applications in chromatography, green chemistry, catalysis, membrane technology and electrochemistry. It has been proposed in thin layer chromatography for separation of nucleic acids and in green chemistry for the generation of green solvents. It is believed that chitosan will play a very important role in these new developments. The utilization of chitosan as a catalyst support is also of particular interest. This application combines several up-to-date techniques (freeze drying, utilization of supercritical CO_2) to increase the surface exchange capabilities and/or utilization of ionic liquids. Chitosan contributes to the implementation of green chemistry principles. The state of the art review of the design of electrochemical biosensor applications based on chitosan and chitin was presented by Suginta et al. (2013) and comprehensively discussed. Membranes are produced by casting chitosan solutions either alone or with suitable ingredients (reagents, polymers) to give desired properties for target applications. Preparation and application of chitosan-based adsorptive membranes for separation and for water purification were reviewed by Salehi et al. (2016) and by Thakur and Voicu (2016), respectively. Chitosan has been proposed for the separation of organic liquid mixtures using evapomeation membranes. This membrane separation technique makes use of the advantage of pervaporation and simultaneously removes a fault of pervaporation. The main applications of chitosan membranes are their use in biomedicine and biotechnology. Albumin blended chitosan membranes have been used in hemodialysis, artificial skin and also drug targeting. Further developments are expected in the near future in these domains (Galiano et al. 2018).

Table 2.20 Applications of chitosan and its derivatives in chemistry

Topic	Form	Applications
Analytical chemistry	Solution	Analytical reagent
Chromatography	Ionic liquids	Reverse osmosis
Dialysis	Powder	Permeability control
Reverse osmosis	Film	Solvent separation
Ultrafiltration	Coating	Organic/organic separation
Gas permeation	Fiber	Alcohol/water selective pervaporation
Pervaporation	Membrane	Transport direction of target molecules
Evapomeation technique	Composite	Membranes for lithium batteries
Carrier transport membranes	Blend	Biosensors, electrochemical devices
Green chemistry	Sensors	CO_2 recovery
Green solvents		Alternative solvents in catalytic organic reactions
Catalysis/Biocatalysis		Adhesive role between metallic surfaces
Adhesives		Corrosion protection of aluminum
Corrosion protection		Ionic liquids
Polymer science		Deep eutectic solvents
Click chemistry		
Electrochemistry		
References		
Goosen (1997), Guibal (2005), Krajewska (2005), Macquarie and Hardy (2005), Li et al. (2008), Crini et al. (2009), Cheba (2011), Dash et al. (2011), Suginta et al. (2013), Mati-Baouche et al. (2014), Carneiro et al. (2015), Salehi et al. (2016), Thakur and Voicu (2016), Osman and Arof (2017), Argüelles-Monal et al. (2018), Galiano et al. (2018), Marpu and Benton (2018), Xie and Yuan (2018), and Zdanowicz et al. (2018)		

2.3.14 Environmental Chemistry

A growing number of papers have been published since the 1980s concerning chitosan for applications in environmental chemistry (Table 2.21). This natural polymer possesses several intrinsic characteristics that make it an effective material for environmental purposes. Its use is justified by four important advantages:(i) its relatively low cost compared with commercial activated carbon or organic resins, (ii) its outstanding pollutant-binding capacities and excellent selectivity, (iii) its versatility, and (iv) its possible biodegradability after use. Indeed, one of the major applications of chitosan is based on its great ability to tightly bind a whole range of pollutants. In addition, chitosan and its derivatives can be used in soluble or insoluble forms including gels, beads, sponges, films and membranes, and fibers through coagulation-, filtration-, flocculation- or adsorption-oriented processes. In a previous review, Crini and Badot (2008) comprehensively discussed the development of chitosan-based materials (grafted and crosslinked derivatives) used as useful adsorbent polymeric matrices for dye removal. Their review highlighted results that have been obtained in their decolorizing application as biosorbents. The effects of various parameters such as chitosan's characteristics, the activation conditions, the process variables, the chemistry of the dye and the experimental conditions used in batch systems, on biosorption were presented and discussed. The authors also reviewed the various adsorption mechanisms involved. They concluded that the biosorbents

Table 2.21 Main applications of chitosan and its derivatives in environmental chemistry (selected reviews)

Topic	Form	Applications
Water treatment Wastewater treatment Coagulation Flocculation Adsorption Biosorption Solid-phase extraction Filtration *Membrane filtration* Remediation Biological denitrification	Solution Gel/hydrogel Powder Microsphere Bead Nanoparticle Fiber Hollow fiber Membrane Sponge	Coagulant/Flocculant: clarification of drinking water, pools and spas, wastewaters Adsorbent/Biosorbent: recovery of precious metals; metal chelation; dye removal; removal of pesticides, phenol derivatives, PCB and radioisotopes Interactions with proteins and amino acids Reduce odors Antifouling agent Polymer-assisted ultrafiltration Sludge treatment and dehydration agent Drilling muds
References		
Hirano (1997), Varma et al. (2004), Crini (2005, 2006, 2015), Krajewska (2005), Tang et al. (2007), Gérente et al. (2007), Alves and Mano (2008), Crini and Badot (2008), Li et al. (2008), Bhatnagar and Sillanpää (2009), Elwakeel (2010), Sudha (2011), Rhazi et al. (2012), Ravichandran and Rajesh (2013), Vakili et al. (2014), Liu and Bai (2014), Boamah et al. (2015), Yong et al. (2015), Azarova et al. (2016), Barbusinski et al. (2016), Kos (2016), Ahmad et al. (2017a, b), Crini et al. (2017), Sudha et al. (2017), Nechita (2017), Alaba et al. (2018), de Andrade et al. (2018), Desbrières and Guibal (2018), El Halah et al. (2018), Pakdel and Peighambardoust (2018), Van Tran et al. (2018), and Wei et al. (2018)		

were efficient in pollutant removal with the additional advantage of being cheap, non-toxic and biocompatible. More recently, Kyzas et al. (2017), Desbrières and Guibal (2018) and Pakdel and Peighambardoust (2018) also indicated that biosorption onto chitosan is a promising alternative to replace conventional adsorbents used for decolorization purposes, and metal and organic removal. Chitosan-based versatile materials are also widely proposed in clarification and water purification, and water and wastewater treatment as coagulating and flocculating agents (Crini et al. 2009). As ecofriendly materials, they can be a potential substitute for metallic salts and synthetic polyelectrolytes in the treatment of water for the removal of both particulate and dissolved substances. However, despite a large number of studies on the use of chitosan for pollutant recovery in the literature, processes are basically at the stage of laboratory-scale study in spite of unquestionable progress. Indeed, these research fields for chitosan have failed to find practical applications on the industrial scale. The actual applications in industry remain rather rare, e.g. Pennofloc™ for water clarification, ChitoVan™ for biofiltration, as concurrent flocculating and adsorbing agents are cheaper. Even if chitosan shows better performances in term of pollutant elimination, the conventional products are sufficient to fulfill current regulatory frameworks.

2.3.15 *Miscellaneous*

Table 2.22 describes applications of chitosan in miscellaneous domains. Due to its optical characteristics, film-forming ability and reactions with silver complexes, chitosan and derivatives found applications in photography. In color photography, chitosan has been proposed as a fixing agent for acid dyes in gelatin and also acts as an aid to improve diffusion (Dutta et al. 2004). Ecological concerns about antifouling paints containing non-green tin and copper compounds have highlighted the need for environmentally friendly alternatives (Pelletier et al. 2009; Banerjee et al. 2011). Novel chitosan-based technologies may prevent fouling by means of unfavorable surface chemical and physical properties or by concentrating antifouling compounds around surfaces. A prototype of antifouling paints was proposed as a possible replacement for traditional antifouling paints by Heuser and co-workers (Heuser et al. 2009; Heuser and Cárdenas 2014). In cement industry, chitosan has been proposed as water proofing and water repellent (Cheba, 2011). Chitosan has been also explored in the production of plastics (Galiano et al. 2018) or in the stabilization of photonic materials (Marpu and Benton 2018).

Table 2.22 Applications of chitosan in miscellaneous domains

Field	Main form	Applications
Photography	Solution	Photographic paper
Detergents	Powder	Film forming ability
Surfactants	Coating	Fixing agent for color photography
Paints	Nanoparticles	Color film
Adhesives	Nanoclusters	Nanoimprinting lithography
Wood industry		Antifouling paints
Cement industry		Thermosensitive materials
Leather		Improvement of wood quality
Plastics		Wood adhesive
Bioplastics		Protection of wood (fungicide)
Cigarette industry		Lithium batteries
Semiconductors		Specific targeting
Luminescent nanoparticles		Cellular imaging
Photonics		Bio-imaging and cancer research
Imaging applications		Bioconjugation to biomolecules
Quantum dots		Sensors and biosensing
Carbon dots		Temperature sensing
		Detection
References		
Struszczyk (2002), Crini et al. (2009), Elsabee et al. (2009), Heuser et al. (2009), Pelletier et al. (2009), Desbrières et al. (2010), Banerjee et al. (2011), Cheba (2011), Heuser and Cárdenas (2014), Mati-Baouche et al. (2014), Al-Naamani et al. (2017), Argüelles-Monal et al. (2017), Galiano et al. (2018), and Marpu and Benton (2018)		

2.4 Conclusion

Isolated from mushrooms in 1811 by Braconnot, chitin is the first polysaccharide identified by man, preceding cellulose by about 30 years, while its deacetylated derivative was discovered by Rouget in 1859. In 1894, Hoppe-Seyler confirmed that the product was deacetylated chitin and named it chitosan. Since, these biopolymers, in particular chitosan, have considerably attracted the interest of scientists and industries in different disciplines including health science, agriculture, chemistry, biochemistry, and environment. The main reasons for this growing interest are its intrinsic biological properties and its versatility as biomaterial. Today, chitosan continue to offer new horizons to scientists and industrials with a wide range of possible modifications and forms. In this chapter, we aim to present an overview of the state of the art in the applications of chitosan, based on a substantial number of relevant references published in the last two decades on various biological, biotechnological, chemical, and physical topics for both academic and industrial applications. Of course, this is an ambitious project and the examples discussed in this chapter are not exhaustive but clearly demonstrate the benefit of chitosan in many fields. The main markets for chitosan are food, pharmaceutical and cosmetic industries. The chitosan market is expected to grow rapidly because of increasing consumption not only in cosmetics but also in water treatment, beverage industry, and nutrition. Indeed, nutraceuticals and cosmeceuticals are growing actual markets. There is also an increased demand for chitosan in emerging countries. Therapeutic and biomedical products are also expected to have a positive impact on the market. It is important to point out that, although numerous papers and patents have been reported in the last two decades, the applications of chitosan in the biomedical area are still limited, mainly due to the extreme difficulty to access sufficient purity and source reliability of the biopolymer. In addition, the development of new materials are rather limited, mainly due to their cost, which remains higher than that of petroleum based polymers with similar properties. Finally, *in vivo* studies are currently limited. Further industrial developments are expected in the near future in the following domains: anticancer drugs, gene delivery, catalysis, sensor applications, wrapping materials and packaging, cosmetotextiles, and bio-imaging.

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