CHITOSAN AS VERSATILE CARRIER IN DRUG DELIVERY SYSTEMS

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.

The crucial factors of purity, degree of acetylation, viscosity, and molecular weight should be taken into account while selecting chitosan for targeted drug delivery.. Drug delivery systems made of chitosan nanoparticles, microspheres, and beads are commonly used. Chitosan microspheres are used to deliver a variety of drugs with controlled release, to improve the bioavailability of substances that degrade

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readily, like protein, or to enhance 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
- To increase the bioavailability and dissolution rate of water-insoluble drugs,
- To enhance the therapeutic efficacy of the low molecular weight drugs.

Because chitosan is chemically inert, it has been combined with other polymers to obtain desired and controlled medication release. Several studies have demonstrated the effectiveness and safety of chitosan and its derivatives (N-tri methyl chitosan, mono-N-carboxy methyl chitosan) as absorption enhancers for enhancing 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. Chitin is estimated to be the second most ubiquitous biomaterial after cellulose. The main component of bacterial cell walls, some fungi, such as aspergillus and mucor, and the protective cuticles of crustaceans like crabs, shrimp, prawns, and lobsters is chitin. Chitin makes up 15% to 20% of the dry weight of the exoskeletons of crustaceans. In terms of inter- and intra-chain hydrogen bonding configurations and biological function, the crystalline structure of chitin has been recognized to be similar to that of cellulose. 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 Alkaline N-deacetylation of chitin results in the formation of chitosan. Chitin monomers and chitosan monomers are the two types of monomers that make it up. A polysaccharide called chitin is made up of (1-4)-linked 2-acetamido-2-deoxy-b-D-glucopyranose. It is made up of (1-4)-linked 2-amino-2-deoxy-b-D-glucopyranose and is known as chitosan. Chitosan contains two free hydroxyl groups and one primary amino group for each C building unit..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 surface of the drug-loaded nanoparticles is conjugated with the targeting moieties. The preparation of chitin and chitosan is given in

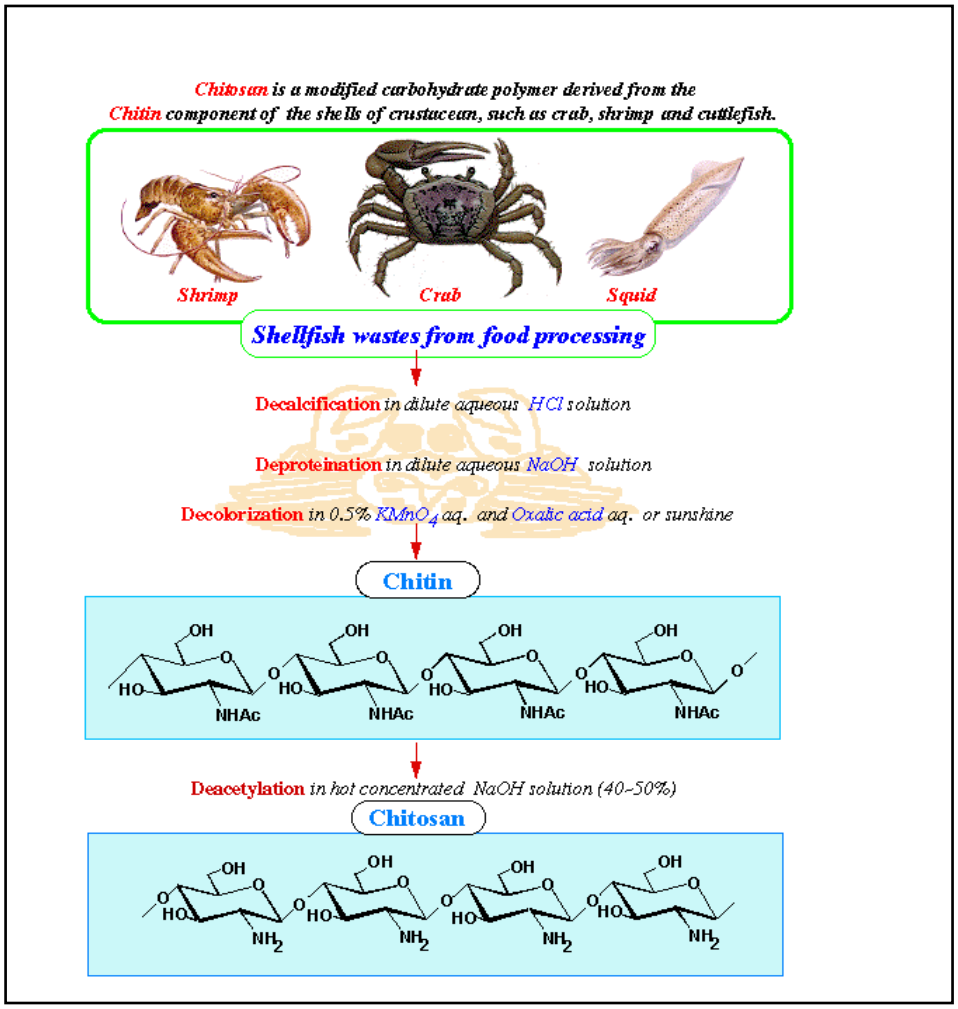

Figure 1: Preparation of Chitosan and Chitin

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. Chitosan's positive charges at neutral pH, which allow for an ionic interaction with the negative charges of sialic acid residues in the mucus, are thought to be responsible for its mucoadhesive qualities.

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 positive charges at neutral pH allow for an ionic contact with

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.

Commercially, chitosan can be purchased as fine powder, solution, and dry flakes. It degrades when fermented; it is safe and simple to remove from the body without causing adverse effects. Applications for chitosan are influenced by its polyelectrolyte nature and the amine groups' chelating properties.the negative charges of mucus sialic acid residues, which is essentially gives it its mucoadhesive properties.

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.

Each of these components can be adjusted according to the particular use of chitosan. For a product to be soluble, de-acetylation is essential. The solubility of hetero-glucans is generally influenced by the distribution of the acetyl groups, the size and polarity of the monomers, the distribution of the monomers along the chain, the flexibility of the chain, branching, charge density, and the molecular weight (50,000 to 2,000,000 Da) of the polymer. Viscosity (10 to 5000 cp) can be modified to each application by modifying the process parameters [12–14].

V. CHITOSAN IN DRUG DELIVERY

1. **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. Chitosan can be employed in ophthalmic drug delivery systems as nanoparticles, microspheres [15,16], gels, colloidal systems coated with chitosan, etc., according to a number of studies.

2. **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.

His might be caused by the chitosan microspheres' tendency to swell. Drug transport and microsphere erosion are impacted by the viscosity of the gel layer as chitosan's molecular weight increases. As polymer concentration rises, drug release from chitosan microspheres decreases.

A variety of chitosan salts, including chitosan lactate, chitosan aspartate, chitosan glutamate, and chitosan hydrochloride, were found to have the nasal sustained release of vancomycin hydrochloride[19]. After a nasal injection of diphtheria toxoid (DT) plus chitosan microparticles, IgG production considerably increases and DT is protected from both a systemic and local immune response [20].

Studies on the release of drug from various nasal vaccine delivery systems have been published. These materials include liposomes, attenuated viruses and cells, cholera toxin, microspheres, nanoparticles, and outer membrane proteins (proteosomes).

3. **Buccal Drug Delivery Systems:** The promising and specific mucoadhesive and absorption-enhancing properties of chitosan have proved to be useful for buccal drug administration. Prolonged adherence to the buccal mucosa is a crucial need of an optimal carrier for successful buccal drug delivery. and deliver the drug in a regulated or sustained manner in a single route toward the mucosa. The device remains in the mouth cavity for a longer durationof time due to mucoadhesive polymers.

It has been proven that chitosan-based buccal patches, pills, and gel formulations carry the drug unidirectionally into the systemic circulation through the buccal mucosa. The chitosan sponges were made for buccal administration of insulin in a different thorough investigation.

The promising and distinctive mucoadhesive and absorption-enhancing capabilities of chitosan have shown that it is suitable for buccal drug delivery. A sustained attachment to the buccal mucosa is a crucial requirement of the perfect carrier for effective buccal drug delivery. and administer the drug via regulated or sustained release in a single path to the mucosa. The device stays in the oral cavity for an extended period of time because of the mucoadhesive polymers.

It has been demonstrated that chitosan-containing buccal patches, pills, and gel formulations deliver the drug uni-directionally into the systemic circulation through the buccal mucosa. In a separate extensive study, chitosan sponges were developed for the buccal delivery of insulin. A quick-hardening paste using chitosan has been developed to replace bone for dental use. By using this paste, you can lessen gum inflammation.

4. **Floating Drug Delivery System:** Floating systems have densities that are less dense than stomach fluid. As a result, the bioavailability of drugs absorbed through the upper GI tract would increase and stomach transit time would decrease. Administering drugs that have a particular absorption site, an area that is insoluble in intestinal fluid, or an area used to treat gastric diseases using intra gastric floating dosage forms is effective. The applicability of chitosan for use in the development of these particular floating drug delivery systems was facilitated by its ionic interaction with the negatively charged surfactant sodium dioctyl sulfosuccinate. Insulin delivery to the colon has been done specifically with chitosan capsules [19–20].

5. **Intestinal Drug Delivery System:** An effective substitute for injectable therapy looks to be the sustained intestinal delivery of drugs like insulin and 5-fluorouracil, which are both used to treat diabetes mellitus and treat colon cancer, respectively. A formulation was developed that could transport the loaded drug into the intestine for a prolonged period of time bypassing the acidity of the stomach by utilizing the bio adhesiveness of polyacrylic acid, alginate, and chitosan [22–23].

6. **Colon Delivery System:** Chitosan was used in the formulation of oral medications to ensure sustained drug release. Recent research has shown that the bacteria in the colon can degrade chitosan. This chemical may therefore have potential for colon-specific drug delivery. Separate reactions with succinic and phthalic anhydrides were performed on chitosan. The resulting semi-synthetic polymers underwent testing for colon-specific, oral drug delivery systems. Acetaminophen (paracetamol), mesalazine (5-ASA), sodium diclofenac, and insulin have all been tested and confirmed to be successful colon delivery systems [24–26].

7. **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. The mucoadhesive performance and release characteristics of the polymer were largely demonstrated using mucoadhesive vaginal gel based on chitosan for lactic acid administration [28].

8. **Transdermal Drug Delivery System:** Chitosan disrupts epithelial tight junctions on the skin, enhancing penetration and promoting drug permeability. This epithelium tear heals quickly and can be reversed. Chitosan-alginate poly electrolyte complex (PEC) is prepared in-situ in beads and microspheres with potential use in packaging, controlled release mechanisms, and wound dressing7. A promising biocompatible and biodegradable medium for local inflammatory treatment is chitosan gel beads. Prednisolone anti-inflammatory drug-containing chitosan gel beads showed sustained drug release with decreased inflammation indices, improving therapeutic efficacy [29]. By carefully controlling the cross-linking of glutaraldehyde with chitosan membranes of different permeabilities to propranolol hydrochloride, drug release in the devices was controlled. Chitosan gel served as the drug reservoir.

9. **Vaccine Delivery:** Various nasal immunizations against chitosan-antigens have been designed. They include the cholera toxin, liposomes, attenuated viruses and cells, microspheres, nanoparticles, and outer membrane proteins (proteosomes). They produced secretory IgA levels that were higher than those produced by parenteral vaccine administration and significant serum IgG responses comparable to those [30]. Chitosan microparticle delivery systems for mucosal immunization have a lot of potential. Significant systemic humoral immune responses were observed after nasal immunization with diphtheria toxoid combined with chitosan microparticles.. Following oral vaccination, diphtheria toxoid conjugated to chitosan microparticles provide a protective local and systemic immune response against diphtheria toxoid as well as a significant rise in IgG production. Chitosan microspheres that had been loaded with BSA and diphtheria toxoid and had been cross-linked with glutaraldehyde showed tissue compatibility and had a long-lasting impact.

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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