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Pharmaceutical Diversity of Chitin and Chitosan: A Review

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Abstract
Chitin and Chitosan are abundant and versatile biomaterials resembling with the properties of cellulose. The deacetylate chitin derivative, chitosan is more useful and functional material of high potential in various fields due to its solubility and reactive free amino group (-NH_2). Based on current research, this review helps to understand the wide range characteristics and applications of chitin and chitosan in various industrial and biomedical areas.

Keywords: biomaterial, chitin, biodegradability, chitosan, medical applications

Introduction [1, 2-7]

Chitin is naturally abundant mucopolysaccharide which is secreted from crustaceans, insects, fungus, algae and related organisms. It is well known to consist of linear monomeric units of 2- acetamido-2-deoxy- D-glucopyranose attached through β-(1-4) linkages.

Its structure is similar to cellulose, but at C_2 position, it has an acetamide group ($NHCOCH_3$). Chitin is non-toxic, non-allergenic, bio renewable, environmentally friendly, biocompatible and biodegradable bio polysaccharide which is beneficial as chelating agent, drug carrier, sensitive adhesive tape and wound healing agent. Chitosan is the N-deacetylated derivative of chitin. Chitosan is considered as most promising materials for future applications because of its excellent biodegradability, biocompatibility, non-toxicity, antimicrobial activity, and its economic advantages. It is biodegradable polymeric material because after being disposed it can be recycled many times before promptly being decomposed by microorganisms or sunlight providing carbon dioxide and water. Chitin and chitosan are of commercial interest due to their high percentage of nitrogen (7.97%) compare to synthetically substituted cellulose. The present review is an attempt to discuss its sources, physical, chemical and biological properties along with its current applications.

What is it that makes it so special [1, 2, 6, 8]?

It is bio polysaccharide, the second most abundant natural carbohydrate on the earth after cellulose and a random mix of deacetylate (D-glucosamine) and acetylated (N-acetyl- D-glucosamine) units which is obtained from shells of crustaceans, such as crab and shrimp. Treating the shells with alkali gives water soluble natural polymer mostly at acidic pH along with excellent biocompatibility. This provide key to its many talent.

Fig 1: Raw chitin of different grade

Composition of chitosan

Table 1: Elemental composition of chitosan

S. No	Elements	% In Chitosan
1.	Carbon	44.11
2.	Nitrogen	7.97
3.	Hydrogen	6.84

Structure

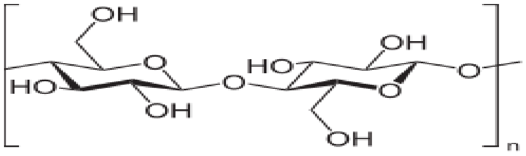

Fig 2: Structure of cellulose

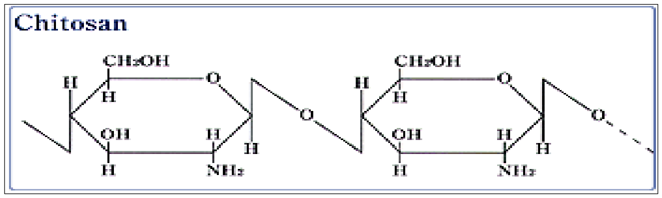

Fig 3: Structure of chitosan

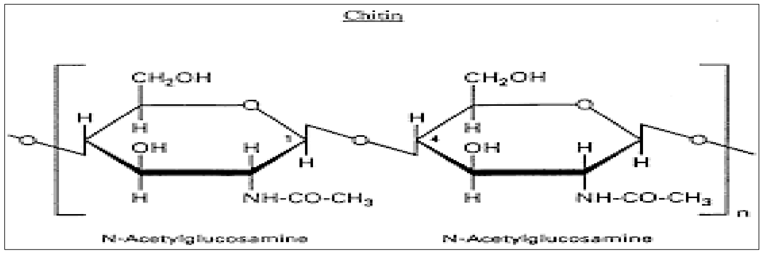

Fig 4: structure of chitin

Chitin and Chitosan Processing [9, 10]

Chitin is easily procured from crab or shrimp shells and fungal mycelia. The treatment of crustacean shells in the presence of alkali mainly involves the removal of proteins and the dissolution of high concentration of $CaCO_3$ which are present in a shell. The use of 40% NaOH for 1-3 h at 120^0C removes the shells protein, calcium carbonate and deacetylates the chitin simultaneously. This treatment is expected to produce 70% of deacetylated chitosan.

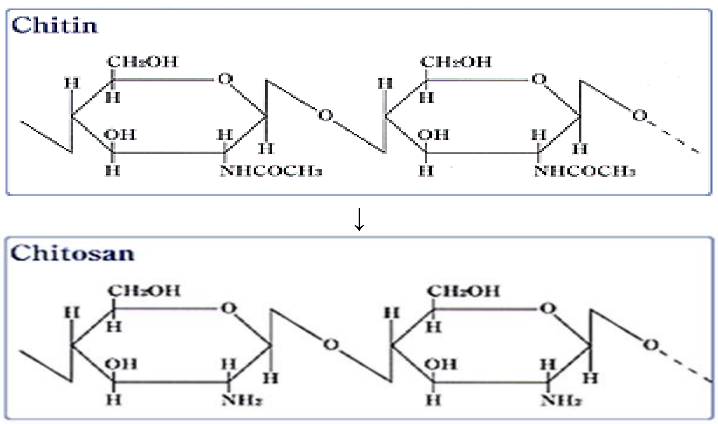

Fig 4

Properties of Chitin and Chitosan

a) Physical properties [1, 6, 9, 11-13]

In its pure, unmodified form, chitin is colourless to off-white, translucent, pliable, resilient, and quite tough nitrogenous polysaccharides. In most arthropods, however, it is often modified, occurring largely as a component of composite materials, such as in sclerotic, a tanned proteinaceous matrix, which forms much of the exoskeleton of insects. Combined with calcium carbonate, as in the shells of crustaceans and molluscs, chitin produces a much stronger composite. This composite material is much harder and stiffer than pure chitin, and is tougher and less brittle than pure calcium carbonate.

The structure of chitosan is very much like to that of cellulose and is the second most abundant natural polymer after cellulose. The solubility, biodegradability and reactivity of chitosan and adsorption of substrates depend on the extent of protonated amino groups in the chain of polymer. Chitosan is incapable of being dissolved in water, organic solvents and aqueous bases however get dissolved after stirring in acetic, nitric, hydrochloric, perchloric and phosphoric acids. The amino group of chitosan is not protonated in alkaline or neutral medium and therefore it is insoluble in water; while in acidic pH it gets the resultant soluble protonated polysaccharide. The molecular weight and degree of deacetylation affected the film properties. The increase in molecular weight of chitosan would increase the tensile strength and elongation as well as moisture absorption of the films, whereas the increase in degree of deacetylation of chitosan would either increase or decrease the tensile strength of the films depending on its molecular weight. Moreover, the higher the degree of deacetylation of chitosan the more brittle and the less moisture absorption the films became. All chitosan films were soluble in HCl-KCl and buffer (pH 1.2). They swelled in phosphate buffer (pH 7.4), and cross-linking between chitosan and phosphate anions might occur Finally, transmission infrared and 13C-NMR spectra supported that chitosan films prepared by using acetic acid as a dissolving were chitosonium acetate films.

b) Chemical properties [9, 10, 14-18]

- Molecular weight of Chitosan- 1526.464 g/mole

- Chitosan is natural linear polyamine with too much nitrogen content and reactive amino and hydroxyl groups.
- It behaves as weak base and its deprotonated amino group acts as a powerful nucleophile (pKa 6.3).
- It can form hydrogen bonds inter molecularly.
- It is high viscous consisting of great reactive groups for cross linking and chemical activation.
- It forms chelates with transitional metal ions like palladium, copper, silver and iodine which are useful as insecticides and in making photography health products.
- Biocompatible and biodegradable to normal body constituents.
- Chitin is insoluble in water and most organic solvents but soluble in hexafluoro-isopropanol, hexafluoroacetone, chloroalcohols in conjugation with aqueous solution of minerals acid. Its deacetylated form chitosan is soluble in DMSO and dilute acid like lactic acid, formic acid & acetic acid.
- Chitosan forms salts with organic and inorganic acids.
- It exhibits the property of ionic conductivity.

c) Biological properties [19-33].

Its unique natural biological properties such as broad antimicrobial activity against both Gram +ve and Gram -ve bacteria, biodegradability, biocompatibility, metal complexation and non-toxicity has gained attention with potential applications in agriculture, food industry, pharmaceuticals and textile industries. In fact, several commercial applications of chitosan take advantage of antimicrobial and bio-stimulating properties. Chitosan has been reported to induce innate immune response in plants against a broad spectrum of microbial species including fungi, bacteria and viruses. These biological properties have been playing a vital role in the field of agriculture. It has also played a significant role in dentistry because of its regenerative effects on connective gum tissue. Its broad spectrum biological activities are as follow: -

Table 2

Biological Activities	Mechanism of Action
Haemostatic: - +ve charge of chitosan allows to mucoadhesion with-vely charge of mucus.	Sorption of plasma Erythrocyte coagulation Platelet adhesion, aggregation & activation occurs. Promotes smooth muscle formation
Bactericidal: -	Due to electrostatic interaction between +ve charge of chitosan and -ve charge of microbial cell membrane cause membrane wall permeability and hydrolysis of the peptidoglycans in the microorganism. Its degradation product, chitoligosaccharide has anti-microbial effect for various MO.
Anti-inflammatory: -	Immune response to biopolymer material leads to aggregation of monocytes at the inflammation site. This monocyte get matured into macrophages and result in secreting various anti-inflammatory cytokines like:- IL-10 which act as healing factor.
Anti-tumour: -	Low molecular weight chitosan exerts anticancer activity through induction of apoptosis and cell cycle arrest in cancer cells.
Accelerates bone formation:	It improves bone forming capacity by increasing mechanical stability and biocompatibility. The release of platelet-derived growth factor-BB (PDGF-BB) from these chitosan matrices exerted significant osteoinductive and osteoconductive effects.
Immunological adjuvants:	By forming electrostatic complexes with anionic blood factors, it promotes platelet activation and stimulates neutrophils to release potent mediators.
Anticholesteremic	Dietary chitosan behaves as polycationic cellulose that forms film with negatively charged surfaces. Hence, negatively charged fatty and bile acid absorption from GIT is reduced.

Some derivatives of chitosan and its uses [10, 34-36]

a) N-Succinyl-chitosan-As a protein delivery and anticancer activity in the colon.
b) Trimethyl-chitosan ammonium- As a flocculating agent in a paper industry.
c) Mono-carboxymethyl-chitosan- As a chelating agent and additionally anti-oxidant.
d) Chitosan 6- O –sulphate- As an anticoagulant
e) N-methylene phosphonic chitosan- As a complexing agents in cosmetics.

Application of chitosan

1. As a pharmaceutical excipients [9, 3-40]

Uses of chitosan are amazingly diverse and has received considerable attention as a possible pharmaceutical excipient in recent time due to its good biocompatibility and low toxicity properties in both conventional dosage form as well as novel applications. Some of the general applications of chitosan in the pharmaceutical fields include: -

- Diluents in direct compression of tablets
- Binders in wet granulation
- Slow release of drugs from tablet and granules
- Films controlling drug release.
- As a wetting agents and improvement of dissolution of poorly soluble drug substances
- As a disintegrants and bioadhesive polymers
- As an implant and microparticles.
- Carrier in relation to vaccine delivery or gene therapy.

2. Wound healing/Wound dressing [21, 22, 41]

Chitosan has been found to have an acceleratory effect on wound healing/wound dressing process. It can be used as a coating on normal biomedical materials. Standard silk and catgut sutures coated with regenerated chitin or chitosan show wound healing activities.

3. Water engineering [6, 42, 43, 44]

Chitosan acts as heavy metal trapper. N-benzyl sulphonate derivatives of chitosan is used as sorbents for removal of metal ions in acidic medium and also be used to remove the colour from dye house effluents as reported by Weltroskiets *et al*. 1996. It acts as flocculent for recycling of food processing waste. It is also found to be effective in removing arsenic from contaminated water and petroleum products from waste water.

4. As a food and nutrition [45-47]
Because of its non-toxic and biocompatibility properties for warm blooded animals, chitosan is well known in food industry. It is used as a natural food preservative for sauces. Microcrystalline chitin (MCC) shows good emulsifying properties and gelling agent for stabilizing foods. It is also used as dietary fibre in baked foods. It could be of special importance for manufacturing protein fortified bread. It is also used in immobilization of enzymes. The N-acetyl glucosamine moiety present in animal milk promotes the growth of bifid bacteria, which impede the growth of other bacteria and generate the lactase required for digestion of milk lactose in human. This property may be of immense importance, since certain group of humans and many animals have lactose intolerance. It is also used to build up the weight of chicks for the commercial point of view.

5. Agricultural Applications [48-51]
Chitin and Chitosan have fungicidal activity against many phytopathogenic fungi. The antiviral and antibacterial properties of bio polysaccharides have been used successfully to control the parasitic nematodes in soil. Chitin treated seed (wheat) were found to have growth accelerating and growth enhancing effects. Covering of fruits and vegetables with a chitosan film grants them anti-septic protection and enhanced shelf life. Chitosan mixed soil also ensures improved germination and higher crop yielding.

6. Photography [52]
Chitosan has important uses in photography due to its resistance to abrasion, its optical characteristics and film forming ability. In colour photography, chitosan has been used as fixing agents for the acid dyes in gelatin and act as an aid to improve diffusion, an important step in developing photographs.

7. Cosmetics [53-55]
Chitin and Chitosan have fungicidal and fungistatic properties. Hence it is used as a preservative in many cosmetic formulations. These materials are used in creams, lotions and permanent waving lotions and several derivatives have also been reported as nail lacquers. It is also used in many healthcare products like shampoos, hair colorants, styling lotions, hair sprays, hair tonics. It can be also used as a salt in toothpaste, mouthwashes and chewing gum to prevent the formation of plaque and tooth decay.

8. Ophthalmology [56, 57, 58]
The diverse characteristics of chitosan fulfil all the parameters required for making an ideal lens: optical clarity, mechanical stability, gas permeability, wettability and immunological 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. The excellent film forming capability make chitosan suitable for development of ocular bandage lens.

9. Paper finishing [9, 59, 62]
Chitosan has been reported to impart wet strength and physical intensity to paper. Hydroxy-methyl chitin and other water-soluble derivatives are useful end additives in paper making. This polymer, although potentially available in large quantities, never became a commercially significant product. The entrepreneur in paper making can utilize this polymer for better finish paper properties. It is used as sizing agent and intensifier. Moreover, it is utilized as paper whiteness.

10. Drug- delivery system [63, 64, 65].
The drug delivery systems offer many advantages in therapy, which include: (a) reduce toxicity, (b) increase therapeutic index of drug and (c) prevent frequent, expensive and unpleasant dosing. Chitosan acts as inactive ingredient added to tablet or capsule to control the release of drug. Chitosan based porous scaffolds and its composite nanoparticles are of controlled microstructure have emerged as 3D matrix in a prolonged topical delivery of drugs.

11. Tissue engineering [66, 67, 68].
Tissue engineering is the development and manipulation of laboratory grown cells, tissue or organs that would replace or support the function of defective or injured parts of the body. This technique commonly need to employ three dimensional supports for initial cell attachment and subsequent tissue formation. Chitosan has similar structural characteristics as glycosaminoglycan's (GAGs) found in the extracellular matrix of several human tissues. Therefore, it has been used a lot in tissue engineering, because it makes cell attachment and the maintenance of differentiating functions easier. The special attention on chitosan has been paid for the repair of articular cartilage.

12. Textile industry [69, 70].
Derivatives of chitin are used to impart antistatic and soil repellent characteristics to the textiles. In textile industry, chitin can be used in printing and finishing preparations, while the chitosan can remove dyes from dye processing effluents. Besides these, chitin and chitosan both have made remarkable contribution to medical related textile sutures, threads, and fibres. The antibacterial and antimicrobial performance is given with the inhibition of bacteria's growth so having an anti- smell function too.

Conclusion
In the light of above fact is concerned, Chitin and Chitosan have diverse range of applications. They are subjected to solve various problems in biomedical engineering. This material can be used as a carrier of a variety of drugs for controlled release and prolonged action on the site of administration. Furthermore, chitin and chitosan exhibits various natural biological activities and pharmaceutical applications. Its formulation with drugs may have dual therapeutic effects. Thanks to nature for providing this world such a versatile polymer.

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