REVIEW ARTICLE

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Chitosan: A Biodegradable and Biocompatible Carrier for Drug Delivery Systems

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ABSTRACT: Chitosan, a natural biopolymer generated from chitin, has attracted a lot of attention as a versatile carrier in drug delivery systems. The properties of chitosan which include biodegradability, biocompatibility, mucoadhesive properties, pH sensitivity, and capacity to interact with other biopolymers make it an inventive option. These properties allow chitosan-based carriers to adjust drug release in response to environmental stimuli, improve targeted delivery, and increase drug stability. The chitosan features pertinent to drug delivery are reviewed in this paper, including its pH-dependent solubility, capacity to attach to mucosal surfaces, and enzymatic breakdown into non-toxic metabolites. The effectiveness of key mechanisms, including hydrogel formation and micro/nanoparticle encapsulation, in preserving therapeutic substances and permitting regulated release is highlighted. Chitosan-based drug delivery system applications in oral, ocular, nasal, pulmonary, wound healing, and cancer therapies are also reviewed. This study highlights the application role of chitosan in modern medicine by analyzing present problems and new potential. It provides insights into how chitosan can change drug delivery and improve therapeutic efficacy across a range of clinical domains.

Keywords: Biocompatibility, Biodegradability, Chitosan, Controlled drug release, Drug delivery system.

INTRODUCTION

A drug delivery system is a formulation or apparatus that allows a medication to selectively enter its site of action while avoiding non-target cells, organs, or tissues (Rojo et al., 2017). Prior to the use of drug delivery systems, drugs were formulated and developed in the form of a pill or capsule. When administered, the drug diffuses through the body and gets absorbed into the bloodstream, and eventually, only a small portion of the drug gets to the needed site of action (Ezike et al., 2023). For example, cytotoxic drugs used in chemotherapy indiscriminately act on both normal cells and tumor cells. Due to these limitations, researchers have considered biopolymers as possible options for creating next-generation drug delivery systems. One of such biopolymers is chitosan (Corrie, 2008).

Chitosan is a deacetylated derivative of chitin – a biopolymer present in the exoskeleton of crustacea, the cuticles of insects, algae, and the cell walls of fungi. Chitosan is a class of linear polysaccharides made up of varying quantities of N-acetyl-2 amino-2-deoxy-D-glucose (glucosamine, GlcN) and 2-amino-2-deoxy-D-glucose (N-acetyl-glucosamine, GlcNAc) residues that are linked by β1→4 (Aranaz et al., 2021). Chitosan has drawn attention among the several biopolymers found in nature because of its innate biological and physiochemical characteristics. Chitosan is a biodegradable, non-toxic polymer with mucoadhesive and absorption-enhancing qualities, excellent biocompatibility, and low immunological response, making it safer for long-term therapeutic applications. These characteristics stem from the polysaccharide's appropriate structure, and they make chitosan have better bio-distribution, higher sensitivity, and specificity, and decreased pharmacological toxicity when used as a drug delivery system. Hence, it is advantageous and is now frequently utilized (Jafernik, 2023). This review seeks to provide a comprehensive overview of chitosan as a biodegradable and biocompatible drug delivery system carrier. It addresses present issues and upcoming prospects, examines the mechanics behind its efficacy, and showcases recent developments and applications. Combining the most recent research, this review highlights how chitosan can revolutionize drug delivery methods and enhance patient outcomes.

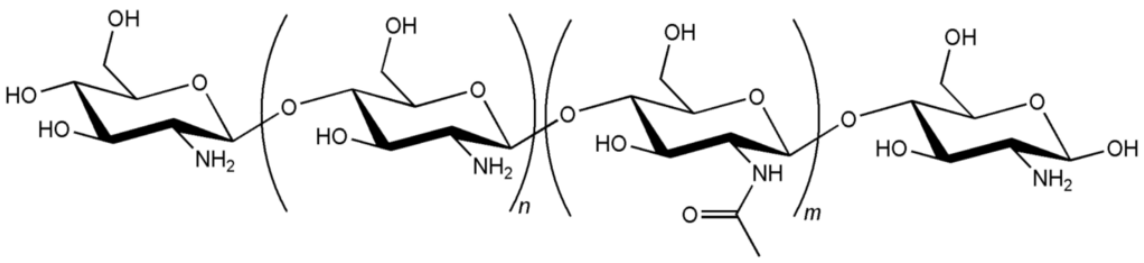

Figure 1. *The chemical structure of chitosan (Ribeiro et al., 2017).*

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The number of repeat units of glucosamine and acetyl-glucosamine in the chain is denoted by the indexes n and m, respectively (n + m denoting the degree of polymerization and m/n + m denoting the degree of acetylation). The polymer is referred to as chitosan when n exceeds fifty percent. Its reactivity is increased by the presence of NH_2 (Ribeiro et al., 2017).

PROPERTIES OF CHITOSAN TO DRUG DELIVERY

Chitosan is the perfect material for drug delivery applications because of its biological and physiochemical characteristics. These characteristics include:

Biodegradability

Biodegradability is a key characteristic that makes chitosan a viable material for drug delivery systems. Chitosan can be naturally broken down by enzyme activity, especially by lysozymes found in the human body (Dash et al., 2011). Studies have shown that the rate of chitosan degradation depends on its molecular weight and degree of acetylation. Enzymatic degradation may also be affected by N-substitution (Kean and Thanou, 2010). Chitosan biodegrades to produce non-toxic oligosaccharides These oligosaccharides may either be excreted or integrated into glycosaminoglycan and glycoprotein metabolic pathways. (Matica et al., 2017). This biodegradation characteristic lowers the possibility of long-term build-up or negative effects by ensuring that chitosan-based drug delivery systems break down into non-toxic metabolites.

Biocompatibility

Biocompatibility refers to the capacity of a material to interact with biological systems without causing toxicity, inflammation, or adverse immunological reactions. Chitosan is a natural polysaccharide that possesses biocompatibility, making it an excellent material for drug delivery. Kim et al. (2011) tested the biocompatibility and biodegradability of chitosan implants in rat spinal cord. Both injured and uninjured spinal cords were used to test the implants. According to the results, chitosan is biocompatible with spinal cord tissue when supplied as a pure, nonporous sheet. In the spinal cord, chitosan has been demonstrated to be a safe and comparatively harmless substance. Because it doesn't cause a persistent inflammatory or immunological reaction, chitosan is an appropriate biomaterial for long-term spinal cord applications. Hirano et al. (1990) researched the biocompatibility of chitosan for oral administration using two groups of rats. Under the same conditions, one group was fed with a basal ration only, while the other group was fed with a basal ration containing 2% chitosan for 239 days. At the end of the study, no significant difference was observed in the two groups concerning their appetite, growth, weight, and appearance, and the color, size, ratio of liver/body weight, fatty deposits, and pathological view of their livers. Hence, it was concluded that chitosan is non-toxic when used for oral administration.

Mucoadhesive Properties

Mucoadhesion refers to the state in which a synthetic surface and a biological surface coated in a mucus layer are held together for a long time to create bonds through interfacial forces (Sandri, et al., 2012). The main constituents of the mucous layer include lipids, water, inorganic ions, and the mucin glycoprotein (Kumar et al., 2016). Conventional formulations are affected by involuntary muscle movement and the effect of extended washing by some body fluids. They cannot resist the pressure from such movements. Due to this limitation, a significant portion of the medications are lost at the application or absorption site. Mucoadhesive polymers stick to the upper respiratory tract and gastrointestinal tract's inner mucous layer. The ability of mucoadhesive medication delivery systems to stick to the mucous membrane's mucus layer lengthens the duration of drug resistance and enhances the concentration gradient, leading to extended therapeutic benefits, increased bioavailability, cost-effective treatment, and controlled drug release (Serra and Peppas, 2009; Ways et al., 2018). The cationic, positively charged chitosan molecules and the anionic, negatively charged mucosal surface form a strong electrostatic sticky force that causes the natural mucoadhesion of chitosan (Lankalapalli and Kolapalli, 2009). The chitosan-based carrier's mucoadhesive property allows it to adhere to the GIT's inner mucosal lining, allowing the medicine or drugs to be released at the appropriate time and pass through the cellular membrane, where the drugs will gradually be released and absorbed (Kim et al., 2015).

pH Sensitivity of Chitosan

One of chitosan's key qualities for controlled drug delivery is its sensitivity to pH. Its chemical structure, in particular, the main amino groups (-NH2) on its glucosamine units, which are susceptible to protonation or deprotonation depending on the pH of the surrounding environment, provides the basis for this property. Because of its distinct responsiveness, chitosan can control the temporal and geographic release of drugs, improving therapeutic efficacy while reducing adverse effects (Kong et al., 2010). Chitosan's sensitivity to pH is essential for overcoming the drawbacks of traditional drug delivery techniques. Acidic conditions in the stomach and neutral to slightly alkaline conditions in the intestines characterize the extremely changing pH environment of the gastrointestinal tract, which is the most practical route of administration for traditional medication delivery. This results in insufficient targeted release of agents, which must be made up for with larger dosages (Choonara et al., 2014). Chitosan can prevent medications from breaking down in the stomach and efficiently releasing them in the intestines because it dissolves in acidic conditions and precipitates or gels in neutral to alkaline pH (Du et al., 2015). In a similar vein, pathological situations like tumors and inflammatory tissues frequently display aberrant pH levels, which pH-sensitive chitosan systems can take advantage of to accomplish site-specific drug delivery. Tığlı and Pulat (2012), evaluated the controlled release of 5-Fluorouracil

encapsulated chitosan nanoparticles based on pH. The 5-Fu encapsulated nanoparticles not only demonstrated a sustained and controlled release but also proved to be a good candidate for tumor-localized drug delivery.

Interaction of Chitosan with Other Biopolymers

Chitosan's distinct chemical structure, which includes reactive amino (-NH_2) and hydroxyl (-OH) groups, drives its interactions with other biopolymers. These groups enable a variety of interactions, such as hydrophobic associations, covalent bonds, hydrogen bonds, and electrostatic attraction, which make it possible for chitosan to work in concert with a variety of natural and synthetic biopolymers, such as collagen, hyaluronic acid, alginate, gelatin, and pectin (Nicolle et al., 2021; Guo et al., 2024). When compared to individual components, the resultant composites frequently show enhanced mechanical strength, stability, and functioning, which makes them ideal for intricate biomedical applications. Chitosan's capacity to create stable complexes with other biopolymers is very beneficial when it comes to drug delivery. These interactions make it possible to create regulated medication delivery systems that can precisely and continuously release therapeutic drugs in response to environmental cues like pH or temperature. For example, mixing chitosan with alginate can produce pH-sensitive nanoparticles for drug delivery through the oral route, and chitosan-hyaluronic acid composites are perfect for drug delivery across mucosal surfaces because of their improved biocompatibility and mucoadhesion (Dhayanandamoorthy et al., 2020; Niculescu and Grumezescu, 2022).

SOME FORMS OF DRUG ENCAPSULATED WITH CHITOSAN

Drug Encapsulation with Chitosan Microparticles/Nanoparticles

Drug encapsulation is a crucial technique in modern medicine that involves embedding a therapeutic agent inside a carrier medium to protect it and enhance its stability, delivery, and efficacy (Klojdová et al., 2023). A good carrier medium for drug encapsulation is nanoparticles. Nanoparticles are solid colloidal matter that range in diameter from 1 to 1000nm and are made up of natural, synthetic, or semi-synthetic polymers that encapsulate a therapeutic molecule. Chitosan has become a popular option for drug encapsulation over other polymers used in drug delivery because of its biological properties–biocompatibility, biodegradability, and low toxicity (Nagpal et al., 2010; Peniche and Peniche, 2011). Chitosan nanoparticles have various benefits, including increased stability, reduced toxicity, easy and gentle manufacturing techniques, a variety of administration routes, ability to regulate the release of active substances, hence there is an increased interest in its use as a drug delivery vehicle (Jafernik et al., 2023). There are two methods by which drugs are loaded into the chitosan nanoparticles. Either through covalent attachment to the polymer backbone or physical entrapment within the polymeric matrix. Physical drug loading can be performed in two ways: incorporation and incubation. Incorporation involves embedding the drugs into the matrix during the preparation of the nanoparticles, while incubation involves embedding the drugs after the preparation of the nanoparticles (Perera and Rajapakse, 2013).

Hydrogels

Hydrogels are networks of cross-linked polymers, either of the same or distinct kinds, that have a high ability to absorb water without dissolving. Hydrophilic functional groups, such as amine (NH_2), amide (-CONH-, -$CONH_2$), hydroxyl [-OH], and sulphate (-SO_3 H), are present in the polymeric structure of hydrogel-forming polymers (Hamidi et al., 2008). The amount of water that hydrogel absorbs causes it to swell and gives it its form (Bhattarai et al., 2010). Hydrogels are ideal drug delivery vehicles due to a number of beneficial properties such as drug protection, high biocompatibility, physiochemical tailor ability, and spatiotemporal control of drug release. It can be gotten from both natural and synthetic sources, with chitosan being a good natural source of hydrogels (Vigata et al., 2020). Chitosan-based hydrogels are used as delivery systems for the controlled release of drugs.

MECHANISMS OF DRUG RELEASE FROM CHITOSAN MICRO/NANOPARTICLES

The drug's release from chitosan micro/nanoparticles (Mp/Np) may be influenced by the Mp/Np formulation, the drug's physicochemical characteristics, and the surrounding environmental factors. Diffusion, degradation, swelling, erosion, and ion exchange are the main mechanisms. Developing effective medication delivery systems with individualized release patterns is made possible by comprehending and controlling the features behind these mechanisms (Herdiana et al., 2021).

Diffusion

This process entails the movement of drug molecules from a region in the Micro/nanoparticles where their concentration is higher to one in the surrounding media where the concentration is lower (Jafernik et al., 2023). The chitosan matrix, environment, and the drug can all have an influence on the concentration gradient. The rate at which the polymer breaks down and the drug's diffusion out of the polymeric matrix regulate the drug release mechanism from the polymeric Micro/nanoparticles (Mikušová and Mikuš, 2021).

Degradation

The rate at which the polymeric matrix degrades determines the medication release. Its degradation can be due to enzymatic, chemical, or environmental stimuli (Islam et al., 2019; Castro et al., 2022). The main enzyme that breaks down chitosan is lysozyme (Jennings, 2017). Usually, enzymes degrade chitosan by eliminating the β-(1 → 4)-linkages that connect the polymer's glucosamine units with N-acetylglucosamine (Poshina et al., 2018).

Swelling

When the chitosan matrix's hydrophilic groups come into touch with water molecules, the matrix swells. The pores of the matrix allow water to enter and enlarge the polymeric matrix, creating enough gaps for the drug molecules to diffuse out of the matrix (Ren et al., 2005). The lower the degree of deacetylation of chitosan, the more the acetyl groups. These acetyl groups attract water, which leads to more water absorption and swelling (Baskar and Kumar, 2009). Higher temperatures also affect swelling behavior by increasing the kinetic energy of water molecules and the pace at which they diffuse into the matrix (Herdiana et al., 2021).

Erosion

Erosion, as opposed to chemical or enzymatic processes, is the physical removal of material from nanoparticles. The erosion process releases medications from chitosan nanoparticles as the polymer matrix gradually breaks down or dissolves (Kamaly et al., 2016). When the rate of erosion exceeds the rate of water penetration, the polymeric substance begins to break down from the outside inward, releasing the medication. Compared to low-molecular-weight chitosan, high-molecular-weight chitosan erodes more slowly because its polymer chains are longer (Sun and Zang, 2010). Also, the degree of cross-linking of the matrix affects the duration and intensity of erosion. A strongly cross-linked matrix results in a slower rate of deterioration (Kesharwani et al., 2024).

APPLICATIONS OF CHITOSAN IN DRUG DELIVERY

Research has demonstrated that chitosan micro/nanoparticles can be a delivery system for a variety of medications, such as antibiotics, anticancer chemical drugs, gene drugs, and protein drugs, through a variety of routes of administration such as ocular, oral, topical, and nasal.

Oral Drug Delivery

The oral route of drug delivery is one of the most popular ways drugs are administered due to its ease of use. However, issues such as low permeability across the gastrointestinal (GI) tract, enzymatic degradation, and inadequate bioavailability can restrict the effectiveness of many medications, especially when transporting protein and peptide drugs through the oral route (Homayun et al., 2019). Chitosan has become a viable excipient in oral drug delivery due to its mucoadhesive, penetration enhancement, and solubility properties (Prego et al., 2005). According to Zang et al. (2010), water-soluble chitosan nanoparticles are a promising protein delivery technology because they improve and prolong the intestinal absorption of bovine serum albumin.

Ocular Drug Delivery

The eye has a complex anatomy and physiological barriers such as blinking, tear generation, and the existence of tight junctions in the corneal epithelium, hence, ocular medication delivery is a difficult field. These obstacles restrict the duration of drug residence and absorption, especially for topical administrations (Bachu et al., 2018). Micro/Nanoparticles appear to be viable carriers for developing novel controlled delivery systems to increase the ocular bioavailability of medications for ocular disorders (Gökçe et al.,2009). Silva et al. (2017) discovered that ceftazidime, which is used to treat severe *Pseudomonas aeruginosa*-caused eye infections like bacterial keratitis, exhibited physiochemical and pharmaceutical properties appropriate for topical ocular administration while maintaining the antimicrobial activity of ceftazidime when encapsulated with chitosan nanoparticles. In the research carried out by Mahmoud et al. (2011), the antifungal effect of ECO-loaded CS/SBE--CD nanoparticles was contrasted with that of ECO solution to examine whether or not the CS nanoparticulate contributed to ocular medication delivery. The evaluated ECO loaded CS/SBE--CD nanoparticles had a stronger antifungal effect on the eye surface than the ECO solution, and demonstrated a sustained drug release mechanism, according to the results.

Nasal and Pulmonary Drug Delivery

Nasal and pulmonary delivery are non-invasive methods of drug administration that target the supplied dose directly to the location where it is needed. There is a low drug metabolizing environment in the lung and nasal cavities, thus pulmonary and nasal delivery avoids the first-pass metabolism seen in oral administration. However, adsorption enhancers are still needed for pulmonary and nasal drugs (Ghadiri et al., 2019). Studies have shown that immunization with chitosan nanoparticle delivery through the nasal route induces humoral and cellular responses. In the study of Soh et al. (2019), mice treated with chitosan nanoparticles encapsulating recombinant B. abortus malate dehydrogenase developed a Th2-related immune response while also producing more IgA. Additionally, the chitosan nanoparticles encapsulating recombinant B. abortus malate dehydrogenase (CNs-Mdh) administered via the nasal cavity increased secretory IgA in the nasal mucosa, vaginal and digestive mucosa, and serum

IgA elevation, which resulted in systemic and mucosal immune responses. Therefore, CNs-Mdh constitute a promising vaccination antigen and delivery mechanism as they effectively promote mucosal immunity when administered intranasally. Dhayanandamoorthy et al. (2020), created chitosan nanoparticles encapsulating an anti-inflammatory medication, ferulic acid (FA), and functionalized with hyaluronic acid (HA). When the HA-functionalized chitosan nanoparticles were used for asthma prophylaxis, they reduced inflammation, hypersensitivity, and airway remodeling. The HA-functionalized chitosan nanoparticles encapsulating the medication resulted in better in vivo therapeutic indices than for free FA.

Wound Healing

Chitosan hydrogel's exceptional biological and physicochemical qualities have made it a ground-breaking substance for wound healing. The capacity of chitosan hydrogel to facilitate blood clot formation and hence aid haemostasis is one of its main benefits. Chitosan influences platelet activation, which encourages surface-induced thrombosis and blood coagulation (Liu et al., 2018). Chitosan-based dressings can speed up the repair of various tissues and control the release of inflammatory mediators such as prostaglandin E, interleukin 1β, and interleukin 8 (Jayakumar et al., 2011). The suitability of a chitosan hydrogel as a wound dressing was assessed by Ribeiro et al. (2009). The cytotoxicity of the hydrogel was evaluated in this study using fibroblast cells that were separated from rat skin. The outcomes demonstrated that chitosan hydrogel might encourage cell growth and adhesion. Hydrogels based on chitosan may be able to eliminate wound exudate, create a moist wound environment, prevent subsequent infections, promote faster wound healing, and result in smoother scarring (Liu et al., 2018).

Cancer Therapy

Chitosan has a positive charge which can neutralize the negative charge on the cell surface of a tumor, hence making chitosan an antitumor property. With their ability to deliver drugs in precise, targeted, and controlled ways, chitosan-based hydrogels and nanoparticles have revolutionized cancer treatment (Zeng, 2011). Chitosan micro/nanoparticles are efficient drug delivery systems for cancer therapy as they encapsulate anticancer medications and target tumor tissues. Their positive charge makes it easier for them to engage non-covalently with biological tissues, improving therapeutic drug delivery and reducing the negative effects of traditional chemotherapy (Ding and Guo, 2022; Atmaca et al., 2024). Manimaran et al. (2022) examined the compatibility of isolongifolene nanoformulation with various polymers. According to preliminary research, the chitosan-based isolongifolene polymeric nanoformulation could serve as a great adjuvant in therapeutics, primarily treating multi-drug resistance in solid tumors. Another study investigated the anticancer efficacy of chitosan on breast cancer cells after creating a novel chitosan derivative by altering the sulfates and phenyls in carboxymethyl benzylamide dextrans with chitosan. Chitosan derivatives reduced FGF-2-induced phosphorylation of ERK in MCF-7 cells and stopped MCF-7 and MDA-MB-231 cells from proliferating, which led to apoptosis (Jiang et al., 2011). Chitosan hydrogels are useful for localized drug delivery because of their pH sensitivity and capacity to create stable networks that can release pharmaceuticals in response to environmental changes. Zhang et al. (2013) carried out a study on chitosan hydrogel, using it in the delivery of Bacillus Calmette–Guérin in the treatment of bladder cancer. It was concluded that a magnetic thermosensitive CS/GP hydrogel is an appropriate matrix for prolonged intravesical BCG administration.

LIMITATIONS AND RECOMMENDATIONS OF CHITOSAN IN DRUG DELIVERY

In drug delivery systems, chitosan has a number of benefits, including mucoadhesive qualities, biocompatibility, and biodegradability. However, there are a few drawbacks that restrict its use, such as:

Solubility

Although chitosan is soluble in weak acids, its solubility is greatly reduced in neutral to alkaline conditions. This restricts its application in physiological pH conditions (pH 7.4), such as blood plasma, where it may precipitate or become ineffective (Garg et al., 2019). However, chitosan can be modified through the introduction of hydrophilic groups to improve its solubility at physiological pH. Feng et al. discovered that the use of carboxymethyl chitosan to encapsulate doxorubicin hydrochloride – an anticancer drug- improved its intestinal absorption (Feng et al., 2016).

Mechanical Resistance

For some drug delivery applications, chitosan's mechanical strength is frequently weak; therefore, it must be modified or additional materials added to improve its qualities. This restriction may affect their integrity and stability when being stored and used, especially in stressful situations (Che et al., 2018). Chitosan's mechanical strength can be improved by the addition of specific chemical precursors. A study focused on the development of a hemostatic dressing that would be more effective at stopping serious bleeding from both internal and external wounds. Chitosan and kaolin, two hemostatic agents, are combined with a surfactant to form the hemostatic composition. In comparison to dressings that use a single hemostatic agent or do not contain a nanoparticularized hemostatic agent, the created composites significantly reduced bleeding to a greater extent (Elsabahy and Hamad, 2021).

Limited Targeting Capability

Without additional modification or in conjunction with other targeting agents, chitosan might not offer adequate targeting capabilities for particular tissues or cells (Mikušová and Mikuš, 2021).

CONCLUSION

Chitosan's versatility encompasses a wide range of uses, such as cancer treatment, wound healing, pulmonary medication administration, oral, ophthalmic, and nasal. Its capacity to combine with other biopolymers to generate hydrogels, nanoparticles, and complex systems improves its functioning and permits targeted and prolonged drug release. Furthermore, chitosan is very useful in site-specific and controlled drug delivery due to its mucoadhesive qualities and pH sensitivity.

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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