



A COMPREHENSIVE REVIEW OF CHITOSAN NANOPARTICLES AND DELIVERY SYSTEMS

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ABSTRACT

Chitosan is a naturally derived, cationic polysaccharide obtained by partial deacetylation of chitin and has become an important platform in modern pharmaceutical technology because of its biodegradability, biocompatibility, mucoadhesion and chemically reactive amino and hydroxyl groups. These characteristics permit the construction of nanoparticles, nanogels, microspheres, hydrogels, films, polyelectrolyte complexes and hybrid nanocarriers capable of improving drug solubility, stability, residence time, cellular uptake and controlled release. This review examines the pharmacological and biopharmaceutical properties of chitosan and discusses the major chitosan-based delivery systems, their preparation principles and their suitability for different routes of administration. Particular emphasis is placed on passive, active and stimulus-responsive targeting, including pH-, temperature-, enzyme-, redox- and light-responsive systems. Recent developments in DNA, RNA, siRNA, mRNA and CRISPR-associated delivery demonstrate the potential of chitosan as a non-viral gene-delivery platform, while hybrid systems extend its utility toward theranostics and multimodal therapy. Despite substantial preclinical progress, clinical translation is limited by variability in molecular weight and degree of deacetylation, formulation reproducibility, colloidal stability, sterilization, scale-up, long-term safety and regulatory characterization. Future progress will depend on standardized pharmaceutical-grade chitosan, quality-by-design approaches, mechanistic understanding of biological interfaces and clinically relevant pharmacokinetic and toxicological studies. Overall, chitosan should be viewed not simply as an excipient but as a tunable delivery platform capable of integrating controlled release, targeting and biological functionality.

KEYWORDS: Chitosan; Chitosan Nanoparticles; Drug Delivery; Targeted Delivery; Stimulus-Responsive Systems; Gene Therapy; Nucleic Acids; Theranostics; Nanomedicine.

INTRODUCTION

Modern pharmacotherapy increasingly requires delivery technologies that can overcome poor aqueous solubility,

rapid degradation, limited membrane permeability, non-specific biodistribution and dose-limiting toxicity. Nanocarriers and other polymeric delivery systems are

therefore being developed to modify the disposition of active pharmaceutical ingredients and to provide spatial and temporal control over drug exposure.^[1,2]

Chitosan is a linear polysaccharide produced mainly by partial deacetylation of chitin. Its repeating units contain D-glucosamine and N-acetyl-D-glucosamine linked through β -(1 $\rightarrow$ 4) glycosidic bonds. The primary amino groups distinguish chitosan from many neutral polysaccharides and provide pH-dependent cationic character, enabling electrostatic interactions with anionic drugs, proteins, nucleic acids and biological surfaces.^[3,4]

Interest in chitosan for pharmaceutical applications arises from the combination of biodegradability, relatively favorable biocompatibility, mucoadhesion, permeability-enhancing activity and chemical versatility. Chitosan can be processed into nanoparticles, nanocapsules, microspheres, films, fibers, hydrogels and polyelectrolyte complexes, allowing the same polymer platform to be adapted to different therapeutic objectives.^[5,6]

Chitosan nanoparticles (ChNPs) are particularly attractive because their nanoscale dimensions provide high surface area, tunable surface charge and opportunities for encapsulation or complexation of small molecules and biological macromolecules. Their properties can be adjusted by changing molecular weight, degree of deacetylation, polymer concentration, crosslinker concentration, pH, ionic strength and surface functionalization.^[7,8]

From a drug-delivery perspective, the biological behavior of chitosan is strongly dependent on the material rather than simply on the polymer name. Molecular weight and degree of deacetylation influence

charge density, solubility, viscosity, degradation, mucoadhesion, particle size and cellular interactions. Consequently, reproducible characterization of the starting polymer is essential for meaningful comparison between studies.^[9, 10]

Chitosan has also progressed beyond conventional carrier functions. Functionalization with hydrophilic polymers, targeting ligands, cell-penetrating peptides or stimuli-sensitive groups can create systems that respond to specific biological environments. Such modifications are being investigated for cancer therapy, infectious disease, inflammatory disorders, brain delivery, vaccination, regenerative medicine and nucleic-acid therapeutics.^[11, 12]

The present review integrates these developments with emphasis on modern pharmacotherapy. It discusses the pharmacological properties of chitosan, major delivery architectures, routes of administration, targeting mechanisms, nucleic-acid delivery and theranostic applications, followed by safety, stability, manufacturing and translational considerations.

Chemical Basis and Structure–Function Relationships

The degree of deacetylation (DD) describes the proportion of glucosamine residues relative to N-acetylglucosamine residues and is one of the most important descriptors of chitosan. Increasing DD generally increases the number of protonatable amino groups, which can enhance cationic interactions and mucoadhesion but may also increase charge-dependent cellular effects. Molecular weight affects chain entanglement, viscosity, particle formation and biological residence time. These parameters interact rather than acting independently.^[3,9]

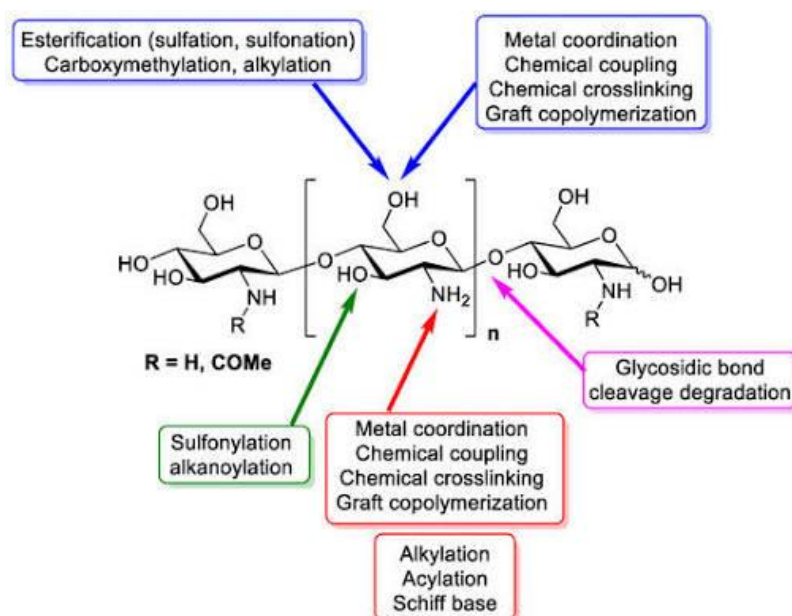


Figure 1: Simplified representation of chitosan structural features relevant to pharmaceutical performance.

Why Chitosan Is Relevant To Modern Pharmacotherapy

- Improvement of dissolution and apparent solubility of poorly water-soluble drugs through nanosizing, encapsulation and interfacial effects.^[2, 13]
- Protection of labile molecules from chemical or enzymatic degradation and modulation of their release rate.^[7, 14]
- Mucoadhesion and transient epithelial interactions that can increase residence time and, for selected systems, improve absorption.^[15, 16]
- Electrostatic complexation with DNA, RNA, siRNA, mRNA and other negatively charged biomolecules, supporting non-viral delivery.^[17, 18]
- Availability of chemically reactive amino and hydroxyl groups for grafting, ligand attachment and stimulus-responsive modification.^[11, 19]

PHARMACOLOGICAL PROPERTIES OF CHITOSAN

Although chitosan is most often discussed as a pharmaceutical excipient or biomaterial, its biological properties contribute directly to therapeutic performance. The magnitude of these effects depends on molecular weight, DD, particle size, surface charge, formulation pH, concentration and route of exposure.^[9, 20]

Mucoadhesion and epithelial interaction

Protonated amino groups permit electrostatic interactions between chitosan and negatively charged mucins. This can prolong residence at mucosal surfaces and create a local concentration gradient favorable to absorption. Chitosan can also transiently alter epithelial tight-junction organization, increasing paracellular permeability for selected molecules.^[15, 16] These effects have supported oral, nasal, buccal, ocular and pulmonary delivery research.

Mucoadhesion is not universally beneficial. Excessive interaction can increase residence but may also cause aggregation, local irritation or altered mucus clearance. Therefore, the objective is usually reversible interaction rather than permanent adhesion. Derivatives such as thiolated, quaternized or carboxylated chitosans are investigated to tune this balance.^[11, 19]

Antimicrobial activity

The cationic character of chitosan can promote interaction with negatively charged microbial cell envelopes, disturbing membrane integrity and altering permeability. Additional mechanisms include binding to microbial DNA or chelation of metal ions. Antimicrobial activity varies with molecular weight, DD, pH and organism, and should not be assumed to be equivalent across all chitosan grades.^[21]

Anti-inflammatory, antioxidant and tissue-supporting effects

Chitosan-containing biomaterials have been investigated in inflammatory conditions, wound repair and tissue engineering. These effects are associated with modulation of cellular responses, moisture retention, antimicrobial protection and support of extracellular-matrix organization. The biological outcome is strongly formulation-dependent, particularly when chitosan is combined with drugs, proteins or inorganic components.^[5, 22]

Biodegradability and biological fate

Chitosan can undergo enzymatic and hydrolytic degradation, with the rate influenced by DD, molecular weight, crystallinity, formulation architecture and physiological environment. In nanoparticulate systems, biodegradation must be considered together with particle dissolution, disassembly, cellular uptake and clearance. The biological interface therefore determines not only efficacy but also the duration of exposure.^[9, 20]

Table 1: Key Material Attributes of Chitosan Delivery System.

Parameter	Typical influence on delivery performance	Pharmaceutical implication
Molecular weight	Affects viscosity, particle formation, degradation and cellular uptake	Must be specified for reproducibility
Degree of deacetylation	Controls charge density, solubility and mucoadhesion	Strongly influences biological interactions
Particle size	Affects uptake, biodistribution and colloidal stability	Requires a controlled size distribution
Zeta potential	Influences membrane interaction and aggregation	Excessive positive charge may increase toxicity
pH / pKa behavior	Controls protonation and solubility	Important for loading, release and mucosal interaction
Crosslinking density	Controls rigidity, swelling and drug diffusion	Determines release kinetics
Surface ligand	Can increase receptor-mediated uptake	Must retain ligand accessibility and specificity

CHITOSAN-BASED DELIVERY SYSTEMS

Chitosan can be transformed into multiple delivery architectures. The choice of system should be based on the drug's physicochemical properties, intended route,

target tissue, required release profile and manufacturing constraints rather than on the polymer alone.^[2, 7]

Chitosan Nanoparticles

ChNPs are commonly prepared by ionic gelation, polyelectrolyte complexation, emulsification, covalent crosslinking, reverse micellar approaches, spray drying, nanoprecipitation and related methods.^[7,23] Ionic gelation is particularly attractive because it can be performed under mild aqueous conditions: positively charged chitosan interacts with multivalent anions such as tripolyphosphate, producing nanoscale crosslinked structures. This avoids harsh organic solvents and is compatible with many sensitive cargos.^[7, 23]

Particle size and polydispersity are governed by polymer concentration, chitosan DD and molecular weight, crosslinker concentration, mixing energy, pH and ionic strength. Optimization is therefore a multivariable formulation problem. Drug loading can occur through entrapment, adsorption, covalent conjugation or electrostatic association, depending on the cargo.^[24]

Nanogels and Hydrogel Systems

Chitosan nanogels combine a hydrated three-dimensional polymer network with nanoscale dimensions. They are particularly useful for hydrophilic molecules, proteins and nucleic acids, while chemical or physical crosslinking can provide tunable swelling and release.^[25] Conventional chitosan hydrogels can provide local drug depots in wounds, mucosal tissues and implanted sites, with release controlled by swelling, diffusion, polymer relaxation and degradation.^[25, 26]

Microspheres and Microparticles

Microspheres offer greater payload capacity and can be advantageous for sustained local delivery or oral dosage

forms. Chitosan microspheres have been investigated for peptides, proteins, antibiotics and anticancer drugs. Their larger size can reduce some nanoscale clearance phenomena but may also limit cellular internalization.^[6,27]

Films, Fibers and Wound-Delivery Matrices

Chitosan films and fibers are useful for topical and wound applications because they combine moisture management, film formation and antimicrobial characteristics. Drug-loaded dressings can provide localized exposure while reducing repeated application.^[22, 28]

Polyelectrolyte Complexes

Polyelectrolyte complexes form when chitosan interacts electrostatically with anionic polymers or biomolecules. This approach is particularly important for DNA and RNA delivery because the cationic polymer condenses and protects nucleic acids from extracellular degradation.^[17, 18]

Hybrid and Surface-Coated Systems

Chitosan can be incorporated into lipid nanoparticles, polymeric nanoparticles, inorganic nanomaterials and nanocomposites. Surface coating can improve mucoadhesion, alter surface charge and facilitate interaction with mucosal barriers, while hybrid cores can provide improved loading of hydrophobic drugs or imaging agents.^[29, 30]

Table 2: Comparison between various delivery systems.

System	Main cargo suitability	Major advantage	Representative limitation
Chitosan NP	Small molecules, peptides, nucleic acids	Versatile nanoscale carrier	Aggregation and batch variability
Nanogel	Proteins, genes, hydrophilic drugs	High water content and tunable release	Crosslinking complexity
Microsphere	Drugs, proteins	Higher payload and depot effect	Limited cellular uptake
Hydrogel	Local drugs, wound agents	Site-specific sustained delivery	Sterilization and mechanical stability
Polyelectrolyte complex	DNA/RNA/siRNA/mRNA	Simple electrostatic loading	Serum and ionic-strength sensitivity
Hybrid NP	Hydrophobic drugs, imaging agents	Multifunctionality	More complex scale-up and characterization

General workflow of a chitosan-based delivery system

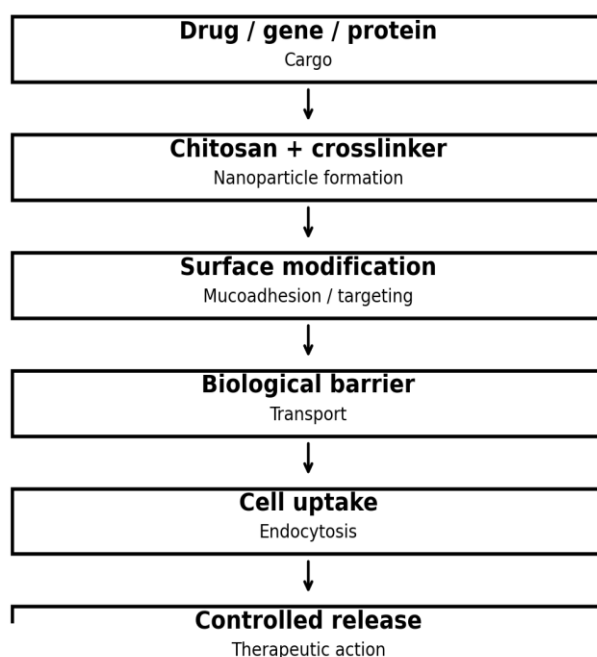


Figure 2: General workflow for development and biological action of a chitosan-based delivery system.

ROUTES OF DRUG ADMINISTRATION

One of the major strengths of chitosan is its adaptability to different routes of administration. Its mucoadhesion, surface charge and ability to form gels or particles make it suitable for both local and systemic delivery.^[5, 15]

Oral Delivery

Oral delivery is the most extensively explored route because chitosan can interact with intestinal mucus and may transiently increase epithelial permeability. Nanoparticles can protect poorly soluble or labile drugs and can provide pH-dependent release. Chitosan systems have also been investigated for colon-targeted delivery, where formulation architecture and environmental responsiveness can be used to shift drug release toward the distal intestine.^[15, 31] However, oral systems must withstand variable pH, digestive enzymes, bile salts, mucus turnover and intestinal fluid shear. A formulation that performs well in simple buffer may behave differently in gastrointestinal fluids. Consequently, biorelevant dissolution and permeability studies are increasingly important during development.^[16]

Nasal and Intranasal Delivery

The nasal route offers a relatively large vascularized surface and avoids first-pass hepatic metabolism. Chitosan's mucoadhesive and permeability-enhancing properties make it attractive for peptides, proteins, vaccines and CNS-oriented delivery. Intranasal chitosan nanoparticles have been studied as a strategy to prolong nasal residence and facilitate epithelial uptake.^[5, 32]

Ocular Delivery

Ocular delivery is limited by tear turnover, blinking and corneal barriers. Chitosan-based nanoparticles and gels can increase precorneal residence and provide sustained drug release. Cationic interactions with ocular mucins can contribute to retention, although excessive irritation or altered vision must be excluded during development.^[33]

Pulmonary Delivery

Pulmonary administration provides direct access to the respiratory epithelium and is relevant to infections, inflammatory diseases, vaccines and gene therapy. Chitosan nanoparticles and nanocapsules can be engineered for aerodynamic delivery and mucus interaction. For nucleic acids, protection from extracellular nucleases and efficient epithelial uptake are central design requirements.^[17, 34]

Transdermal and Topical Delivery

The stratum corneum is a major barrier to systemic transdermal delivery. Chitosan is therefore frequently used in topical formulations and in combination with permeation-enhancing strategies. Films, hydrogels and nanoparticles can maintain local drug concentration and support wound treatment. For true systemic transdermal delivery, additional technologies such as microneedles or physical enhancement may be required.^[22, 28]

Parenteral and Intravenous Delivery

Intravenous administration permits direct systemic exposure but places the highest demands on sterility, endotoxin control, hemocompatibility, colloidal stability and predictable biodistribution. Chitosan nanoparticles

can be functionalized for prolonged circulation or targeting, but strong positive charge may increase nonspecific protein adsorption and cellular interactions.^[20,35]

Buccal, Vaginal and Other Mucosal Routes

Buccal and vaginal delivery benefit from prolonged residence and local drug action. Chitosan films, gels and nanoparticles have been investigated for antimicrobial agents, hormones, proteins and vaccines. The formulation must account for mucin composition, fluid turnover, local pH and patient acceptability.^[5, 36]

DRUG DELIVERY BY PASSIVE, ACTIVE AND STIMULUS-RESPONSIVE TARGETING

Targeted delivery seeks to increase the ratio between drug exposure at the desired site and exposure in non-target tissues. Chitosan is useful in this context because its surface chemistry can be modified without changing the polymer backbone completely.^[11, 19]

Passive Targeting

Passive targeting relies on physicochemical behavior, vascular characteristics, local retention and biological transport rather than a specific ligand-receptor interaction. In oncology, nanoparticle accumulation has historically been discussed in relation to the enhanced permeability and retention effect; however, the magnitude and reproducibility of this effect vary across tumors, patients and animal models.^[37] Therefore, passive targeting should be regarded as a probabilistic strategy rather than a guaranteed tumor-homing mechanism.

Particle size, surface charge, hydrophilicity and protein corona formation can influence circulation and tissue distribution. PEGylation or other hydrophilic coatings may reduce nonspecific interactions, whereas excessive shielding can also reduce cellular uptake. Chitosan's surface charge therefore needs to be balanced against the desired biological interface.^[29, 35]

Active Targeting

Active targeting adds ligands capable of recognizing receptors overexpressed on target cells. Folate, transferrin, antibodies, peptides, sugars and other ligands have been attached to chitosan nanoparticles. The intention is to increase receptor-mediated endocytosis after the nanoparticle has reached the relevant tissue.^[11,38] Active targeting does not eliminate the need for appropriate biodistribution. A ligand cannot bind its receptor if the carrier never reaches the tissue, and receptor expression can vary between patients or change during disease progression. Ligand density, orientation, stability and potential immunogenicity must therefore be considered during optimization.^[38]

Stimulus-Responsive Delivery

Stimulus-responsive systems release cargo when exposed to a defined environmental signal. Chitosan-based

systems have been designed to respond to pH, temperature, enzymes, redox conditions, light and, in hybrid systems, magnetic fields.^[19, 39]

- pH-responsive systems exploit protonation/deprotonation and changes in polymer swelling or crosslinking to alter release.
- Thermo-responsive systems combine chitosan with temperature-sensitive polymers or crosslinkers to trigger gelation or drug release near a selected temperature.
- Enzyme-responsive systems use degradable linkers or matrix components that are preferentially cleaved in diseased tissues or intracellular compartments.
- Redox-responsive systems incorporate disulfide or related bonds that can be destabilized under intracellular reducing conditions.
- Light- or magnetic-responsive hybrid systems can provide externally triggered release, particularly when chitosan is combined with photothermal or magnetic components.^[19, 39]

GENE THERAPY, NUCLEIC ACID DELIVERY AND THERANOSTICS

Nucleic-acid therapeutics require carriers because DNA, RNA and related molecules are large, hydrophilic and negatively charged, are susceptible to nuclease degradation and generally have poor passive cellular uptake. Chitosan provides a non-viral platform capable of condensing nucleic acids through electrostatic interactions.^[17, 18]

DNA Delivery

Plasmid DNA can associate with protonated chitosan to form polyplexes that protect the nucleic acid and facilitate cellular uptake. Transfection efficiency depends on molecular weight, DD, N/P ratio, particle size, surface charge, pH and the presence of serum. An optimized system must balance strong DNA binding with intracellular release; excessively stable complexes can protect DNA extracellularly but hinder cytosolic availability.^[17]

siRNA and miRNA Delivery

Small interfering RNA and microRNA require cytoplasmic access for gene-silencing activity. Chitosan can protect these molecules from nucleases and can be modified with targeting ligands or endosomal-escape components. The formulation must facilitate dissociation or release after uptake so that the nucleic acid can interact with the RNA-induced silencing machinery.^[18,40]

mRNA Delivery

mRNA is particularly sensitive to enzymatic degradation and requires efficient cytoplasmic release. Chitosan-based complexes can provide a non-viral alternative for mRNA delivery, although transfection efficiency and endosomal escape remain important challenges. Recent formulation approaches use derivatives, helper polymers and hybrid systems to improve stability and intracellular delivery.^[17, 18]

CRISPR/Cas and Genome-Editing Cargo

CRISPR/Cas systems create additional delivery complexity because the cargo may consist of plasmid DNA, messenger RNA, guide RNA, Cas protein or combinations thereof. Chitosan has been investigated as a carrier because its cationic backbone can complex with nucleic acids and can be functionalized for targeting. The principal challenge is achieving sufficient editing in target cells while minimizing off-target exposure and inflammatory responses.^[41]

Endosomal Escape

Following endocytosis, nucleic-acid carriers may become trapped in endosomal compartments. Chitosan has been associated with pH-dependent protonation and buffering behavior that can contribute to endosomal escape; however, the extent of this effect is formulation-specific and should not be assumed solely from the presence of chitosan.^[17, 41]

Theranostics and Multimodal Systems

Theranostic platforms combine diagnosis or imaging with therapy. Chitosan can serve as the polymeric

component of systems containing fluorescent probes, magnetic nanoparticles, gold nanostructures or other imaging agents, while simultaneously carrying drugs or nucleic acids. Such systems can potentially enable image-guided delivery and treatment monitoring, but increasing functional complexity also increases manufacturing and regulatory burden.^[12, 42]

SAFETY, STABILITY AND TRANSLATIONAL CHALLENGES

The favorable safety reputation of chitosan should not be generalized automatically to every chitosan nanoparticle. Nanoparticle behavior is determined by size, surface charge, DD, molecular weight, dose, route, impurities and degradation products. Highly cationic systems may improve cellular interaction while also increasing membrane disruption or nonspecific protein adsorption.^[20, 35]

Table 3: Challenges and their recommended development response.

Challenge	Why it matters	Recommended development response
Polymer variability	Changes particle formation and biological behavior	Define MW, DD, purity and source
Particle aggregation	Changes dose and biodistribution	Monitor size/PDI and develop stability-indicating methods
High positive charge	Can increase uptake and toxicity	Optimize surface charge rather than maximize it
Residual impurities	May alter immunological response	Pharmaceutical-grade purification and release testing
Sterilization	May alter polymer and nanoparticles	Validate sterilization/aseptic strategy early
Scale-up	Mixing and mass transfer change with scale	Use QbD and design-of-experiments
Regulatory complexity	Nanocarriers need extensive characterization	Define CQAs, CPPs and clinically relevant assays
Clinical translation	Preclinical behavior may not predict human outcomes	Prioritize PK, biodistribution and safety studies in relevant models

CONCLUSIONS AND FUTURE DIRECTIONS

Chitosan has evolved from a conventional natural polymer into a versatile platform for modern pharmacotherapy. Its cationic character, biodegradability, mucoadhesion and chemical reactivity enable a wide range of delivery architectures, from simple gels and films to sophisticated nanoparticles, hybrid carriers and nucleic-acid polyplexes.^[2,11] The most important future opportunity is not simply the production of more chitosan nanoparticles but the development of reproducible, mechanism-based systems in which polymer characteristics are directly linked to pharmacokinetics, biodistribution and therapeutic response. Molecular weight and DD should be treated as critical material attributes, while particle size, surface charge, encapsulation efficiency, release behavior and biological interaction should be controlled as product-

specific quality attributes.^[43,44] Targeting strategies are likely to become increasingly integrated. Passive accumulation can be combined with receptor-mediated uptake and stimulus-responsive release to create multi-stage systems. However, greater complexity should be justified by measurable therapeutic benefit because every additional component introduces new manufacturing, stability, safety and regulatory requirements.^[38, 39]

Nucleic-acid delivery represents a particularly important frontier. Chitosan provides an attractive non-viral platform, but improvements in endosomal escape, transfection efficiency, serum stability and intracellular cargo release are still needed. Derivative chemistry, hybrid nanocarriers and rational surface engineering may address these limitations.^[17, 18, 41]

Translation will also depend on standardized analytical methods. Reporting only mean particle size and zeta potential is insufficient; future studies should provide polymer MW and DD, particle-size distribution, morphology, surface chemistry, loading, release, stability, residual solvents or crosslinkers, endotoxin where relevant, and clinically meaningful biological endpoints.^[20, 43]

In conclusion, chitosan is best considered a tunable pharmaceutical platform rather than a single excipient. Its future in pharmacotherapy will depend on convergence between polymer science, nanomedicine, pharmacokinetics, immunology, manufacturing science and regulatory engineering. If reproducibility and biological predictability can be improved, chitosan-based delivery systems could move from predominantly preclinical research toward more defined and clinically useful nanomedicines.

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