
Chitosan: A Natural Polymer for Health

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ABSTRACT

This review aim to present recent research trends and prospects in chitosan with special emphasis highlighting some of its special pharmaceutical and biomedical applications. Chitosan is one of the natural multifunctional polymers with unique and versatile properties. It is well-known for its significant biological and chemical properties. It is regarded as a useful compound in medical and pharmaceutical technology; widely used in nanomedicine, biomedical engineering and development of new therapeutic drug delivery systems with enhanced bioavailability, specificity and reduced pharmacological toxicity. Extensive applications of polymers in drug delivery have been realized because polymers offer unique properties which so far have not been attained by any other materials. Chitosan is very useful in everyday life in adsorption, cosmetics, pharmaceuticals, flocculants, anticancer and antimicrobial. The pharmaceutical industry is currently busy with variety of problems, e.g. capsule shell. The main ingredient of making current commercial capsule shell is gelatin; chitosan can be processed into capsule shell giving succor to this problem. Chitosan in modern industry is widely useful in food, detergents, textiles, leather, paper, pharmaceuticals and cosmetics industries.

Key words: Chitosan, Polymer, Health.

INTRODUCTION

Chitosan is the deacetylated derivative of chitin, which is chemically defined as a copolymer of α -(1,4) glucosamine ($C_6H_{11}O_4N$)_n, having different number of N-acetyl groups (Zvezdova, 2010). It is white to light red solid powder, insoluble in water but soluble in organic acids. According to Fernández, et al., 2006, chitosan provides antibacterial activity (E. coli, S. aureus, Pseudomonas aeruginosa and Salmonella paratyphi B).

In preparation of chitosan, sample is macerated, demineralized, deproteinized and washed with distill water to neutral pH. Chitin immersed in 12.5 M NaOH, and washed with distill water to neutral pH and dried to obtain powdered chitosan (Alhafi 2013 and Maulin's 2017). In the field of controlled drug delivery, biodegradable polymers offer tremendous potential either as a drug delivery system alone or in conjunction to functioning as a medical device (Gilding, and Reed, 1979, Kohn, and Langer, 1996).

It is hoped that the design and synthesis of novel combinations of polymers will expand the scope of new drug delivery systems in the future. Biodegradable polymers have been widely used in biomedical applications because of their known biocompatibility and biodegradability. Biodegradable polymers can be classified into synthetic and natural polymers. Both synthetic and natural biodegradable polymers have been used for drug delivery, and some of them have been successfully developed for clinical applications (Pietrzak, 1997).

Florence, and Jani, (1994) and Robert, et al., (2006) suggested that advances in organic chemistry and nano/micro fabrication/manufacturing methods has enabled continuous progresses in better utilization of a wide range of novel biodegradable polymers in drug delivery. For the ongoing fact about HIV novel drug delivery systems have been found to present an opportunity for formulation scientists to overcome the many challenges associated with antiretroviral (ARV) drug therapy. The currently available anti-HIV drugs are classified into the nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors and recently fusion integration inhibitors. Most of these drugs have some significant drawbacks such as relatively short half-life, low bioavailability, poor permeability and undesirable side effects. Efforts have been made to design drug delivery systems for antiretroviral therapy as reducing dosing frequency, increase bioavailability, decrease degradation/metabolism in Gastrointestinal tract (GIT), improve Central Nervous System (CNS) penetration and inhibit CNS efflux, delivering them to target cells and selectively minimal side effects.

Antiviral drugs are a class of medication used specifically for treating viral infections. Like antibiotics for bacteria, specific anti-viral are used for specific viruses. Unlike most antibiotics, antiviral drugs do not destroy their target pathogen; instead they inhibit their development. In this trend nanoparticles show a fast development from out of total novel drug delivery systems. Nanoparticles are stable, solid colloidal particles consisting of macromolecules materials and ranging in size from 10 to 1000nm. Drugs can be absorbed on the particle surface or can be entrapped or dissolved in the particle matrix. Thus using nanotechnology, engineering researchers have developed a small but powerful device capable of enhancing the targeted delivery of drugs to treat life-threatening illnesses (Mahajan, et al., 2015).

Various types of biopolymers particularly of carbohydrate origin have been found to have a very promising industrial application in various forms (Singh, 2011). Chitin is the second most abundant biopolymer after cellulose, existing in the exoskeletons of crabs, prawns, and insects and the cell walls of fungi. Although chitin is produced in Nature at a rate of 10¹⁰ to 10¹¹ tons per year, most chitin is thrown away as commercial waste (Gopalan, and Dufresne, 2003). This is obvious due to the low workability of the biopolymer, since commercially available chitin powder is not soluble in any solvent but precipitates immediately. A large body of knowledge exists today on the use of chitosans as safe biomaterials for a variety of applications (Yang, T.L. 2011).

Chitin and chitosan with beneficial biological and antimicrobial properties and high valuable potential for wound healing are attractive for wound care. In recent years, a large number of research groups are dedicated to produce a new, improved wound dressing by synthesizing and modifying biocompatible materials (Ulubayram, et al., 2001).

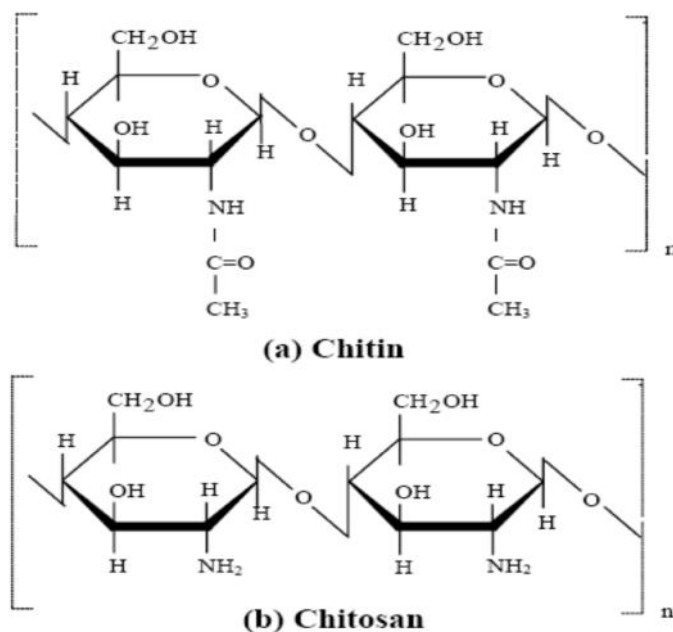


Figure 1: Structure of chitin and chitosan

CHEMICAL PROPERTIES OF CHITOSAN

This biopolymer has a number of chemical properties that make it suitable for several biomedical applications. Some of them are listed below (Dutta, *et al.*, 2004).

1. Chitosan is a linear polyamine which grants it several properties like antimicrobial activity, antitumor activity and so on.
2. It has reactive amino groups ($-NH_2$) which allow chemical substitution reactions to get various derivatives more potent than chitosan.
3. There is availability of reactive hydroxyl groups ($-OH$).
4. It has chelating ability for many transitional metal ions in water purification, binding to trace elements causing the essential nutrients unavailable for normal growth of microbes (Roller, 1999).

BIOLOGICAL PROPERTIES OF CHITOSAN

Besides the various chemical properties, chitosan shows diverse biological properties which are summarized by Venter, *et al.*, 2006, Younes, & Rinaudo, 2015 as follows:

1. Biocompatible:
 - i. Natural polymer
 - ii. Safe and non-toxic
 - iii. Biodegradable to normal body constituents
2. Binds to mammalian and microbial cells aggressively
3. Regenerative effect on connective gum tissue
4. Accelerates the formation of osteoblast responsible for bone formation
5. Haemostatic (stop bleeding)
6. Fungistatic (inhibiting the growth of fungi)
7. Spermicidal (birth control)
8. Antitumor or Anticancer (inhibiting the growth of tumor or cells)

9. Anticholesteremic (cholesterol lowering agent)
10. Central nervous system depressant (slow down the brain activity)
11. Immunoadjuvant (involved in the improvement of immune response)

Pharmacokinetics

Pharmacokinetics is an area of pharmacology concerned with the time course of absorption, distribution, metabolism and excretion (ADME) of drugs from biological systems in order to understand the effect of the drug, or of the organism, on the drug's impact. Experimental evidence suggests that chitosan is partially digested and absorbed owing to the acidic environment of the stomach, enzymes present in saliva and gastric juice, and bacterial enzymes in the large intestine. Oral intake of 1g/day of chitosan increases the serum concentration of *N*-acetyl-D-glucosamine. Serum levels remain high 48h after ingestion (Muzzarelli, 1999).

Interactions

Theoretically, there has been concern that chitosan could bind fat-soluble vitamins and deprive the body of these essential nutrients. It has been suggested that vitamin supplements should be taken at a separate time from chitosan in order to avoid any potential interaction (Muzzarelli, 1999). Absorption of vitamins E (Muzzarelli, 1999; Pittler, et al., 1999), D, and A and β -carotene is not altered by chitosan intake (Pittler, et al., 1999). A study found that vitamin K levels were significantly higher after 4 weeks of treatment with chitosan but were not outside the normal range (Pittler, et al., 1999). Theoretically, this could lead to a decrease in the efficacy of warfarin (blood thinner). There is some concern that taking chitosan might increase the blood thinning effects of warfarin (Coumadin). Taking chitosan with warfarin could increase the chance of bruising or bleeding. If you take warfarin, avoid taking chitosan. It was also once thought that chitosan might interfere with intestinal absorption of trace metal ions such as iron and zinc (Muzzarelli, 1999) and mineral salts (Colombo, and Sciutto, 1996).

APPLICATIONS OF CHITOSAN AND ITS DERIVATIVES

In drinking water and wastewater treatment; Chitosan is used as flocculating and chelating agents, for the removal of heavy metals and dyes, as an ecological polymer (eliminates synthetic polymers and reduces odours) (Gerente, *et al.* 2007; Guibal, 2004; Rinaudo, 2006; Wan, *et al.*, 2004; Wu, *et al.*, 2000).

Chitosan is used in food industries for clarification of juices, production of biodegradable packaging films, antimicrobial agents, beverage clarification additives, flavour extenders and colour and texture stabilizers (Krajewska, 2005). Its nanoparticles (NP) are also used as anti-thrombogenic materials for controlled release and drugs encapsulation (Nadapdap, et al., 2014 and Oliveira, 2013).

It is also used for the delivery of anti-infectives such as antibacterial, antiviral, antifungal drugs (Jianglian, Shaoying 2013 and Hajidoun and Jafarpour 2013). Chitosan exhibits anti-fungal property against *Aspergillus niger*, *Rhizopus stolonifer*, *Rhizopus oryzae* etc., in its free polymer form. Chitosan nanoparticles can be a major source for the delivery of various drugs like heparin, chondroitin sulphate through oral route (Thi 2012, Mahmood, 2012 and Sarkar, 2012). Chitosan nanoparticles, being extremely low toxic are used as efficient vectors for gene delivery. Used as a potential adjuvant for vaccines against influenza, hepatitis (de Assis et al., 2012, Yu, et al., 2012).

Chitosan NP is also used in the dentistry to eliminate caries (i.e. decay and crumbling of a tooth or bone) (Mahoney et al., 2012). It is used as an additive in antimicrobial textile industry for producing clothes for health care professionals. The nanoparticles have also been proven to show skin regenerative properties, hence, they can be used in anti-aging skin care products (Moussa, 2011 and Nassif, 2012).

Health Benefits of Chitosan

For the lowering of serum cholesterol, in enzyme and cell immobilizations and as a material for the production of contact lenses or eye bandages (Synowiecki, 1986; Sandford, 1989; Bodnar, et al., 2007; Malafaya et al., 2007). It is further applied in drug delivery (Honarkar, and Barikani, 2009); enzyme immobilization (Kuo, et al., 2004); gene delivery vehicle, orthopedics, contact lenses, cosmetics, bacteriostatic agent, hemostatic agent, anticoagulant, antitumor agent (Özbas-Turan, et al., 2003); encapsulation of sensitive drugs (Alishahi, and Aider, 2012); medical textiles, suture, surface modification, guided bone regeneration (Ohkawa, et al., 2006); Scaffold for nerve tissue regeneration, wound healing (Kucharska, et al., 2007); wound care, dialysis membrane, antitumoral (Dhanikula, and Panchagnula, 2004); semi-permeable film for wound dressing, artificial skin (Kucharska, et al., 2011); adsorbent for pharmaceutical and medical devices, Surgical glove powder, enzyme immobilization, Mucosomal hemostatic dressing, enzyme entrapment Excipient (Illum, 1998) and spermicidal (Felse, Panda, 1999 and (Pereira, et al., 2005).

The design of artificial kidney systems has made possible repetitive hemodialysis and the sustaining life of chronic kidney failure patients. Chitosan membranes have been proposed as an artificial kidney membrane because of their suitable permeability and high tensile strength (Domard, and Domard, 2003). A series of membranes prepared from chitin and its derivatives improved dialysis properties (Lin, et al., 2003).

The development of efficient and safe gene carrier systems that are capable of transferring DNA in the cells is a major goal of the gene therapy. Several literature surveys show that chitosan is a suitable material for efficient non-viral gene therapy (Jayakumar, et al. 2010). Besides many good characteristics, chitosan has growth-inhibition effect on tumor cells (Carreno-Gomez, & Duncan, 1997). The ligand-targeted approach is expected to deliver drugs to tumor tissues selectively with high efficiency. Although *in vivo* studies of targeted chitosan nanoparticles are currently limited, results from *in vitro* studies have demonstrated their promise for applications in cancer treatment and diagnosis (Hang, 2010).

As chitosan shows antimicrobial activity, so its film has shown great promise for their applications in food preservation. The antimicrobial activity limits or prevents microbial growth by extending the interval period and reducing the growth rate or decreasing live counts of microorganisms (Han, 2000) which support the chitosan film for its potentiality in the packaging of food items and food preservation.

Gavhane, et al. (2013) reported wide biomedical applications of chitin and chitosan, however, he also highlighted some limitations such as allergy and constipation. Furthermore, people with intestinal mal-absorption syndroms should not use chitosan. Its adverse effects on the growth of children and on the outcome of pregnancy was also reported. However, application of chitin and chitosan have faced some limitation with high viscosity and low solubility at neutral pH (Kim, & Dewapriya, 2014).

The different properties like antimicrobial, anti-inflammatory and biomedical applications of chitosan based materials particularly wound dressings have been explored. Owing to its antimicrobial and anti-inflammatory nature, chitosan has shown to be a potential biomaterial to be used in potential wound healing (Shakeel, and Ikram, 2016). Effective dressings should have characteristics optimized for a particular type of wound at a reasonable low cost and with minimum inconvenience to patients. Many results have been reported, but complete and standard characterization of such materials is required.

Most materials formed in nature during the life cycles of green plants, animals, bacteria and fungi are polymers or polymer matrix composites. Biopolymers include the polysaccharides such as cellulose, starch, the carbohydrate polymers produced by bacteria and fungi and animal protein based biopolymers such as wool, silk, gelatin and collagen; biopolymers, especially the carbohydrate origin, have been found very promising industrial application in various forms (Akhilesh, and Singh, 2011).

DISCUSSION

Modification and enhancement of natural and environmental friendly polymers for replacing synthetic polymers is of interest for many scientists. Chitosan is a safe and friendly substance for the human organism; therefore, it has become of great interest not only as an underutilized resource, but also as a new functional material of high potential in various fields. Some unique properties make chitosan an excellent material for the development of new industrial applications and recent progress in chitosan material is quite noteworthy.

Polymer chemists and chemical engineers, pharmaceutical scientists are engaged in bringing out design predictable, controlled delivery of bioactive agents. Biodegradable polymers have been widely used in biomedical applications because of their known biocompatibility and biodegradability. In the biomedical area, polymers are generally used as implants and are expected to perform long term services. These improvements contribute to make medical treatment more efficient and to minimize side effects and other types of inconveniences for patients.

The main ingredient of making current commercial capsule shell is gelatin. Gelatin in use is generally obtained from cow bones and pork skin. Weakness of shell gelatin capsules of pork skin is that this product cannot be consumed by some, while gelatin made from bovine bones makes people worried about contracting mad cow disease from the cow. Therefore, the need of an alternative that can be used as the manufacture of gelatin capsule shell apart from pig skin or cow bone. Chitin/chitosan is processed into a capsule shell with high effectiveness. The magnitude of the benefits of chitin and chitosan as well as the availability of raw materials abundant shrimp shell, even a waste that can pollute the environment and damage the aesthetic environment, then these compounds need to get the most attention, especially in terms of efforts to use, research processes and products, as well as pollution prevention. Useful shrimp waste to produce chitosan products of high economic value as raw materials pharmaceutical industry, such as anti-hypercholesterol, and minimize pollution by industrial waste processing and utilizing frozen shrimp industry in order to create a clean and friendly environment (Sanusi 2004).

The special attention on chitosan has been paid for the repair of articular cartilage. Articular cartilage is particularly vulnerable to injury trauma, disease or congenital abnormalities because of its avascular, alymphatic and aneural nature. Once damaged, it has

little capacity for intrinsic repair. Although many repair techniques have been attempted in the past, but none has succeeded to regenerate long-lasting hyaline cartilage tissue to replace defected or damaged cartilage. Recently, preliminary studies on chitosan-glycosaminoglycan (CGAG) composite and its biologically interaction with articular chondrocytes showed promising results. Chitosan and its derivatives are being extensively used for bone tissue engineering and central nervous system (Francis, and Mathew, 2000).

Chitosan has been found to have an acceleratory effect on wound healing/wound dressing process. Regenerated chitin fibres, non-woven mats, sponges and films exhibit an increase in wound healing by over 30 percent. Chitin can also be used as a coating on normal biomedical materials. Standard silk and catgut sutures coated with regenerated chitin or chitosan show wound healing activities only slightly lower than the all-chitin fibres. Surgical gauze coated with regenerated chitin demonstrates a substantially greater amount of activity than an uncoated control group (Francis, and Mathew, 2000).

Chitosan is a promising candidate for burn treatment. This is true since chitosan can form tough, water-absorbent, biocompatible films. These films can be formed directly on the burn by application of an aqueous solution of chitosan acetate. Another advantage of this type of chitosan treatment is that it allows excellent oxygen permeability. This is important to prevent oxygen-deprivation of injured tissues. Additionally, chitosan films have the ability to absorb water and are naturally degraded by body enzymes. This fact means that chitosan needs not be removed. In most injuries (and specially burns), removing the wound dressing can cause damage to the injury site.

The design for artificial skin, applicable to long-term chronic use focuses on a non-antigenic membrane which performs as a biodegradable template for the synthesis of neodermal tissue. It appears that chitosan polysaccharides having structural characteristics similar to glycosamino-glycans can be considered for developing such substratum for skin replacement (Mucha, 1997). Nowadays the investigation on brain-scal damage, plastic skin surgery are being made by the use of chitosan.

Chitosan has replaced the synthetic polymers in ophthalmological applications. Chitosan possesses all the characteristics required for an ideal contact lens; optical clarity, mechanical stability, sufficient optical correction, gas permeability, partially towards oxygen, wettability, and immunologically compatibility. Contact lenses are made from partially depolymerized and purified squid pen chitosan by spin casting technology, and these contact lenses are clear, tough, and possess other required physical properties such as, modulus, tensile strength, tear strength, elongation, water content, and oxygen permeability. Antimicrobial and wound healing properties of chitosan along with excellent film forming capability make chitosan suitable for development of ocular bandage lens (Jing et al., 1996).

CONCLUSION

Chitin and chitosan can readily be derivatized by utilizing the reactivity of the primary amino group and the primary and secondary hydroxyl groups to find applications in diversified areas. In this review, attempt has been made to increase the understanding of the importance and characteristics of the chitin/chitosan by describing various aspects, including the chemical properties, biological properties, pharmacokinetic, interaction, processing, and applications. It is regarded as a useful compound in medical and pharmaceutical technology. It is widely used in nanomedicine, biomedical engineering and development of new therapeutic drug delivery

systems with enhanced bioavailability, specificity and reduced pharmacological toxicity. In view of this, this review will attract the attention of entrepreneurs, industrialists, academicians, environmentalists, medical scientist and the general populace.

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