AN OVERVIEW OF CHITOSAN NANOPARTICLES AS DRUG CARRIERS

Abstract

Many traditional diseases may have greater potential if new drug delivery methods are developed. Chitosan has been preferred as a drug delivery vehicle due to its beneficial properties such as biodegradability, biocompatibility, non-toxicity, non-immunogenicity, non-carcinogenicity and antibacterial ability. In addition, it has attracted great interest as a new drug delivery method because it is widely used in the transport of protein, gene and antibody drugs, as well as in many ways such as mouth, nose, urine, injection. The second most abundant polysaccharide after cellulose is chitosan, which is abundant in nature. Chitin can be produced by partial deacetylation in alkaline solution. Chitosan is good and absorbs well. The most important feature of chitosan is that it can easily combine with substances such as glutaraldehyde, tripolyphosphate and polyaspartic acid sodium salt to form nanoparticles that can dissolve in macromolecules with a pH value below 6.5. Most organic acidic solutions.

Keywords: Chitosan, Non-Immunogenicity, Drug Therapy, Tripolyphosphate.

Authors

Dr. B.K. Jain
Faculty, Pharmacy
Kalaniketan Polytechnic College
Jabalpur, Madhya Pradesh, India.
jainbhaanukumar@gmail.com

Dr. Ankita Alice Singh
Faculty, Pharmacy
Kalaniketan Polytechnic College
Jabalpur, Madhya Pradesh, India.

Dr. Kaminee Sahu
Professor, Pharmacy
Gyan Ganga Instt. of Science and Technology
Jabalpur, Madhya Pradesh, India.

Dr. Seema Kohli
HOD, Pharmacy
Kalaniketan Polytechnic
Jabalpur, Madhya Pradesh, India.

I. INTRODUCTION

Drug therapy is receiving increasing attention in the treatment of various diseases such as arterial disease, malignancy, osteoporosis, type 2 diabetes and hypertension. The lack of stability, insoluble in water, limited selectivity, excessive pollution and poor quality of cause the explosion of many chemicals. A good drug carrier is essential to solve these problems. Chitosan nanoparticles are a drug carrier with growth potential, which has the advantage of slow and controlled release of drugs, can increase drug solubility and stability, improve curative effect and reduce toxicity. Due to their small size, drugs can be sent to the treatment center, increasing their efficiency, allowing them to pass through the biological system. Other properties of modified nanoparticles include better drug handling. When enzymes work in living organisms, biodegradable nanoparticles can produce water and carbon dioxide without harming them.

II. CHITOSAN: THE BASIC PROPERTIES

Chitosan are obtained by removing the acetic acid portion of chitin by strong alkali hydration. It is a copolymer containing -(1,4)-2-acetylamino-D-glucose and -(1,4)-2-amino-D-glucose units (Figure 1). Most dilute acids can dissolve chitosan. After the amino group is protonated, chitosan dissolves in water in an acidic environment and provides a good charge, gelation and film formation. The hemialdosidic linkage of chitosan renders it unstable in acid and causes it to hydrolyze in this environment, reducing its viscosity and molecular weight. The molecular weight and degree of deacetylation of chitosan are important determinants of its physical and chemical properties. 2 Since chitosan is a natural product, its adhesion increases in neutral and acidic environments. The higher the molecular weight and degree of deacetylation of chitosan, the stronger its adhesion and adhesion. It is easy to change some chitosan groups, such as thiols, to increase adhesion (1).

III. BIODEGRADABILITY AND SAFETY OF CHITOSAN

The biodegradability of chitosan is important for its application in drug delivery. Chitosan with appropriate molecular weight can be divided into parts that can be removed from the kidney in the body, while chitosan with high molecular weight is suitable for removal of the kidney. 4 As the degree of deacetylation increases, the rate of degradation also increases. The amino group of chitosan is a prerequisite for enzymatic catalysis, another degradation process. 4 Chitosan is now considered a non-toxic and safe medicinal product. However, as the charging rate increases, the toxicity of chitosan also increases. 4 Blood clots from too much chitosan can be fatal (3).

IV. PREPARATION OF CHITOSAN NANOPARTICLES

The most popular methods used to produce chitosan-based nanoparticles include ionic gelation, microemulsions, emulsified solvent diffusion, and emulsion-based solvent evaporation. Some of the key benefits most of these processes provide are the use of less organic solvents and less energy. The molecular weight and degree of acetylation of chitosan are important factors affecting the size and value of chitosan nanoparticles produced by this process. Drugs can be retained in polymer matrices by a variety of methods, including electrostatic contact, hydrogen bonding, and hydrophobic interactions. The physiological

environment of the nanoparticles application and distribution site must be considered, including factors such as pH stability, ionic strength, salt content, and the presence of salts, enzymes, and proteins.

1. **Ionic Gelation:** This is a simple process in which the chitosan solution (well-charged) is dissolved in acetic acid or polyanionic solutions with or without stabilizers such as poloxamers. During mechanical mixing at room temperature, nanoparticles are easily formed due to the complexation of positive and negative charge types, causing the chitosan to split into spherical particles of different sizes and surface charges. Generally stated size ranges are 20 to 200 and 550 to 900 nm. Chitosan-TPP/vitamin C nanoparticles were prepared by ionic gelation of the amino group of chitosan-TPP and vitamin C with continuous stirring for 1 hour at room temperature (3,4). Simple process these eight are about achieving good results. With or without the addition of stabilizing agents such as chitosan, poloxamers, charged amino-charged chitosan in acetic acid or other negatively charged polyanion. Chitosan breaks down into small fragments of various sizes and surface loads due to the combination of good and bad species during mechanical agitation at ambient temperature. The reported size is generally between 20 and 200 nm and between 550 and 900 nm. Chitosan-TPP/vitamin C nanoparticles were produced in just one hour by continuous mixing at room temperature by ion transport gelation of the amino groups of chitosan-TPP and vitamin C (3, 4). Ionic gelation has many advantages such as small operation and use of aqueous media, low toxicity and the ability to reduce variation in the encapsulation process. The main disadvantage of this method is that high molecular weight drugs are difficult to penetrate and do not work well in acidic environments (5,6).

2. **Complex Coacervation Method:** Coagulation is a technique used to separate cylinders by mixing electrostatically driven fluids. DNA-chitosan nanoparticles are formed by the combination of positively charged amine groups and negatively charged DNA phosphate groups in chitosan (7,8). Encapsulation efficiency and drug release are determined by the molecular weight of the two polymers (9,10). The advantage of the coacervation method is that the process can be carried out completely in liquid at low temperature. This provides a better way to store the functionality of the encapsulated object. The main disadvantage of this method is the poor stability of nanoparticles, low drug loading and synthesis of complexes by the toxic substance glutaraldehyde (4,11,12). The separation of spherical particles by electrostatic coupling of liquids is called agglomeration. The positively charged amine groups of chitosan combine with the negatively charged phosphate groups of DNA to form DNA-chitosan nanoparticles (7,8). The molecular weight of the two polymers controls the efficiency of drug retention and release (9,10). The advantage of complex coacervation is that the entire process can be done in a hot water environment. This makes it possible to control the effect of the encapsulated drug. The disadvantages of this method include limited drug loading, poor nanoparticle stability, and the need to crosslink the complex with hazardous chemicals such as glutaraldehyde. (4, 11, 12). In the Polyelectrolyte complex (PEC) method, a cationic polymer (such as a solution of chitosan dissolved in acetic acid, gelatin, and polyethyleneimine) is added to an anionic solution (such as dextran sulfate DNA solution), mechanical mixing of the chamber. gold as the neutralization rate. The simplicity of the method, the lack of weight, and the produced nanoparticles are always

positive (4,5) Charged nanoparticles with in vitro sustained release properties show an average diameter of about 200 nm (4).

3. **Co-Precipitation Method:** Easily Dispersed nanoparticle group acid solution, it is added to a high pH 8.5-9.0 solution such as ammonium hydroxide. High encapsulation efficiency can be used to produce nanoparticles as small as 10 nm in diameter (4,11)]. This method reveals many different dimensions that can be misleading. Lactic acid grafted chitosan (LA-g-chitosan) nanoparticles were produced by a coagulated method using ammonium hydroxide to form coagulated droplets. Spherical and uniformly dispersed nanoparticles can be produced using this technique (13).

4. **Microemulsion Method:** In this method, a surfactant is mixed with glutaraldehyde in an organic solvent such as chitosan and hexane in an acetic acid solution. After synthesis was complete, the mixture was placed at room temperature with continuous stirring to allow the nanoparticles to grow overnight. The organic solvent was then removed by low evaporation. At this time, the product contains an excess of surfactant, which can be removed by centrifugation after precipitation of calcium chloride. The final suspension of nanoparticles was then dialyzed and lyophilized (14)]. With this technique, a very narrow gap can be observed and its size can be adjusted by changing the concentration of glutaraldehyde used in nanoparticle synthesis. This process produces small nanoparticles (15). Some disadvantages of this method include the use of organic solvents, lengthy procedures and difficult cleaning steps.

5. **Emulsion Solvent Diffusion Method:** O/W emulsion (16) is prepared by mixing the stabilizer solution containing organic solvent and chitosan under mechanical mixing and high pressure homogenization. Dimensions of 300-500 nm can be obtained with this technique. When more water is added to the emulsion, the polymer precipitates, forming nanoparticles. This method is best for hydrophobic substances where the encapsulation efficiency is very high. The biggest disadvantage of this method is the use of high cutting force.

6. **Emulsion Based Solvent Evaporation Technique:** Uses this technique with a slight modification of the above technique, but avoids high shear forces. Particles smaller than 300 nm can be produced with this device. Chitosan and surfactants are dissolved in organic solvents and the mixture is sonicated to form an emulsion. The resulting emulsion is then mixed with a surfactant solution, forming nanoparticles when the organic solvent evaporates. The nanoparticles are then washed, centrifuged several times to remove excess surfactant, and then lyophilized to produce lyophilized nanoparticles (17,18).

7. **Back Micellar Method:** After the surfactant has dissolved in the organic solvent, the drug and the cross-linker chitosan are added and the mixture is continuously mixed by vortexing overnight. The organic solvent evaporated, leaving a translucent dry material. To precipitate the surfactant, the product is dissolved in water and a small amount of salt is added (19,20). Small-sized nanoparticles can be seen when organic solvents are used (21). Chitosan nanoparticles loaded with doxorubicin-dextran conjugate were produced using reverse micelle technique. During this process, the surfactant sodium bis (ethylhexyl) sulfosuccinate (AOT) is dissolved in n-hexane. Continue mixing the AOT solution with liquid ammonia, 0.01% glutaraldehyde, 0.1% chitosan in acetic acid

solution at room temperature and add the doxorubicin-dextran conjugate to the AOT solution with continuous stirring at room temperature to produce nanoparticles (22, 23).

V. DRUG RELEASE FROM CHITOSAN NANOPARTICLES

As shown in Figure 1, polymer swelling (24), drug diffusion from the polymer matrix, drug diffusion, polymer erosion or degradation, and erosion and degradation (25) If the polymer swells, forms pores, or the drug diffuses on the polymer surface, the chitosan nanoparticles Chitosan nanoparticles also show pH-dependent drug release due to their solubility (27). Chitosan derivatives affect the pharmacokinetic profile of the loaded drug by changing the way the drug is released from nanoparticles (28).

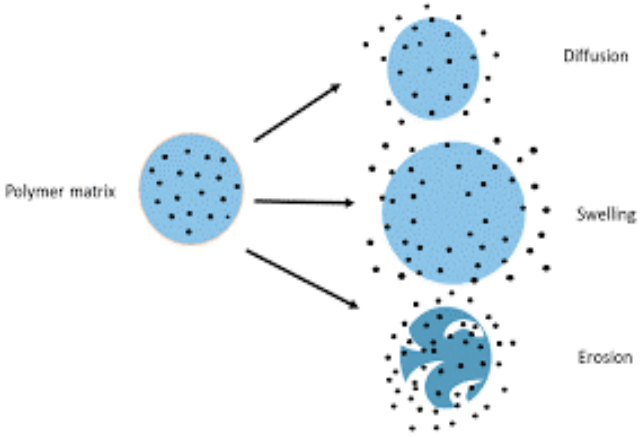

Figure 1: Diagram representing the possible mechanisms of drug release by diffusion, swelling and erosion of polymer (chitosan) matrix

In diffusion-controlled release, the drug penetrates through the polymer matrix into the surrounding environment. The release of the drug is slowed down by the gap barrier formed by the polymer chain, which makes the flow of the drug difficult. In addition, polymer erosion or swelling can inhibit expansion. Fick's law of diffusion provides a mathematical description of diffusion. F is the flux rate per unit of cross-sectional area, c is the chemical concentration, and D is the diffusion coefficient (diffusion rate), where F = D c x (1).

To deduce the limits of Fick's law, the following assumptions need to be made: the buffer is always supplied by the environment around the nanoparticles, the so-called state is stored at the time of injection, and the diameter of said drug. The diffusion mean is smaller than that of the drug passing through the polymer matrix (29). Water is absorbed into the polymer until the polymer dissolves, causing the polymer to swell. The solubility of a polymer in water or biological media is a defining feature of the drug release mechanism. When polymer chains come into contact with the surrounding environment, they dissolve and begin to expand. Drug release then occurs from this region of the polymer matrix. The drug release film is mainly affected by the hydrophilicity of the polymer, the swelling = of the polymer, and the density of the polymer chain (30). Thus, this will affect the amount of drug in the transport membrane or cellular uptake, which in turn will affect the amount of drug absorbed from the body. Co-erosion and degradation of polymers. Sometimes physical

erosion can occur due to the breakdown of materials due to polymer decomposition. Polymer erosion is a complex process involving swelling, diffusion and fragmentation. There are two types of erosion: homogeneous erosion and heterogeneous erosion. In contrast to inhomogeneous erosion from the surface to the inner core, uniform erosion occurs throughout the matrix at the same rate. Enzymes or mediators in this region will be responsible for the degradation of the polymer. The composition of the copolymer, the pH of the surrounding environment, and the water absorption of the polymer are all factors that affect the rate of polymer degradation. The type and interconnections of the polymer, any additional materials (chitosan derivatives), and the shape and size of the nanoparticles, because it indicates the area and degree of freedom of that domain (31).

VI. PROPERTIES OF CHITOSAN NANOPARTICLES

Nanoparticles are solid colloidal particles at 1-1000 nm. Due to their small size, nanoparticles are more mobile than micron particles and can easily enter cells and accumulate at the site of inflammation. Therefore, the cellular uptake rate is high. Through the denaturation and dissolution of chitosan, drugs contained in chitosan nanoparticles can be released, causing a slow reaction. Different types of nanoparticles can be used to control drug release because chitosan has different molecular weights and levels of deacetylation, they degrade at different rates and take longer to degrade. It can also be modified to provide a controlled release of chitosan.

1. **In Vivo Metabolism of Chitosan Nanoparticles:** Antibodies produced by the body see foreign nanoparticles and absorb them. Adsorbed plasma proteins, lipoproteins, immune system and additional protein C in plasma accelerate the reorganization of the reticuloendothelial system. Macrophages engulf the nanoparticles and remove them from the body circulation. Plasma proteins deposited on the surface of nanoparticles form a bridge between nanoparticles and macrophages. The amount of nanoparticles affects their ability to absorb plasma, which affects plasma proteins that can be transported by macrophages. In vivo, polar, highly surface-capable, amphiphilic and hydrophilic nanoparticles circulate longer and are less phagocytized.

2. **Targeting Chitosan Nanoparticles:** Good amount of chitosan on the surface of tumor cells has a specific adsorption and neutralization effect. It acts as a drug carrier and targets the liver, spleen, lungs and intestines (32). Vinyl chitosan nanoparticles have long circulation and are highly selective for tumor cells. (33). These effects have also been reported in high molecular weight vinyl chitosan nanoparticles. Doxorubicin-chitosan polymer micelles have excellent drug-carrying capacity, are suitable for targeting the liver and spleen, and reduce toxicity to the heart and kidneys. (34).

3. **Application of Chitosan Nanoparticles:** According to Nam et al. (35) revealed that modified ethylene glycol-chitosan nanoparticles are distributed into different species in all cells compared to unmodified nanoparticles. In vivo, drug-loaded chitosan nanoparticles decompose into free chitosan and drugs. To produce a therapeutic effect, the drug enters tissues and cells. During this process, lysozyme and bacterial enzymes in the large intestine often cause the chitosan to break down. The kidneys remove the chitosan from the blood and the rest is excreted in the faeces. The rate and level of degradation of chitosan in the body are also affected by its molecular weight and degree

of deacetylation. (36.37). According to studies, chitosan nanoparticles can transport various drugs through the mouth, nose, drainage and eyes. These drugs include genes, proteins, anti-cancer drugs and antibiotics.

4. **Oral Administration:** Oral administration is the most accurate form of administration because it is easy to administer. However, oral administration poses many problems, including changes in pH (the stomach is acidic), presence of enzymes, first pass effects in the liver, and gastrointestinal effects on drug absorption. These difficulties prevent it from entering the body (38). Nanoparticle technology is increasingly used in formulations to overcome limitations in oral drug delivery (39,40). The small size, large surface area and flexible surface of nanoparticles are just some of the advantages. Small particles are known to cause rapid breakdown of the drug. In addition to these benefits, nanoparticles can also improve the stability of acid-sensitive drugs in the gastrointestinal tract compared to other drug delivery methods such as liposomes and lipid systems (41). As illustrated in the various examples below, chitosan can be formulated into polymeric nanoparticles for a variety of oral drug applications.

5. **Nasal Delivery Nasal Delivery:** Is a method that does not interfere with the delivery of drugs to the lungs, brain and/or body organs. Mucociliary clearance of drugs poses an important problem in nasal delivery. Also because of their low permeability to nasal epithelium, hydrophilic substances, proteins and peptides, nucleic acids and polysaccharides. Nasal breathing is important for the drug to work well. Molecular weight, lipophilicity, and price are examples of physical properties of drugs that control nasal absorption. Drugs that cannot pass through the nasal mucosa are removed by the mucociliary route. The development of mucoadhesive systems can overcome this limitation. Chitosan adheres to mucus, is biodegradable, biocompatible, has very low toxicity, opens nasal membrane connections, and is biocompatible. Because of these properties, chitosan can be applied to the nasal cavity (42) and nasal absorption can occur in three different ways: via transcellular, paracellular and trigeminal neurons (43). The ability of the drug to cross the blood-brain barrier (BBB). Carbamazepine treat epilepsy. Carbamazepine nanoparticles have been reported to improve the bioavailability and brain targeting of oral carbamazepine. When carbamazepine was administered intra-nasally as chitosan nanoparticles, the brain/plasma ratio was 150% (24). Gender is a risk factor for Alzheimer's disease (AD), and women with AD have lower 17-estradiol levels. AD can be prevented and treated with the powerful sex hormone estradiol. For estradiol to work, it must reach enough tissue in the brain. When given orally, estradiol levels in the CSF are relatively low. When estradiol was administered intra-nasally in the form of chitosan nanoparticles, higher levels were found in the cerebrospinal fluid than in the blood. These findings show that estradiol is delivered directly to the brain, while chitosan, which is nanoparticles, is administered through the nose. Another example is the discovery that leuprolide, which is used in the treatment of hormonal disorders and prostate cancer, is more bioavailable when thiolated chitosan nanoparticles (43) are synthesized as leuprolide-thiolated chitosan, nanoparticles and chitosan nanoparticles. When leuprolide was formulated as chitosan nanoparticles or thiolated chitosan nanoparticles, drug transport across the nasal mucosa of pigs was increased 2-5 times compared to leuprolide solution. For thiolated chitosan nanoparticles, there is a 6.9-fold increase in drug exposure measured by area in plasma concentration compared to AUC time (44).

6. **Pulmonary Drug Transport:** Pulmonary Drug Transport can cause local and systemic effects. Pulmonary drug delivery has many advantages over other methods, such as rapid and prolonged drug delivery, high efficiency, and absence of primary liver disease. The large surface area, tissue vascularity, and poor absorption of the lungs result in better transport of the drug from the lungs (38). Bronchial mucus layer, alveolar lining fluid, epithelial cells, macrophage clearance and proteolytic degradation are some of the factors affecting the lungs. medicine. transported to the lungs (40).

7. **The Carrier of the Drug Gene:** As carriers of the gene, normal bacteria have some disadvantages such as low infection rate, high cytotoxicity and significant immunity (45). Chitosan is a non-bacterial material with good biocompatibility and biodegradability, and this has increased the use of chitosan nanoparticles in providing genetic modification (46,47). Wang et al. It has received great interest as a potential therapeutic agent in the treatment of diseases caused by genetic defects (46). However, its use is limited due to its rapid degradation and lack of cellular uptake. By using chitosan nanoparticles, drugs can be delivered to the lungs. According to the researchers, chitosan has mucoadhesive properties that facilitate the transport of drugs in the lungs due to its good surface area. This adhesion to the lung mucosa increases the chance of drug absorption; The nanoparticles produced by Katas and Alpar ionic (46) gelled up to 100%, thus protecting the siRNA from nuclease damage. Liu (46) et al. synthesized stable siRNA nanoparticles by directly combining the green fluorescent protein-inhibiting siRNA using electrostatic interactions of polyelectrolytes as carriers with a compound ratio of 83% to 94%. This study also showed that the molecular weight and deacetylation level of siRNA and chitosan can make nanoparticles more stable at good cost.

8. **Carriers of other Drugs:** Chitosan nanoparticles are hormones, anti-allergic drugs, anti-inflammatory drugs, etc. It can also be loaded with other drugs such as Hao and Deng (48) prepared acyclovir chitosan nanoparticles with 17.8% drug load and 87.5% encapsulation efficiency using ion crosslinking technology. Li and Luan (49) prepared tranilast-loaded chitosan nanoparticles with 82.4% encapsulation efficiency and 285.5 nm particle size for allergic diseases.

9. **Anti-Tumor Effect of Chitosan:** Chitosan can directly affect tumor cells, affect metabolism, slow growth or induce apoptosis. It also has anti-cancer properties by strengthening the immune system (50). Maeda and Kimura (51) showed that low molecular weight chitosan and oligochitosan inhibited tumor growth in S180-bearing mice. According to Torzsas et al., chitosan-containing foods can reduce the growth of intestinal bacteria caused by the azomethane molecule. In vitro anti-tumor testing of chitosan nanoparticles showed that the inhibition rate of Hela uterine cancer at 500 mg/L concentration was 27%, the inhibition rate of liver cancer SMMC-7721 cells was 23%, and the intestinal inhibition rate was 23%. cancer BGC-823 cells are 27%. For MCF-7 breast cancer, this rate is 55% (52). These studies provide evidence that chitosan has anti-inflammatory properties in vitro and in vivo, and provide a good opportunity for its use as an adjunct agent for antineoplastic drugs and drug carriers. Studies have also shown that there are significant differences in anti-inflammatory activity and selectivity for tumor cells of chitosan nanoparticles produced by different manufacturers (53).

VII. CONCLUSION

Chitosan nanoparticles are preferred as drug carriers due to their excellent biocompatibility, degradability and non-toxicity. Chitosan nanoparticles can be used to deliver protein, gene and other drugs and protect them from the destruction of enzymes in vivo due to their better drug absorption and bioavailability. Currently, chitosan nanoparticles are being modified for targeted, controlled release. The development of specific chitosan carriers to promote/control the release of phyto-pharmaceuticals is another area of future research as antimicrobial compounds for phytotherapy continue to be sought and designed. The application of chitosan nanoparticles as drug carriers has been well developed, but there are still some important problems to be overcome. For example, due to the poor quality of chitosan, only a few hydrophilic substances can be encapsulated unchanged within chitosan nanoparticles. Although it is easy to modify chitosan to encapsulate hydrophobic drugs, more research is needed to determine whether the modified chitosan and its derivatives are biocompatible. As a result, chitosan and its derivatives have the potential to be used more widely as drug carriers. Chitosan is a biocompatible, sustainable supplement. The use of chitosan and its derivatives as drug carriers has great potential.

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