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Recent advancement in Chitosan based formulations and its pharmaceutical application

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ABSTRACT

Chitosan is a cationic natural polysaccharide obtained by deacetylation of chitin, the second most abundant polysaccharide in nature. Most important characteristics of chitosan are that it is biologically safe, biocompatible, biodegradable polysaccharide and non-toxic natural polymer that exhibits excellent film forming ability. Chitosan and their nanoparticles have gained more attention as drug delivery carriers because of their better stability, low toxicity, simple and mild preparation method. Recent applications of chitosan are in ophthalmic, nasal, sublingual, buccal, periodontal, gastrointestinal, colon-specific, vaginal, transdermal drug delivery and as mucosal-vaccine and gene carrier. The objectives of this review are to summarize the available derivatives of chitosan and formulation based on chitosan and to discuss importance of chitosan in numerous delivery systems.

Keywords: Chitosan, chitin, microspheres, biodegradable polymer, Drug delivery carriers.

INTRODUCTION

Chitosan is a natural polymer obtained by the hydrolysis of chitin, a native polymer present in shellfish. Together with chitin, chitosan is considered the second most abundant polysaccharide after cellulose. The use of chitosan as an excipient in pharmaceutical formulations is a relatively new development. The polymer differs from chitin in that a majority of the N-acetyl groups in chitosan are hydrolyzed. The degree of hydrolysis (deacetylation) has a significant effect on the solubility and rheological properties of the polymer. The amine group on the polymer has a pKa in the range of 5.5 to 6.5, depending on the source of the polymer [1]. At low pH, the polymer is soluble, with the sol-gel transition occurring at approximate pH 7. The pH sensitivity, coupled

with the reactivity of the primary amine groups, make chitosan a unique polymer for oral drug delivery applications. Chitosan obtained from partial deacetylation of chitin, is a polysaccharide comprising copolymers of glucosamine and N-acetylglucosamine.

Chitosan is commercially available in several types and grades that vary in molecular weight between 10000 and 1000000 and vary in degree of deacetylation and viscosity [2]. Technically speaking, chitosan is a naturally occurring substance that is chemically similar to cellulose which is a plant fiber. Like plant fibers, chitosan possesses many of the same properties as fiber, however unlike plant fiber; it has the ability to significantly bind fat, acting like a "fat sponge" in the digestive tract. It attracts the bio-hazardous substances like greases, oils, heavy metals and other potentially toxic substances from the water and it is used for detoxifying water. Chitosan is used for this purpose in water purification plants throughout the nation [3].

Chitosan is a cationic polyelectrolyte present in nature. Chitosan has shown favorable biocompatibility characteristics [4] as well as the ability to increase membrane permeability, both *in-vitro* [5] and *in-vivo* [6] and be degraded by lysozyme in serum.

From a biopharmaceutical point of view, chitosan has the potential of serving as an absorption enhancer across intestinal epithelial for its mucoadhesive and permeability enhancing property. It has been proved that chitosan could enhance insulin absorption across human intestinal epithelial cells without injuring them [7-9]. Chitosan has been used in preparing films, beads, intragastric floating tablets, microspheres and nanoparticles in the pharmaceutical filed [10-16]. Chitosan (poly[-(1,4)-2-amino-2-deoxy-D-glucopiranose] has a structure as shown in Figure

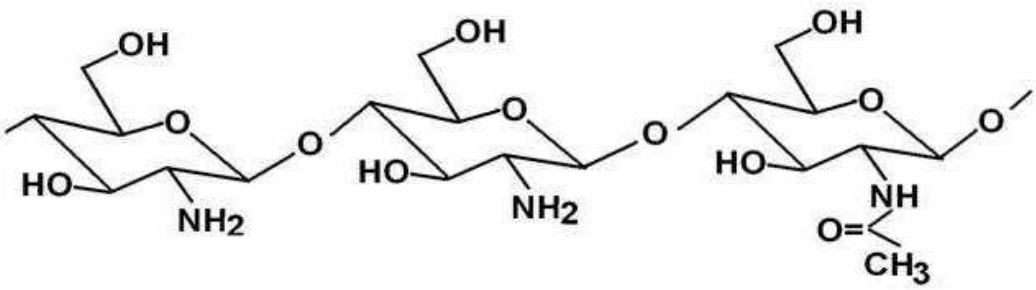

Fig 1 : Chemical Structure of Chitosan

Chitosan opens the tight junction of the mucosal barrier and facilitates the paracellular transport of hydrophilic macromolecules [17-18]. The strong mucoadhesive properties of chitosan point to its potential as a permeation enhancer for mucosal drug delivery. [19-20] Due to mucoadhesive properties of chitosan drug strongly adheres to mucosa and MCC is decreased thus increasing the residence time of drug in nasal cavity which results in increase in absorption.[21-22]

Chitosan has found a number of applications in several drug delivery systems, by virtue of its high biocompatibility, biodegradability and lack of toxicity associated with gel- and film-forming abilities, bioadhesiveness, dissolution and transmucosal penetration enhancer properties [23-24]. Chitosan first attracted the attention of biopharmaceutical scientists as a mucoadhesive

polymer that could be useful for peptide drug delivery. Furthermore, its antacid and antiulcer activities were exploited to reduce gastric irritation caused by active compounds, such as anti-inflammatory drugs [25]. Chitosan is widely used as a dissolution enhancer for poor solubility drugs, the low cost and abundant availability of chitosan offers high flexibility for pharmaceutical scientist to use chitosan as an excipient of choice in drug delivery system [26-27].

Derivatives of chitosan

Chitosan provides a number of excellent properties, further derivatization of the amine functionalities can be carried out to obtain polymers with a range of properties. A number of approaches, both chemical and enzymatic, have been tried to exploit the reactivity of the amine functional groups [1].

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. 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.

Chitosan Esters

Chitosan esters, such as chitosan succinate and chitosan phthalate have been used successfully as potential matrices for the colon-specific oral delivery of sodium diclofenac[28]. By converting the polymer from an amine to a 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 [29]. A similar colon-targeting application was suggested for this polymer as well.

Chitosan Conjugates

Reactivity of the amine functionality can be exploited to covalently conjugate functional excipients to the polymer backbone. For example, Guggi and Bernkop attached an enzyme inhibitor to chitosan. The resulting polymer retained the mucoadhesivity of chitosan and further prevented drug degradation by inhibiting enzymes, such as trypsin and chymotrypsin [30]. This conjugated chitosan demonstrated promise for delivery of sensitive peptide drugs, such as calcitonin.

Water-soluble derivative of chitosan at neutral pH

Chitosan and its derivatives soluble in pH values of lower than 6.0 may not be desirable for usage in medicine, cosmetics and food [31] . To improve its solubility at neutral pH, it is first

derivatized with substituents containing quaternary amino group [32], caboxymethylation and then sulfatation by adding strongly hydrophilic substituent [33]

N- sulfonated derivatives of chitosan

These are amphoteric in nature. They can be prepared under heterogeneous reaction condition using 2-sulfobenzoic acid anhydride [34]. N-sulfonato-N,O-carboxymethylchitosan: a novel polymeric absorption enhancer for the oral delivery of macromolecules [35].

Quaternarized derivatives

The simplest derivative is the trimethyl ammonium salt of chitosan. A repeated treatment of chitosan in N-methyl-2 pyrrolidone containing sodium iodide and methyl iodide with chloride ion in presence of sodium hydroxide results into the trimethyl ammonium salt of chitosan with high degree of substitution [36]. Anionic changes of iodide with chloride ion are necessary for stabilization. The resulting product is water soluble at neutral pH [37].

Caboxyalkylation

The process of caboxyalkylation introduces acidic group on the polymer backbone. This derivative exhibits amphotericity due to the presence of native amino group. These derivatives also exhibit an isoelectric point as that of other amphoteric molecules. Water solubility is attained at pH values above or below the isoelectric point. Formation of N- carboxyalkylation uses carboxyaldehyde in a reductive amination sequence [38]. The reaction is carried out under homogeneous condition provided that the aldehyde used is water, allowing for greater degree of substitution distribution along the polymer back-bone. However, sequential substitution giving rise to the formation of bis-carboxymethyl derivatives have been observed using glyoxalic acid [39].

Stability and storage condition

Chitosan powder is a stable material at room temperature, although it is hygroscopic after drying. It should be stored in cool, dry place; preferably at a temperature of 2-8 $^{\circ}$C. Chitosan is incompatible with strong oxidizing agent [40].

Specifications & characteristics of pharmaceutical-grade chitosan

The pharmaceutical requirements for chitosan include: a white or yellow appearance (powder or flake), particle size < 30 m, density between 1.35 and 1.40 g/cm^3, a pH of 6.5 to 7.5, moisture content < 10%, residue on ignition <0.2%, protein content <0.3%, degree of deacetylation 70% to 100%, viscosity <5 cps, insoluble matter <1%, heavy metals (As) <10 ppm, heavy metals (Pb) <10 ppm and no taste and smell [41].

Formulations based on chitosan

Chitosan Pellets

The extraction of chitosan with a degree of deacetylation of >99% led to a stable process at a fixed power consumption level of 120W. Other chitosan properties made it necessary to adjust the power consumption to a higher level. The extrusion of chitosan with a degree of deacetylation of 90 % at a power consumption level of 120 W resulted in a lack of granulation liquid in the wet powder mass.

Consequently, the mass accumulated in front of the die plate and blocked the holes; therefore, the extrusion had to be stopped. As indicated by the low standard deviation of the power consumption, a stable extrusion process was only possible at a 99.9% degree of deacetylation. With a decreasing degree of deacetylation of the used chitosan, the extrusion process became unstable [42].

Chitosan Microporous semipermeable membrane coating

Chitosan in acetone containing different levels of pore forming agent (chitosan) is used as coating formulation. The weight gains of microporous semipermeable membrane are 10%, 12% and 14%, respectively. PEG 400 (25% of total coating materials) acted as a hydrophilic plasticizer and is added to enhance the physical–mechanical property of chitosan membrane. The coating conditions are as follows: stainless steel pan, 200mm diameter; 4 baffles; rotation rate of the pan, 40 rpm; nozzle diameter of spray gun, 1 mm; spray rate, 3mL/min; spray pressure, 2 bar; drying temperature, 40° C. The surface morphology of the coated tablets is a little bit rough even though the fine micronized chitosan powder (400 mesh 98% pass, mean particle size 35µm) is used. After coating, the tablets are dried for 12 h at 50 °C to remove residual solvent [43].

Chitosan Microparticle

Chitosan is dissolved in 0.5% acetic acid solution at 1% (w/v) concentration. Rizatriptan benzoate is dissolved at 1% (w/v) concentration in 96% ethanol [44]. This solution is then mixed with chitosan solution and subjected to spray drying under optimized process parameters. Increasing concentrations of chitosan are used .The prepared microparticles are then collected from drying chamber and cyclone separator carefully and then stored in dry atmosphere.

Chitosan solution of different pH

Typical chitosan/β-GP solution is obtained by dissolving 200mg of chitosan in 10ml of acetic solution (0.1mol.mL). 560mg of β-GP powder is then added to the incubated solution in ice bath under stirring. The mixing is then continued for 30—60min [45―47]. The final pH of this system is adjusted to 7.2—7.4 by dropwise addition of saturated disodium hydrogen phosphate solution. Chitosan with different molecular weight and deacetylation degree is used according their chitosan specification.

Chitosan Nanoparticles

Chitosan nanoparticles are prepared by ionic gelation method. Different concentrations of polymer, ranging from 0.10 to 0.75 %w/v, are dissolved in 1.5 %v/v acetic acid solution. Sodium tripolyphosphate solution is also prepared in distilled water in concentrations ranging from 0.10 to 0.75 %w/v. Sodium tripolyphosphate solution is added dropwise with a syringe to chitosan solution while stirring, followed by sonication for 20 min. The resulting suspension is subsequently centrifuged at 15000 rpm for 10 min. The pellets obtained are re-suspended in deionised water by sonication, centrifuged and dried at room temperature .Drug-loaded chitosan nanoparticles are formed spontaneously upon dropwise addition of 12 ml of 0.4 % aqueous sodium tripolyphosphate solution to 20 ml of 0.35%w/v chitosan solution containing 2 – 5 mg/ml of the drug under magnetic stirring, followed by sonication. The resulting nanoparticle suspensions are centrifuged 4 times (15 min each) at 15000 rpm washed with distilled water and dried [48].

Insulin formulations

Chitosan is dispersed in deionized water and hydrochloric acid is added into the above system under agitation until chitosan is dissolved completely. The pH of this solution is about 4.0. Insulin-chitosan nanoparticles can be 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[49].

Preparation of micro spheres

A novel cellulose acetate/chitosan multimicrospheres are prepared by the method of w/o/w emulsion. The concentration of cellulose acetate and the ratio of cellulose acetate /chitosan had influence on the cellulose acetate chitosan multimicrospheres size and appearance. Ranitidine hydrochloride loading and releasing efficiency in vitro were investigated. 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 cellulose acetate chitosan multimicrospheres was 40 % during 48 hr in buffers [50].

Nasal morphine chitosan solution formulation

Nasal morphine chitosan solution are prepared by dissolving 50 mg of chitosan glutamate in 10 ml of 0.5% sodium chloride solution (pH adjusted to 4 with 1 M HCl) and filtering through a 0.2-μm membrane filter (Satorius) [51-53]. Morphine hydrochloride (150 mg) is added to 5 ml of this chitosan solution. The final formulation contained 30 mg/ml morphine hydrochloride in an isotonic (osmolality of 0.301 Osmol/kg) 0.5% chitosan glutamate solution at pH 3.81.

Nasal morphine chitosan microsphere

The nasal morphine chitosan microsphere formulation is prepared by suspending 800 mg of cross-linked chitosan microspheres (prepared using a conventional water-in-oil emulsification technique) in 10 ml of distilled water and adding 5 ml of a 24.0 mg/ml morphine hydrochloride solution and 38 ml of distilled water. The mixture is stirred for 20 min and freeze-dried by using an Edwards Modulyo 4 K freeze-dryer [52-53]. The powder is stored desiccated at 4°C until use.

Pharmaceutical applications of chitosan polymer in drug delivery system

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 [54]. 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 [55]. 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 [56]. The duration of efficacy of the ofloxacin was increased by using high MW (1930 kd) chitosan [57].

Gene delivery

Gene delivery systems include viral vectors, cationic liposomes, polycation complexes, and microencapsulated systems [58-59]. 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 [60]. 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 [61] 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.

Intratumoral and local drug delivery

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. [62]

Oral drug delivery

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 [63].

Nasal drug delivery

The nasal mucosa presents an ideal site for bioadhesive drug delivery systems. Chitosan based drug delivery systems, such as micro spheres, liposomes and gels have been demonstrated to

have good bioadhesive characteristics and swell easily when in contact with the nasal mucosa increasing the bioavailability and residence time of the drugs to the nasal route. Various chitosan salts such as chitosan lactate, chitosan aspartate, chitosan glutamate and chitosan hydrochloride are good candidates for nasal sustained release of vancomycin hydrochloride [64]. Nasal administration of Diphtheria Toxoid incorporated into chitosan microparticles results in a protective systemic and local immune response against Diphteria Toxoid with enhanced IgG production. Nasal formulations have induced significant serum IgG responses similar to secretory IgA levels, which are superior to parenteral administration of the vaccine [65]. Nasal absorption of insulin after administration into chitosan powder were found to be the most effective formulation for nasal drug delivery of insulin in sheep compared to chitosan nanoparticles and chitosan solution.

Buccal drug delivery

Chitosan is an excellent polymer to be used for buccal delivery because it has muco/bioadhesive properties and can act as an absorption enhancer [66]. Buccal tablets based on chitosan microspheres containing chlorhexidine diacetate gives prolonged release of the drug in the buccal cavity improving the antimicrobial activity of the drug[67]. Chitosan microparticles with no drug incorporated have antimicrobial activity due to the chitosan. The buccal bilayered devices (bilaminated films, palavered tablets) using a mixture of drugs (nifedipine and propranolol hydrochloride) and chitosan, with or without anionic crosslinking polymers (polycarbophil, sodium alginate, gellan gum) has promising potential for use in controlled delivery in the oral cavity[68].

Gastrointestinal drug delivery:

Chitosan granules having internal cavities prepared by deacidification when added to acidic and neutral media are found buoyant and provided a controlled release of the drug prednisolone [69]. Floating hollow microcapsules of melatonin showed gastroretentive controlled-release delivery system. Release of the drug from these microcapsules is greatly retarded with release lasting for 1.75 to 6.7 hours in simulated gastric fluid. Most of the mucoadhesive microcapsules are retained in the stomach for more than 10 hours e.g., Metoclopramide and glipizide loaded chitosan micro-spheres [70].

Peroral drug delivery:

As chitosan and most of its derivatives has a mucoadhesive property, a presystemic metabolism of peptides can be strongly reduced leading to a strongly improved bioavailability of many perorally given peptide drugs, such as insulin, calcitonin, and buserelin [71]. Unmodified chitosan has a permeation-enhancing effect for peptide drugs. A protective effect for polymer-embedded peptides towards degradation by intestinal peptidases can be achieved by the immobilization of enzyme inhibitors on the polymer. The mucoadhesive property of chitosan gel can be enhanced by threefold to sevenfold by admixing chitosan-glyceryl mono-oleate. Drug release from the gel followed a matrix diffusion controlled mechanism [72]. Nifedipine embedded in a chitosan matrix in the form of beads have prolonged release of drug compared to granules [72].

Vaginal drug delivery

Chitosan, modified by the introduction of thioglycolic acid to the primary amino groups of the polymer, embeds clotrimazole, an imidazole derivative, is widely used for the treatment of mycotic infections of the genitourinary tract. By introducing thiol groups, the mucoadhesive properties of the polymer are strongly improved and this is found to increase the residence time of the vaginal mucosa tissue (26 times longer than the corresponding unmodified polymer), guaranteeing a controller drug release in the treatment of mycotic infections [73]. Vaginal tablets of chitosan containing metronidazole [74] and acriflavine have showed adequate release and good adhesion properties [75].

Transdermal drug delivery

Chitosan has good film-forming properties. The drug release from the devices is affected by the membrane thickness and cross-linking of the film [76]. Chitosan-alginate polyelectrolyte complex has been prepared in-situ in beads and microspheres for potential applications in packaging, controlled release systems and wound dressings [77]. Chitosan gel beads are a promising biocompatible and biodegradable vehicle for treatment of local inflammation for drugs like prednisolone which showed sustained release action improving therapeutic efficacy [78]. The rate of drug release was found to be dependent on the type of membrane used. A combination of chitosan membrane and chitosan hydrogel containing lidocaine hydrochloride, a local anesthetic, is a good transparent system for controlled drug delivery and release kinetics.

Colonic drug delivery

Chitosan has been used for the specific delivery of insulin to the colon [79]. The chitosan capsules were coated with enteric coating (Hydroxy propyl methyl cellulose phthalate) and contained, apart from insulin, various additional absorption enhancer and enzyme inhibitor. It was found that capsules specifically disintegrated in the colonic region. It was suggested that this disintegration was due to either the lower pH in the ascending colon as compared to the terminal ileum or to the presence bacterial enzyme, which can degrade the chitosan.

Multiparticulate delivery system

H.Steckel and F. Mindermann-Nogly [80] have prepared chitosan pellets using the extrusion/spheronization technology. Microcrystalline cellulose was used as additive in concentrations range from 0-70 %. The powder mixtures was extruded using water and dilute acetic acid in different powder to liquid ratios. The study showed that chitosan pellets with a maximum of 50 %(m/m) could be produced with demineralized water as granulating fluid. The mass fraction of chitosan within in the pallets could be increased to 100% by using dilute acetic acid for the granulation step.

Importance of chitosan polymer in pharmaceutical field

Chitosan polymer play a very important role in current drug delivery systems described as:-

- 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)

The positively charged polysaccharide chitosan is able to increase precorneal residence time of ophthalmic formulations containing active compounds when compared with simple aqueous solutions [81]

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[81].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 [82].

The chitosan/β-GP thermosensitive gel forming system has the potential to benefit not only the long-term drug delivery system of birth control, general hormone-replacement, immunization and cancer chemotherapy, but also the tissue engineering and cell transportation. However , this pre-gel solution has low pH (~ 7.15) and low mechanical strength, which leads to slow gel-forming and rapid drug release

Other important utilizations of chitosan polymer

Cholesterol-lowering effects

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 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 [81]

Increase stability of drug
Chitosan polymer is used to increase the stability of the drug in which the drug is complexed 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 [82].

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 substantial, 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
Chitosan have been recognized to accelerate wound healing to attain an aesthetically valid skin surface, and to prevent excess scar formation. In dental medicine, 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. 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 [83].

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 [84]. 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, hereby 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 [85].

Effect of chitosan: citric acid ratio on drug release
It has been demonstrated that polymer with appropriate viscosity and expanding property can be used as osmotic agents for the release of water-insoluble drug [86]. Due to its high molecular weight and a linear unbranched structure, chitosan is completely biodegradable, toxicologically

harmless and low cost, and exhibits an excellent gelation characteristic [87]. Hence the potential for chitosan to be used as a polymeric osmotic agent in osmotic pump is obvious. The hydration and gel formation of chitosan are very much dependent on the pH of surroundings. It is insoluble at an alkaline and neutral pH but soluble at acid condition. Upon dissolution, amine groups of the polymer become protonated, forming a resultant viscous and soluble polysaccharide. Inclusion of citric acid as pH-regulating excipient in the developed formulations was expected to decrease the microenvironmental pH of the core to a suitable level at which chitosan could form appropriate viscous gelling solution and hence, to enhance the osmotic pressure of core tablets.

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Enhanced bone formation by transforming growth factor (TGF-pl)

Chitosan composite microgranules were fabricated as bone substitutes for the purpose of obtaining high bone-forming 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 [89].

Direct compressible excipients and as binder

Chitosan has an excellent property as excipients for direct compression of tablets where the additions of 50% chitosan result in rapid disintigration. The degree of deacetylation determine the extent of moisture absorption [90].Chitosan higher then 5%, was superior to corn starch and microcrystalline cellulose as a disintigrant .The efficiency was dependent on chitosan crystalinity, degree of deacetylation, molecular weight and particle size [91] Chitosan is found to be excellent tablet binder as compared to other excipients with the rank order co-relation for binder efficiency. Hydroxy propyl methyl cellulose >chitosan> Methyl cellulose>Sodium carboxy methyl cellulose [92].

Wound healing properties

Efficacy of chitosan in the promotion of wound healing was first reported in 1978 [93]. Chitosan acetate films, which were tough and protective, had the advantage of good oxygen permeability, high water absorptivity and slow enzymatic degradation.

CONCLUSION

Chitosan is biocompatible and show the activities such as antimicrobial and antifungal activities, which makes it a favorable option for biomedical applications. It has been proven to be useful in tissue growth, in tissue repair and accelerating wound-healing and bone regeneration. Chitosan polymer are incorporated into hydro gels and micro spheres which demonstrate large potentials in delivery systems for drugs proteins and genes.

Chitosan has strong positive charge and this charge helps it to bind fats and cholesterol and initiates clotting of red blood cells. Chitosan have fiber like properties which can be used to replace calories in foods.

It can also be used in the pharmaceutical industry in direct tablet compression, as tablet disintegrant, for the production of controlled release solid dosage form or for the improvement of drug dissolution.

Chitosan has been postulated in numerous areas of biopharmaceutical research such as mucoadhesion, permeation enhancement, vaccine technology, gene therapy and wound healing. Recent applications of chitosan are in ophthalmic, nasal, sublingual, buccal, periodontal, gastrointestinal, colon-specific, vaginal, transdermal drug delivery and mucosal-vaccine and gene carrier.

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