RESEARCH PAPER

# Functionalized Chitosan Nanoparticles for Cancer Drug Delivery: Current Advances and Future Perspectives

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*ABSTRACT*

Cancer chemotherapy remains limited by poor drug targeting specificity, rapid clearance, and dose-dependent systemic toxicity. Chitosan-based nanoparticles represent a promising biocompatible platform for overcoming these challenges. This narrative review synthesizes recent advances in functionalized chitosan systems designed to improve cancer drug delivery through enhanced encapsulation, controlled release, prolonged circulation, and active targeting. We examine chemical modifications of chitosan, including carboxymethylation, phosphorylation, thiolation, and quaternization, alongside surface functionalization with targeting ligands such as folate, hyaluronic acid, and aptamers. Current preclinical evidence demonstrates significant improvements in tumor accumulation and therapeutic efficacy. However, critical challenges remain regarding nanotoxicity assessment, manufacturing scalability, and optimal matching of nanoparticle chemistry with individual cancer omics profiles. This review identifies emerging opportunities for precision medicine approaches that integrate cancer genomics with rational nanoparticle design while highlighting regulatory considerations essential for clinical translation.

**Keywords:** Chitosan, nanoparticles, cancer drug delivery, targeted therapy, nanomedicine.

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## 1. Introduction

Cancer remains a leading cause of mortality globally, with current chemotherapy limited by poor pharmacokinetics and pronounced off-target toxicity (Zaiki et al., 2023). Conventional anti-cancer drugs, including alkylating agents, topoisomerase inhibitors, and cytotoxic antibiotics, demonstrate high efficacy against tumor cells but lack selectivity, causing severe adverse effects in healthy tissues (Qi et al., 2017). The fundamental challenge in cancer therapeutics is achieving sufficient drug concentration at tumor sites while minimizing systemic exposure.

Nanoparticulate drug delivery systems have emerged as a promising strategy to address these limitations (Shi et al., 2020). The enhanced permeability and retention (EPR) effect, wherein nanoparticles preferentially

accumulate in tumors due to leaky vasculature and impaired lymphatic clearance, provides a passive targeting mechanism (Ding et al., 2020). Nanoparticles in the 50-200 nm range can exploit tumor vasculature gaps spanning 100-780 nm, achieving higher local drug concentrations than free drugs (Bar-Zeev et al., 2017). However, rapid clearance by the mononuclear phagocyte system (MPS), protein corona formation, and non-specific interactions with plasma components limit efficacy (Ilinskaya & Dobrovolskaia, 2016).

Chitosan, a deacetylated derivative of chitin, has garnered considerable attention as a biodegradable nanoparticle matrix material (Adhikari & Yadav, 2018). Its cationic nature, biocompatibility, and amenability to chemical modification make it uniquely suited for cancer drug delivery applications. This review examines advances in functionalized chitosan systems, analyzing chemical strategies to enhance drug encapsulation, reduce premature clearance, and improve cancer cell targeting. We critically evaluate the current evidence base while addressing translational challenges that must be resolved to advance these promising systems toward clinical reality.

## 2. Chitosan: Structure, Properties, and Inherent Anti-Cancer Activity

### 2.1 Chemical Composition and Manufacturing

Chitosan is produced through alkaline deacetylation of chitin, the second most abundant biopolymer in nature after cellulose (Kim & Park, 2015). Industrial processing typically involves treatment with 450 g/L sodium hydroxide at 100°C for 2 hours, yielding polymers with reduced molecular weight and degree of acetylation (Maeda & Kimura, 2004). This harsh chemical process, while efficient, produces heterogeneous deacetylation patterns that may compromise drug delivery precision.

Enzymatic deacetylation represents an emerging alternative approach utilizing chitin deacetylases from fungi including *Mucor rouxii* and *Aspergillus nidulans* (Kaczmarek et al., 2019). Enzymatic processing prevents irregular deacetylation and reduces uncontrolled molecular weight reduction, producing more uniform polymers with superior functionalization properties. Further depolymerization using chitooligosaccharide deacetylases yields low-molecular-weight chitooligosaccharides (<3.9 kDa) with exceptional aqueous solubility previously unattainable by standard chitosan (Liaqat & Eltem, 2018).

### 2.2 pH-Dependent Solubility and Cationic Properties

A defining characteristic of chitosan is its solubility in acidic aqueous solutions (pH <6.5) owing to protonation of primary amino groups (Roy et al., 2017). The tumor microenvironment, characterized by pH 6.0-6.5 due to anaerobic metabolism and lactic acid accumulation, provides optimal conditions for chitosan solubilization and cationic charge acquisition (Yang et al., 2018a). With ζ-potentials exceeding +30 mV in acidic conditions, chitosan molecules adopt uncoiled linear configurations that efficiently interact with negatively charged cancer cell membranes (Mourya & Inamdar, 2009). This electrostatic targeting mechanism selectively permeabilizes cancer cells while sparing normal cells maintained at physiological pH 7.4, where chitosan remains less cationic.

### 2.3 Intrinsic Anti-Cancer Mechanisms

Chitosan exhibits direct anti-cancer activity independent of drug payload (Adhikari &

Yadav, 2018). Low-molecular-weight chitooligosaccharides activate 5′ adenosine monophosphate-activated protein kinase (AMPK) and suppress NF-κB signaling, inhibiting tumor progression (Mattaveewong et al., 2016). Administration of chitooligosaccharides at 500 mg/kg/day in colorectal cancer-bearing mice achieved 60% tumor size reduction through cyclin D1 downregulation and matrix metalloproteinase 9 (MMP9) suppression.

Chitosan nanoparticles additionally activate antitumor immune responses through dendritic cell activation and T lymphocyte stimulation (Castro et al., 2019). Particles of 183 nm diameter from 300 kDa chitosan increased interleukin-6, interleukin-12, tumor necrosis factor-α, and interferon-γ expression in human dendritic cells, enhancing macrophage proliferation and tumor inhibition. These intrinsic immunostimulatory properties, absent in conventional chemotherapy, represent a unique advantage for combination immunotherapy approaches.

## 3. Functionalization Strategies to Overcome Drug Delivery Barriers

### 3.1 Improving Drug Encapsulation and Controlled Release

Unmodified chitosan exhibits limited ability to encapsulate hydrophobic chemotherapeutics efficiently. Chemical functionalization with charged and hydrophobic moieties enhances drug loading while enabling pH-responsive release at tumor microenvironments.

Carboxymethylation introduces negative surface charges through reaction with chloroacetic acid (Jiang et al., 2015). The resulting amphoteric derivatives maintain negative charge at physiological pH 7.4 while acquiring positive charge through amino group protonation at acidic pH 6.5. This charge-reversal mechanism prevents plasma protein interaction in circulation while promoting rapid intracellular drug release within acidic tumor and endosomal compartments. Carboxymethyl chitosan-based nanoparticles demonstrated superior tumor inhibition compared to unmodified chitosan in H22 hepatocellular carcinoma models (Qi et al., 2016).

Phosphorylation via phosphorus pentoxide at 0-5°C introduces acidic phosphate groups enhancing encapsulation of large hydrophobic drugs such as curcumin and α-lipoic acid (Gogoi et al., 2020). Phosphorylated chitosan nanoparticles achieved 17% higher drug loading with 10-hour prolonged release at pH 5.0 versus pH 7.4, demonstrating robust pH-sensitivity essential for tumor-specific delivery.

Zwitterionic functionalization combines negatively charged carboxyl groups with positively charged amino moieties, enabling dual pH-responsiveness and lysosomal escape (Cheng et al., 2015). Thiolated zwitterionic glycol chitosan stably complexes cationic melittin peptides at physiological pH, preventing hemolysis while enabling rapid intracellular release in acidic lysosomes (pH 5) due to inter-polymeric charge repulsion. In vitro treatment of colorectal cancer cells demonstrated 100% cell death with melittin-loaded nanoparticles versus negligible toxicity with drug-free formulations.

### 3.2 Preventing Premature Clearance

Early MPS-mediated elimination fundamentally limits nanoparticle efficacy. Multiple functionalization approaches reduce immunogenic surface properties and extend systemic circulation.

Stealth coating with polyethylene glycol (PEG) remains the gold standard for mitigating opsonization (Fam et al., 2020).

Hydrophilic PEG chains form hydrogen-bonded hydration layers that sterically hinder opsonin protein interaction. PEG-functionalized chitosan-alginate nanoparticles achieved 63.1% transfection efficiency and enhanced anti-tumor responses against 4T1 breast cancer and CT26 colorectal cancer cells by simultaneously downregulating immunosuppressive adenosine A2A receptors and CTLA-4 on T cells (Ghasemi-Chaleshtari et al., 2020).

Hybrid lipid-chitosan formulations combine phosphatidylcholine lipids with chitosan to reduce both hydrophobic character-induced aggregation and cationic charge-mediated MPS clearance (Alhajamee et al., 2022). Hybrid nanoparticles of tamoxifen and curcumin demonstrated 6-fold higher cellular uptake in A2780 ovarian cancer cells and significantly improved bioavailability and systemic residence time compared to lipid or chitosan nanoparticles alone.

3.3 Enhancing Cancer Cell Membrane Permeability

Cell membrane penetration critically determines intracellular drug bioavailability. Chitosan functionalization with cell-penetrating peptides and membrane-interactive molecules overcomes this barrier.

Quaternization via N-methylation of amino groups yields water-soluble N,N,N-trimethyl chitosan with enhanced cell membrane permeation capacity (Pathak et al., 2021). Trimethyl chitosan conjugated with carboxymethyl dextran delivered BV6 and STAT3 siRNA synergistically, achieving 71% higher transfection efficiency and 50% higher cytotoxicity in breast cancer, colon cancer, and melanoma cells compared to free siRNA (Nikkhoo et al., 2020).

TAT peptide functionalization leverages the HIV transactivator of transcription peptide (GRKKRRQRRR) containing multiple cationic lysine and arginine residues (Zaiki et al., 2023). Dual functionalization of thiolated-trimethyl chitosan with TAT peptide and hyaluronic acid achieved 3-fold higher cancer cell penetration and 30-45% higher cytotoxicity against breast cancer and melanoma cells, with 20-day extended survival in xenograft models.

## 4. Active Targeting Through Ligand Functionalization

Passive accumulation via EPR effect achieves limited specificity, with only 0.7% of systemically administered nanoparticles reaching solid tumors (Mahmoudi, 2018). Active targeting through cell receptor-specific ligands dramatically improves precision.

### 4.1 Small Molecule Ligands

Folate receptor targeting exploits elevated folate receptor-α expression on many cancer cells due to increased DNA synthesis (Norton et al., 2020). Folate-functionalized chitosan nanoparticles carrying interferonγ-inducible protein-10 gene achieved 59% tumor volume reduction and 44% higher survival in hepatocellular carcinoma-bearing mice compared to non-targeted controls (Lai et al., 2014). However, recent evidence demonstrates that excessive folate conjugation (≥20%) paradoxically increases protein corona formation and MPS-mediated clearance (Nemati et al., 2021), necessitating optimization of ligand density.

Estrone conjugation targets estrogen receptors on both cell surface and nuclear membranes, enabling dual-level targeting (Kurmi et al., 2020). Estrone-modified chitosan nanoparticles achieved 3-fold higher bioavailability and 1.2-fold

increased tumor tissue accumulation with 40% reduced accumulation in heart, liver, and kidneys compared to free doxorubicin.

### 4.2 Peptide and Antibody Ligands

**Monoclonal antibodies** provide exceptionally high binding specificity with in vivo serum stability (Sabra et al., 2019). Dual-functionalized chitosan nanoparticles bearing anti-HER2 and anti-human mammaglobin antibodies achieved 35% higher cytotoxicity against metastatic breast cancer cells compared to non-functionalized formulations without affecting normal cell viability (Helmi et al., 2021).

**Peptide ligands** including RGD and K237 peptides target integrin and VEGFR2 receptors respectively (Bajracharya et al., 2022). RGD-functionalized chitosan nanoparticles delivered ZEB1 and CD73 siRNA, achieving 64% tumor volume reduction and 100-day extended survival in BALB/c mice bearing xenografts (Alzamely et al., 2021).

### 4.3 Aptamer-Based Targeting

DNA and RNA aptamers—short single-stranded oligonucleotides (25-90 nucleotides)—fold into unique 3D structures with high receptor binding affinity (Sheikh et al., 2022). DNA aptamers offer superior stability compared to RNA aptamers, which are susceptible to ribonuclease degradation despite enhanced transfection potential. The AS1411 nucleolin-targeting aptamer achieved 67% reduction in toll-like receptor 4 messenger RNA and 32% reduction in $IC_{50}$ value against A549 lung cancer cells when delivered via chitosan-polyethyleneimine-urocanic acid nanomicelles (Carvalho et al., 2019).

### 4.4 Tumor Microenvironment and Stromal Cell Targeting

Emerging evidence emphasizes that tumor-associated macrophages and stromal cells critically regulate therapeutic response. Dual-targeting strategies address both cancer cells and immunosuppressive stromal components. Mannose- and hyaluronic acid-functionalized carboxymethyl chitosan-protamine nanoparticles carrying CpG oligodeoxynucleotides reverted tumor-associated macrophages to proinflammatory M1 phenotype, achieving 91.3% tumor inhibition in 4T1 breast cancer-bearing mice through synergistic cancer cell targeting and immune reactivation (Song et al., 2018).

## 5. Emerging Strategies and Precision Medicine Integration

### 5.1 pH and Redox-Responsive Drug Release

Beyond pH-responsiveness, reducing redox microenvironments within cancer cells offer additional targeting specificity. Disulphide-bonded conjugates undergo rapid cleavage in the glutathione-rich cytoplasm (2-10 mM) versus extracellular environment (2-10 μM), achieving 100-fold differential activation (Gamcsik et al., 2012). Core-shell nanoparticles with glycol chitosan-polyethyleneimine cores linked via reducible disulphide bonds demonstrated 90% higher tumor targeting and 66% lower liver toxicity compared to free DNA plasmid in PC3 metastatic prostate cancer models (Cheng et al., 2022).

### 5.2 Stimuli-Responsive Hydrogels for Local Delivery

Chitosan-based thermosensitive hydrogels undergo temperature-responsive phase transitions at physiological temperature, enabling prolonged local drug retention. Intra-tumoral injection of paclitaxel-loaded chitosan-β-glycerophosphate hydrogels in EMT-6 breast cancer-bearing mice

achieved 40% higher tumor growth inhibition and reduced systemic toxicity compared to intravenous free drug (Ruel-Gariépy et al., 2004).

### 5.3 Integration with Cancer Omics for Personalized Nanomedicine

The concept of precision nanomedicine—matching nanoparticle design with individual cancer genomic and proteomic profiles—remains largely unexplored (Gan et al., 2022). Cancer receptor expression patterns vary dynamically with age, gender, ethnicity, and tumor microenvironment conditions. Selection of constituent materials, targeting ligands, permeation enhancers, and stealth coats should rationally align with specific cancer omics profiles. This requires individual omics diagnosis defining cancer receptor and metabolizing enzyme expression, with nanoparticles developed using optimal "right" therapeutics for molecular targets, "right" ligands for overexpressed receptors, and "right" matrix materials resistant to premature biodegradation.

## 6. Critical Challenges and Regulatory Considerations

### 6.1 Manufacturing Standardization and Quality Control

Achieving nanoparticles with identical surface elemental and chemical composition remains technically challenging despite standardized procedures (Sazali et al., 2023). Storage conditions and environmental factors induce aggregation, dissolution, sorption, and corrosion, altering size, charge, crystallinity, and surface roughness—parameters critically affecting biodistribution and pharmacodynamics. Regulatory pathways for personalized nanomedicine produced in small batches remain undefined.

### 6.2 Nanotoxicity Assessment

Nanotoxicity represents a fundamental barrier to clinical translation (Akçan et al., 2020). Chitosan-based nanoparticles exhibit dose-dependent immune activation that may precipitate inflammatory complications. Comprehensive safety assessment protocols require standardization across nanoparticle types and constituents.

### 6.3 Route of Administration and Bioavailability

Chitosan's cationic character predisposes to protein corona formation and particle aggregation in blood, rendering intravenous administration problematic (Hattori & Ishihara, 2015). Non-intravenous routes including oral, intranasal, and pulmonary administration offer advantages but face mucosal barrier limitations. Optimal route selection requires integration with nanoparticle design.

## 7. Future Perspectives

The field of chitosan-based cancer nanomedicine stands at a critical juncture. Preclinical evidence demonstrates remarkable therapeutic potential, yet translational success requires addressing fundamental challenges. Future directions must encompass:

1. Cancer omics-integrated design: Establishment of clinical pipelines integrating individual cancer genomic analysis with rational nanoparticle development
2. Manufacturing innovation: Development of scalable, green manufacturing approaches ensuring batch-to-batch consistency
3. Regulatory framework clarification: Collaborative development of

regulatory pathways for precision nanomedicines

4. Long-term safety monitoring: Comprehensive nanotoxicity assessment protocols and post-marketing surveillance
5. Combination strategies: Integration with immunotherapy, targeted therapy, and conventional chemotherapy
6. Biomimetic approaches: Cancer cell membrane-coated nanoparticles exploiting homologous cell targeting

## 8. Conclusion

Functionalized chitosan nanoparticles represent a paradigm-shifting platform for overcoming critical limitations of conventional cancer chemotherapy. Chemical modifications enabling controlled drug release, extended circulation, and active targeting have demonstrated impressive preclinical efficacy across diverse cancer types. The inherent immunostimulatory properties of chitosan add unique advantages for combination immunotherapy approaches. However, advancement toward clinical reality requires resolution of manufacturing standardization, nanotoxicity assessment, and regulatory clarification. Integration with cancer precision medicine—matching nanoparticle design with individual tumor omics profiles—promises to maximize therapeutic specificity and minimize off-target toxicity. Collaborative efforts among biotechnologists, medical scientists, chemists, and regulatory agencies will be essential to translate these promising laboratory findings into transformative clinical benefits for cancer patients.

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