A review on chitosan nanoparticles applications in drug delivery

Sheetal G Roy, Namrata S Shirsat, Ashish C Mishra, Sandeep O Waghulde and Mohan K Kale

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Abstract
Chitosan is a polymer naturally obtained by deacetylation of chitin. It is a polymer which is biodegradable and biocompatible regarded as safe for human dietary use and also approved for wound dressing applications. Because of their better stability, low toxicity, simple and mild preparation method and providing versatile routes of administration, chitosan nanoparticles have gained more attention as drug delivery carriers. Nanoparticles (NP) are prepared with chitosan and its derivatives possess a positive surface charge and mucoadhesive properties such that can adhere to mucus membranes and release the drug payload in a sustained release manner. Their sub-micron size is suitable for various applications in non-parenteral drug delivery for the treatment of cancer, gastrointestinal diseases, pulmonary diseases, drug delivery to the brain and ocular infections.

Keywords: Nanoparticles, drug delivery carriers, chitosan, polymer

Introduction
The efficacy of many drugs especially pharmacognosy drugs is often limited by their potential to reach the site therapeutic action. In most of the cases, small amount of administered dose reaches the target site and the majority of the drug distributes throughout the rest of the body in accordance with its physicochemical and biological properties. In recent times there are many new drug molecules showing therapeutic activity are discovered but its of minimal use if majority of its active ingredients fails to reach target site. Therefore developing a drug delivery system that optimizes the pharmaceutical actions of drug while reducing its toxic side effects in vivo is a challenging risk. Nanoparticles can be used to target the herbal medicines to individual organ which improves the selectivity, solubility, drug delivery safety, effectiveness and reduces the frequent dose. Nanoparticle size drug delivery increases the entire surface area of the drugs therefore leads to quicker dissolution in the blood. The enhanced permeability and retention of nanoparticles can cross Blood Brain Barrier (BBB). Nanoparticles are solid colloidal particles with diameters ranging from 1-1000nm. Chitosan act as a penetration enhancer by opening a tight junctions of the epithelium. Chitosan can transport drug both paracellularly and transcellular Chitosan interacts with mucus (negatively charged) to form a complex by ionic or hydrogen bonding as well as through hydrophobic interactions. There are many processes that can be used to encapsulate drugs within chitosan matrixes such as ionotropic gelation, spray drying, emulsification-solvent evaporation and coacervation. Since ancient times, herbal remedies and natural products are being used to cure the diseases. The herbal medicines have thousands of constituents that all work simultaneously against the diseases. Incorporation of the herbal extracts into new formulation systems have added advantages, such as their bulk dosing and absorption issues can be overcome which is the major problem being faced, enticing the attention of major pharmaceutical corporation. Thus, the nano-sized delivery systems of herbal drugs have a potential future. Hence, integration of the nanocarriers as a drug delivery system in the traditional medicine system is essential to conflict more chronic diseases like asthma, diabetes, cancer and others [1-4].
**Chitosan**

Chitosan is a modified natural carbohydrate polymer prepared by the partial N-deacetylation of chitin, a natural biopolymer derived from crustacean shells such as crabs, shrimps and lobsters. Chitosan is also found in some microorganisms, yeast and fungi (Illum, 1998). The primary unit in the chitin polymer is 2-deoxy-2-(acetylamino) glucose units combined by (1, 4) glycosidic linkages forms a long chain linear polymer. Although chitin is insoluble in most solvents, chitosan is soluble in most organic acidic solution a pH less than 6.5 including formic, acetic, tartaric it is insoluble in phosphoric and sulphuric acid \(^5\)-\(^6\).

![Fig 1](image)

Before reaching to the blood, many constituents of the herbal and allopathic drugs will be smashed in the highly acidic pH of the stomach another constituents might be metabolized by the liver. Therefore, the optimum quantity of the herbal drugs may not reach the blood. If the drug fails to reach in the optimum amount to the infected region at minimum effective level, then there will be no means to show the therapeutic effect of the drug. Nano carriers applying to herbal and allopathic remedies will carry optimum amount of the drug to their site of action bypassing all the barriers such as acidic pH of stomach, liver metabolism and increase in the prolong circulation of the drug into the blood due to their small size. Because of the following properties herbal remedies were selected as feasible drug candidate for delivery through a nano delivery system:

- Chloroform, petrol, acetone and methanolic extracts are available which may be unsuitable for delivery as such
- Dose reduction is intended as they are the bulk drugs
- Recent formulations lack target specificity for various chronic diseases.
- Some other side effects are associated with currently marketed formulations.
- Patient non-compliance due to large doses less effectiveness with the available formulations \(^7\).

**Drug Release from Chitosan Nanoparticles**

There are several mechanisms which govern drug release from chitosan nanoparticles such as: swelling of the polymer, diffusion of the adsorbed drug, drug diffusion through the polymeric matrix, polymer erosion or degradation and a combination of both erosion and degradation as represented in Figure 2. The initial burst release from the chitosan nanoparticle is either because of swelling of the polymer, creating pores, or diffusion of the drug from the surface of the polymer. Chitosan nanoparticles also exhibit pH-dependent drug release because of the solubility of chitosan. Chitosan derivatives alter the release of drug from the nanoparticle, affording tunable drug release and impacting the pharmacokinetic profile of the loaded drug.

![Fig 2: Diagram representing the mechanism of drug release by diffusion swelling and erosion of polymer (chitosan) matrix](image)

In diffusion control release, the drug permeates through the interior of the polymeric matrix to the surrounding medium. Polymer chains form the diffusion barrier making it unsuitable for the drug to pass through and this barrier serves as the rate limiting membrane for drug release. It may also be associated with polymer swelling or erosion. The swelling of the polymer is characterised by the imbibition of water into the polymer until the polymer dissolves. The mechanism of drug release is characterized by the solubility of the polymer in water or the surrounding biological medium. When the polymer encounters the surrounding medium and swelling commences, the polymer chain detangle. This can be followed by drug release from that region of the polymer matrix.

Erosion and degradation of polymers are interrelated features. Sometime, degradation of the polymer may cause subsequent physical erosions as bonds break. Erosion of polymers involves swelling, diffusion and dissolution. Erosion occurs in two ways: homogeneous and heterogeneous. Homogeneous erosion is erosion of the polymer at the same rate throughout the matrix whereas heterogeneous erosion is erosion of the polymer from the surface towards the inner core. The degradation of polymer may be due to the surrounding media or the presence of enzymes, pH of the surrounding media, the copolymer composition and water uptake by the polymer. Drug release depends on the type of polymer and the internal bonding, any additives (chitosan derivatives), as well as the shape and size of the nanoparticles as this reflects surface area and free energy \(^8\).

**Preparation of Chitosan Nanoparticles**

There are atleast four important methods available:

- Ionotropic Gelation
- Microemulsion
- Emulsification solvent diffusion
- Polyelectrolyte complex

These methods offer many advantages such as simple and mild preparations method without the use of organic solvent or high shear force. The drug is mostly bound with chitosan via electrostatic interaction, hydrogen bonding and hydrophobic interaction.
Ionotropic Gelation
Chitosan NP prepared by Ionotropic Gelation technique was first reported by Cavlo et al. and has been widely examined and developed. The mechanism of chitosan NP formation is based on electrostatic interaction between amine group of chitosan and negatively charged group polyanion such as tripolyphosphate. It offers a simple and mild preparation method in the aqueous environment. First, chitosan can be dissolved in acetic acid in the absence or presence of stabilizing agent, such as poloxamer, which can be added in the chitosan solution before or after the addition of polyanion. Polyanion or anionic polymers were added and nanoparticles were spontaneously formed under mechanical stirring at room temperature. Chitosan-TPP/vitamin C nanoparticles were prepared via Ionotropic Gelation between the positively charged amino groups of chitosan-TPP and the vitamin C, with constant stirring at room temperature for just one hour [9].

Micro emulsion method
In micro emulsion method, chitosan in acetic acid solution and glutaraldehyde are added to a surfactant in an organic solvent such as hexane. The mixture is kept on continuous stirring at room temperature, which allows the nanoparticles to form overnight as the cross-linking process is completed. Organic solvent is after this which is removed by evaporating under low pressure. The product at this point has excess surfactant can be removed by precipitating with calcium chloride followed by centrifugation. The final nanoparticle suspension is dialyzed and then undergo lyophilization. A very narrow size distribution is seen with this method and the size in formation of small sized nanoparticles. Some disadvantages with this method include usage of organic solvent, a lengthy process and a complex washing step [9].

Emulsification solvent diffusion method
It has been reported as chitosan NP prepared by emulsion solvent diffusion method, (which originally developed by Niwa et al. employing PLGA. The emulsification solvent diffusion method is based on the partial miscibility of an organic solvent with water. An o/w emulsion is obtained upon injection an organic phase into chitosan solution containing a stabilizing agent such as poloxamer under mechanical stirring, following high pressure homogenization. The emulsion is then diluted with a water to overcome organic solvent miscibility in water. Polymer precipitation occurs as a result of the diffusion of organic solvent into water, followed by the formation of nanoparticles. This methodist suitable for hydrophobic drug. The major drawbacks of this method include harsh processing conditions (e.g., the use of organic solvents) and the high shear forces used during nanoparticle preparation [9].

Polyelectrolyte complex
Polyelectrolyte complex or self-assemble polyelectrolyte is a term to describe complexes formed by self-assembly of the cationic charged polymer and plasmid DNA. Mechanism of Polyelectrolyte complex formation involves charge neutralization between cationic polymer and DNA leading to decrease in hydrophilicity. Several cationic polymers (i.e., gelatin, polyethyleneimine) also posses this property. Usually, this technique offers simple and mild preparation method without harsh conditions involved. The nanoparticles spontaneously formed after addition solution of DNA into chitosan dissolved in acetic acid solution, under mechanical stirring at or under room temperature. The complexes size lies from 50 nm to 700nm [9].

Drug delivery routes
1. Chitosan in oral drug delivery
Catechin and Epigallocatechin are the flavonoids present in green tea and behaves as strong antioxidants. They undergo degradation in intestinal fluid and are poorly absorbed across intestinal membranes. The intestinal absorption of catechin and epigallocatechin gallate can be enhanced by encapsulating them in chitosan nanoparticles. Tamoxifen San anti-cancer drug, is poorly water soluble and a good candidate for oral cancer drug delivery. By formulating tamoxifen into lecithin chitosan nanoparticles, permeation of tamoxifen across the intestinal epithelium was increased. Chitosan and carboxymethyl chitosan NP were found to be excellent carriers for oral vaccine delivery of extracellular products V. anguillarum (pathogenic bacteria) [10].

2. Chitosan in nasal drug delivery
Carboxymethyl chitosan NPs of carbamazepine used in the treatment of epilepsy have found to enhance the bioavailability and brain targeting via the nasal route. In Alzheimer’s disease (AD), Estradiol, a potent sex hormone, has been used in the prevention and treatment of AD. The CSF levels of estradiol in brain were found to be high compared to plasma levels when estradiol was administered intranasally as chitosan NPs. The three pathways of nasal absorption is mainly by transeellular pathway, paracellular pathway and trigeminal nerves. The bioavailability of leuprolide which is used in the treatment of prostate cancer and hormone-dependent diseases, was found to be increased when administered as thiolated-chitosan NPs. There was a 2-5 fold increases in drug transport across porcine nasal mucosa when leuprolide was formulated as chitosan NPs or thiolated - chitosan NP, respectively, compared to leuprolide solution. [10].

3. Chitosan in Pulmonary Drug Delivery
A nanoparticle dry powder inhalation (DPI) of rifampicin, an antitubercular drug, was formulated with chitosan as the polymer. This NP formulation has shown sustained drug release until 24 hours and no toxicity at both cell and lungs. Itraconazole is an antifungal drug which, when administered orally, suffers from low solubility. The pulmonary deposition of itraconazole was shown to be increased when formulated as spray-dried microparticles containing itraconazole loaded chitosan NP [10].

Pharmacokinetics of chitosan based formulations
The most important property of chitosan to be exploited is its ability of mucoadhesion. A pharmacokinetic study was done in beagle dogs to assess the bioavailability of cyclosporin-A (CY-A) encapsulated into NPs which consist of chitosan, gelatin-A or sodium glycocholate (SGC). The standard oral micro-emulsion formulation (Neoral®) was received by the control group. The Cmax was significantly increased in the case of both the chitosan as well as gelatin NP formulations while there was decrease in Cmax of SGC NPs as compared to Neoral. There was a 2.6-fold increase in the AUC of Cy-A from chitosan NPs compared to SGC NPs and 1.8-fold increase in AUC from gelatin NPs compared to SGC NPs [9].

Delivery of vaccines
While clinical use of oral or mucoadhesive drug formulations containing chitosan remain on the horizon, there are already human vaccines in the development which use chitosan as an adjuvant. Nanoparticles often exhibit significant adjuvant
effects in parenteral vaccine delivery since they may be readily taken up by antigen presenting cells. The sub-micron size of nanoparticles allows them to be taken up by M cells, in mucosa associated lymphoid tissue (MALT). Activation of macrophages is initiated after uptake of chitosan and also have applications in DNA mucosal vaccines. This system showed high antibody level in mice after intranasal administration[10-11].

Limitations
In neutral and alkaline pH chitosan has low solubility. For GI applications, its mucoadhesion and permeation enhancer properties are strongest in the duodenal area, which can be modulated by chitosan derivatives. To date, chitosan has shown little or no toxicity in animal bodies and there have been no reports of major adverse effects in healthy human volunteers [12].

Conclusions and future work
Due to versatility of chitosan, it has many potential applications in drug delivery. A chitosan based nasal formulations of morphine is currently in phase 2 clinical trials (UK and EU) and phase 3 clinical trials in US. Nanoparticles drug delivery system has a promising future and also the versatility of chitosan, it has many potential applications in drug delivery via the gastrointestinal tract, nasal, pulmonary routes as explained in this review[12].

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References