Review

Chitosan in Modern Pharmacotherapy: From Drug Encapsulation to Targeted Delivery Systems

Robertas Lažauskas *, Inga Stanevičienė, Lolita Kuršvietienė

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Chitosan in Modern Pharmacotherapy: From Drug Encapsulation to Targeted Delivery Systems

Robertas Lažauskas [1,*], Inga Staneviciene [2] and Lolita Kursvietiene [2]

[1] Institute of Physiology and Pharmacology, Medical Academy, Lithuanian University of Health Sciences, LT-50161 Kaunas, Lithuania.

[2] Department of Biochemistry, Medical Academy, Lithuanian University of Health Sciences, A. Mickeviciaus St. 9, LT-44307, Kaunas, Lithuania.

* Correspondence: robertas.lazauskas@lsmu.lt

Abstract

During the previous decade, chitosan has emerged as a highly valued biopolymer with diverse uses in the field of pharmacy. This review is intended to present information published during the recent years on the pharmacological properties of chitosan, multiple chitosan-based delivery systems and routes of drug administration of chitosan nanoparticles. Recent scientific research demonstrates that chitosan represents a valuable candidate for designing non-invasive drug delivery strategies. Chitosan nanoparticles are capable of optimizing drug pharmacokinetics, increasing local drug concentrations, and reducing overall systemic toxicity. Chemical and biological properties of chitosan make it suitable for a wide range of drug administration pathways, from conventional oral systems to advanced gene therapy approaches. Despite promising preclinical results, clinical application faces several challenges such as production standardization and regulatory hurdles.

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1. Introduction

Chitosan is a natural polysaccharide derived from the partial deacetylation of chitin, and it is highly valued for its biocompatibility, biodegradability, and versatility for chemical modifications [1,2]. Research has also highlighted the multi-functional potential of its derivatives in biomedicine [3]. Over the past decade, chitosan has garnered exceptional attention as a multi-purpose biopolymer in the pharmaceutical field. Its positively charged amino groups give it unique properties, including mucoadhesion, the ability to open epithelial tight junctions, and strong interactions with negatively charged biological membranes, which helps increase the bioavailability of drugs, especially biotechnological molecules [4]. Beyond its role in drug delivery, chitosan also has antimicrobial, anti-inflammatory, antioxidant, and tissue-regenerating effects, making it a valuable therapeutic component [5]. Since 2015, scientists have increasingly focused on chitosan derivatives, such as thiolated, quaternized, or carboxymethylated polymers, to improve their solubility, stability, and targeted biological efficacy [6;7]. Recent advances in chitosan-based nanocarriers have been particularly significant, with applications in drug encapsulation, gene therapy, and the treatment of oncological and inflammatory diseases, as well as in vaccinology [8,9]. Given this rapid growth, the goal of this review is to systematically present scientific achievements from 2015 to 2025 related to the use of chitosan in pharmacotherapy, covering its pharmacological properties, various delivery systems, targeted strategies, potential in gene therapy, and the translational challenges involved.

2. Pharmacological Properties of Chitosan

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Chitosan is a natural poly-(1→4)-2-amino-2-deoxy-β-D-glucose polymer derived from the partial deacetylation of chitin, a polysaccharide found in the cells of crustaceans, insects, and fungi [2]. This biopolymer is insoluble in neutral solutions but dissolves in certain organic acids (e.g., acetic, lactic) and inorganic acids (e.g., hydrochloric acid), where its protonated amino groups acquire a positive charge [2]. This protonation in an acidic environment gives chitosan a polycationic character. The positively charged chains interact strongly with negatively charged components of cell membranes and mucosa, leading to its exceptional mucoadhesive properties [4]. This property, combined with its ability to temporarily open intercellular tight junctions in the epithelium, leads to increased drug permeation across the mucosal barrier, which is particularly beneficial for large-molecule drugs like peptides [10–13].

The control over chitosan's solubility and other physicochemical parameters depends on its structural features, including its crystalline structure, degree of deacetylation, molecular weight, and the distribution of acetyl groups along the chain [2]. Modulating these parameters through chemical modification (e.g., by quaternizing, carboxymethylating, or thiolation of the polymer) can significantly alter chitosan's properties, allowing it to be tailored for specific pharmacotherapeutic needs [6,7]. Another key property is its ability to form polyelectrolyte complexes with nucleic acids. This allows for the stable encapsulation of siRNA, mRNA, and plasmid DNA into polyplexes, protecting them from nuclease degradation - an essential requirement for gene therapy [14,15].

Recent research shows that chitosan not only functions as an auxiliary carrier but also exhibits various pharmacological activities. It is biocompatible, biodegradable, non-toxic, and has very low allergenicity [2]. A broad spectrum of its biological effects has been observed: chitosan inhibits the growth of numerous microorganisms, providing an antimicrobial and antifungal effect by damaging microbial membranes, causing changes in permeability and loss of cellular content [11,16]. It also possesses antioxidant properties, promotes tissue regeneration (used in wound healing), and can have antineoplastic and even anti-diabetic effects [**5**]. Because of these properties, chitosan is considered a versatile biopolymer in biomedicine. Its biocompatibility, biodegradability, ability to chelate metal ions, and environmental stability are particularly emphasized [2]. These characteristics, combined with its pH-sensitivity and the possibility of introducing new functional groups into the polymer chain, have led to a surge of interest in chitosan derivatives for developing innovative drug carriers in recent years [6,7].

3. Chitosan-Based Delivery Systems

The chemical structure of chitosan (a linear β-(1→4)-glucosamine chain) allows for the formation of diverse drug delivery systems. Due to its polymeric nature and abundance of reactive amino groups, chitosan can be cross-linked with a variety of reagents and polymers to form carriers of different shapes, including nanoparticles (1–1000 nm), microparticles (1–1000 μm), hydrogels, nanogels, fibers, and films [17]. These forms exhibit different drug loading and release kinetics. For example, chitosan nanoparticles can efficiently encapsulate hydrophobic active compounds, increasing their solubility and stability in an aqueous environment [14], while hydrogels and films provide the capability for sustained, long-term drug release, which is beneficial for applications like wound dressings [17]. Due to their large surface area and ease of chemical modification, chitosan carriers can be adapted to transport and protect both hydrophilic and hydrophobic drugs from degradation within the body [6,7].

In the last decade, chitosan nanoparticles (ChNPs) have emerged as one of the most intensively studied drug delivery systems. In 2015, approximately 1500 scientific papers were published on this topic, and by 2024, this number had grown to nearly 5000, which clearly demonstrates the increasing interest in chitosan-based nanocarriers [7]. This progress is linked to the advantages that ChNPs offer: they help to improve the pharmacokinetics of active molecules (extending their circulation time in the bloodstream and reducing undesirable clearance), their pharmacodynamics (by increasing drug concentration in the target tissue), and drug solubility [7].

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The development of chitosan nanodrugs considers numerous design parameters - including particle size, shape, surface charge, and degree of cross-linking - as these factors determine the drug release rate and distribution within the body [6]. Research indicates that by optimizing these parameters (e.g., using techniques like ionic gelation, emulsification, and coacervation), it's possible to encapsulate both hydrophilic and hydrophobic compounds, protecting them from premature degradation and ensuring controlled release at the desired location [16,18]. Therefore, chitosan delivery systems are versatile and can be applied to transport a wide variety of active substance classes.

3.1. Nanoparticles and Microspheres

Chitosan nanoparticles are most commonly produced via ionotropic gelation, where positively charged amino groups interact with multivalent anions, such as tripolyphosphate (TPP). This cross-linking process results in stable nanoparticles with high drug encapsulation efficiency [11,16].

Another strategy is the formation of polyelectrolyte complexes with polyanions, like alginate, which provides nanoparticles with stability through electrostatic interactions and controlled release [11,16].

Self-assembly methods, in which chitosan is chemically modified with hydrophobic groups or mixed with phospholipids, allow for the creation of amphiphilic nanoparticles suitable for the transport of lipophilic drugs [18,19]. Microspheres obtained by spray drying offer controlled drug release, making them particularly suitable for oral administration [11,12].

3.2. Hydrogels and Nanogels

Chitosan-based hydrogels can be adapted to respond to physiological stimuli, especially changes in pH. For example, they remain stable in the acidic environment of the stomach but swell and release the drug in the neutral or alkaline environment of the intestine. Such systems are particularly useful in colonic therapy for treating inflammatory bowel diseases and colorectal cancer [11,20].

Nanogels, formed by cross-linking chitosan chains at the nanoscale, create a hydrated environment that effectively protects proteins and peptides from enzymatic degradation [14].

3.3. Hybrid and Stimuli-Responsive Systems

Recent trends focus on hybrid systems, where chitosan is combined with inorganic or synthetic materials to achieve multifunctionality. For instance, chitosan-iron oxide hybrids can be directed by a magnetic field, while chitosan-PEG conjugates prolong circulation time by reducing clearance through the reticuloendothelial system [21].

Growing research interest in stimulus-responsive chitosan-lipid hybrid carriers (CLBCs) underscores their potential as next-generation systems for targeted cancer treatment [22]. In acidic tumor microenvironments, pH-sensitive chitosan releases drugs, while under redox conditions with elevated GSH levels, carriers disintegrate, ensuring intracellular drug delivery [23, 24]. Additionally, their thermo-responsive properties allow phase changes at physiological temperatures, enhancing drug delivery efficiency [25]. Incorporation of enzyme-recognition motifs further enables selective enzymatic degradation, supporting controlled and targeted drug release [26].

4. Routes of Drug Administration

Chitosan nanoparticles have been studied for various routes of administration due to their mucoadhesive and permeation-enhancing properties. Because of these characteristics, chitosan is highly promising for developing non-invasive drug delivery methods.

The oral route is one of the most widely researched. The addition of chitosan to oral formulations helps protect active compounds from the acidic environment of the stomach and from enzymatic degradation, thereby improving their absorption in the small intestine [11,12,17]. For example, chitosan nanocapsules have been shown to significantly increase the absorption of the peptide

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hormone salmon calcitonin and prolong its therapeutic effect. This occurs because the polymer adheres to the intestinal epithelium and temporarily increases its permeability [27]. This property is particularly crucial for peptide drugs like insulin, which are typically degraded rapidly in stomach acid [28].

Intranasal (nasal) drug delivery has also advanced significantly with the use of chitosan carriers. Positively charged chitosan nanoparticles adhere to the nasal mucosa and can transport drugs - including small molecules and nucleic acids - directly to the central nervous system via the olfactory region, bypassing the blood-brain barrier [10,13,14]. Animal studies have shown that chitosan-based nasal formulations prolong the residence time of a drug in the nasal cavity due to strong polymer adhesion to mucin, which increases the bioavailability of the active substance in brain tissue [10].

Chitosan is also applied in ophthalmology. Chitosan-enriched eye drops allow for a longer interaction between the drug and the corneal surface. This increases the bioavailability of the drug in eye tissues and ensures a longer-lasting effect [29]. An example is the experimental formulation Lacrimera®, whose clinical trials have demonstrated good tolerance and effectiveness in treating dry eye, ensuring a longer retention of the active ingredient in the tear film [29].

For pulmonary delivery, inhaled chitosan nanoparticles have shown success in lung cancer models. They provide a localized effect while reducing systemic toxicity [11,30].

Chitosan carriers are also successfully applied through local and parenteral routes.

Transdermal delivery (via the skin) utilizes chitosan hydrogels and films in pharmacotherapy, for instance, in wound dressings. Here, the polymer performs multiple functions: it forms a moist, protective film, has hemostatic (blood-clotting) properties, and protects against infections due to its antimicrobial activity [17,31].

Parenteral (injectable) delivery of chitosan hydrogels or nanoparticles is being researched as a carrier for anti-cancer drugs. When injected intravenously, the particles can selectively accumulate in tumor tissue by leveraging the Enhanced Permeability and Retention (EPR) effect and their prolonged circulation time in the bloodstream [7]. Combining this with active targeting - for example, by attaching specific ligands to the particle surface - allows a higher drug concentration to reach the tumor while minimizing systemic toxicity. For these reasons, chitosan nanotechnology is considered an advanced delivery platform for various routes of administration. Essentially, all drug forms (oral, nasal, ophthalmic, transdermal, injectable) can be improved by using chitosan derivatives [17].

5. Targeted Delivery and Disease Therapy

A key goal in modern pharmacotherapy is to ensure that a drug reaches the diseased tissue at the highest possible concentration while minimizing its effect on healthy organs. Chitosan nanocarriers contribute to this goal by enabling both passive and active drug targeting. Passive targeting is particularly relevant in oncology: once in the bloodstream, chitosan particles of approximately 100 nm in size tend to accumulate in tumors due to the defective structure of their blood vessel walls, a phenomenon known as the Enhanced Permeability and Retention (EPR) effect [7]. This effect leads to a higher drug concentration at the tumor site.

Furthermore, engineering techniques allow for the active targeting of chitosan nanoparticles to a specific site. By functionalizing the polymer's surface with ligands such as folic acid, antibodies, or peptides, the particles can selectively recognize and bind to cells that express specific receptors [6]. For example, many epithelial cancer cells overexpress folate receptors (FR) on their surface. Folic acid-coated chitosan nanoparticles can specifically bind to these cells and deliver cytotoxic drugs inside, increasing the effectiveness of the therapy [32,33]. Similar studies have been conducted with transferrin or antibody conjugates to achieve specific cellular uptake [19,34]. The literature indicates that FR expression remains high even during chemotherapy, so attaching folate to nanoparticles helps overcome chemotherapy resistance mechanisms and improves treatment outcomes [32].

Another significant advantage is that encapsulating hydrophobic anti-cancer drugs in chitosan nanoparticles allows them to be delivered without harsh solvents or surfactants, which reduces

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unwanted side effects. Chitosan nanoparticles can "load" poorly soluble chemotherapeutic compounds into their core, improving their solubility and permeability. This enables a higher drug concentration in the tumor without the excipient-related toxicity [14]. Additionally, these nanoparticles can be designed for slow drug release, allowing the anti-cancer drug to remain in the tumor tissue for a longer period, which enhances the therapeutic effect and may reduce the frequency of dosing [14].

The tumor microenvironment, which is characterized by hypoxia, acidity, and a high concentration of reactive oxygen species, provides opportunities for stimuli-responsive chitosan carriers to selectively release active compounds [34]. In the case of brain tumors, chitosan-based carriers have been shown to cross the blood-brain barrier and deliver doxorubicin and siRNA into glioblastoma cells [15].

Chitosan-based targeted delivery systems are not just being explored in oncology; they are also being applied to a wide range of diseases. Recent reviews note that chitosan formulations are being developed for treating bacterial and viral infections (e.g., for delivering antimicrobial peptides or antiviral drugs), managing inflammatory diseases (e.g., ulcerative colitis), controlling metabolic disorders (e.g., obesity, diabetes), and even for gastroesophageal reflux disease (e.g., a chitosan gel that binds stomach acid) [17].

Furthermore, biomaterials derived from chitosan can function as immunotherapy adjuvants (by stimulating a local immune response, for example, in vaccines) and are useful in regenerative medicine (e.g., promoting cartilage regeneration in osteoarthritis) [17]. Interestingly, chitosan's antibacterial properties are even being exploited in the food industry to create antimicrobial packaging impregnated with chitosan to protect food products from pathogen growth [17]. This interdisciplinary application of chitosan highlights its potential as a versatile biopolymer platform for the therapy of various diseases.

6. Gene Therapy and Nucleic Acid Delivery

In the field of gene therapy, chitosan is emerging as a promising non-viral gene delivery vector. The positive charge of the polymer backbone allows it to electrostatically complex with negatively charged DNA or RNA molecules, forming polyelectrolyte complexes (polyplexes). These chitosan-DNA complexes protect the genetic material from degradation by nucleases and facilitate its entry into cells via endocytosis [8,10]. Chitosan nanoparticles exhibit excellent biocompatibility and lower cytotoxicity than many classic gene carriers (e.g., pure polyethyleneimine), making them widely used to transport plasmid DNA, siRNA, mRNA, and even complex CRISPR/Cas9 components into cells [8,9].

Importantly, innovations over the last decade have significantly improved the transfection efficiency of chitosan vectors. For example, modifying chitosan with polycationic polymers like polyethyleneimine (PEI) has led to hybrid carriers that achieve more effective gene transfer than traditional PEI vectors alone [35]. It has also been reported that attaching specific targeting ligands to chitosan (e.g., the AS1411 aptamer, which recognizes tumor cells) can ensure highly efficient delivery of plasmid DNA into targeted cancer cells [36]. These achievements pave the way for the use of CRISPR/Cas9 gene-editing technologies. Chitosan nanoparticles have successfully delivered CRISPR/Cas9 plasmids into cancer cells, reducing the expression of a targeted oncogene and slowing tumor invasiveness [9]. Thus, chitosan-based gene carriers are considered one of the most advanced approaches for safe and effective gene therapy in a clinical setting.

However, effective gene therapy requires endosomal escape for the material to reach the cytoplasm. Modifications such as thiolated chitosan or chitosan conjugation with imidazole groups increase the buffering capacity, promoting a "proton sponge" effect and subsequent endosomal membrane disruption. Comparative studies show that chitosan derivatives often have lower toxicity than synthetic polycations like polyethyleneimine while providing similar transfection efficiency.

7. Safety, Stability and Translational Challenges

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The toxicological profile of chitosan as a pharmaceutical adjuvant is generally favorable. Most studies indicate that the polymer is non-toxic to mammalian cells, non-mutagenic, and exhibits low cytotoxicity at typical doses [2]. Furthermore, meticulous manufacturing processes ensure that chitosan is virtually free of protein impurities, resulting in low immunogenicity. Researchers state that its allergenic potential is minimal [2]. Nevertheless, rare cases of hypersensitivity reactions to poorly purified chitosan have been reported in patients with shellfish allergies, underscoring the critical importance of selecting and purifying the raw material to ensure safety [37].

Despite numerous successful laboratory and preclinical studies, integrating chitosan into routine clinical practice faces several challenges.

First, there are difficulties with production standardization and reproducibility. Natural chitosan, depending on its source (e.g., shrimp, crabs), can have varying degrees of deacetylation (DDA), molecular weight (MW), and impurities. This leads to batch-to-batch variability in the polymer's properties, which complicates scaling up from laboratory synthesis to industrial production. It is difficult to ensure consistent safety and efficacy of nanoparticles across different batches [38]. Scientists propose using Quality-by-Design (QbD) principles and rigorous characterization (specifying DDA, MW, and polydispersity) to ensure these parameters are controlled and reproducible [38].

Second, regulatory barriers pose a significant hurdle. Chitosan-based nanocarriers do not have a long history of use as approved drug products, which requires extensive preclinical and clinical data on their pharmacokinetics, toxicology, and long-term effects [39]. Both the U.S. FDA and the European Medicines Agency (EMA) emphasize the need for precise definitions of the polymeric carrier's composition and properties. This is complex for natural polymers where batch-to-batch variations are possible [38,39]. Currently, few chitosan-containing medical products are registered (most are medical devices, such as hemostatic wound dressings), and complex chitosan nanodrugs are still in the clinical evaluation stage. The main barriers remain scalability, stability, and regulatory compliance [39].

Nevertheless, with ongoing intensive research and improving manufacturing technologies, these challenges will likely be overcome in the near future, allowing chitosan-based drug delivery solutions to find their rightful place in clinical practice [39]. Overcoming these limitations requires standardized characterization methods, unified regulatory guidelines, and comprehensive clinical trials [40].

8. Conclusions and Future Directions

Resent studies have clearly demonstrated that chitosan is one of the most promising biopolymers in modern pharmacotherapy. Chitosan nanoparticles are characterised by great drug encapsulation efficiency and steady drug release profile [41]. Unique chemical and biological properties of chitosan allow this polymer to be used across various routes of drug administration, ranging from oral formulations to targeted gene therapy delivery [4,27]. Current research has shown that chitosan nanoparticles can improve drug pharmacokinetics, increase the concentration of active compounds in target tissues, and reduce systemic toxicity [7,32].

On the other hand, while chitosan-based carriers have broad applicability, their translation into clinical practice remains limited. The major hurdles are related to standardizing polymer production, eliminating batch-to-batch variability, and providing evidence of long-term safety [38,39].

Nevertheless, advancements in technology, new chemical modification methods, and an increasing number of clinical trials suggest that in the coming years, chitosan will become an increasingly important platform not only for drug delivery but also in broader biomedical fields, from tissue engineering to immunotherapy [17,42].

In conclusion, over the past decade, chitosan has evolved from a polymer that was primarily an excipient into one of the most significant subjects of scientific research in pharmacotherapy. Its clinical potential is immense, and the remaining challenges open the door for further innovation.

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