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Exploring the Potential of Chitosan in Drug Delivery: A Review of Current Research and Future Directions

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Abstract

Chitosan is a flexible polysaccharide that has generated much interest as a potential component for drug delivery systems. The article emphasizes recent discoveries in formulation tactics, targeted delivery methodologies and biological applications as well as future directions for chitosan-based drug delivery systems. Important developments include chitosan modifications to increase mucoadhesion and enable targeted distribution to certain tissues or cells as well as the creation of chitosan nanoparticle and nanocapsules for enhanced drug solubility and bioavailability. Furthermore, chitosan use in sustained and combination treatment has increased due to its incorporation into hydrogels and co-delivery systems. Moreover, advancements in in-vivo research and chitosan-based gene delivery vectors highlight the material's potential for use in regenerative medicine and gene therapy. Biocompatibility, scalability, and clinical translation are examples of challenges. In addition, chitosan's promise in gene therapy and regenerative medicine is highlighted by advancements in in-vivo studies and chitosan-based gene delivery systems. Factors like scalability, biocompatibility, and clinical translation are also addressed, as potential paths forward for enhancing chitosan-based drug delivery systems to satisfy the requirements of contemporary medications.

1. Introduction:

Since chitosan entered the pharmaceutical field in the early 1990s, it has inspired academic and industrial research teams to generate novel more effective therapeutic systems based on it. Apart from applications such as slimming, wound dressing, and tissue engineering, chitosan showed promising features as an auxiliary agent in drug delivery. In contrast to all other biodegradable polymers having a monograph in a pharmacopoeia, chitosan is the only one exhibiting a cationic character rendering it unique among all others [1]. This cationic character being based on its primary amino groups is responsible for various properties and subsequently for its use in drug delivery systems. In the following, these properties are highlighted in more detail [2]. Chitosan (CS) is one of the most functional natural biopolymers widely used in the pharmaceutical field due to its biocompatibility and biodegradability. These privileges have led to its application in the synthesis of nanoparticles for the drug during the last two decades [3]. Chitosan, a natural-based polymer obtained by alkaline deacetylation of chitin, is nontoxic, biocompatible, and biodegradable. These properties make chitosan a good candidate for conventional and novel drug delivery systems. Chitosan (CS) is one of the most exploited polymers in biomedical science, and it is the second most abundant next to cellulose, a naturally occurring amino polysaccharide. It is produced from chitin (present in the exoskeleton of insects and marine aquatic animals, and microorganisms such as fungi, yeast, and microalgae) by partial deacetylation in an alkaline environment [4]. The properties of chitosan include biocompatibility in which chitosan is compatible with living tissue and makes it capable of medical application. Other properties like biodegradability,mucoadhesive,non-toxicity,solubility,etc.

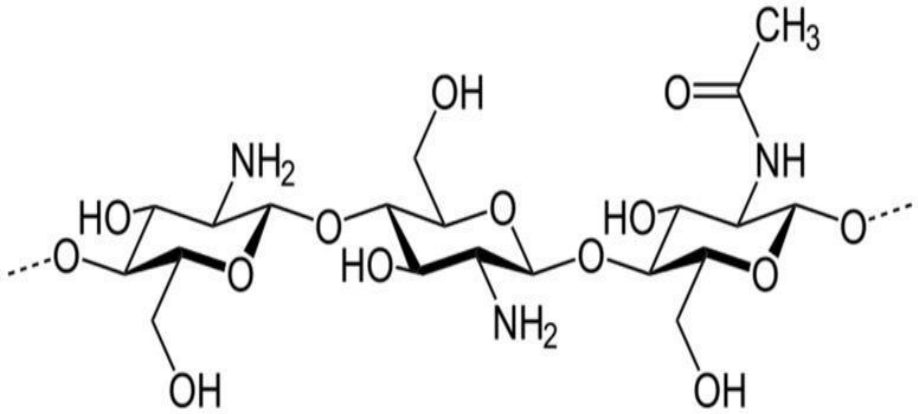

Fig1 Chemical structure of chitosan

2. Type of chitosan-based drug delivery system

Chitosan-based drug delivery systems are versatile and have been extensively studied due to their properties. Various types of chitosan-based drug delivery systems include-

a. Nanoparticles: These are small particles where the drug is either encapsulated within or adsorbed onto the chitosan matrix. They are used for controlled and targeted drug delivery. There is another version of nanoparticles which is nanocapsules. These have a core-shell structure

where the drug is enclosed within polymeric shells. This kind of structure helps protect the drug from degradation and also provides controlled drug release.

The applications of nanoparticles in pharmaceutical industries are increasing day by day. The small size of nanoparticles makes them capable of moving through various biological barriers (like brain barrier) bringing drugs to the target site and enhancing its efficacy [5]. Chitosan nanoparticles (CsNPs) act as excellent drug carriers because of some intrinsic beneficial properties such as biocompatibility, biodegradability, non-toxicity, bioactive, and relatively to some extent target specific triggered by its cationic character. Several methods have been reported for the preparation of chitosan nanoparticles, such as emulsion, coacervation or precipitation, ionic gelation, reverse micellar method, sieving method, and nanoprecipitation etc. [6–8]. The applications of nanoparticles in pharmaceutical industries are increasing day by day. The small size of nanoparticles makes them capable of moving through various biological barriers (like brain barrier) bringing drugs to the target site and enhancing its efficacy [6]. The nanoparticles prevent the enzymatic degradation of labile drugs in the gastrointestinal tract. Several review articles have been published on chitosan nanoparticle-based drug delivery systems [9–11]. In which the author highlighted the advantages and advanced properties of nano-sized chitosan in drug delivery applications. Mitra et al. investigated CsNPs as a tumor-targeted carrier for dextran-doxorubicin (DOX) conjugate [12]. Doxorubicin a cancer therapy drug usually shows many side effects like cardiotoxicity, however, conjugation with dextran minimizes its side effect, and encapsulation of this conjugate in chitosan hydrogel nanoparticle increases drug efficacy.

b. Hydrogel: Chitosan hydrogels are the 3D network that can absorb large amounts of water or biological fluids. They are used for localized drug delivery, wound dressings, and tissue engineering.

c. Films: Thin layers of chitosan that can be used as wound dressings or for transdermal drug delivery. They offer a sustained release of the drug at the application site. Chitosan displays excellent film-forming capability and finds many applications in drug delivery systems as a carrier for bioactive agents ranging from small molecules like antibiotics to macromolecules like nucleic acid and proteins [13]. Chitosan, due to its bacteriostatic property known to enhance wound healing rate and also possesses hemostatic properties [14]. Thus chitosan films have been considered as wound dressing material. Generally, solution-casting methods have been used to prepare chitosan films. The preparation of both simple chitosan and cross-linked chitosan films was reported by researchers for various applications. Cross-linking improves both physical and mechanical properties of chitosan like tensile strength, thermal stability, water-resistant property, color and moisture retaining capacity, etc. [15–18]. Chitosan and cross-linked films have been investigated as drug delivery devices in several fields like oral mucosal delivery [18–20], buccal delivery, transdermal delivery, sublingual delivery, and periodontal delivery [21,22].

Tang et al. prepared and investigated chitosan films loaded with ibuprofen using a super critical solution impregnation method for oral mucosal delivery [23]. The in vivo study confirms that 70% drug was released from the matrix in 460 min across the rabbit mucosa. Also, the new supercritical impregnation method provides a low solvent residual, controlled, and sustained

release profile. In another effort, varshosaz et al. [24] developed and studied the release behavior of Lidocaine a local anesthetic agent from cross-linked chitosan films for oral mucosal delivery. Tripolyphosphatpenta sodium salt was used as cross cross-linker. Three different Mw of chitosan were used. The flux rate of lidocaine was increased by high Mw and concentrated solution of chitosan. However, upon increasing the concentration of cross-linker the flux and release rate decreases of the drug [25].

d. Microsphere: The practice of a microsphere-based delivery system allows control over the drug release profile and specific target site by carefully tailoring the formulation of various polymer-drug combinations [17]. This type of delivery system provides an increased life span, controlled release rate, and targets specific drugs. Different methods for the formation of microspheres include interaction with counter ions like anions (sulfate, phosphates, hydroxides), cross-linking, solvent evaporation, ionic gelation, spray drying, emulsion polymerization, and precipitation/coacervation, etc[26–29]. Jameela et. al. prepared glutaraldehyde cross-linked chitosan microspheres aimed as a long-lasting biodegradable delivery device using mitoxantrone, a novel antineoplastic agent [18]. The drug release rate was found to depend on the extent of crosslinking. Using a highly crosslinked microsphere it is found that only 25% of the incorporated drugs were released for 36 days. The prepared microsphere showed good biocompatibility but did not display significant biodegradability even after 3 months in the skeletal muscle of rats. Chitosan microspheres were also prepared by precipitation method using sodium sulfate as precipitant, as well as precipitation controller. Prednisolone sodium phosphate was used as an anti-inflammatory model drug. The drug release rate was found to be dependent on the polymer-drug ratio [30].

e. Liposome: Chitosan-coated liposome combines the benefits of liposome and chitosan, providing enhanced stability, bioadhesiveness, and controlled release for drug delivery [31].

3. Application of chitosan-based drug delivery systems

a. Oral drug delivery

Chitosan is a non-viral vector that can be used for immunization and gene therapy. Chitosan can transport proteins and peptides as well as vaccination antigens and medications even ones with low bioavailability [32]. Drugs can be delivered to cancer cells using chitosan reducing adverse effects. Because chitosan increases the solubility and permeability of medications across the intestinal epithelium it can increase their bioavailability [33]. Chitosan can be used to direct medication to particular bodily parts, such as the small intestine or colon. Sustained-release formulations that release medication over an extended period can be created using chitosan [34]. It is possible to create mucoadhesive formulations using chitosan that stick to the mucus layer [35].

b. Topical drug delivery

Chitosan promotes the growth and multiplication of three-dimensional cells and facilitates quick healing by regulating the deposition of collagen. When designing scaffolds for tissue engineering applications, chitosan has demonstrated enormous potential as a functional biomaterial, allowing

for the regeneration of diverse tissues. Numerous medications have been investigated for transdermal administration using chitosan [36]. Chitosan-based drug delivery vehicles have mucoadhesive qualities because the positive charge of the ionizable amino group of chitosan encourages electrostatic contact with the negatively charged mucosal surfaces[37]. Sustained-release formulations that release medicine over an extended period can be created using chitosan. Drugs may be directed to certain bodily parts, such as the skin, using chitosan. Chitosan increases the solubility and permeability of medications, enhancing their bioavailability[38].

c. Ocular drug delivery

Chitosan is added to ophthalmic solutions to slow down their elimination rate. Chitosan is used in making mucoadhesive microspheres that increase the retention time of the drug[39]. Chitosan is used in making a thermo-sensitive gel that increases ocular contact time and bioavailability of drugs. Chitosan promotes wound healing by enhancing keratinocyte migration, leading to rapid collagen synthesis[40]. Chitosan increases corneal permeability by promoting the proliferation of corneal epithelium during wound healing. Chitosan-based scaffolds are used in tissue engineering to develop artificial corneas that adhere to native cornea[41,42].

d. Pulmonary drug delivery

Nanoparticles that improve pulmonary medication delivery are made with chitosan. Nanocarriers based on chitosan have been a significant area of study[43]. As significant means of enhancing pulmonary medication delivery, polymeric nanoparticles, liposomes, dendrimers, microspheres, nanoemulsions, solid lipid nanoparticles, carbon nanotubes, and other modified effective targeting systems compete. Because of its numerous special physicochemical characteristics, strong biocompatibility, and adequate biodegradability, chitosan is a promising choice for pulmonary drug administration[44]. Microspheres that extend the medication's retention period in the lungs have been created using chitosan. Chitosan has been utilized to create liposomes that improve medication administration to the lungs[45]. Chitosan is utilized in targeted drug delivery, which lowers clearance and lengthens the medication's half-life in the lungs[46].

4. Recent Advances In Chitosan-Based Drug Delivery Systems:

The effectiveness, adaptability, and targeting capabilities of chitosan-based drug delivery systems have been the focus of recent developments [47]. The capacity of chitosan nanoparticles and nanocapsules to increase medication solubility, stability, and bioavailability has made them more well-known. Both hydrophilic and hydrophobic medications may be encapsulated in these nanostructures, enabling targeted administration and controlled release[48]. To better customize chitosan's physical properties and to improve its interaction with pharmaceuticals and biological systems, numerous chemical modifications have been investigated, including quaternization, grafting with polymers, and conjugation with targeted ligands (e.g., antibodies, and peptides). Due to its mucoadhesive qualities, chitosan can be used in mucosal medication delivery applications such as gastrointestinal, buccal, ophthalmic, and nasal[49]. Mucoadhesive formulation improvement has been the focus of recent research to enhance absorption and extend the time of medication residence[50]. Since chitosan-based carriers may condense nucleic acids into nanoparticles and are biodegradable and biocompatible they are currently being studied for

use in gene therapy[51]. Developments in this field are intended to target certain tissues or cells and improve transcription efficiency[52]. Chitosan hydrogels have been created for delivering drugs both locally and permanently. These hydrogels provide a flexible foundation for tissue engineering, wound healing, and the controlled release of medicinal substances. They may be injected or treated externally [53-55].

The overall goal of further study into chitosan-based drug delivery systems is to utilize the unique characteristics of chitosan to create novel therapeutic solutions while overcoming issues including biocompatibility, stability, and reproducibility[56].

5. Future direction:

Because of their special qualities and adaptability in handling different drug delivery problems, chitosan drug delivery systems (or CDDS) have a bright future ahead of them. Here are some significant prospective advancements and future outlooks for CDDS:

a. Hybrid system: To improve mechanical qualities and drug delivery efficacy, hybrid drug delivery systems that combine chitosan with other biocompatible polymers, including PLGA or alginate, are being developed. Development of chitosan-based systems for accurate and on-demand drug release that react to outside stimuli (such as pH, temperature, and magnetic fields)[57].

b. Biocompatibility and safety: Chitosan was modified through research to increase its biocompatibility and decrease its immunogenicity, enabling a greater variety of medicinal uses. Comprehensive in vivo and clinical studies to ensure the safety and efficacy of chitosan-based drug delivery systems[58].

c. Advanced drug delivery: Development of micelles and nanoparticles made of chitosan to deliver drugs specifically to desired tissues or cells while reducing negative effects and enhancing the effectiveness of treatment also the development of hydrogels and films based on chitosan to release medications gradually and under control, improving therapeutic results and patient compliance[59].

d. Regenerative Medicine and Tissue Engineering: tissue engineering applications using chitosan scaffolds to encourage cell proliferation and differentiation for tissue regeneration and repair. Innovative films and dressings based on chitosan for improved wound healing and infection prevention[60].

e. Sustainable and Cost-effective Production: adoption of sustainable and ecologically friendly chitosan production techniques to cut costs and negative environmental effects. Development of scalable production methods to satisfy the pharmaceutical industry's rising need for chitosan-based medication delivery systems[61].

6. Conclusion:

In the biomedical industry, controlled and targeted drug delivery systems are intriguing, and there's a growing need for time due to the availability of highly specialized drugs that must be taken to prevent adverse effects. The biocompatible and biodegradable polymer chitosan is

crucial for such application. For medications intended for particular targets, the chitosan nanocomposites further provide improved qualities with a stimulus-responsive matrix that is programmable. Various combinations of inorganic nanoparticles and chitosan improve the solubility of insoluble medications, producing stable complexes and ensuring their safe transport to the intended location. Additional uses for chitosan nanocomposite include tissue engineering, wound dressing, bioimaging, biosensors, packaging, and other applications. Chitosan drug delivery systems have a bright future ahead of them, with opportunities for innovation and growth in a variety of medical domains. Continuous research and development, in conjunction with developments in materials science and nanotechnology, should result in more individualized, safe, and efficient drug delivery systems, eventually enhancing patient care and treatment results.

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