



Challenges in Development of Nanoparticle-Based Therapeutics

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Abstract

In recent years, nanotechnology has been increasingly applied to the area of drug development. Nanoparticle-based therapeutics can confer the ability to overcome biological barriers, effectively deliver hydrophobic drugs and biologics, and preferentially target sites of disease. However, despite these potential advantages, only a relatively small number of nanoparticle-based medicines have been approved for clinical use, with numerous challenges and hurdles at different stages of development. The complexity of nanoparticles as multi-component three dimensional constructs requires careful design and engineering, detailed orthogonal analysis methods, and reproducible scale-up and manufacturing process to achieve a consistent product with the intended physicochemical characteristics, biological behaviours, and pharmacological profiles. The safety and efficacy of nanomedicines can be influenced by minor variations in multiple parameters and need to be carefully examined in preclinical and clinical studies, particularly in context of the biodistribution, targeting to intended sites, and potential immune toxicities. Overall, nanomedicines may present additional development and regulatory considerations compared with conventional medicines, and while there is generally a lack of regulatory standards in the examination of nanoparticle-based medicines as a unique category of therapeutic agents, efforts are being made in this direction. This review summarizes challenges likely to be encountered during the development and approval of nanoparticle-based therapeutics, and discusses potential strategies for drug developers and regulatory agencies to accelerate the growth of this important field.

Keywords: Nano medicines, Nanoparticle-based therapeutics, Drug delivery, Bio distribution, Safety and efficacy, Regulatory challenges, Clinical development

1. Introduction

Nanotechnology continues to revolutionize the way therapeutic agents are delivered by offering unique platforms for targeted drug delivery with improved efficacy and reduced toxicity. Nano-based drug delivery systems are engineered technologies that utilize nanoparticles to encapsulate, protect, and transport therapeutic compounds to specific target sites in the body. These systems hold the promise of minimizing side effects and reducing both dosage and frequency of administration by allowing for controlled and sustained drug release. Moreover, the ability of nanoparticles to traverse biological barriers such as the blood–brain barrier (BBB) and their potential to integrate diagnostic functions (theranostics) have further elevated their significance in modern medicine.

This comprehensive review critically examines the recent advances, materials, mechanisms, and applications in nano-based drug delivery systems. By reflecting on the strides made in nanomedicine for targeted drug delivery, this article also highlights the challenges faced in formulation, characterization,

manufacture, pharmacology, safety, regulatory compliance, and environmental aspects. In doing so, we synthesize information from multiple supporting sources to provide an updated perspective on the state-of-the-art in nanoparticle drug delivery. The research scope bridges fundamental scientific principles with clinical applications in areas such as oncology, neurology, regenerative medicine, and infectious disease management.

Nano-based drug delivery systems have evolved from the basic encapsulation of chemical entities in nanoscale carriers to sophisticated systems with multiple functionalities, including active targeting and controlled release. As the field matures, conventional carriers such as liposomes have been augmented by polymeric nanoparticles, inorganic nanoparticles, viral particles, and albumin-bound systems. This review delves into each of these platforms, examines their unique design characteristics, and discusses the underlying mechanisms that drive targeted delivery and therapeutic outcomes.

2. Recent Advances in Nano-Based Drug Delivery Systems

Recent strides in nanomedicine have expanded the horizons of drug delivery beyond the conventional boundaries. Advances in material science and nanofabrication have enabled the design of nanoparticles with tailored physicochemical properties, including size, shape, and surface chemistry, and functionalization, which directly affect their bio distribution, cellular uptake, and pharmacokinetics.

2.1. Advances in Materials and Functionalization

Nanoparticles can be engineered with specific surface properties that allow them to selectively target diseased cells, thereby increasing therapeutic efficacy while simultaneously reducing the adverse effects commonly associated with systemic drug administration. Controlled surface functionalization is achieved by conjugating targeting ligands such as antibodies, peptides, or small molecules (e.g., folate) to the nanoparticle surface. This ligand-mediated active targeting is particularly important in the context of cancer therapy, where receptors overexpressed on tumor cells can be selectively bound to enhance drug accumulation in the tumor microenvironment.

In parallel, advances in the development of stimuli-responsive nanoparticles have garnered significant attention. These systems are designed to release their therapeutic payload only upon encountering a specific trigger, such as changes in pH, temperature, or ionic strength. For example, nanoparticles that respond to the acidic conditions of the tumor microenvironment can achieve rapid drug release at the target site while remaining stable during circulation.

2.2. Theranostic Approaches

A particularly exciting development is the emergence of theranostic nanoparticles—platforms that combine therapeutic and diagnostic capabilities within a single, multifunctional nanostructure. Theranostic systems can not only deliver drugs but also provide real-time imaging feedback on drug distribution, accumulation, and therapeutic response. These advances pave the way for personalized medicine strategies, where treatment regimens can be optimized based on the observed bio distribution and pharmacodynamics responses of the nanocarrier.

2.3. Integration with Clinical Therapeutics

The application of these advanced systems is clearly exemplified by FDA-approved formulations such as the liposomal encapsulation of chemotherapeutic agents (e.g., Doxil™ and Myocet®) and albumin-bound nanoparticle formulations like Abraxane® (nab-paclitaxel). These products demonstrate enhanced therapeutic indices by leveraging the unique properties of nanoparticles to circumvent traditional delivery challenges. Research has consistently shown improved accumulation in target

tissues, enhanced cellular uptake, and reduced systemic toxicity compared to conventional drug formulations.

Recent clinical studies have explored the utilization of nanoparticles in various therapeutic areas, including cancer treatment, brain disorders, and inflammatory diseases. Despite the excitement surrounding nanotechnology, it is important to note that the translation from experimental systems to clinical practice remains a gradual process, often hampered by challenges in reproducibility, large-scale manufacturing, and regulatory approval.

3. Materials and Platforms in Nano-Based Drug Delivery Systems

Nano-based drug delivery platforms can be broadly classified based on their composition and properties. The choice of platform depends on the nature of the therapeutic agent, the target site, and the desired pharmacokinetic profile. The most common platforms include liposomes, polymeric nanoparticles, inorganic nanoparticles, viral nanoparticles, lipid-based nanoparticles, and albumin-bound (nab) systems.

3.1. Liposomes

Liposomes are spherical vesicles composed primarily of phospholipids and cholesterol, which allow for the encapsulation of both hydrophilic and hydrophobic drugs within their aqueous core or lipid bilayer, respectively. They are widely used due to their biocompatibility, ease of preparation, and ability to reduce the toxicity of encapsulated drugs. Clinically approved liposomal formulations such as Doxil™ (liposomal doxorubicin) have demonstrated efficacy in treating AIDS-related Kaposi sarcoma and ovarian cancer by taking advantage of the enhanced permeability and retention (EPR) effect.

3.2. Polymeric Nanoparticles

Polymeric nanoparticles, made from synthetic polymers like polylactic-co-glycolic acid (PLGA) or natural polymers such as chitosan and alginate, offer excellent biocompatibility and biodegradability. These systems can be engineered for controlled drug release, improved stability, and enhanced mucoadhesive properties. They are particularly useful in developing sustained-release formulations that maintain therapeutic drug levels over extended periods.

3.3. Inorganic Nanoparticles

Inorganic nanoparticles, including gold nanoparticles, silver nanoparticles, iron oxide nanoparticles, and silica-based systems, leverage unique optical, electrical, and magnetic properties. For instance, gold nanoparticles have been extensively studied for their photo thermal therapy capabilities and imaging applications due to their strong surface plasmon resonance. The inherent stability and tunable properties of inorganic nanoparticles make them attractive for dual-function applications (diagnosis and therapy).

3.4. Viral Nanoparticles

Viral nanoparticles are derived from non-infectious viral capsids and are engineered to deliver therapeutic agents by exploiting their natural cellular tropism. These platforms offer precise control over particle size and surface functionality. Although less common in clinical use, viral nanoparticles hold promise for gene therapy and vaccine delivery due to their efficient intracellular delivery mechanisms.

3.5. Lipid-Based Nanoparticles and Nab Technology

Lipid-based nanoparticles include systems such as solid lipid nanoparticles and nanostructured lipid carriers that provide advantages of simplicity, scalability, and good tolerance. In addition, nab (nanoparticle albumin-bound) technology, which uses endogenous albumin as a carrier, has been successfully exploited in formulations like Abraxane®. Albumin facilitates drug delivery by binding to

specific receptors (e.g., gp60) on endothelial cells, thereby enhancing transcytosis and preferential accumulation in tumor tissues.

3.6. Summary Table of Nano-Based Drug Delivery Platforms

Platform	Material Examples	Key Properties/Applications	Clinical Examples
Liposomes	Phospholipids, cholesterol	Encapsulate hydrophilic/hydrophobic drugs; allow for passive/active targeting	Doxil™, Myocet®
Polymeric Nanoparticles	PLGA, chitosan, alginate	Biocompatibility, biodegradability, controlled release, mucoadhesion	Experimental formulations
Inorganic Nanoparticles	Gold, silver, silica, iron oxide	Unique optical/magnetic properties; stimuli-responsive imaging and therapy	Investigational agents
Viral Nanoparticles	Engineered viral capsids	Natural cellular tropism; high payload capacity; potential for gene/drug delivery	Preclinical studies
Lipid-Based Nanoparticles Nab	Solid lipid nanoparticles; Albumin	Biodegradable carriers; enhanced circulation time; receptor-mediated transcytosis	Abraxane®

Table 1: Comparison of Nano-Based Drug Delivery Platforms and Their Clinical Applications

4. Mechanisms of Drug Delivery

The efficacy of nano-based drug delivery systems is predicated on their ability to overcome biological barriers and deliver therapeutic agents selectively to target sites. Two major mechanisms facilitate this selective delivery: passive targeting and active targeting. Controlled and stimuli-responsive release mechanisms further enhance the precision of drug therapy.

4.1. Passive Targeting: Enhanced Permeability and Retention (EPR) Effect

Passive targeting exploits the natural pathophysiological characteristics of tumor vasculature. Tumor tissues often exhibit leaky blood vessels with fenestrations ranging from 0.2 to 1.2 μm , coupled with poor lymphatic drainage, which leads to the accumulation and retention of nanoparticles in the tumor interstitium—a phenomenon known as the Enhanced Permeability and Retention (EPR) effect. The small size of nanoparticles (typically below 200 nm) enables them to extravasate from the circulation into the tumor microenvironment, where they remain for extended periods, thereby enhancing local drug concentration.

4.2. Active Targeting: Ligand-Mediated Specificity

Active targeting involves modifying the surface of nanoparticles with ligands that have a high affinity for receptors expressed on the surface of target cells. For example, folate receptors, highly expressed in certain cancers, can be targeted by conjugating folate to the nanoparticle surface. Similarly, antibodies, peptides, and other biological ligands can be attached to facilitate receptor-mediated endocytosis, ensuring that nanoparticles are internalized selectively by the target cells. Such targeting not only increases the concentration of the therapeutic agent within the intended site but also minimizes its uptake by healthy tissues, reducing systemic toxicity.

4.3. Transcytosis and Intracellular Delivery

Some nano-based systems are designed to harness active transport pathways, such as transcytosis. Albumin-bound nanoparticles, for instance, leverage the gp60 receptor on endothelial cells to initiate caveolae-mediated transcytosis, thus crossing the endothelial barrier more efficiently. This mechanism is particularly beneficial for delivering drugs across tight biological barriers like the BBB.

4.4. Controlled and Stimuli-Responsive Release Mechanisms

In addition to targeting strategies, controlled release is essential for maintaining therapeutic drug levels over time and reducing dosing frequency. Drug release can be engineered to occur via several mechanisms:

- **Diffusion-Controlled Release:** The drug slowly diffuses from the nanoparticle matrix based on concentration gradients.
- **Degradation-Controlled Release:** The polymer matrix degrades over time, gradually releasing the encapsulated drug.
- **Stimuli-Responsive Release:** Nanoparticles designed to respond to external stimuli—such as pH, temperature, light, or magnetic fields—can trigger rapid drug release at the target site. For instance, the acidic microenvironment of tumors can be exploited to induce drug release from pH-sensitive nanoparticles.

4.5. Visualizing the Mechanisms of Targeting and Drug Release

Below is a Mermaid diagram that summarizes the core processes involved in nanoparticle-mediated drug delivery, highlighting both passive targeting via the EPR effect and active targeting through ligand-receptor interactions:

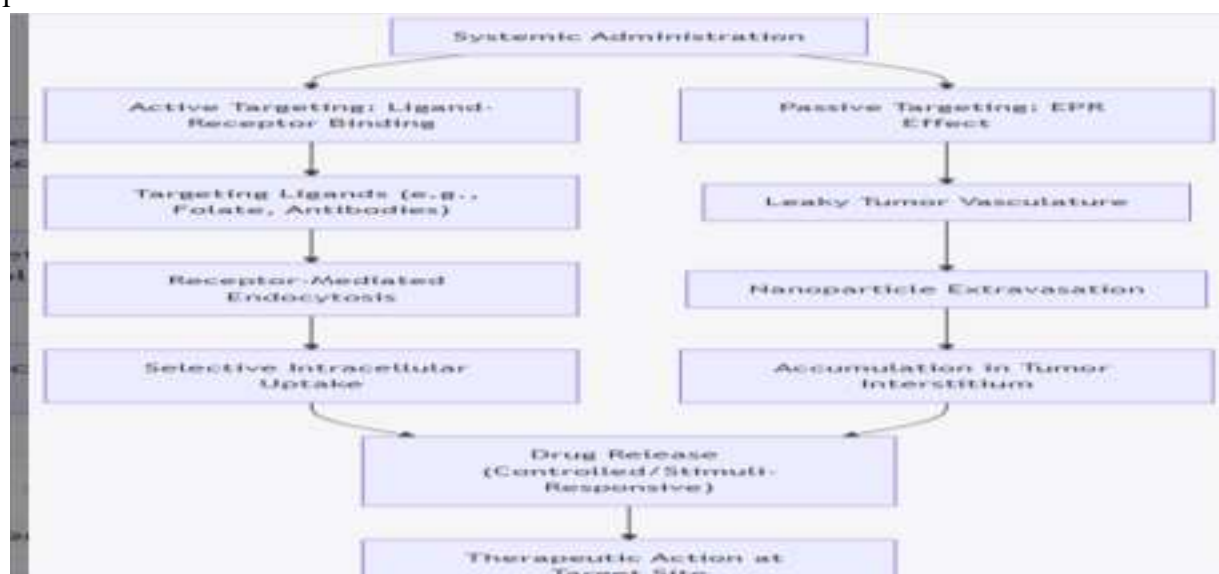


Figure 1: Flowchart Illustrating Passive and Active Targeting Mechanisms in Nano-Based Drug Delivery

5. Applications and Therapeutic Areas

Nanotechnology in drug delivery is most notably applied in the treatment of cancer, but its applications extend to a broad array of therapeutic areas including neurological disorders, infectious diseases, and regenerative medicine.

5.1. Cancer Therapy

Cancer remains the primary focus of nano-based drug delivery research owing to the myriad advantages

that nanoparticles provide in the selective targeting of tumor tissues. Leveraging both passive and active targeting strategies, nanoparticles can deliver chemotherapeutic agents more efficiently to tumor cells while reducing systemic side effects. For example, liposomal formulations of doxorubicin (Doxil™) and albumin-bound paclitaxel (Abraxane®) have been approved by regulatory agencies for the treatment of various cancers, demonstrating improved pharmacokinetic profiles, enhanced tumor accumulation, and reduced toxicity compared to conventional formulations.

Moreover, theranostic nanoparticles offer dual functionality by simultaneously delivering drugs and enabling tumor imaging. These multifunctional platforms can help in the early detection and monitoring of tumor response during chemotherapy, facilitating personalized treatment approaches.

5.2. Neurological Disorders

The delivery of therapeutic agents to the brain poses a significant challenge due to the BBB. Nanoparticles have shown potential in overcoming this barrier by employing both passive diffusion and receptor-mediated transcytosis. Recent research has focused on designing nanoparticles that can cross the BBB to deliver neuroprotective agents, anti-inflammatory drugs, and gene therapies for conditions such as Alzheimer's disease, Parkinson's disease, and brain tumors.

5.3. Regenerative Medicine

In regenerative medicine, nanoparticles serve as carriers for growth factors, cytokines, and genetic material crucial for tissue repair and regeneration. Nanomaterials can be engineered to provide localized, sustained release of these agents at sites of injury, thereby enhancing the repair process and reducing systemic exposure. Furthermore, nanoparticles can be integrated into scaffold materials to improve cell adhesion, proliferation, and differentiation—all key factors in tissue engineering.

5.4. Treatment of Infectious Diseases and Antimicrobial Applications

Nanoparticles, particularly those constructed from metals such as silver and copper, have inherent antimicrobial properties. Silver nanoparticles (AgNPs) have been applied as coatings on medical devices and clothing materials to prevent postoperative infections and combat antibiotic-resistant bacterial strains. This dual approach of pathogen detection and eradication enhances the safety and efficacy of medical interventions.

5.5. Additional Applications

Other promising applications of nano-based drug delivery include:

- **Diabetes Management:** Controlled release formulations to maintain steady insulin levels.
- **Autoimmune Diseases:** Targeted delivery to modulate immune responses without widespread immunosuppression.
- **Cardiovascular Diseases:** Nanoparticles designed for delivering drugs that repair damaged blood vessels or alleviate thrombosis.

Each of these applications takes advantage of the unique ability of nanoparticles to improve drug stability, promote targeted uptake, and modulate release kinetics, ultimately leading to enhanced therapeutic efficacy and reduced adverse effects.

6. Challenges in Development and Translation

Despite the remarkable potential of nano-based drug delivery systems, significant challenges remain in their development, characterization, manufacturing, and regulatory approval. Addressing these challenges is essential for the smooth translation of innovative nanoparticle formulations into clinical practice.

6.1. Formulation and Manufacturing Challenges

The production of nanoparticle formulations is a complex, multistep process that requires precise control over several parameters. Factors such as particle size, surface charge, composition, and the spatial arrangement of components are crucial for ensuring the desired therapeutic outcome. Even subtle deviations in these parameters can lead to significant variations in pharmacokinetics and efficacy. Mass production poses additional challenges:

- **Reproducibility:** Ensuring batch-to-batch consistency is essential, as slight variances may impact therapeutic performance and safety.
- **Scale-Up:** Translating laboratory-scale synthesis to commercial-scale manufacturing requires robust, reproducible processes and in-process quality controls.
- **Sterilization:** Many nanoparticles are sensitive to standard sterilization techniques (e.g., gamma irradiation, autoclaving), which may affect their integrity, particularly those containing biological molecules.

6.2. Characterization and Analytical Challenges

Due to their complex and multicomponent nature, nanoparticles require sophisticated characterization techniques to fully elucidate their physicochemical properties. Standard analytical methods may not suffice in determining key attributes such as:

- **Size Distribution and Morphology:** Techniques like dynamic light scattering (DLS), transmission electron microscopy (TEM), and cryo-TEM are necessary to ascertain size and shape.
- **Surface Chemistry and Charge:** Methods such as zeta potential measurements and X-ray photoelectron spectroscopy (XPS) are used to assess surface functionalization.
- **Drug Loading and Release Profiles:** It is critical to quantify both active and inactive components and their spatial distribution within the nanoparticle to predict performance reliably.

Owing to these factors, the level of analytical characterization required for nano-based therapeutics is more extensive and time-consuming than for conventional drugs.

6.3. Pharmacology and Safety Considerations

The complex interplay of nanoparticle properties has profound implications for their pharmacokinetic (PK) and safety profiles:

- **Pharmacokinetic Variability:** Nanoparticles can exhibit non-linear PK behavior owing to their unique biodistribution and clearance mechanisms. Parameters such as size, charge, and surface chemistry affect clearance rates by the mononuclear phagocytic system (MPS) and renal filtration.
- **Immunotoxicity:** Nanoparticles can induce immune responses, including complement activation, hypersensitivity, and immunogenicity. For example, PEGylated systems may elicit anti-PEG antibodies, leading to accelerated blood clearance upon repeated dosing.
- **Long-Term Safety:** The persistence of nanoparticles in certain tissues, along with potential chronic toxicities like hemolysis or thrombogenicity, requires thorough preclinical and long-term clinical evaluation.

6.4. Regulatory and Generic Approval Challenges

Regulatory agencies such as the FDA and EMA continue to grapple with the unique challenges posed by nanomedicines:

- **Lack of Standardization:** There is currently no universally accepted set of standards or guidelines explicitly tailored to nanoparticle-based formulations. Each product tends to be evaluated on a product-by-product base.

- **Bioequivalence Testing:** The complexity of nanomedicines makes traditional bioequivalence studies insufficient. Even formulations that appear similar in composition can exhibit markedly different behaviors in vivo, posing significant challenges for generic drug manufacturers.
- **Manufacturing and Quality Control:** Due to the sensitive nature of nanoparticle formulations, regulators demand rigorous control of manufacturing processes, including in-process tests and critical quality attribute.

6.5. Environmental and Occupational Health Issues

The handling and manufacturing of nanoparticles also raise concerns regarding environmental safety and occupational exposure:

- **Airborne Nanoparticles:** Dry nanoparticles can become airborne and pose respiratory hazards. Strict control measures are necessary during production to avoid inhalation and dermal exposure.
- **Waste Disposal:** The long-term environmental impact of nanoparticles, particularly those not readily biodegradable, necessitates further research and the development of sustainable waste management practices.

6.6. Summary Table of Challenges in Nano-Based Drug Delivery

Category	Challenges
Formulation & Manufacturing	Subtle compositional changes, batch-to-batch reproducibility, scale-up difficulties, sterilization and process control issues
Characterization & Analysis	Need for multiple orthogonal analytical methods; determining size, morphology, surface chemistry, and functional attributes accurately
Pharmacology & Safety	Non-linear pharmacokinetics, immunotoxicity, complement activation, potential long-term toxicities such as hemolysis and thrombogenicity
Regulatory Challenges	Inconsistent standards, difficulties in establishing bioequivalence for generics, and extensive documentation required for clinical approval
Environmental & Occupational Health	Airborne exposure risks, environmental persistence, safe handling and disposal practices

Table 2: Key Challenges in the Development and Translation of Nanoparticle-Based Therapeutics

7. Future Prospects and Directions

Looking forward, the field of nano-based drug delivery systems is poised for further advancements driven by ongoing research and interdisciplinary collaboration. Several key trends and future directions are emerging that are likely to shape the next generation of nanomedicines.

7.1. Personalized Medicine and Targeted Therapies

The integration of nanotechnology with personalized medicine approaches has the potential to revolutionize patient care. By harnessing advanced diagnostic tools—such as theranostic nanoparticles that combine imaging and therapy—clinicians can identify patient subgroups that are most likely to benefit from specific therapies. Personalized nanomedicine may enable:

- **Tailored Drug Dosing:** Adjusted based on real-time imaging and biomarker feedback.
- **Predictive Response Monitoring:** Using theranostic platforms to monitor drug accumulation and therapeutic response within target tissues.

- **Reduced Toxicity:** Achieving high drug concentration at the target site while sparing healthy tissues, thereby minimizing side effects.

7.2. Smart and Stimuli-Responsive Delivery Systems

Future nanocarriers are expected to incorporate smart, stimuli-responsive features that allow for precise control over drug release. These systems may respond to a variety of internal and external triggers such as:

- **pH and Redox Conditions:** Exploiting differences between healthy and diseased tissues (e.g., tumor microenvironment).
- **Temperature and Light:** Utilizing hyperthermia or photothermal effects to trigger drug release.
- **Magnetic and Ultrasound Fields:** Employing external forces to direct nanoparticles and stimulate drug release at specific target sites.

The development of these smart systems will require further refinement of nanoparticle surface chemistry and polymer design to ensure robustness and responsiveness in complex biological environments.

7.3. Enhanced Barrier Crossing and Delivery to Challenging Sites

A major hurdle in drug delivery is the traversal of biological barriers such as the BBB and dense tumor stroma. Future research is likely to focus on:

- **Improved Transcytosis:** Engineering nanoparticles with enhanced ligand affinity for receptors mediating transcytosis (e.g., gp60, transferrin receptors) to facilitate more efficient passage across barriers.
- **Multi-Stage Delivery Systems:** Designing nanoparticles that release secondary carriers upon reaching the target site, thereby further improving tissue penetration and intracellular delivery.

7.4. Integration with Emerging Technologies

The convergence of nanotechnology with other technological domains is expected to yield innovative hybrid systems:

- **Integration with Artificial Intelligence (AI):** AI algorithms can guide the design of nanoparticles, optimize their properties based on predictive models, and analyze complex datasets from preclinical studies to accelerate development.
- **Microfluidic Fabrication:** Advanced manufacturing methods, such as microfluidic-based nanoparticle synthesis, allow for high-precision, scalable production with tight control over particle characteristics.
- **Gene Editing and RNA Therapies:** Nanoparticles will be critical in delivering CRISPR systems, siRNA, and mRNA therapies, enabling targeted genetic modifications and personalized treatments for previously intractable diseases.

7.5. Addressing Regulatory and Environmental Challenges

Efforts are underway to develop comprehensive guidelines and standardized testing protocols for nanomedicines. Collaborative initiatives between industry, academia, and regulatory bodies are essential to:

- **Harmonize Standards:** Establish robust criteria for nanoparticle characterization, bioequivalence, and quality control to streamline the approval process.
- **Environmental Risk Assessment:** Invest in research focused on evaluating the long-term environmental impacts of nanoparticles and developing sustainable manufacturing and disposal practices.

- **Risk Mitigation Strategies:** Develop strategies to manage immunotoxicity and other safety concerns through improved formulation, better in vivo models, and enhanced monitoring during clinical trials.

7.6. Future Directions Diagram

The following Mermaid diagram summarizes the anticipated trajectory of future developments in nano-based drug delivery systems:

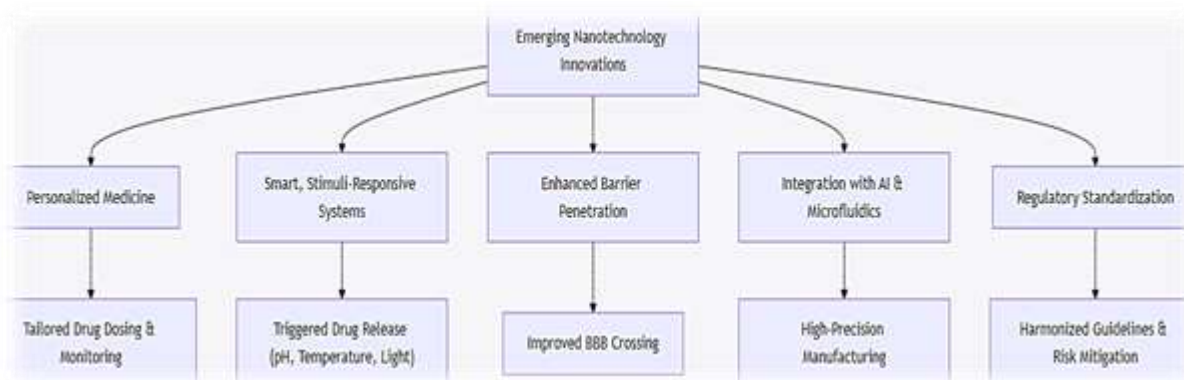


Figure 2: Future Trajectory of Nano-Based Drug Delivery Innovations

8. Conclusions

Nano-based drug delivery systems represent a transformative leap in the capability to target therapeutic agents with precision and efficiency. This review has outlined the evolution from traditional drug formulations to advanced nano carriers that employ both passive and active targeting strategies. The critical advances in materials science have enabled the development of diverse platforms—including liposomes, polymeric nanoparticles, inorganic nanoparticles, and albumin-bound systems—each offering distinct advantages for clinical applications.

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14. Key insights from this review include:
15. Innovation in Materials:
 - Nanoparticles can be tailored by adjusting size, shape, and surface chemistry to optimize drug delivery and minimize side effects .
 - The incorporation of targeting ligands enhances selective uptake by diseased cells and improves therapeutic indices.
16. **Mechanistic Insights:**
 - Passive targeting via the EPR effect and active targeting through ligand-receptor interactions work synergistically to enhance drug accumulation in target tissues .
 - Stimuli-responsive formulations enable controlled and on-demand drug release, which is critical for maintaining therapeutic drug levels.
17. **Challenges and Future Directions:**
 - Reproducibility in formulation and scale-up remains a major challenge, as does the need for comprehensive characterization and regulatory standards .
 - Future prospects point toward personalized medicine, smart nano-delivery systems, and integration with cutting-edge technologies such as AI and microfluidic fabrication.
18. **Clinical and Environmental Considerations:**
 - While many nano-based therapies have already entered the clinic, on going research is needed to address long-term safety, immunotoxicity, and environmental impact.