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CHITOSAN: A BIOCOMPATIBLE POLYMER FOR PHARMACEUTICAL APPLICATIONS IN VARIOUS DOSAGE FORMS

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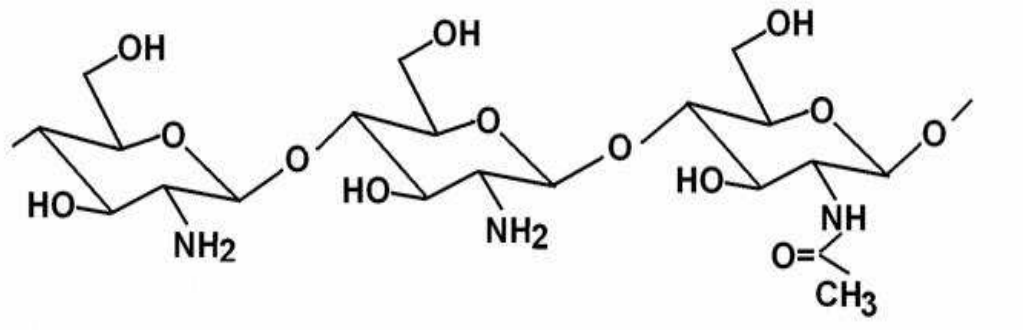
Abstract:

Chitosan is a weak cationic polysaccharide composed essentially of β(1→4) linked glucose amine units together with some acetyl glucose amine units. It is obtained by extensive deacetylation of chitin, a polysaccharide common in nature. Chitosan is biocompatible, biodegradable, and non toxic natural polymer that exhibits excellent film forming ability. As a result of its cationic character, chitosan is able to react with polyanions giving rise to polyelectrolyte complexes. Therefore, because of these interesting properties, it has become the subject of numerous scientific reports and patents on the preparation of micro spheres and microcapsules. The techniques employed to microencapsulate with chitoson include, among others, ionotropic gelation, spray drying, emulsion phase separation, simple and complex coacervation, and polymerization of vinyl monomer in the presence of chitosan. The aim of the work is to review some of the more common techniques used and to put forward the results obtained in preparing chitosan-based microcapsules: for taste masking and improving the stability of nutritional oil, the sustained release of drugs, as well as the preparation of chitosan super paramagnetic microcapsules for immobilization of enzymes.

Key Words: Chitosan, Drug delivery, Hydro gel, Micro encapsulation.

Chemical structure of chitosan:

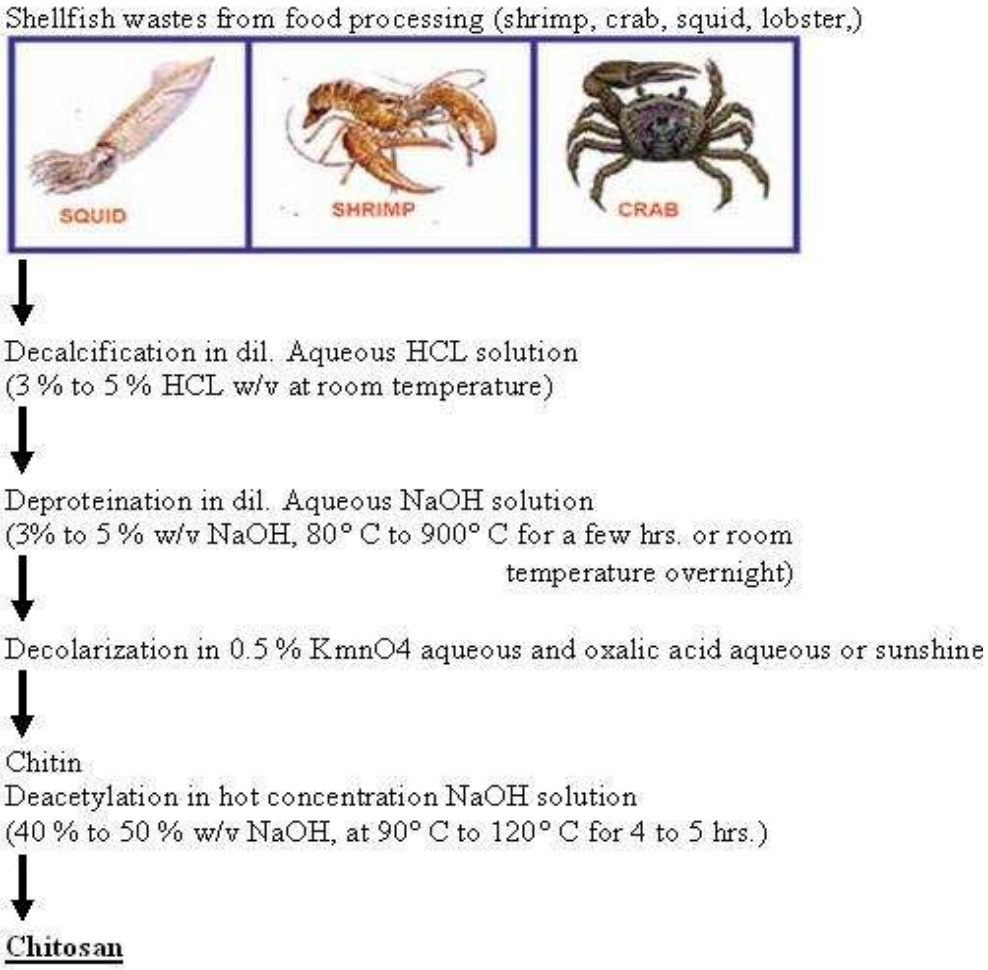


Introduction:

Chitosan is a polysaccharide obtained by deacetylating chitin, which is the major constituent of the exoskeleton of crustaceous water animals. Chitin accounts for approximately 70% of the organic components in such shells. Chitosan was reportedly first discovered by Rouget in 1859, when he boiled chitin in concentrated potassium hydroxide solution. This resulted in the deacetylation of chitin. In 1934, two patents one for producing chitosan from chitin and other for making films and fibers from chitosan was obtained by Rigby. Unlike oil and coal, chitosan is a naturally regenerating resource (e.g., crab and shrimp shells) that can be further enhanced by artificial culturing. Chitosan can selectively bind desirable materials such as cholesterol, fats, metal ions, proteins and tumor cells. Chitosan has also shown affinity for proteins, such as wheat germ agglutinin and trypsin. Other properties that make chitosan very useful include inhibition of tumor cells, antifungal effects, acceleration of wound healing, stimulation of immune system, and acceleration of plant germination. [1].

Preparation of Chitosan:

Figure 1: preparation of chitin and chitosan shellfish wastes from food processing (shrimp, crab, lobster, squid)



The crude chitosan is dissolved in aqueous 2 % w/v acetic acid. Then the insoluble material is removed giving a clear supernatant solution, which is neutralized with NaOH solution resulting in a purified sample of chitosan as a white precipitate. Further purification may be necessary to prepare medical and pharmaceutical-grade chitosan.

Different studies on Chitosan and its derivatives:

1) Tozaki and coworkers utilized Chitosan capsules for colon-specific delivery to treat ulcerative colitis. A 5-amino salicylic acid was encapsulated in chitosan capsules and delivered in vivo to male wistar rats after induction of colitis. It was observed that chitosan capsules disintegrated specifically in

the large intestines as compared to the control formulation (in absence of chitosan), which demonstrated absorption of drug in small intestine. This data is a representative example of utility of chitosan for colon- specific delivery. [2]

2) Glipizide microspheres containing Chitosan were prepared by simple emulsification phase technique using glutaraldehyde as a cross-linking agent. Results of preliminary training indicate that volume of cross-linking agent, time for cross linking, polymer to drug ratio, and speed of rotation affected characteristics of microspheres. Microspheres were discrete, spherical and free flowing. The Microspheres exhibit good mucoadhesive property in the in-vitro wash off test and showed high percentage drug entrapment efficiency. [3]

3) Insulin-chitosan nanoparticles were prepared by the ionotropic gelation of chitosan glutamate and tripolyphosphate pentasodium and by simple complexation of insulin and chitosan. The nasal absorption of insulin after administration in chitosan nanoparticle formulations and in chitosan solution and powder formulations was evaluated in anaesthetised rats and/or in conscious sheep. Insulin-chitosan nanoparticle formulations produced a pharmacological response in the two animal models, although in both cases the response in terms of lowering the blood glucose levels was less (to 52.9 or 59.7% of basal level in the rat, 72.6% in the sheep) than that of the nasal insulin chitosan solution formulation (40.1% in the rat, 53.0% in the sheep). The insulin-chitosan solution formulation was found to be significantly more effective than the complex and nanoparticle formulations. The hypoglycaemic response of the rat to the administration of post-loaded insulin-chitosan nanoparticles and insulin-loaded chitosan nanoparticles was comparable. As shown in the sheep model, the most effective chitosan formulation for nasal insulin absorption was a chitosan powder delivery system with a bioavailability of 17.0% as compared to 1.3% and 3.6% for the chitosan nanoparticles and chitosan solution formulations, respectively. [4]

4) Intratumoral and local drug delivery strategies have gained momentum recently as a promising modality in cancer therapy. In order to deliver paclitaxel at the tumor site in therapeutically relevant concentration, Chitosan films were fabricated. Paclitaxel could be loaded at 31% (w/w) in films, which were translucent and flexible. Chitosan films containing paclitaxels were obtained by casting method with high loading efficiencies and the chemical integrity of molecule was unaltered during preparation according to study. [5]

5) The positively charged polysaccharide chitosan is able to increase precorneal residence time of ophthalmic formulations containing active compounds when compared with simple aqueous solutions. The purpose of the study was to evaluate tear concentration of tobramycin and ofloxacin after topical application of chitosan-based formulations containing 0.3% wt/vol of antibiotic and to compare them with 2 commercial solutions: Tobrex® and Floxal®, respectively[6].

6) Metronidazole was formulated in mucoadhesive vaginal tablets by directly compressing the natural cationic polymer chitosan, loosely cross-linked with glutaraldehyde, together with sodium alginate with or without microcrystalline cellulose (MCC). Sodium carboxymethylcellulose (CMC) was added to some of the formulations. The drug content in tablets was 20%. Drug dissolution rate studies from tablets were carried out in buffer pH 4.8 and distilled water. Swelling indices and adhesion forces were also measured for all formulations. The formula containing 6% chitosan, 24% sodium alginate, 30% sodium CMC, and 20% MCC showed adequate release properties in both media and gave lower values of swelling index compared with the other examined formulations. This also proved to have good adhesion properties with minimum applied weights. Moreover, its release properties (percentage dissolution efficiency, DE) in buffer pH 4.8, as well as release mechanism (n values), were negligibly affected by aging. Thus, this formula may be considered a good candidate for vaginal mucoadhesive dosage forms [7].

7) In controlled released drug matrices cross linked chitosan sponges has been used as drug carrier system. Here Tramadol hydrochloride, a centrally acting analgesic, was used as a model drug. The sponges were prepared by freeze drying 1.25% and 2.5% (w/w) high and low molecular weight chitosan solution,respectively, using glutaraldehyde as a cross linking agent. The formulation made by this sponges has shown the release data followed the Higuchi model over 12 hours [8].

8) The antimicrobial activity of chitosan in lipid emulsions as well as in aqueous solution was investigated. It was originate that lipid emulsions containing 0.5% chitosan conformed to the requirements of the preservation efficacy test for topical formulations according to the European Pharmacopoeia while the emulsion without chitosan and a lactic acid solution with and without the biopolymer did not conform. In hemolysis studies on human erythrocytes, the hemolytic activity of the lipid emulsions with chitosan was assessed. These emulsions showed a negligible hemolytic behavior. The results point toward a use of chitosan as antimicrobial preservative in emulsion formulations for mucosal as well intended for parenteral applications [9].

Chitosan Esters:

Chitosan esters such as Chitosan succinate and Chitosan phthalate have been used successfully as potential matrices for colon-specific oral delivery of sodium diclofenac[10]. converting the polymer from an amine to succinate form, the solubility profile is changed significantly. The modified polymers were insoluble under acidic conditions and provided sustained release of the encapsulated agent under basic conditions. The same researchers also synthesized an iron cross-linked derivative of hydroxamated Chitosan succinate, as a matrix for oral theophylline beads. A similar colon-targeting application was suggested for this polymer as well [11].

Chitosan conjugates:

Reactivity of the amine functionality can be exploited to covalently conjugated functional exceipients to the polymer backbone. For example , Guggi and Bernkop attached an enzyme inhibitor to chitosan. The resulting polymer retained the mucoadhesivity of the chitosan and further prevented drug degradation by inhibiting enzymes such as trypsin and chymotrypsin[12]. This conjugated chitosan demonstrated delivery of sensitive peptide drugs such as Calclitonin.

N-Trimethylene chloride chitosan (TMC):

A number of studies demonstrated that the charge on chitosan has a role in providing intestinal permeability. Hence, a quaternary derivatized chitosan (N-trimethylene chloride chitosan) was shown to demonstrate higher intestinal permeability than chitosan alone. The TMC derivative was used as a permeation enhancer for large molecules, such as octreotide, a cyclic peptide. Hamman and coworkers showed that the degree of quaternization of TMC influences its drug absorption-enhancing properties [13]. Polymers with higher degrees of quaternization (> 22%) were able to reduce the transepithelial electrical resistance and thereby epithelial transport (in vitro) in a neutral environment (pH 7.4). The maximum reduction in transepithelial resistance was reached with TMC with a degree of quaternization of 48%. This degree of quaternization was also seen to be optimum for in vitro transport of model drugs across a Caco-2 monolayer.

General pharmaceutical applications of Chitosan:

Due to its good biocompatibility and low toxicity properties in both conventional exciepient applications as well as in novel application, chitosan has received considerable attention as a pharmaceutical exceipient in recent decades. Some of the general applications of chitosan in pharmaceutical fields are [14]:

- Drug carrier in micro particle systems
- Slow release of drugs from tablets and granules
- Bioadhesive polymer
- Disintegrant and biodegradable polymer (implants, micro particles)
- Binder in wet granulation
- Diluents in direct compression of tablets
- Films controlling drug release
- Carrier in relation to vaccine delivery or gene therapy
- Site-specific drug delivery (e.g. to the stomach or colon)
- Absorption enhancer (e.g. for nasal or oral drug delivery)

Pharmaceutical applications of Chitosan in various dosage forms:

In conventional solid dosage forms:

Chitosan's film forming abilities lend itself well as a coating agent for conventional solid dosage forms such as tablets. Furthermore its gel- and matrix-forming abilities make it useful for solid dosage forms, such as granules, microparticles, etc. Sakkinen and coworkers studied microcrystalline chitosan as a gel-forming excipient for matrix-type drug granules. Crystallinity, molecular weight, and degree of deacetylation were seen to be factors that affected the release rates from the chitosan-based granules. Combination of positively charged chitosan with negatively charged biomolecules, such as gelatin, alginic acid, and hyalouronic acid, has been tested to yield novel matrices with unique characteristics for controlled release of drugs.

Increase stability of drug:

Chitosan polymer is use to increase the stability of the drug in which the drug is complexes with chitosan and make slurry and kneading for 45 minutes until dough mass. This dough mass is pass through sieve no.16 and make a granules is completely stable at different condition.

Orthopaedic patients:

Chitosan is a biopolymer that exhibits osteo conductive, enhanced wound healing and antimicrobial properties which make it attractive for use as a bioactive Coating to improve Osseo integration of orthopedic and craniofacial implant devices. It has been proven to be useful in promoting tissue growth in tissue repair and accelerating wound-healing and bone regeneration.

Cosmetics industry:

Cosmetic compositions are disclosed for the treatment of hair or skin, characterized by a content of new quaternary chitosan derivatives of the formula. The chitosan derivatives have a good substantively, particularly to hair keratin, and prove to have hair strengthening and hair conditioning characteristics. e.g.; Hair setting lotion, Oxidation Hair-coloring Composition, Hair-toning Composition, Skin Cream, Hair-treatment Composition, Gel-form.

Dental Medicine [10]:

Chitin / chitosan have been recognized to accelerate wound healing to attain an aesthetically valid skin surface, and to prevent excess scar formation. In dental medicine, chitin / chitosan is also applied as a dressing for oral mucous wound and a tampon following radical treatment of maxillary sinusitis. Furthermore, it is being investigated as an absorbing membrane for periodontal surgery.

Chitin / chitosan has a variety of biological activities and advertised as a healthy food that is effective for improvement and/or care of various disorders, arthritis, cancer, diabetes, hepatitis, etc. In Japan , it is renowned since a three-year old Russian boy whose skin was burnt 90 % in total area

dramatically recovered thanks to the chitin / chitosan dressing (Beschitin-WR, Unitika , Japan) in August, 1990.

For oral drug delivery: Preliminary study on film dosage form

The potential of chitosan films containing diazepam as an oral drug delivery was investigated in rabbits. The results indicated that a film composed of a 1:0.5 drug-chitosan mixture might be an effective dosage form that is equivalent to the commercial tablet dosage forms. The ability of chitosan to form films may permit its use in the formulation of film dosage forms, as an alternative to pharmaceutical tablets. The pH sensitivity, coupled with the reactivity of the primary amine groups, make chitosan a unique polymer for oral drug delivery applications.

Chitosan as Permeation Enhancer:

It has been reported that chitosan, due to its cationic nature is capable of opening tight junctions in a cell membrane. This property has led to a number of studies to investigate the use of chitosan as a permeation enhancer for hydrophilic drugs that may otherwise have poor oral bioavailability, such as peptides [15]. Because the absorption enhancement is caused by interactions between the cell membrane and positive charges on the polymer, the phenomenon is pH and concentration dependant. Furthermore increasing the charge density on the polymer would lead to higher permeability.

Chitosan as Mucoadhesive Excipient:

Bioadhesivity is often used as an approach to enhance the residence time of a drug in the GI tract, thereby increasing the oral bioavailability. A comparison between chitosan and other commonly used polymeric excipients indicates that the cationic polymer has higher bioadhesivity compared to other natural polymers, such as cellulose, Xantham gum, and starch[16].

Ophthalmic Drug Delivery:

Chitosan exhibits favorable biological behavior, such as bioadhesion, permeability-enhancing properties, and interesting physico-chemical characteristics, which make it a unique material for the design of ocular drug delivery vehicles [17]. Due to their elastic properties, chitosan hydro gels offer better acceptability, with respect to solid or semisolid formulation, for ophthalmic delivery, such as suspensions or ointments, ophthalmic chitosan gels improve adhesion to the mucin, which coats the conjunctiva and the corneal surface of the eye, and increase precorneal drug residence times, showing down drug elimination by the lachrymal flow. In addition, its penetration enhancement has more targeted effect and allows lower doses of the drugs [18]. In contrast, chitosan based colloidal system were found to work as transmucosal drug carriers, either facilitating the transport of drugs to the inner eye (chitosan-coated colloidal system containing indomethacin) or their accumulation into the corneal/conjunctival epithelia (chitosan nanoparticulate containing cyclosporine). The micro particulate drug- carrier (micro spheres) seems a promising means of topical administration of acyclovir to the eye [19]. The duration of efficacy of the ofloxacin was increased by using high MW (1930 kd) chitosan [20].

Gene Delivery:

The course of many hereditary diseases could be reversed by gene delivery. In addition, many acquired diseases such as multigenetic disorders and those diseases caused by viral genes could be treated by genetic therapy [21]. Gene delivery systems include viral vectors, cationic liposomes, polycation complexes, and microencapsulated systems [22,23]. Viral vectors are advantageous for gene delivery because they are highly efficient and have a wide range of cell targets. However, when used in vivo they cause immune responses and oncogenic effects. To overcome the limitations of viral

vectors, non-viral delivery systems are considered for gene therapy. Non-viral delivery system has advantages such as ease of preparation, cell/tissue targeting, low immune response, unrestricted plasmid size, and large-scale reproducible production [24]. Chitosan has been used as a carrier of DNA for gene delivery applications. Also, Chitosan could be a useful oral gene carrier because of its adhesive and transport properties in the GI tract. MacLaughlin et al [25]. Showed that plasmid DNA containing cytomegalo virus promoter sequence and a luciferase reporter gene could be delivered in vivo by Chitosan and depolymerized Chitosan oligomers to express a luciferase gene in the intestinal tract.

Preparation of micro spheres:

A novel cellulose acetate/chitosan multimicrospheres (CA/CM) was prepared by the method of w/o/w emulsion. The concentration of cellulose acetate (CA) and the ratio of CA/chitosan (CS) had influence on the CACM size, and appearance. Ranitidine hydrochloride loading and releasing efficiency in vitro were investigated. The optimal condition for preparation of the microspheres was CA concentration at 2% and the ratio of CA/CS at 3:1. The microspheres size was 200–350 μm. The appearance of microspheres was spherical, porous, and non aggregated. The highest loading efficiency was 21%. The ranitidine release from the CACM was 40% during 48 hr in buffers.

Cholesterol-lowering effects [26]:

Fibres with a range of abilities to perturb cholesterol homeostasis were used to investigate how the serum cholesterol-lowering effects of insoluble dietary fibres are related to parameters of intestinal cholesterol absorption and hepatic cholesterol homeostasis in mice. Cholestyramine, chitosan and cellulose were used as examples of fibres with high, intermediate and low bile acid-binding capacities, respectively. The serum cholesterol levels in a control group of mice fed a high fat/high cholesterol (HFHC) diet for 3 weeks increased about 2-fold to 4·3mM and inclusion of any of these fibres at 7·5%

of the diet prevented this increase from occurring. In addition, the amount of cholesterol accumulated in hepatic stores due to the HFHC diet was reduced by treatment with these fibres. The three kinds of fibres showed similar hypocholesterolaemic activity; however, cholesterol depletion of liver tissue was greatest with cholestyramine. The mechanisms underlying the cholesterol-lowering effect of cholestyramine were,

1) Decreased cholesterol (food) intake,

2) Decreased cholesterol absorption efficiency, and

3) Increased faecal bile acid and cholesterol excretion.

The latter effects can be attributed to the high bile acid-binding capacity of cholestyramine. In contrast, incorporation of chitosan or cellulose in the diet reduced cholesterol (food) intake, but did not affect either intestinal cholesterol absorption or faecal sterol output. The present study provides strong evidence that above all satiation and satiety effects underlie the cholesterol-lowering.

Taste masked by spray drying:

Chitosan polymer and drug are dissolved in suitable solvent. Sonication done by ultracentrifuge, after stirring 24 hrs with magnetic stirrer, after completely loading polymer to drug, it way from sprays drying the complexes and evaluate for taste masking, threshold concentration of bitterness was determine and complexes was characterization with the help of XRPD, FT-IR, DSC and SEM. If Complexation was achieve, % of drug content was determine and equivalent weight of complexes taken and formulate it. Dissolution of the chitosan – drug complexes tablet give sustain released effect.

Enhanced bone formation by transforming growth factor [11] :

Chitosan composite microgranules were fabricated as bone substitutes for the purpose of obtaining high bone-forming efficacy. The microgranules have the flexibility to fill various types of defect sites with closer packing. The interconnected pores formed spaces between the microgranules, which

allowed new bone ingrowth and vascularization. In addition, the transforming growth factor-beta 1 (TGF-pl) was incorporated into the microgranules in order to improve bone-healing efficacy. The chitosan microgranules were fabricated by dropping a mixed solution into a NaOH/ethanol solution. TGF-pl was loaded into the chitosan microgranules by soaking the microgranules in a TGF-pl solution. Scanning electron microscopy (SEM) observations and experiments examining the release of TGF-pl from chitosan and the collagen/chitosan microgranules were performed. SEM was used to examine the cell morphologies on the microgranules and cell proliferation was evaluated using a dimethylthiazole tetrazolium bromide assay. The differentiated cell function was assessed by measuring the alkaline phosphatase (ALPase) activity as well as detecting an osteocalcin assay. The in vivo bone-regeneration experiments were performed using a rabbit calvarial defect model. TGF-pl was released from the collagen/chitosan microgranules at a therapeutic concentration for 4 weeks. SEM indicated that the seeded osteoblastic cells were firmly attached to the microgranules and proliferated in a multilayer manner. The proliferation of the osteoblasts on the TGF-pl-loaded microgranules was the highest among the different types of microgranules tested. The ALPase activity and osteocalcin level of all the samples increased during the culture period, and the TGF-pl-loaded microgranules had a significantly higher ALPase activity and osteocalcin content than the other microgranules. The TGF-pl-loaded microgranules demonstrated a higher bone-regenerative capacity in the rabbit calvarial defects after 4 weeks than the TGF-pl-unloaded microgranules.

Chitosan is an attractive material for multiple applications including the following:

Application	Summary
Biomedical	
Cell delivery Drug delivery Orthopedics	Chitosan is biocompatible [27-28]. Shows antimicrobial and antifungal activities [2-29], which makes it a favorable option for biomedical applications.
Skin treatment Wound healing Surgical sutures	It has been proven to be useful in tissue growth in tissue repair and accelerating wound-healing and bone regeneration[15,16].
Ophthalmology Bone healing Dentistry Pharmaceuticals	Chitosan can be incorporated into hydro gels and micro spheres which demonstrate large potentials in delivery systems for drugs proteins and genes.
Nutritional	
Cholesterol-lowering effects	Chitosan has strong positive charge; studies indicate that chitosan's charge helps it bind to fats and cholesterol and initiates clotting of red blood cells[30].
Fiber and weight loss Effects	It acts as fiber; the fiber like properties can be used to replace calories in foods.
Cosmetics	
Skin care Hair care Oral care	Chitosan's strong positive charge allows it to bind to negatively charged surfaces such as hair and skin which makes it a useful ingredient in hair and skin products.

Conclusion:

Biologically degradable polymers can be loosely distinct as a class of polymers, which degrade to smaller fragments due to chemicals present inside the body. Natural polymers are always biodegradable because they undergo enzymatically promoted degradation. Chitosan is one of them which exhibit biodegradability, scrawny antigeneity and better quality biocompatibility compared with supplementary natural polymer. Chitin in fact, is one of the most important polysaccharide bring into being in nature, assembly Chitosan a plentiful and moderately inexpensive product. Chitosan has recently sparked significance in tissue-engineering field. Chitosan has been used in the blueprint of many different types of drug carriers for various administration rules such as oral, bucal, nasal, transdermal, parenteral, cervical, vaginal, intrauterine and rectal. It can be engineered into poles apart shapes and geometrics such as nanoparticles, micro spheres, membrane, sponge and rods. On drug delivery special preparation techniques are used to put in order chitoan drug carriers by culturing such parameters as cross linker concentration, chitosan molecular weight, drug/polymer ratio and processing conditions all of which impinge on the morphology of chitosan drug carriers and release rate of loaded drugs.

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