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Original Article

Recent Advances in Nanoparticles-Based Drug Delivery Systems

Pokale Shraddha*, Bhise Gorakhnath, Salve Aniket, Ghuge Tanuja, Kolhe Vishakha

Vidya Niketan Institute of Pharmacy and Research Centre

ABSTRACT

Nanoparticle-based drug delivery systems have emerged as a transformative approach in modern pharmaceutics, offering precise, controlled, and targeted delivery of therapeutic agents. Conventional drug delivery methods often suffer from poor solubility, limited bioavailability, and nonspecific distribution, leading to reduced efficacy and adverse effects. Nanoparticles overcome these limitations through their tunable size, surface modification, and ability to encapsulate both hydrophilic and hydrophobic drugs. Recent advancements focus on polymeric nanoparticles, lipid-based carriers, dendrimers, metallic nanoparticles, and hybrid nanostructures designed for site-specific delivery and sustained release. Functionalization with ligands and stimuli-responsive systems further enhance therapeutic outcomes by enabling active targeting and controlled release in response to physiological triggers. Applications extend across oncology, infectious diseases, neurodegenerative disorders, and gene therapy, where nanoparticles have shown remarkable potential in improving therapeutic indices. Despite significant progress, challenges such as large-scale manufacturing, regulatory approval, long-term toxicity, and cost-effectiveness remain critical barriers to clinical translation. This review highlights current developments, therapeutic applications, and future prospects of nanoparticle-based drug delivery systems, emphasizing their role in bridging the gap between laboratory innovation and clinical practice.

Keywords: Nanoparticles, Drug delivery systems, Nanomedicine, Targeted drug delivery, Controlled release, Biocompatibility, Stimuli-responsive nanocarriers, Personalized medicine

INTRODUCTION

Drug delivery is a critical component of therapeutic success, as the effectiveness of any drug is not only determined by its pharmacological activity but also by its ability to reach the desired site of action in a safe and controlled manner. Conventional drug delivery systems such as tablets, capsules, and injections often face limitations including poor solubility, low bioavailability, rapid clearance, and non-specific distribution. These drawbacks may lead to reduced therapeutic efficacy and unwanted side effects, necessitating the development of advanced systems capable of overcoming these challenges. Nanotechnology has emerged as a revolutionary platform in pharmaceutical sciences, providing innovative solutions to the limitations of traditional drug delivery methods. Nanoparticles, typically ranging from 1 to 100 nanometers in size, possess unique physicochemical properties such as high surface area-to-volume ratio, tunable surface chemistry, and the ability to encapsulate a wide variety of drugs. These features make them ideal carriers for both hydrophilic and hydrophobic therapeutic agents. By modifying surface functionalities, nanoparticles can be engineered for targeted drug delivery, sustained release, and reduced toxicity. Over the last decade, extensive research has focused on different types of nanoparticles including polymeric nanoparticles, lipid-based systems (liposomes, solid lipid nanoparticles, nanostructured lipid carriers), dendrimers, metallic nanoparticles, and hybrid nanostructures. Each of these systems offers distinct advantages, such as improved drug stability, controlled pharmacokinetics, and enhanced patient compliance. For instance, liposomes have gained FDA approval for cancer chemotherapy, while polymeric nanoparticles are increasingly used for controlled release formulations. Recent advances also include smart nanoparticles that respond to stimuli

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such as pH, temperature, or enzymes, thereby enabling site-specific and on-demand drug release. Nanoparticle-based delivery systems have demonstrated significant promise in the treatment of cancer, infectious diseases, cardiovascular disorders, neurological conditions, and in the delivery of biomolecules such as proteins, peptides, and nucleic acids. In oncology, for example, nanoparticles have enabled targeted delivery of chemotherapeutics to tumor tissues, reducing systemic toxicity. Similarly, in gene therapy, nanoparticles act as non-viral vectors for safer and more efficient nucleic acid delivery. Despite these remarkable advances, several challenges hinder the full-scale clinical translation of nanoparticle-based drug delivery. These include issues related to large-scale manufacturing, reproducibility, long-term stability, potential toxicity, regulatory hurdles, and cost-effectiveness. Addressing these challenges through innovative research and robust regulatory frameworks is essential to move from experimental success to The field of drug delivery has evolved remarkably over the past few decades, shifting from simple dosage forms to sophisticated platforms designed to maximize therapeutic efficacy and minimize adverse effects. Conventional delivery approaches, while widely used, often suffer from limitations such as rapid systemic clearance, poor penetration into biological barriers, and non-specific biodistribution. These shortcomings are particularly critical in the treatment of chronic and life-threatening diseases like cancer, neurological disorders, and infectious diseases, where precise delivery of therapeutic agents is essential. Nanotechnology has emerged as a transformative solution to these challenges, giving rise to nanoparticle-based drug delivery systems (NDDS). Nanoparticles, due to their nanometer-scale dimensions, exhibit unique properties including enhanced permeability, improved solubility of poorly water-soluble drugs, and the potential to cross biological barriers such as the blood–brain barrier. Moreover, their surfaces can be tailored with ligands, antibodies, or polymers to achieve active targeting, thereby directing the therapeutic payload specifically to diseased tissues while sparing healthy ones. A significant advantage of NDDS lies in their ability to provide controlled and sustained release of drugs. By manipulating particle size, surface charge, and composition, researchers can design carriers that release drugs in response to specific physiological stimuli, such as pH gradients in tumors or enzymatic activity in diseased tissues. This adaptability makes nanoparticles a highly versatile platform across multiple therapeutic areas. Recent research has expanded the scope of nanoparticles from traditional liposomes and polymeric carriers to advanced systems like dendrimers, solid lipid nanoparticles, metallic nanocarriers (e.g., gold and silver nanoparticles), and hybrid systems that combine organic and inorganic components. These novel systems have shown great promise in areas like immunotherapy, gene delivery, and vaccine development. For example, the success of lipid nanoparticles (LNPs) in delivering mRNA vaccines against COVID-19 has demonstrated the clinical relevance and scalability of nanoparticle technology on a global level. Another important dimension of nanoparticles is their role in overcoming multidrug resistance (MDR), a major challenge in cancer therapy and infectious diseases. By co-delivering multiple therapeutic agents or incorporating efflux pump inhibitors, nanoparticles can enhance intracellular drug retention and improve therapeutic outcomes. Similarly, in neurological disorders, nanoparticles facilitate the delivery of drugs across the blood–brain barrier, opening new avenues for the treatment of conditions such as Alzheimer's disease and Parkinson's disease. Despite the undeniable progress, translating nanoparticle-based systems into clinical practice is not without hurdles. Critical issues include nanoparticle stability in biological fluids, potential immunogenicity, large-scale reproducibility, and the high cost of production. Furthermore, the regulatory landscape for nanomedicine remains complex, requiring extensive toxicological and pharmacokinetic studies before clinical approval. Addressing these challenges requires interdisciplinary collaboration among chemists, pharmacologists, material scientists, and regulatory agencies. In light of these advancements and challenges, nanoparticle-based drug delivery represents a dynamic and rapidly expanding area of pharmaceutical research. This review paper explores the recent developments in nanoparticle design, fabrication techniques, therapeutic applications, and translational hurdles, with a focus on how these systems are shaping the future of precision medicine.

This review aims to provide a comprehensive overview of the recent advances in nanoparticle-based drug delivery systems, with emphasis on their design, types, therapeutic applications, challenges, and future perspectives in modern medicine.

Mechanisms of Drug Delivery Using Nanomaterials:

Nanoparticles act as versatile carriers that transport therapeutic agents to the site of action with high precision. Their drug delivery mechanisms can be broadly categorized into passive targeting, active targeting, and stimuli-responsive release, each governed by unique physicochemical and biological interactions.

1) Passive Targeting:

Based on the Enhanced Permeability and Retention (EPR) effect, commonly seen in tumors and inflamed tissues.

Nanoparticles accumulate at diseased sites due to:

- Leaky vasculature with wide fenestrations.
- Poor lymphatic drainage, which reduces clearance.

Example: Liposomes and polymeric nanoparticles used for anticancer drug delivery exploit the EPR effect to enhance local drug concentration.

2) Active Targeting:

Involves surface modification of nanoparticles with ligands (antibodies, peptides, aptamers, sugars) that recognize and bind to specific receptors on target cells. This receptor-mediated binding promotes cellular uptake via endocytosis and ensures site-specific delivery.

Example: Folic acid–conjugated nanoparticles selectively target folate receptors, which are overexpressed in many cancer cells.

3) Cellular Uptake Mechanisms:

Nanoparticles enter cells through multiple endocytic pathways:

- Clathrin-mediated endocytosis → uptake into clathrin-coated vesicles.
- Caveolae-mediated endocytosis → uptake through lipid raft–associated invaginations.
- Macropinocytosis → engulfment of extracellular fluid and nanoparticles. Once inside, nanoparticles release drugs into the cytoplasm or bypass lysosomal degradation to deliver biomolecules like DNA and RNA.

4) Stimuli-Responsive Release:

Nanomaterials can be engineered to release drugs in response to specific triggers:

- pH-sensitive systems → release drugs in acidic tumor microenvironments or endosomes.
- Enzyme-sensitive systems → degrade in the presence of disease-specific enzymes.
- Temperature-sensitive nanoparticles → release drugs when exposed to hyperthermia at diseased sites.
- Redox-responsive systems → triggered by high intracellular glutathione levels.
- Example: pH-sensitive polymeric nanoparticles carrying doxorubicin release the drug specifically in tumor tissues.

5) Controlled and Sustained Release:

Nanoparticles provide a reservoir effect, slowly releasing drugs over time.

- Mechanisms include diffusion through the matrix, erosion of biodegradable polymers, or swelling-controlled release.
- Example: Poly (lactic-co-glycolic acid) (PLGA) nanoparticles provide sustained delivery of hydrophobic drugs.

6) Transcytosis Across Biological Barriers:

Certain nanocarriers (e.g., lipid nanoparticles, polymeric micelles) can cross difficult barriers like the blood–brain barrier (BBB) via receptor-mediated or adsorptive-mediated transcytosis. This property expands therapeutic possibilities for central nervous system (CNS) disorders.

7) Co-Delivery and Combination Therapy:

Nanoparticles can encapsulate multiple drugs or drug-gene combinations, releasing them either simultaneously or sequentially.

Inorganic Nanomaterials in drug delivery:

1) Carbon-Based Nanomaterials in Drug Delivery:

Carbon nanomaterials, such as carbon nanotubes (CNTs), graphene, fullerenes, and nanodiamonds, have unique structural, electrical, and mechanical properties that make them excellent drug carriers.

- High surface area → allows high drug loading.
- Π–π interactions → useful for attaching aromatic drug molecules.
- Functionalization → can be modified with hydrophilic groups, ligands, or polymers for improved biocompatibility and targeting.

Applications:

- Carbon Nanotubes (CNTs): Efficient carriers for anticancer drugs, peptides, and nucleic acids. Their needle-like shape helps in cellular penetration.
- Graphene Oxide (GO): Used for pH-sensitive and photothermal-triggered drug release. Excellent in tumor-targeted chemotherapy.
- Fullerenes: Exhibit antioxidant properties; also explored as antiviral and anticancer carriers.
- Nanodiamonds: Biocompatible and useful for sustained release of anticancer drugs like doxorubicin.

Limitations:

- Potential toxicity and poor biodegradability.
- Need for surface functionalization to avoid aggregation.

2) Silica-Based Nanomaterials in Drug Delivery:

Silica nanoparticles, especially Mesoporous Silica Nanoparticles (MSNs), are among the most studied inorganic carriers.

- Large surface area and pore volume → enable high drug-loading capacity.
- Tunable pore size → allows encapsulation of both small molecules and biomacromolecules.
- Biocompatibility and stability → suitable for systemic administration.
- Surface modification → functional groups can be added for targeted and stimuli-responsive release.

Applications:

- Cancer therapy: MSNs deliver chemotherapeutic agents directly to tumors with controlled release.
- Gene delivery: Silica nanoparticles are used to deliver DNA, RNA, and siRNA.
- Smart release systems: pH, enzyme, and redox-responsive MSNs are designed for site-specific delivery.
- Theranostics: MSNs can be loaded with both imaging agents and drugs for combined diagnosis and therapy.

Limitations:

- Risk of accumulation in organs due to slow biodegradation.
- Need for careful surface engineering to avoid toxicity.

3) Iron Oxide Nanoparticles in Drug Delivery:

Iron oxide nanoparticles (IONPs), including magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3), are well known for their superparamagnetic properties.

- Magnetic responsiveness → enables site-specific delivery using external magnetic fields
- Dual functionality → used in both therapy and imaging (MRI contrast agents).
- Biocompatibility → can be coated with polymers, lipids, or silica for stability and reduced toxicity.

Applications:

- Magnetic Drug Targeting: Drugs are loaded on IONPs and directed to diseased sites using external magnets.
- Cancer Hyperthermia: IONPs generate localized heat under alternating magnetic fields, killing tumor cells.
- Gene Delivery: Modified IONPs are carriers for plasmid DNA, siRNA, and antisense oligonucleotides.
- Imaging + Therapy (Theranostics): Used as MRI contrast agents combined with chemotherapeutic delivery.

Limitations:

- Potential aggregation and instability in biological fluids.
- Risk of oxidative stress and cytotoxicity at high doses.
- Clearance and long-term safety require further investigation.

Recent Advances and Innovations in Nanoparticle-Based Drug Delivery Systems:

Nanoparticle-based drug delivery systems (NDDS) have undergone remarkable evolution over the past decade, shifting from simple drug carriers to multifunctional, intelligent, and patient-tailored therapeutic platforms. The convergence of nanotechnology, materials science, and biotechnology has driven several innovations that improve drug solubility, stability, targeting efficiency, and therapeutic outcomes.

1) Stimuli-Responsive Nanoparticles:

- Smart nanocarriers are engineered to release drugs in response to internal (pH, enzymes, redox state) or external (temperature, light, magnetic fields, ultrasound) stimuli.
- Example: pH-sensitive polymeric nanoparticles that release chemotherapeutics specifically in the acidic tumor microenvironment.
- Advantage: Minimizes systemic toxicity and improves site-specific action.

2) Hybrid and Multifunctional Nanoparticles

- Development of hybrid systems combining polymers, lipids, and inorganic nanomaterials.
- Enables dual or multiple functionalities such as controlled release, imaging, and therapy (theranostics).
- Example: Lipid-polymer hybrid nanoparticles co-loaded with drugs and imaging probes for cancer diagnosis and therapy.

3) Theranostic Nanoparticles

- Integration of diagnostic imaging agents with therapeutic payloads.
- Iron oxide nanoparticles serve as both MRI contrast agents and drug carriers.
- Application: Real-time monitoring of drug distribution and therapeutic response.

4) Nanoparticles for Gene and Nucleic Acid Delivery

- Safe alternatives to viral vectors for delivering siRNA, mRNA, plasmids, and CRISPR-Cas9.
- Lipid nanoparticles (LNPs) gained prominence during COVID-19 mRNA vaccine development.
- Current innovations focus on targeted delivery of genetic materials to hard-to-reach tissues (e.g., CNS, tumors).

5) Targeted and Personalized Nanomedicine:

- Functionalization with ligands (antibodies, peptides, aptamers) for active targeting.
- Tailoring nanoparticle formulations based on individual patient genetics, disease type, and drug metabolism profile.
- Supports the move toward precision medicine.

6) Biodegradable and Safe Nanomaterials:

- Focus on developing biocompatible and biodegradable nanocarriers to reduce long-term toxicity and organ accumulation.
- Example: Biodegradable mesoporous silica nanoparticles and polymeric micelles.

8) Nanoparticle-Mediated Immunotherapy:

- Nanocarriers delivering immune modulators (checkpoint inhibitors, cytokines, vaccines) to reshape the tumor microenvironment.
- Example: Nanoparticles used in cancer immunotherapy and mRNA vaccine delivery.

9) Clinical Translation and Scalable Manufacturing:

- Advances in Good Manufacturing Practices (GMP)-compliant nanoparticle production for large-scale use.
- Several nanoformulations are FDA-approved or in late-stage clinical trials (e.g., liposomal doxorubicin, albumin-bound paclitaxel, lipid nanoparticles for vaccines).
- Ongoing innovations aim to address cost-effectiveness, reproducibility, and regulatory challenges.

Safety and Toxicity Challenges in Nanoparticle-Based Drug Delivery Systems:

While nanoparticle-based drug delivery systems (NDDS) offer remarkable opportunities for improving therapeutic efficacy, their translation from laboratory to clinic is significantly hindered by safety and toxicity concerns. Nanoparticles interact with biological systems in complex ways due to their small size, high surface area, and surface reactivity. These properties, though advantageous for drug delivery, can also lead to unintended biological effects.

1) Biodistribution and Accumulation:

- Nanoparticles may accumulate in organs such as the liver, spleen, lungs, and kidneys, leading to long-term toxicity.
- Poor biodegradability and slow clearance of inorganic nanoparticles (e.g., gold, carbon nanotubes, iron oxide) raise concerns about chronic toxicity.
- The reticuloendothelial system (RES) often sequesters nanoparticles, reducing efficacy and altering immune responses.

2) Cellular and Molecular Toxicity:

- Nanoparticles can generate reactive oxygen species (ROS), causing oxidative stress, DNA damage, mitochondrial dysfunction, and apoptosis.
- Positively charged nanoparticles often disrupt cell membranes, leading to cytotoxicity and inflammation.
- Surface coatings or stabilizers (e.g., surfactants, polymers) may also induce unexpected toxicity.

3) Immunotoxicity and Hypersensitivity:

- Nanoparticles may activate the complement system and trigger immune reactions such as complement activation-related pseudoallergy (CARPA).
- Repeated administration can cause immune suppression or hyperactivation, complicating long-term therapies.
- Unmodified nanoparticles are often recognized as foreign agents, leading to rapid clearance and reduced therapeutic benefits

4) Hematological and Cardiovascular Effects:

- Certain nanoparticles interact with blood proteins and platelets, causing hemolysis, thrombosis, or altered blood coagulation.
- Surface-modified nanoparticles may cross endothelial barriers, potentially disturbing vascular homeostasis.

5) Dose and Exposure-Dependent Toxicity:

- At low doses, nanoparticles may be well tolerated, but cumulative exposure can lead to chronic toxicity.
- Long-term studies are limited, making it difficult to predict delayed or lifelong effects.

6) Reproducibility and Batch Variability:

- Differences in size, shape, surface chemistry, and zeta potential between batches can alter toxicity profiles.
- Lack of standardized protocols complicates safety evaluation across different laboratories and clinical settings.

7) Regulatory and Ethical Concerns:

- Limited regulatory guidelines for assessing nanoparticle safety compared to conventional drugs.
- Ethical concerns arise from using nanomaterials with unknown long-term risks in vulnerable patient populations.

8) Strategies to Mitigate Safety Concerns:

- Surface functionalization with biocompatible polymers (PEG, chitosan) to reduce toxicity and immune recognition.
- Development of biodegradable nanoparticles (polymeric, lipid-based, silica with controlled degradation).
- Use of in vitro and in vivo predictive models to evaluate toxicity before clinical translation.
- Standardization of toxicological testing protocols and harmonization of global regulatory frameworks.

Future Perspectives of Nanoparticle-Based Drug Delivery Systems:

Nanoparticle-based drug delivery systems (NDDS) represent one of the most transformative innovations in modern medicine, yet their full potential is still unfolding. With ongoing advances in nanotechnology, material science, and molecular biology, NDDS are expected to become more precise, intelligent, and patient-centered in the future.

1) Precision and Personalized Nanomedicine:

- Integration of genomics, proteomics, and AI-driven predictive models will allow nanoparticles to be tailored for individual patients.
- Patient-specific nanocarriers could optimize drug dose, release profile, and targeting, reducing adverse effects and improving therapeutic outcomes.

2) Smart and Stimuli-Responsive Nanoparticles:

- Development of next-generation intelligent nanocarriers that respond to multiple stimuli (pH, redox, enzymes, light, ultrasound, magnetic fields).
- These "on-demand" systems will enable site-specific and time-controlled drug release, particularly in cancer, neurodegenerative, and inflammatory diseases.

3) Theranostic Nanoplatforms:

- Combining therapy and diagnostics in a single nanoparticle platform.
- Future systems will integrate imaging (MRI, PET, fluorescence) with therapeutic agents, enabling real-time monitoring of treatment efficacy.
- This will improve early detection, personalized dosing, and adaptive treatment strategies.

4) Nanoparticles in Gene and Nucleic Acid Therapy:

- Expansion beyond mRNA vaccines to siRNA, CRISPR-Cas9, and DNA-based therapies.
- Nanoparticles will serve as safe, non-viral carriers for genome editing and regenerative medicine.
- Could revolutionize treatments for genetic disorders, cancers, and neurological diseases.

5) Overcoming Safety and Regulatory Barriers:

- Future research will focus on biodegradable, non-toxic, and immunologically safe nanomaterials.
- International efforts will likely establish standardized safety protocols and regulatory frameworks to ensure consistency and patient safety.
- Development of predictive in silico toxicology models to accelerate approval processes.

6) Advanced Manufacturing and Scalability:

- Adoption of microfluidics, 3D printing, and automated nanoformulation techniques for large-scale, reproducible production.
- GMP-compliant and cost-effective manufacturing methods will enhance clinical translation.
- Could make nanoparticle-based therapies more accessible in low- and middle-income countries.

7) Integration with Emerging Technologies:

- Artificial intelligence (AI) for nanoparticle design, optimization, and prediction of therapeutic outcomes.
- Bioprinting and organ-on-chip models for preclinical testing of nanoformulations.
- Nanorobotics for precise delivery of drugs at the cellular or subcellular level.

CONCLUSION:

Nanomaterial-based drug delivery has advanced from a theoretical concept to practical clinical applications. Inorganic nanomaterials-including carbon-based, silica-based, and iron-oxide carriers-offer unique advantages in stability, targeting, and multifunctionality. Recent innovations in smart and hybrid nanocarriers, combined with green synthesis strategies, promise to improve their safety and translational potential. However, challenges such as toxicity, regulatory approval, and large-scale manufacturing must be addressed. The integration of Al-driven nanodesign, patient-specific personalization, and sustainable synthesis approaches will pave the way for the next generation of nanomedicine.

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