Chitosan as Versatile Carrier in Drug Delivery Systems

***Dr B. K. Jain, Faculty at Pharmacy,**
K.N.Polytechnic College,
Jabalpur. (M.P.)
India
jainbhaanukumar@gmail.com

Dr Ankita Alice Singh, Faculty at Pharmacy,
K.N.Polytechnic College,
Jabalpur, (M.P.), India

Dr. Seema Kohli, HOD, Pharmacy,
K.N.Polytechnic College,
Jabalpur, (M.P.), India

Dr. Kaminee Sahu, Professor at Pharmacy,
Gyan Ganga Instt. Of Pharmacy,
Jabalpur, (M.P.), India

ABSTRACT

Chitosan is a strong, biocompatible, biodegradable, and non-toxic linear polysaccharide that can be used in a various pharmaceutical drug delivery application. Chitosan possesses special physicochemical and biological properties that are necessary for the development of safe and effective drug delivery systems. Chelation is one of chitosan's most useful characteristics. It can selectively bind to specific substances, including protein, tumour cells, metal ions, lipids, and cholesterol. Additionally, because it is biodegradable by nature, it does not result with allergic responses or rejection. The human body entirely produces armless product during metabolism. Since chitosan is an effective cationic polymer for membrane synthesis, it can also be used to create artificial kidney membranes. In addition to these properties, it has a number of medicinal uses, including analgesic, hypo-cholesterolemic, hemostatic antitumor, anti-oxidant spermicidal, CNS depressant, immune adjuvant properties, antacid, antiulcer activities, wound and burn healing action, and has been found to be suitable for immobilizing enzymes and living cells in ophthalmology. The development of nasal, vaginal, ophthalmic, transdermal & topical, buccal, parenteral, colon-specific, and implantable drug delivery systems are important uses of chitosan in the pharmaceutical field.

When using chitosan for accurate drug administration, the important chitosan properties such as purity, degree of acetylation, viscosity, and molecular weight should be taken into account. Drug delivery systems made of chitosan nanoparticles, microspheres, and beads are commonly used. Chitosan microspheres are used to deliver numerous medications with controlled release, to increase the bioavailability of compounds that break down easily, like protein, or to speed up the uptake of hydrophilic substances via epithelial layers. Targeted medication delivery employs magnetic chitosan microspheres so that drugs are kept at target site while being affected by an external magnetic field.

Due to its abilities to increase absorption and penetration, chitosan has been also utilized for the oral delivery of genes and peptides.

Keywords: Chitosan, Structure, Drug delivery, Pharmaceutical applications

I. INTRODUCTION

As drug carriers, a variety of substances including lipids, surfactants, natural or synthetic polymers, and dendrimers have been used [1-4]. Usually, synthetic polymers are expensive, non-biodegradable, and non-biocompatible. In particular, polysaccharides have drawn more attention due to their exceptional physical and biological characteristics [5]. Natural polymers like chitin and chitosan are devoid of these problems, making them a potential carrier for the development of specific drug delivery systems. Due to its widespread availability, special muco adhesiveness, inherent pharmacological properties, and other advantageous biological properties like biocompatibility, biodegradability, non-toxicity, and low-immunogenicity, cationic polysaccharide chitosan has a wide range of pharmaceutical and biomedical applications in the field of pharmaceutical sciences [6–8]. Chitosan has also been utilized as a novel bio adhesive polymer for the drugs having antibacterial properties.

When choosing chitosan for targeted drug delivery, the critical variables of purity, degree of acetylation, viscosity, and molecular weight should be considered. Chitosan nanoparticles, microspheres, and beads have gained widespread acceptance as drug delivery systems. Chitosan microspheres are used to control the release of numerous drugs and to improve the bioavailability of degradable substances such as protein, as well as to increase the uptake of hydrophilic molecules through the epithelial layers. Magnetic Chitosan microspheres are used in targeted medicine delivery to keep drugs in target site capillaries under the influenced by an external magnetic field.

Due to its absorption and penetration boosting abilities, chitosan has been employed for the oral administration of genes and peptides. Chitosan's particular affinity for biomolecules has been used to decrease pharmacological adverse effects. Chitosan membranes have been demonstrated to be more permeable to acidic drugs than basic drugs. Because of its unique properties in the world of pharmaceutical sciences, chitosan can be used as a preferred formulation excipient among medicinal applications such as binding agent,

- Disintegrating agent,
- Stabilizing agent,
- Suspending agent,
- Tablet coating and film forming material
- Drug carrier for sustained release formulations
- Co-grinding diluents for the improvement of dissolution rate and bioavailability of water insoluble drugs.
- To improve the therapeutic efficacy of the low molecular weight drug compounds

Because chitosan is chemically inert, it has been combined with other polymers to obtain desired and controlled medication release. Numerous studies have shown that chitosan and its derivatives (N-tri methyl chitosan, mono-N-carboxy methyl chitosan) are effective and safe absorption enhancers for improving mucosal (nasal, peroral) delivery of hydrophilic macromolecules like peptides, proteins, and heparins, as well as their antimicrobial and wound-healing properties. Chitosan is a hemostatic agent, and some of its derivatives, such as sulfated chitosan, are anticoagulants. Chitosan bandages and sponges are manufactured for surgical therapy and wound protection by exploiting the haemostatic action.

Chitosan's low toxicity, combined with its broad applicability, makes it an attractive candidate not just for drug delivery of a variety of pharmacological moieties such as anti-inflammatory medicines, peptides, and so on, but also as a biologically active agent. The objective of this article is to examine the existing and prospective applications of chitosan in the pharmaceutical industry [9-11].

II. CHEMICAL STRUCTURE AND PREPARATION

Chitin is a renewable bioresource [12,13,14] that is extensively distributed in nature. After cellulose, chitin is thought to be the second most abundant biomaterial. Chitin is the primary component of the protective cuticles of crustaceans such as crabs, shrimp, prawns, and lobsters, as well as bacterial cell walls and some fungus such as aspergillus and mucor. Crustacean exoskeletons are composed of 15% to 20% chitin by dry weight. Chitin's crystalline structure has been found to be similar to cellulose in terms of inter- and intra-chain hydrogen bonding arrangements and biological function.

Both types of monomers are present in commercial chitin and chitosan. Chitosan, to a lesser extent than chitin, is present in nature. Chitosan's physicochemical and biological properties are considerably influenced by its molecular weight and degree of de-acetylation.

Chitin is a straight homo-polymer made up of b-(1-4)-linked N-acetyl-glucosamine units, whereas chitosan is made up of glucosamine and N-acetyl glucosamine copolymers. Chitosan is a polysaccharide with approximately 5000 glucosamine units and a molecular weight of over one million Daltons. Chitosan is made by through the alkaline N-de-acetylation of chitin. It is made up of two kinds of monomers: chitin monomers and chitosan

monomers. Chitin is a polysaccharide that is composed of (1-4)-linked 2-acetamido-2-deoxy-b-D-glucopyranose. Chitosan is a polysaccharide that is composed of (1-4)-linked 2-amino-2-deoxy-b-D-glucopyranose. For each C building block, chitosan has one main amino group and two free hydroxyl groups.

Chitosan's chemical alteration gives amphiphilicity, which is a key property for the development of self-arranged nanoparticles that could be used in drug delivery system. The targeting moieties are conjugated to the surface of drug-loaded nanoparticles.

The preparation of chitin and chitosan is given in

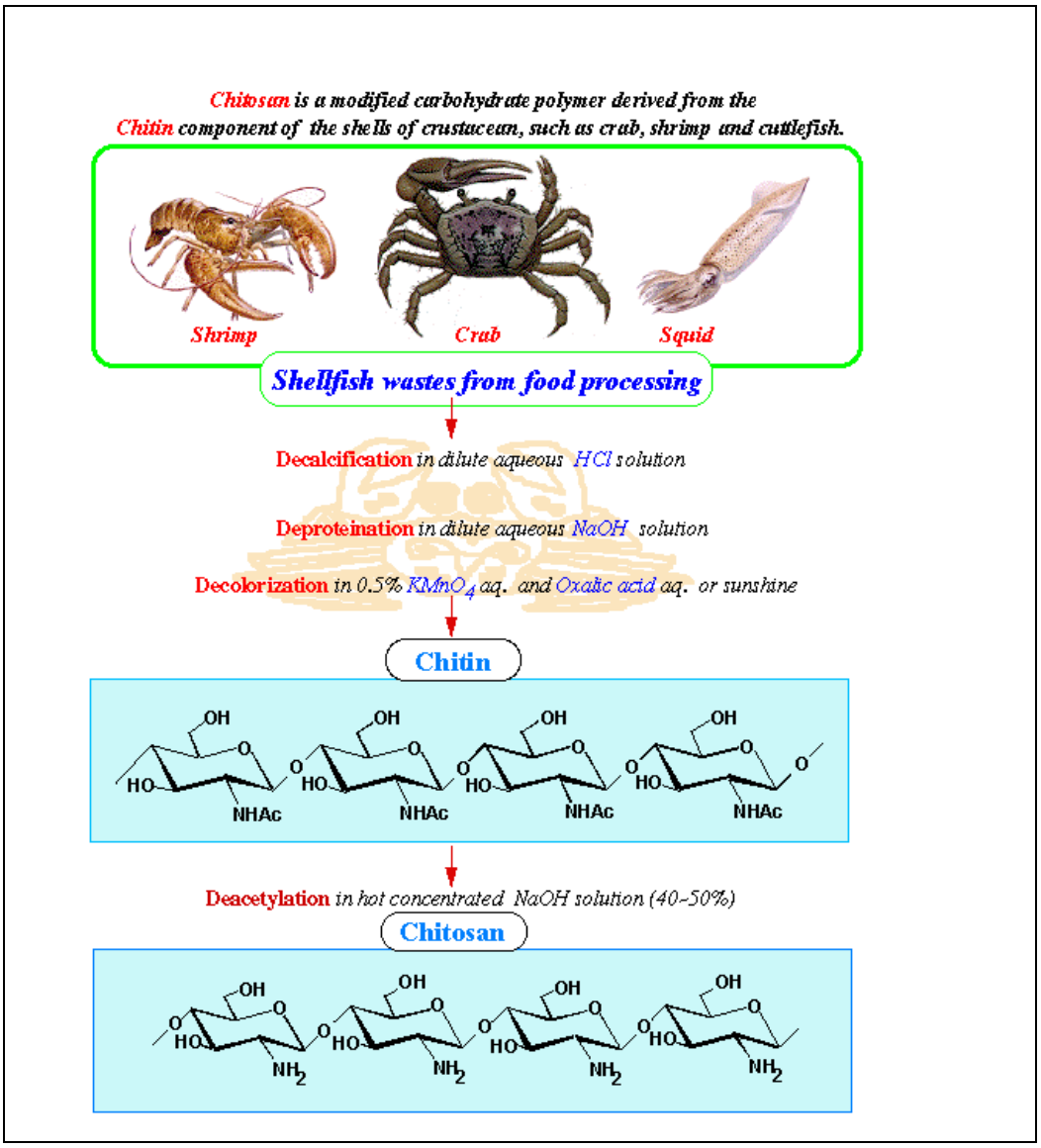

Figure 1: Preparation of Chitosan and Chitin

III. PROPERTIES OF CHITOSAN

The qualities and properties of chitosan products such as purity, viscosity, de-acetylation, molecular weight, and polymorphs structure may differ with manufacturing process variables that in turn influence the characteristic of the pharmaceutical formulations. The mucoadhesive properties of chitosan are attributed to its positive charges at neutral pH that enable an ionic interaction with the negative charges of sialic acid residues of the mucus.

In addition to muco adhesive property, chitosan also posses binding, disintegrating, and tablet coating properties. These properties may be attributed to Purity, viscosity, de-acetylation, molecular weight, and polymorphs structure of chitosan products may fluctuate depending on production process variables, which in turn influence the characteristics of medicinal formulations. Chitosan's mucoadhesive qualities are related to its positive charges at neutral pH, which allow for an ionic contact with the negative charges of mucus sialic acid residues.

These characteristics could be related to -

- Strong hydrogen bonding groups like-OH, -COOH
- Strong charges
- High molecular weight
- Sufficient chain flexibility and
- Surface energy properties favoring spreading into mucus.

Chitosan is commercially available in the form of dry flakes, solution, and fine powder. It degrades when fermented; it is harmless and easily removed from the organism without causing concurrent side reactions. Chitosan's applications are determined by its polyelectrolyte nature as well as the chelating ability of the macromolecule's amine groups.

IV. CHARACTERIZATION OF CHITOSAN

Chitosan is generally characterized by the following parameters:

- Degree of de-acetylation in %,
- Dry matter in %,
- Ash in %,
- Protein in %,
- Viscosity in Centipoises’,
- Intrinsic viscosity in ml/g,
- Molecular weight in g/mol, and

- Turbidity in NTU units.

All of these factors can be tailored to the specific application for which chitosan is employed. De-acetylation is critical for obtaining a soluble product. In general, the distribution of the acetyl groups, the polarity and size of the monomers, the distribution of the monomers along the chain, the flexibility of the chain, branching, charge density, and molecular weight (50,000 to 2,000,000 Da) of the polymer all influence the solubility of hetero- glucans. By adjusting the process parameters, viscosity (10 to 5000 cp) can be tailored to each application [12-14].

V. CHITOSAN IN DRUG DELIVERY

A. Ophthalmic Drug Delivery Systems:

Because chitosan has the ability to form films, it has been proposed as a biopolymer of choice for the development of contact lenses used as protective devices for acutely or chronically injured eyes. Chitosan has been discovered to be a unique substance for building ocular drug delivery vehicles due to its outstanding features. Because of chitosan's elastic properties, chitosan gels have great adherence to mucin, which coats the conjunctiva and the corneal surface of the eye. Chitosan has been shown to improve drug retention and bio-distribution in the ocular cavity. It is also said to have eye tolerance, low or no toxicity, and low allergenicity. Several studies have shown that chitosan can be used in the ophthalmic drug delivery systems as nanoparticles, microspheres [15,16], gels, colloidal systems coated with chitosan etc.

B. Nasal Drug Delivery Systems:

Because of the enormous surface area and high vascularity of the nasal mucosa, it is an attractive target for bio-adhesive drug delivery devices. Microspheres, beads, liposomes, and gels have been shown to be promising bio-adhesive drug delivery methods. Chitosan is non-toxic and non-irritating; thus it can be administered to the nasal epithelium. In an aqueous environment, it swells and produces a gel-like layer, which is suitable for the conversion of polymer and glycoprotein chains into mucus. Chitosan has high bio adhesive properties and can limit the rate of drug clearance from the nasal cavity by enhancing the bioavailability of the drug incorporated in it. [16-18]. Chitosan microspheres have typically demonstrated that drug release decreases with increasing chitosan molecular weight.

This could be due to the swelling characteristic of chitosan microspheres. As the molecular weight of chitosan increases, so does the viscosity of the gel layer, which effects drug transport and microsphere erosion. Drug release from chitosan microspheres diminishes as polymer concentration increases.

The nasal sustained release of vancomycin hydrochloride was observed in a range of chitosan salts (chitosan lactate, chitosan aspartate, chitosan glutamate, and chitosan hydrochloride)[19.] Diphtheria toxoid (DT) combined with chitosan micro particles leads in a protective systemic and local immune response against DT, as well as increased IgG production significantly after nasal injection [20]

Drug release studies from different types of nasal vaccine systems have been described to include cholera toxin, microspheres, nanoparticles, liposomes, attenuated virus and cells, and outer membrane proteins (proteosomes).

C. Buccal Drug Delivery Systems:

The promising and distinctive mucoadhesive and absorption enhancing quality of chitosan has confirmed its suitability for the buccal drug delivery for efficient buccal drug delivery, prolonged adherence to the buccal mucosa is the vital requirement of an ideal carrier. And release the drug in a unidirectional way toward the mucosa in a controlled- or sustained-release manner. Mucoadhesive polymers extends the residence time of the device in the oral cavity.

Buccal patches, tablets, and gel formulations prepared with chitosan have been reported to effectively deliver the drug unidirectional into systemic circulation through buccal mucosa. In another extensive study the chitosan sponges were developed for buccal administration of insulin.

Chitosan's promising and distinct mucoadhesive and absorption boosting properties have verified its appropriateness for buccal drug delivery. For optimal buccal drug delivery, prolonged adherence to the buccal mucosa is a critical need of an ideal carrier. And deliver the medicine uni-directionally to the mucosa via controlled or sustained release. Mucoadhesive polymers prolong the device's residence time in the mouth cavity.

Buccal patches, pills, and gel formulations containing chitosan have been shown to carry the medicine uni-directionally into systemic circulation via the buccal mucosa. Chitosan sponges were produced for buccal administration of insulin in another lengthy investigation. As a bone substitute for dental purposes, chitosan-containing quick-hardening paste was produced. The use of this paste will reduce gum inflammation.

D. Floating Drug Delivery System:

The density of floating systems is lower than the density of gastric fluid. As a result, stomach transit time and hence bioavailability of medications absorbed in the upper GI tract would be improved. Intra gastric floating dosage forms are effective for administering medications that have a specific absorption site, an area that is insoluble in intestinal fluid, or an area used to treat gastric disorders. The ionic interaction of chitosan and negatively charged surfactant sodium dioctyl sulfosuccinate resulted in the suitability of using chitosan in the creation of these specific floating drug delivery systems. Chitosan capsules have been utilized to deliver insulin to the colon specifically [19-20]

E. Intestinal Drug Delivery System:

Sustained intestinal delivery of medications like 5-fluorouracil (a treatment option for colon cancer) and insulin (for diabetes mellitus) appears to be a viable alternative to injectable therapy. Using the bio adhesiveness of poly acrylic

acid, alginate, and chitosan [22-23], a formulation was produced that could bypass the acidity of the stomach and deliver the loaded drug for long periods of time into the intestine.

F. Colon Delivery System:

Chitosan was utilized in oral medication formulations to provide drug release that was sustained. Chitosan has recently been discovered to be destroyed by the bacteria found in the colon. As a result, this molecule may hold promise for colon-specific medication delivery. Chitosan was reacted with succinic and phthalic anhydrides separately. The semisynthetic polymers that resulted were tested for colon-specific, orally given medication delivery systems. Colon administration systems containing acetaminophen (paracetamol), mesalazine (5-ASA), sodium diclofenac, and insulin have been examined and found to be effective [24-26]

G. Vaginal Drug Delivery System:

Anti-infective medications incorporating mucoadhesive vaginal formulations based on chitosan have been effectively described in several literatures, demonstrating the best properties of this polymer for vaginal drug delivery [27]. A chitosan vaginal tablet containing metronidazole, acriflavine, and other medicines provided adequate release, therapeutic effect, and good adherence. Apart from vaginal tablets and films, the its also includes pH- or temperature-sensitive delivery systems, nano carriers, and implants. Mucoadhesive vaginal gel based on chitosan for lactic acid delivery was used primarily to demonstrate the polymer's mucoadhesive performance and release profiles [28].

H. Transdermal Drug Delivery System:

Chitosan, as a penetration enhancer, breaks epithelial tight junctions on the skin, facilitating drug permeability. This epithelial rupture is short-lived and reversible. In situ preparation of chitosan-alginate poly electrolyte complex (PEC) in beads and microspheres for possible uses in packaging, controlled release systems, and wound dressing[7]. Chitosan gel beads are a promising biocompatible and biodegradable medium for local inflammatory therapy. Chitosan gel beads containing the anti-inflammatory medication prednisolone demonstrated sustained drug release with lower inflammation indices, resulting in better therapeutic efficacy [29]. Chitosan membranes with varying permeabilities to propranolol hydrochloride were employed to control drug release in the devices via controlled cross-linking with glutaraldehyde. The drug reservoir was made of chitosan gel.

I. Vaccine Delivery

Several chitosan-antigen nasal vaccinations have been developed. Cholera toxin, microspheres, nanoparticles, liposomes, attenuated virus and cells, and outer membrane proteins (proteosomes) are among them. They elicited strong serum IgG responses comparable to and secretory IgA levels superior to those induced by parenteral vaccination delivery [30]. Chitosan micro particles have the potential to be very effective mucosal vaccination

delivery technologies. Following nasal vaccination with diphtheria toxoid coupled with chitosan micro particles, significant systemic humoral immune responses were seen. Diphtheria toxoid conjugated to chitosan micro particles induces a protective systemic and local immune response against diphtheria toxoid following oral vaccination, as well as a considerable increase in IgG production after nasal delivery. Chitosan microspheres cross-linked with glutaraldehyde were loaded with BSA and diphtheria toxoid and demonstrated tissue compatibility with a long-lasting effect.

VI. Conclusion

It is a versatile polymer with applications ranging from weight loss supplements to biomedical and pharmaceutical compositions. Chitosan is an appealing biopolymer for delivering a wide variety of drugs in a controlled/sustained manner due to its biocompatibility, nontoxicity, lack of allergenicity, and biodegradability. It can also be successfully targeted for site specific drug delivery and gene drug delivery. Chitosan is an excellent carrier for microsphere drug delivery. Chitosan microspheres are a well-studied drug delivery technology for the controlled release of medicines, antibiotics, antihypertensive agents, proteins, peptide medications, anti-inflammatory, steroids, anti-diuretics, amino acids, and vaccines. Chitosan has shown a significant improvement in the dissolution rate of poorly soluble pharmaceuticals and can thus be used to improve the bioavailability of poorly water soluble medication.

It gradually degrades to harmless byproducts (amino sugars) that are totally absorbed by the human body. The use of such biopolymers can eliminate/reduce problems associated with dose dumping, burst out effect, and unavoidable fluctuations in drug concentrations (mostly associated with conventional dosage form), resulting in enhanced efficacy and lower incidences of adverse drug effects. Chitosan has numerous applications in agriculture, textiles, nutritional enhancement and food processing, waste water management, and cosmetics.

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