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CHITOSAN NANOPARTICLES AS A THERAPEUTIC DELIVERY SYSTEM

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ABSTRACT
Chitosan is a cationic polymer derived from chitin found in insects and crustaceans. In it's nanosize form chitosan has shown to be very effective as targeted delivery system with wide applications. The remarkable properties of chitosan such as biodegradability, biocompatibility and bioavailaibilty make's it very suitable as a carrier for therapeutic molecules. In addition the properties like controlled release of the molecule or protein at the carrier site, easy modification of the chitosan surface and attachment to ligand's makes it an excellent choice as a delivery system. Chitosan nanoparticles can be used as vaccine vectors because of its muco-adhesiveness. It attaches to the mucosal surfaces of the body like gastrointestinal, respiratory and the nasal tract. This review explores the properties and therapeutic uses of chitosan nanoparticles as a delivery system for drugs, anti-microbials, vaccine , anti-cancer agents and wound healing polymer.

KEYWORDS: Chitosan nanoparticles, Biomaterial, drug delivery system, antimicrobial delivery system, vaccine vector, wound healing.

INTRODUCTION
Chitin is a naturally occurring polymer found in wide variety of organisms like algae, fungi, yeast, shells of insects and crustaceans.[1] A non-toxic polymer chitosan is formed on deacetylation of chitin. Chitosan nanoparticles exhibit antibacterial activity as the positive charge on the chitosan nanoparticles react with the negative charge on the bacterial surface resulting in bacterial cell lysis.[2] Chitosan nanoparticles also interact with the fungus cell membrane and impair the fungal cell.[3]

Chitosan nanoparticles (colloidal particles in the size range from 10-1000 nm in diameter) have been prepared by various methods like ionic gelation, emulsion solvent diffusion, reverse micellisation, emulsification, nanoprecipitation, spray drying, cross linking by aldehyde, tripolyphosphate geniptin, carboxylic groups, polyelectrolyte complex (PEC) method, coprecipitation method.[4] The applications of chitosan nanoparticles has increased tremendously in recent times for encapsulation in pharmaceutical drugs, anti-cancer agents, anti-microbial agents, pesticides and herbicides in agriculture and food packaging in food industries. This review discusses the current applications of chitosan nanoparticles in pharmaceuticals, loading antimicrobials and therapeutic agents.

The dual nature of chitosan as a linear polyamine having a number of free amine groups which are available for cross-linking and as cation which can cross-link with multivalent anions makes it very suitable for preparation of nanoparticles for controlled drug delivery system. Chitosan nanoparticles are increasingly being used as drug –delivery system because of the following factors.

a) Bio-degradibility- The important advantage of using chitosan as a biomaterial is its bio-degradibility due to which it can be easily and safely eliminated from the human body. Chitosan undergoes bio-degradation by enzymatic hydrolysis and acidic dissolution. Enzymes like lysozyme, chitinase and chitonase in saliva, blood, tears and macrophages can cleave glycosidic bond in chitosan.[5] Chitosan solubilizes in acidic environment of stomach or lysosomes. It is not soluble in alkaline or neutral pH. Chitosan degrades to oligosaccharides and monosaccharides of glucosamine which are non-toxic and can be safely eliminated from the body.[6]
b) Muco-adhesion- Chitosan is a muco-adhesive material which can attach to the body's mucosal sites such as gastro-intestinal tract, respiratory tract, ocular and vaginal tract. This increases the drug – delivery and bioavailability of the drug by penetrating the mucosal membranes.[7]

c) Surface modifiability- Chitosan bound nanoparticles can be surface modified to positively charged particles. They then become a highly efficient delivery which is more stable, soluble and bioavailable.[8]
d) Stimuli-responsiveness- The flexibility of chitosan nanoparticles to respond to various stimuli like pH, light, temperature, enzymes, redox potential makes it suitable to encapsulate and deliver drugs.[9] The efficient delivery by chitosan nanoparticles across different physiological barriers such as blood brain barrier, interstitial fluid pressure, extracellular matrix is due to small size of 10 to 200nm.[10] Since chitosan nanoparticles respond to internal and external stimuli their efficiency can be increased as a controlled drug delivery system.

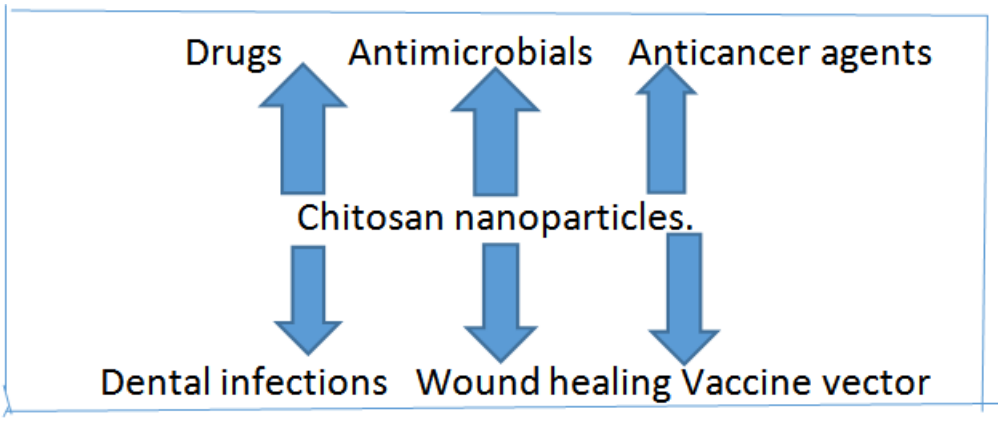

Fig 1: Therapeutic applications of Chitosan nanoparticles.

Application in loading drugs and antimicrobials: Chitosan nanoparticles in the size range of (119±9 nm to 227±18nm) have been used to load antihistaminic drug olapatidine hydrochloride by the method of spray drying. Chitosan nanoparticles loaded with resveratrol by liquid –liquid dispersion method improved sustained release of resverastrol in gastro intestinal fluids because of its mucoadhesive effect.[11] Similarly lithium loaded chitosan nanoparticles enabled controlled release of lithium to treat pulmonary pheochromocytoma cells as compared to direct use of lithium carbonate which caused pulmonary toxicity.[12] Khalil *et al* prepared propranolol loaded chitosan nanoparticles for the treatment of infantile hemangioma by double emulsion technique. Propranolol loaded chitosan were effectively absorbed two times more as compared to direct application on the skin.[13] Chitosan nanoparticles have been also used as efficient hemostatic agent. Epinephrine loaded chitosan nanoparticles were capable of inducing red blood cell absorption and aggregation thereby resulting in increased blood coagulation.[14]

Chitosan nanoparticles are now increasingly being used for loading and delivering antimicrobials including antibacterial, antiviral agents and as vaccine vector. Because of the many properties of polymer such as biocompatibility, bioavailability, biodegradability, non-toxicity and the most important its muco adhesiveness it is permeable and diffuses across cell membranes. Ciprofloxacin loaded chitosan nanoparticles were prepared against pathogenic *Pseudomonas aeruginosa*.[15] In another study rifaximin loaded chitosan nanoparticles were used to treat inflammatory bowel disease (IBD) so as to improve the drug solubility and controlled release in the bowel.[16] An increase in therapeutic efficacy for vulvo-vaginal candidiasis was observed using miconazole loaded chitosan nanoparticles versus topical cream application.[17] Parasites have also been targeted using chitosan nanoparticles. Tachzoites in liver, spleen and brain found in human toxoplasmosis were targeted with spiramycin –loaded chitosan nano particles and a 90% reduction in tachzoites was observed. Chitosan nanoparticles loaded with amphotericin were used in a study for leishmaniasis treatment.[18] Chitosan nanoparticles loaded with ciprofloxacin, colistin have been studied against drug resistant *Staphylococcus aureus* and *Escherichia coli* showing a significant decrease in minimum inhibitory concentration values. Chitosan nanoparticles loaded with levofloxacin were used in therapy for eye infection by *Pseudomonas aeruginosa* and *Staphylococcus aureus* and a higher bacterial clearance was reported.[19] In dentistry also studies on chitosan nanoparticle for disinfection of contaminated gutta-percha cones showed no CFU units at 1-5 min of immersion time. The topographical changes on the gutta percha cones observed by atomic force microscopy were also significant as compared to control.[20] Mausavi *et al* loaded chitosan nanoparticles with phages to combat drug resistant bacteria. Cp-1 phage loaded CNP's have been used against drug-resistant *Streptococcus pneumoniae*.[21] In our study *Enterococcus faecalis* phages were loaded in chitosan-alginate nanoparticles and studied as a delivery system to combat drug-resistant oral biofilms.[22] The encapsulated phages were observed to have the potential to be used as phage therapy in oral diseases.

Chitosan nanoparticles drug delivery system has also been explored for viral diseases. Pegylated chitosan

nanoparticles loaded with different doses of lamivudine have been used to inhibit HIV virions.[23] In another study Si RNA coupled with antibody –modified chitosan nanoparticles was delivered across the blood-brain barrier to target HIV-infected brain cells and inhibit HIV multiplication.[24] Hepatitis C virus has been targeted with chitosan –curcumin loaded nanoparticles and were found to be effective.[25]

Application in loading anticancer agents

Cancer is one of the leading cause of death worldwide presently and by the year 2030 will be the top cause.[26] The anticancer agents have poor bioavailability and greater side effects. Many studies have been conducted using anticancer drug's utilizing chitosan nanoparticles. These drugs include Paclitaxel, Trastuzumab, Pembrilizumab, Vinblastine, Doxorubicin, Methotrexate, Rosmaninic acid, Kaempferol. These studies have demonstrated improved bioavailability, controlled and targeted release of the drug thereby overall improving the efficacy and minimum toxicity.[27] To further increase the efficacy of anti- cancer loaded drug chitosan – nanoparticles they have been bound to ligands like antibodies, aptamers, peptides, folate. Chitosan was liganded to folate and used in adeno-carcinoma cell lines.[28] Doxorubicin and Piperine P-gp inhibitors were bound and loaded in chitosan nanoparticles to target doxorubicin tumour. Controlled drug release was observed. Chitosan-alginate nanoparticles loaded with doxorubicin by water in oil (w/o) emulsion was targeted for murine breast cancer cell line and controlled release was observed.[29] Similarly chitosan- alginate has been utilized for curcumin diethyl diglutarate showing better efficacy then curcumin diethyl diglutarate alone.[30] Biotin-avidin liganded chitosan nanoparticles against pulmonary melanoma had a higher uptake efficiency.[31] Succinate bound chitosan nanoparticles showed 2 times more uptake for Docetaxel then used alone.[32] There are recent reports of pre-clinical research using chitosan nanoparticles loaded SiRNA to target prostate cancer cells.[33] Use of chitosan nanoparticles biosensors to detect biomarkers for cancer such as CA 125 or PSA has shown improved imaging.[34]

Applications in vaccines and wound healing

Chitosan nanoparticles were first used in nasal vaccine for influenza A as carriers by conjugating H1 N1 antigen. To overcome the variation in influenza A virus vaccine was made using chitosan nanoparticles conjugated to hemagglutinin subunit 2 and nucleoprotein (NP).[35] Chitosan polymers are being tried in nasal vaccination for Hepatitis B. Mucosal vaccines using chitosan encapsulated EIT (a recombinant protein) to target hemolytic uremic syndrome caused by *E.coli* (EHEC) 0157:H7 having a high mortality rate have been designed. romp22 a protein from *Acinetobacter baumanii* which is a multi-drug resistant pathogen have been loaded in chitosan –PLGA nanoparticles and tried as mucosal vaccine candidate.[36] Antigen from *Brucella abortus*, Mdh (malate dehydrogenase)has also been used for nasal vaccination in murine.[37] The muco-adhesiveness of chitosan makes it a suitable material for wound healing. Carboxy methyl chitosan (CMC)/oxidized dextran hydrogel for wound dressing with improved wound healing properties. Gelatin based alginate –chitosan hydrogel has been tried efficiently. Gold nanoparticles (Au NPs) bound with chitosan nanoparticles in treatment of diabetic ulcer have been formulated. Chitosan coated on gold nanoparticles has been successfully used for the control of cariogenic bacteria in the oral cavity. These nanoparticles exhibited a strong antimicrobial activity against *Streptococcus mutans* ATCC 25175 and *Streptococcus sobrinus* ATCC 33402 with an inhibition zone of 15.90 and 14.25 mm.[38] The vast applications of chitosan nanoparticles have been demonstrated but limitations like toxicity profile of chitosan nanoparticles is still under investigation. Similarly the chitosan nanoparticle need to be more aptly designed for an efficient encapsulation, minimum immunotoxicity and the waste generated during making need to be disposed of more efficiently.

Conclusion and future research

Chitosan nanoparticles as a delivery system have shown promising results. Reduced to nanosize the chitosan particles have shown remarkable properties which can be used in therapeutics. This biomaterial has versatile properties including bioavailability, biodegradability, biodegradability, biocompatibility making it a very suitable therapeutic agent with minimal systemic toxicity. Chitosan moiety can be modified by binding various ligands resulting in controlled release of the drug thereby an effective treatment. Because of muco-adhesion of chitosan nanoparticles it can be administered through nasal and oral route for vaccination. Pre- clinical and clinical trials using chitosan nanoparticles as delivery system to combat drug resistance, effective vaccination, targeted anti-cancer agents and therapeutics needs to be focused in future research study.

Conflict of Interest

The authors declare no conflict of interest.

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