Academic Sciences

International Journal of Current Pharmaceutical Research

ISSN- 0975-7066 Vol 7, Issue 2, 2015

Review Article

CHITOSAN: A MULTIFACET POLYMER

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Received: 05 Mar 2015, Revised and Accepted: 30 Mar 2015

ABSTRACT

Objective: Chitosan is considerably versatile and promising biomaterial. It is a natural, tough, cationic, nontoxic, biodegradable, and biocompatible polymer obtained by alkaline deacetylation of chitin. Chitin is a polysaccharide obtained from exoskeletons of crustaceans and sea insects such as crab, krill, shrimp and crawfish etc. Besides the formerly mentioned resources it is also obtained from some fungi and bacterial cell walls.

Methods: Chitosan has found wide applicability in conventional pharmaceutical devices as a potential formulation excipient, some of which include binding, disintegrating, stabilizing, suspending, tablet coating, and film forming material. Chitosan has been comprehensively investigated for its suitability for its controlled release characteristics in various studies. Chitosan presents remarkable absorption and penetration enhancing properties that makes it a good candidate for the delivery of genes and peptide.

Results: It is possessing tremendous mucoadhesive and inherent anti-microbial properties, so that it can be used as a carrier for novel drug delivery. In addition to the above mentioned reasons, tailoring the controlled release and to improve the therapeutic efficacy of the low molecular weight drug compounds can also be achieved by this polymer and moreover in combination with various polymers is feasible due its compatibility i.e. low chemical reactivity.

Conclusion: This brief editorial epitomizes the potential application of chitosan in the development of drug delivery systems.

Keywords: Chitosan, Drug delivery, Gene delivery, Pharmaceutical applications.

INTRODUCTION

Chitin, the second most abundant natural polysaccharide, is a straight homopolymer composed of β (1, 4)-linked GlcNAc (N-acetyl glucosamine) units with a three dimensional α-helical configuration stabilized by intramolecular hydrogen bonding [1]. Partial deacetylation of chitin results in the production of chitosan, which is a polysaccharide comprising copolymers of glucosamine and N-acetyl glucosamine.

Since chitosan exhibits favorable biological properties such as non-toxicity, biocompatibility, and biodegradability, it has attracted widespread interest in the pharmaceutical and biomedical fields [2, 3]. Along with these properties it also possesses some medical applications such as antimicrobial, hypocholesterolemic, antitumor, anti-inflammatory, antioxidant, angiotensin-I-converting enzyme (ACE) inhibition, excluding toxins from the intestines, reducing heavy-metal poisoning in humans, mucoadhesive, haemostatic, analgesic, radio-protective properties, preventing tooth decay and tooth diseases and immunity enhancing activities [4]. It is also widely used in biomedical industries for enzyme immobilization and purification, in chemical plants for wastewater treatment and in food industries for food formulations as binding, gelling, thickening and stabilizing agent [5].

The term chitosan is used to describe a series of chitosan polymers with different molecular weights (50 kDa to 2000 kDa), viscosity and degree of deacetylation [3]. The chemical structure of chitin and chitosan is shown in (fig. 1).

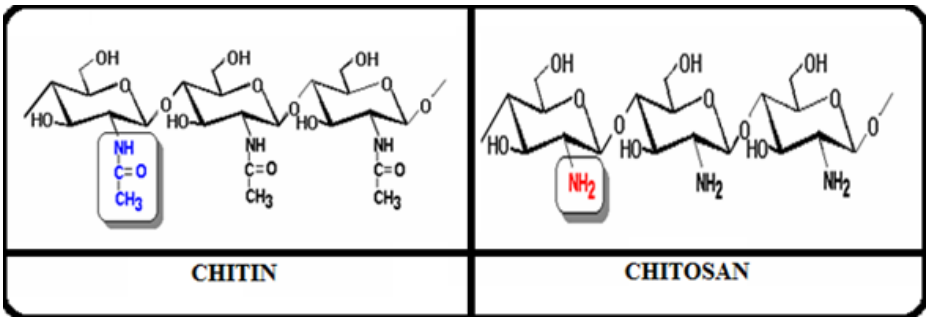

Fig. 1: Chemical structure of chitin and chitosan [6]

Application in drug delivery

Chitosan is widely used for nasal, vaginal, ophthalmic, transdermal & topical, buccal, parenteral, colon-specific and in implantable drug delivery etc. due to its favorable biological properties. Purity, the degree of acetylation, viscosity and molecular weight are the imperative factors of the chitosan ought to be taken in to consideration while selecting chitosan for the precise drug delivery. For the reason that, these qualities of this polymer decides the selection of an apt grade of chitosan as a material/carrier for a specific drug delivery [7].

This biodegradable polymer can be dissolved in mineral acid and organic acid aqueous solutions at particular conditions i.e. soluble in dilute acidic solutions below pH 6 [8-10]. The polyelectrolytic natures as well as chelating ability of the amine groups of the macromolecule determine the applications of chitosan. The amine groups of chitosan are protonated to NH_3^+ in acidic solution, and accordingly chitosan's polyelectrolytic and chelating properties are essentially dominated by the acidity of the-NH_3^+[11]. It is used in the form of tablets, gels etc. (table 1).

Table 1: **List of chitosan based formulations prepared by different methods [12]**

Types of systems	Methods of preparation	Drugs
Tablets	Matrix	5-ASA, Diclofenac Sodium, Theophylline, Mesalamine, Glipizide.
	Coating	Propranolol HCl.
Capsules	Capsule shell	Insulin.
Microspheres/Microparticles	Emulsion cross-linking	Gentamicin Sulphate, Hemoglobin, Diclofenac, Clarithromicin.
	Coacervation/precipitation	Propranolol-HCl.
	Spray-drying	Cimetidine, Famotidine, Bovine serum albumin.
	Ionic gelation	Bovine serum albumin.
	Sieving method	Clozapine.
Nanoparticles	Emulsion-droplet coalescence	Gadopentetic acid.
	Coacervation/precipitation	Bovine serum albumin, Ovalbumin.
	Ionic gelation	Ascorbic acid, Cyclosporine A.
	Reverse micellar method	Doxorubicin.
Beads	Coacervation/precipitation	Bovine serum albumin, Insulin.
Films	Solution casting	Ofloxacin, Paclitaxel.
Gel	Cross-linking	5-Fluorouracil.

Ophthalmic drug delivery system

The potential use of chitosan-based ophthalmic drug delivery systems is enhanced retention and biodistribution of drugs applied topically onto the eye. Chitosan is a suitable material for the design of ocular drug delivery systems mainly because it has admirable bio adhesion and penetration enhancing properties together with appropriate ocular tolerability and less or non-toxicity and allergenicity. Chitosan-based formulations used for ophthalmic drug delivery are hydrogels [13], nanoparticles [14], colloidal systems coated with chitosan [15] etc.

De Campos *et al.* [14] demonstrated the potential of chitosan nanoparticles with incorporated cyclosporine A in improving the delivery of drugs to the ocular mucosa.

Furthermore, chitosan-based colloidal systems were found to work as trans mucosal drug carriers, either facilitating the transport of drugs to the inner eye or their accumulation into the corneal epithelia. The use of chitosan-based colloidal suspensions *in vivo* showed a significant increase in ocular drug bioavailability [15, 16].

Calvo *et al.* [15], for instance, combined the features of polycaprolactone nanocapsules as ocular carriers with the advantages of the cationic mucoadhesive chitosan and poly-L-lysine (PLL) coating. Even though PLL and chitosan displayed a similar positive surface charge, only chitosan-coated nanocapsules enhanced the ocular penetration of indomethacin with respect to uncoated nanocapsules. The authors suggested that an undetermined property of chitosan was responsible for this enhanced uptake.

Genta *et al.* [16] indicated that acyclovir-loaded chitosan microspheres offer significantly sustained ocular drug release *in vivo*. According to the authors, in addition to its mucoadhesive properties, chitosan is effective in retarding the rate of drug release.

Nasal drug delivery system

Chitosan, a cationic bioadhesive natural polymer has remarkable influence in augmenting the transport of polar drugs, peptides and proteins across epithelial surfaces was established in various studies. There are two central effects of chitosan delivery systems on nasal mucosa that influence the permeation of drugs across it.

- Firstly, clearance of the formulation from the nasal cavity is abridged by the cations present in the chitosan bind to negatively charged sialic residues tenders excellent mucoadhesive properties consequently lead to prolonged contact time.

- Secondly, its reversible and momentary action on epithelial tight junctions between cells actually steps up the drug transportation paracellularly.

Morphine administered intranasally to humans, as a simple solution, is only absorbed to a limited degree, with a bioavailability in the order of 10%, compared with intravenous administration. Morphine associated with chitosan was rapidly absorbed, with a t_{max} of ≥15 minutes and a bioavailability of nearly 60%, and can result in a non injectable opioid formulation capable of offering patients rapid and efficient pain relief [17]. Morphologic and histologic evaluation of the rat nasal mucosa following a 2-week daily administration indicated that chitosan produced only mild to moderate irritation [17, 18].

Akbar Bayat *et al.* [19] studied the effect of insulin-loaded Chitosan nanoparticles on bioavailability of insulin and it was observed that insulin-loaded Chitosan nanoparticles enhanced the nasal absorption of insulin and shown the sustained effect.

In addition, Fisher *et al.* [20] developed fentanyl nasal spray formulations with pectin, chitosan, and chitosan–poloxamer 188 for clinical evaluation to provide rapid absorption and subsequently increased bioavailability. The study was conducted in 18 healthy adult volunteers and revealed significantly increased systemic exposure as well as reduced times to peak plasma values for all formulations compared with oral transmucosal fentanyl citrate lozenge.

Buccal drug delivery system

Prolonged adherence to the buccal mucosa is the vital requirement of an ideal carrier for efficient buccal drug delivery. Buccal patches, tablets, and gel formulations prepared with chitosan have been effectively delivered the drug unidirectionally into systemic circulation through buccal mucosa.

In another extensive study the chitosan sponges were developed for buccal administration of insulin, exposed efficient unidirectional delivery of insulin and demonstrated its excellent mucoadhesive properties. The promising unique mucoadhesive and absorption enhancing quality of this polymer further confirmed its aptness for the buccal drug delivery [21].

Gels of chitosan (at 1 or 2% concentration), containing 0.1 or 0.2% chlorhexidine gluconate, release the antifungal agent chlorhexidine gluconate for 3 hours; a prolonged release was also observed with film formulations. No lag-time was observed in the release of chlorhexidine gluconate from either gels or films. The highest antifungal activity was obtained with 2% chitosan gel containing 0.1% of the drug [22]. The loading of chlorhexidine into chitosan to improve the anti-microbial activity of the drug was also confirmed by different formulations [23]. An additional antifungal effect was thought to be achieved since chitosan also inhibits the adhesion of Candida albicans to human buccal cells. A 0.5% wt/v solution depressed the fungal adherence on a surface according to the sequence: low Molecular weight (MW) chitosan>phosphorylated chitosan>amorphous chitosan>carboxymethyl chitosan.

The buccal bilayered devices (bilaminated films, bilayered tablets) using a mixture of drugs Nifedipine and Propranolol hydrochloride and chitosan, with or without anionic cross linking polymers (polycarbophil, sodium alginate, gellan gum), demonstrated that

these devices show promising potential for use in controlled delivery of drugs to the oral cavity [24].

In another study, the potential of thiolated chitosan for peptide delivery systems via the buccal mucosa was investigated in pigs [25]. The therapeutic peptide PACAP was applied to pigs, and its bioavailability was determined in order to facilitate the treatment of type 2 diabetes. Due to its strong permeation enhancing properties, tablets based on thiolated chitosan raised continuously the plasma level of this peptide drug, allowing therapeutic range levels to be maintained over the whole period of application.

Oral drug delivery system

Oral ingestion of drugs is the most common route of administration, but unfortunately the gastrointestinal tract represents a barrier for absorption of peptides and proteins. Chitosan, displaying enzyme inhibiting and absorption enhancing activity, appears to be a suitable adjuvant for this purpose, and chitosan derivatives have been evaluated to bypass the gastric medium and operate at neutral pH values, such as those found in the intestinal tract [26].

Trimethyl chitosan chloride, at different degrees of quaternization, increases the permeation and/or absorption of neutral and cationic peptide analogs across intestinal epithelia. Mono-carboxymethylated chitosan, a poly ampholytic polymer able to from visco-elastic gels in aqueous environments or with anionic macromolecules at neutral pH values, appears to be less potent than the quaternized derivative. Nevertheless, mono-carboxymethylated chitosan was found to increase the permeation and absorption of low MW heparin across intestinal epithelia. The mechanism by which Trimethyl chitosan chloride enhances intestinal permeability is similar to that of the protonated chitosan; it reversibly interacts with components of the tight junctions, widening the para cellular routes, without permanent damage to the cell membrane and without altering the viability of intestinal epithelial cells [27]. A sustained or delayed ampicillin release can be provided by delivery systems containing such a polymer [28].

Bioadhesive tablets for intraoral drug delivery were prepared by directly compressing a drug with a mixture of chitosan and sodium alginate in weight ratios of 4: 1, 1: 1 and 1: 4, and the adhesion and release characteristics of the prepared systems were evaluated *in vitro* and *in vivo*. The plasma concentration curves for the tablet with a 1: 4 chitosan/alginate ratios showed a sustained release 3 hours after administration [29]. The percentage of ampicillin release, embedded in a chitosan matrix was much higher in an acidic solution compared with the phosphate solution, probably due to the gelation properties of the matrix at low pH [28]. The release rate of the drug from the chitosan matrix was slower for beads than granules, thereby offering the possibility of modifying the formulation to obtain the most convenient oral sustained delivery system [28].

Thanou *et al.* [30], for instance, demonstrated that intra duodenally applied buserelin results in 0.8% absolute bioavailability in rats, whereas co-administrations with trimethylated chitosans resulted in average bioavailability values between 6% and 13%. In contrast, chitosan HCl did not significantly increase the intestinal absorption at pH 7.2.

Colon-specific drug delivery system

Chitosan is a well accepted and a promising polymer for drug delivery in colonic part, since it can protect the active agents from the hostile conditions of the upper gastrointestinal tract and release the entrapped agent specifically at the colon through degradation of the glycosidic linkages of chitosan by colonic microflora [31]. Chitosan can be modified by reacting with succinic and phthalic anhydride to prepare matrices resistant to dissolution under acidic conditions. Improved drug release profiles under basic conditions suggested that these matrices are suitable for colon-specific delivery of orally administered drugs [32].

M. L. Lorenzo-Lamosa *et al.* [33] proposed the design of microencapsulated chitosan microspheres for colonic drug delivery. He prepared the pH-sensitive multicore microparticulate system containing Chitosan micro-cores entrapped into enteric acrylic microspheres. Chitosan micro-cores in which sodium diclofenac was entrapped and then it was microencapsulated into Eudragit (L-100 and S-100) to form a multi reservoir system have been prepared. *In vitro* release study revealed no release of the drug in gastric pH for 3 h and after the lag-time, a continuous release for 8-12 h was observed in the basic pH.

Formulation parameters showed significant influence on drug release pattern. Zinc–pectin–chitosan composite microparticles were designed and developed as colon specific carrier [34]. The formulation was prepared at pH 1.5, 1% chitosan, 120 min cross-linking time, and pectin: drug at 3:1 ratio demonstrated colon-specific drug release. Resveratrol was used as model drug due to its potential activity on colon diseases. *In vivo* pharmacokinetics of the zinc-pectinate particles was compared with the zinc–pectin–chitosan composite particles in rats. Pharmacokinetics study indicated *in vivo* colon-specific drug release from the zinc–pectin–chitosan composite particles only. Cross-linking solution pH, cross-linking time, and chitosan concentration in the cross-linking solution exhibited major influence on drug release pattern.

Jitendra kawadkar *et al.* [35] prepared the Chitosan coated microsphere matrix system for the treatment of ulcerative colitis-A. In these studies, the microspheres of Chitosan HCl was directly compressed with the drug 5-aminosalisylic acid (5-ASA), into matrices. These matrices were compressed into tablets or introduced into capsules and coated. The release of 5-ASA from these compressed matrices by the polymer degrading action of the caecal microflora was evaluated *in vitro* using rat caecal microflora in virtue of the similarity with human intestinal microflora and it provides better release of 5-amino salicylic acid in the colon having ulcerative colitis.

Chitosan capsules containing insulin entered the colon 8 hours after administration, as evaluated by transit time experiments, starting the hypoglycemic effect from that time [36, 37].

Vaginal drug delivery system

Anti-infective drugs incorporated mucoadhesive vaginal formulations based on chitosan have been reported successfully in various literatures substantiated the best qualities of this polymer for the vaginal drug delivery [38, 39]. Apart from the vaginal tablets and films, pH-or temperature-sensitive delivery systems, nanocarriers, and inserts are also in the investigation.

Mucoadhesive vaginal gel based on chitosan for the delivery of lactic acid was exclusively illustrated the polymer's mucoadhesive performance and release profile [40].

Chitosan, modified by the introduction of thioglycolic acid to the primary amino groups of the polymer, embeds clotrimazole, an imidazole derivative widely used for the treatment of mycotic infections of the genitourinary tract. By introducing thiol groups, the mucoadhesive properties of the polymer were strongly improved and this resulted in an increased residence time of the vaginal mucosa tissue (26 times longer than the corresponding unmodified polymer), guaranteeing a controlled drug release in the treatment of mycotic infections [41].

Amal El-kamel *et al.* [42] prepared CS based vaginal tablets containing metronidazole by directly compressing the natural cationic polymer Chitosan, loosely cross-linked with glutaraldehyde. The batch 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. It also proved to have good adhesion properties with minimum applied weights. Moreover, its release properties (% dissolution efficiency, DE) in buffer pH 4.8, as well as the release mechanism (n values), were negligibly affected by aging. Thus, this formula may be considered a good candidate for vaginal mucoadhesive dosage forms.

In another study, Sandri *et al.* [43] evaluated the mucoadhesive and permeation enhancing properties of four different chitosan derivatives: 5-methyl-pyrrolidinone chitosan, two low molecular

mass chitosans, and a partially re-acetylated chitosan via the vaginal and buccal mucosa using acyclovir as the model drug. Methyl-pyrrolidinone chitosan showed the highest mucoadhesive and permeation enhancing properties in both vaginal and buccal environments. The capability of enhancing the permeation/penetration of acyclovir was decreased by partial depolymerization of chitosan and disappeared after partial re-acetylation. The antimicrobial properties of chitosan, however, might have a negative impact on the vaginal microflora [44]. Its vaginal use for treatment of chronic diseases has therefore to be seen with caution.

Transdermal drug delivery system

Owing to its irreplaceable film forming capacity, penetration enhancing competence without causing much stress to the skin, skin compatibility and good adhesive properties etc. [45, 46], Prompted the researchers to conduct plenteous studies that have been done extensively and reported on the skin permeation ability of the drugs by using this natural biopolymer chitosan. The electrostatic interaction of the positively charged chitosan mediates protracted contact with the epithelium and the negatively charged glycoprotein residues on the cell surface smooth the progress of the passive diffusion results in the successful absorption of the drug into the underlying epithelium [47, 48]. As a penetration enhancer chitosan disrupts the epithelial tight junctions on the skin and facilitates the drug permeation. This epithelial disruption is very brief and within a diminutive period of time altogether it is reversible [49, 50].

Jaleh Varhosaz *et al.* [51] prepared the gel containing lidocaine (LC) as a local anesthetic agent with three different MW and concentrations of Chitosan for prolonging anesthetic effect of this drug for transdermal delivery. Lecithin was used as permeation enhancer. Viscosity, bio-adhesion, drug release from synthetic membranes, drug permeation through the biological barrier (rat skin) was studied. It was found that by increasing the concentration and MW of Chitosan, there was an increase in both the rate and extent of drug release and was probably because of the increase in repulsive forces between LC and chitosan cations.

Topical systems for controlled delivery of glycolic acid were prepared to optimize the cosmetic properties of the acid, thereby reducing its adverse effects. Two types of liposomes were investigated: the addition of chitosan into the lipidic bilayer during liposome preparation; and coating of already formed liposomes with chitosan [52]. The results showed that liposomes always modulated glycolic acid release and that the best condition to achieve this control was obtained by the liposomal systems in which the glycolic acid/lipid molar ratio was 5: 1. On the contrary, chitosan microspheres are not able to control glycolic acid release, even after cross-linking [52].

Thacharodi and Rao *et al.* [53–55] reported permeation-controlled transdermal drug delivery systems (TDS) using chitosan. Studies on Propranolol hydrochloride (prop-HCl) delivery systems using various chitosan membranes with different cross link densities as drug release controlling membranes and chitosan gel as the drug reservoir has been performed. The physicochemical properties of the membranes have been characterized and the permeability characteristics of these membranes to both lipophilic and hydrophilic drugs have been reported [53, 54]. *In vitro* evaluations of the TDS devices while supported on rabbit pinna skin were carried out in modified Franz diffusion cells [55]. The *in vitro* drug release profiles showed that all devices released prop-HCl in a reliable, reproducible manner. The drug release was significantly reduced when cross linked chitosan membranes were used to regulate drug release in the devices. Moreover, the drug release rate was found to depend on the crosslink density within the membranes. It was observed that the device constructed with a chitosan membrane with a high crosslink density released the minimum amount of drug. This is due to the decreased permeability coefficient of cross linked membranes resulting from the crosslink points.

Gastro retentive drug delivery system

Gastro retentive drug delivery systems increase the retention of a per-oral dosage form in the stomach and offer numerous advantages for drugs exhibiting an absorption window in the GI tract, drugs that are poorly soluble in the alkaline medium (Verapamil), and drugs that are intended for local action on the gastroduodenal wall [56]. Chitosan has a high potential in the development of a successful gastro retentive drug delivery system because it combines both bioadhesion and floating capabilities [57], especially for drugs that are poorly soluble in intestinal medium and readily soluble in acidic medium. Chitosan could be ideal for use in formulations intended to release drugs slowly in the stomach, since the gel formation by cationic chitosan that is pronounced at acidic pH levels results in marked retardant effects on drug release. Orally administered formulations are initially exposed to the acidic milieu of the stomach, especially if they have been administered to subjects in fasted states, in whom gastric pH is likely to range from approximately 1 to 2. Mucoadhesive ability could result in formulations containing chitosan being retained in the stomach. Adhesion would be expected to be particularly marked under the acidic conditions in the stomach, where cationic chitosan would be highly charged.

The chitosan beads can serve as depot reservoir that allows the continuous gradual release of small amounts of Verapamil in solution to the upper part of the small intestine (the main site of absorption), leading to higher and more uniform blood levels of the drug. Thus, reduced adverse effects are highly expected.

Floating hollow microcapsules of melatonin showed gastro retentive controlled-release delivery. Release of the drug from these microcapsules is greatly retarded, with release lasting for 1.75–6.7 h in simulated gastric fluid. Most of the mucoadhesive microcapsules are retained in the stomach for more than 10 h (e. g., Metoclopramide and Glipizide-loaded chitosan microspheres) [58].

In an additional endeavor chitosan granules prepared with prednisolone demonstrated good buoyancy and controlled release when it was added to acidic and neutral media provide evidence of its appropriateness in making such category of formulations [31].

Gene delivery

Chitosan is the most prominent among natural polymer-based gene delivery vectors, due to its biodegradability, biocompatibility, and degradation potential [59]. Chitosan's cationic qualities have the aptitude to interact with negative molecules such as DNA and form complexes, facilitate transfection and inhibit degradation of the same. Chitosan as (safer to other non-viral vectors) non-viral vector for gene delivery put forward quite a few advantages that are not producing endogenous recombination, oncogenic and immunological effects.

Microcapsules containing calf thymus DNA and prepared by interfacial polymerization of chitosan, and alginate microspheres formed by emulsification/internal gelation, were recovered intact from rat feces following gastrointestinal transit. This is the first report of microcapsules or microspheres containing DNA being passed through the gastrointestinal tract with the potential for substantial recovery [60].

In a study by Erbacher *et al.* [61], formulation of plasmid DNA with chitosan resulted in a homogeneous population of complexes that were stable and had a diameter of approximately 50-100 nm. These complexes were found to effectively transfect HeLa cells, independently of the presence of serum (10%) without the need for the presence of an endosomolytic agent. The gene expression was also observed to gradually increase over time (from 24-96 h). At 96 h, chitosan was found to be 10-times more efficient than polyethylene-imine-mediated transfection.

Roy *et al.* [62] described an immunoprophylactic strategy using oral allergen-gene immunisation to moderate peanut antigen induced murine anaphylactic responses. Oral administration of DNA nanoparticles synthesized by complexing plasmid DNA with chitosan resulted in transduced gene expression in the intestinal epithelium, thus indicating the probable use of chitosan-DNA nanoparticles in murine anaphylactic responses.

The molecular mass and deacetylation extent of the chitosan, chitosan to DNA/siRNA charge proportion (N/P ratio) and its

strength, the chitosan salt form utilized, pH, serum, additives, chitosan/nucleic acid particles preparation process and routes of administration and diverse formulation allied factors influence the transfection efficiency [63].

As the Mw increased, transfection efficiency also improved [64]. Moderate DD increases the transfection efficiency. A pH of 6.8–7.0 is found to be optimum to achieve a high level of transfection [65]. Higher gene transfer efficiency was achieved in HEK293 cells as compared to other cell types [66]. But, the major drawback of chitosan is its low transfection efficiency. Numerous chemical modification like quaternization [67], deoxycholic acid modification [68], galactosylation [69], PEI grafting [70], and thiolation [71] have been carried out by various groups in an attempt to improve transfection efficiency.

Vaccine delivery

Chitosan is a mucoadhesive polymer that is able to open tight junctions and allow the paracellular transport of molecules across mucosal epithelium, and is therefore suitable for the mucosal delivery of vaccines [72]. Chitosan microparticles were able to associate large amounts of Ovalbumin (model vaccine) and diphtheria toxoid (DT). They are not disintegrated in an acidic environment and protect the antigen against degradation by entrapping it into their porous structure [73]. The chitosan microparticles were only taken up by the follicle-associated epithelium (FAE), in which microfold cells (M-cells) are present. This result was from oral delivery studies in mice, in which chitosan microparticles were found to transport associated Ovalbumin into the Peyer's patches [74]. Oral efficacy studies with DT associated to chitosan microparticles demonstrated that they were able to induce strong DT-specific systemic and local immune responses (IgG and IgA titers, respectively) [75]. The amount of neutralizing antibodies in mice vaccinated with DT-loaded chitosan microparticles was also high; the levels were considered to be protective in man.

Chitosan is shown to be a promising candidate in mucosal vaccine delivery for protein vaccines such as Bacillus anthracis [76], diphtheria [77], and influenza [78]. Chitosan derivative trimethylated chitosan/tripolyphosphate/ovalbumin (TMC/TPP/ OVA) nanoparticles have previously been shown to be very effective nasal vaccine carriers. Replacing TPP by CpG as a cross linking agent to obtain TMC/CpG/OVA nanoparticles modulated the immune response towards a Th1 (T helper cell 1) response after nasal vaccination, while maintaining the strong systemic and local antibody responses observed with TMC/TPP nanoparticles. TMC/CpG nanoparticles are therefore an interesting nasal delivery system for vaccines requiring broad humoral as well as strong Th1-type cellular immune responses [79]. In another study, Ovalbumin was encapsulated in alginate-coated chitosan nanoparticles and delivered via the oral route to Peyer's patches [80].

Jain *et al.* [81] observed high secretory IgA concentrations and better immune response with nanoparticulate vesicular formulation upon oral administration. Chitosan microparticles show suitable *in vitro* and *in vivo* characteristics for oral vaccination and are therefore a promising carrier system for this particular purpose. Fluorescently labeled chitosan microparticles can be taken up by the epithelium of murine Peyer's patches. Since uptake by Peyer's patches is an essential step in oral vaccination, these results show that the presently developed porous chitosan microparticles are a very promising vaccine delivery system. Chitosan particles have been described as a potential oral vaccine carrier [82] and transport of these particles by M-cells has been observed. A drawback of chitosan is its water solubility. With a pKa of 6.2, at physiological pH the primary amine groups of chitosan are protonated and, consequently, OVA/chitosan nanoparticles lose their repulsive surface charge and show colloidal instability. The slightly acid environment of the jejunum will promote the stability of chitosan nanoparticles, but as soon as these particles are transported to the sub epithelial space to interact with immune cells, the physiological pH will be deleterious for its stability. Because TMC carries a permanent positive charge, OVA/TMC nanoparticles will not be affected by small pH shifts and may be a more suitable carrier for mucosal vaccination [83]. An intraduodenal immunization study with OVA/chitosan nanoparticles, OVA/TMC nanoparticles, and unencapsulated OVA was performed to analyze the extent and type of immune response elicited.

Commercial application of chitosan

(Table 2) shows commercial applications of chitosan

Table 2: Commercial applications of chitosan [84, 85]

Fields of application	Examples
Water & waste treatment	Flocculant to clarify water (drinking water, pools).
	Removal of metal ions.
	Ecological polymer (eliminate synthetic polymers).
	Reduce odors.
Pulp and paper	Surface treatment.
	Photographic paper.
	Carbonless copy paper.
	Purification of water wastes, wet-strength improve agent and chitosan-coated papers.
Medical and pharmaceutical materials	Bandages, sponges.
	Blood cholesterol control.
	Tumor inhibition.
	Membranes.
	Dental/plague inhibition.
	Skin burns/artificial skin.
	Contact lens.
	Control release drugs.
	Bone disease treatment.
	Surgical sutures.
Cosmetics & toiletries	Maintain skin moisture.
	Treat acne.
	Improve suppleness of hair.
	Reduce static electricity in hair.
	Tone skin.
	Oral care (toothpaste, chewing gum).
Biotechnology	Enzyme immobilization.
	Protein separation.
	Chromatography, cell recovery.
	Cell immobilization.
	Electrodes and sensors.

Agriculture	Defensive mechanism in plants.
	Stimulation of plant growth.
	Seed coating.
	Frost protection.
	Time release of fertilizers and nutrients into the soil.
Food & beverages	Not digestible by human (dietary fiber).
	Bind lipids (reduce cholesterol).
	Preservative.
	Thickener and stabilizer for sauces.
	Protective, fungistatic, antibacterial.
	Coating for fruit.
Textile	Sanitary fibrous materials.
	Surgical threads.
	Textile material.
Membranes	Reverse osmosis.
	Permeability control.
	Solvent separation.
Biopharmaceutics	Immunologic.
	Antitumoral.
	Hemostatic and anticoagulant
	Healing.
	Bacteriostatic.

CONCLUSION

Chitosan is an abundant natural based polymer, obtained by alkaline N-deacetylation of chitin. The physical and chemical properties of chitosan, such as inter and intramolecular hydrogen bonding and the cationic charge in acidic medium, makes this polymer attractive for the development of conventional and novel pharmaceutical products. So far, a number of chitosan based colloidal systems have been revealed as very promising carriers for bioactive molecules. Being a bioadhesive polymer and having antibacterial activity, chitosan is a good candidate for oral cavity drug delivery. Also, because of its favorable biological properties such as nontoxicity, biocompatibility, and biodegradability, chitosan is a promising candidate for the enhancement of absorption of drugs using a buccal delivery system. Chitosan microspheres can reside longer in the stomach and allow for stomach-specific drug delivery. Chitosan acts as an absorption enhancer in the intestine by increasing the residence time of dosage forms at mucosal sites, inhibiting proteolytic enzymes, and increasing the permeability of protein and peptide drugs across mucosal membranes. Chitosan can be degraded by the micro-organisms, which are present in the colon. Therefore, this polymer could have promising application in a colon-specific drug delivery. A number of in-vitro and in-vivo studies showed that chitosan is a suitable material for efficient non-viral gene and DNA vaccine delivery. As a result of the physical, chemical, and biological properties, chitosan has been used in many different formulations for drug and gene delivery in the gastrointestinal tract.

So going through the applications of chitosan for the beneficial of human being it is not surprising at all to call it a “Multifacet polymer”.

CONFLICT OF INTERESTS

Declared None

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