# NANOTECHNOLOGY IN PARENTERAL DRUG DELIVERY: OPPORTUNITIES AND FUTURE PERSPECTIVES REVIEW

Ms. Sharayu P. Jadhav[1], Prof V.M. Waghulkar[2], Ms Aditi A. Mhasatkar[3]

1 *M Pharmacy Quality Assurance , Vidyabharti College Of Pharmacy ,Amravati Maharashtra India*

2Professor , Department of Quality Assurance ,Vidya Bharti College Of Pharmacy, Amravati, Maharashtra, India

*3M Pharmacy Quality Assurance , Vidyabharti College Of Pharmacy ,Amravati, Maharashtra, India*

## ABSTRSACT

*The paper presents a comprehensive review of the advancements in parenteral drug delivery systems, emphasizing the role of nanotechnology in enhancing drug efficacy and targeting. Parenteral administration remains crucial for delivering therapeutics with narrow therapeutic indices and poor bioavailability, particularly in unconscious patients. The integration of nanotechnology has led to innovative drug delivery platforms, including liposomes, polymeric nanoparticles, and dendrimers, which enhance the solubility, stability, and bioavailability of drugs, while minimizing side effects through targeted delivery mechanisms. The paper discusses the challenges associated with traditional parenteral routes, such as patient discomfort and physiological barriers, including the reticuloendothelial system and blood-brain barrier. Moreover, it highlights the mechanisms of passive and active targeting, controlled drug release strategies, and the potential for combination therapies. The review also addresses safety and toxicological concerns related to nanoparticle immunogenicity, biodistribution, and long-term effects. Finally, it outlines future perspectives in personalized medicine, smart nanocarriers, and the integration of emerging technologies in the development of effective nanomedicines for various disease conditions, particularly in cancer and infectious diseases. Overall, the study underscores nanotechnology's transformative impact on parenteral drug delivery, paving the way for enhanced therapeutic outcomes and improved patient compliance.*

**Keyword:-** *Nanotechnology, Parenteral Drug Delivery, Liposomes, Lipid Nanparticle, Inorganic Nanoparticle Etc*

## 1.Introduction

Parenteral drug administration is widely regarded as one of the most reliable methods for delivering medications, especially in cases where drugs have a low oral bioavailability or a narrow therapeutic range. This route is essential for treating patients who are unconscious or unable to take medicine by mouth. In hospital settings, parenteral formulations are a cornerstone of patient care. Methods such as intravenous, intramuscular, subcutaneous, intradermal, and intra-arterial injections offer efficient drug absorption and ensure that the medication reaches systemic circulation effectively. Despite these advantages, repeated injections are often necessary to maintain therapeutic levels, which may result in discomfort for the patient. To address this, modern pharmaceutical research has focused on developing advanced parenteral formulations capable of controlled, sustained, and targeted drug release. Since these products bypass the body's natural barriers and enter directly into the bloodstream, strict sterility and the absence of pyrogens are essential to ensure safety and effectiveness.(1)

Nanotechnology is a rapidly advancing discipline focused on the engineering of materials typically ranging from 5 to 200 nanometers in size. Its applications extend across numerous sectors, including medicine, where it has

shown great promise in enhancing therapeutic drug delivery and the treatment of various diseases. In this approach, drugs are encapsulated within biodegradable nanoparticles that are specifically engineered to both carry the therapeutic agents and shield them from enzymatic and chemical degradation. Nanotechnology enables the precise delivery of active pharmaceutical compounds to targeted areas in the body, ensuring site-specific action and accurate dosing. One of the most significant advantages of using nanotechnology in drug delivery systems is the reduction of side effects, as the drug is concentrated at the diseased site rather than being distributed systemically. Nanoparticles can be fabricated from diverse materials, including proteins, synthetic polymers, and polysaccharides. The choice of material is influenced by several factors, such as particle size, the nature of the drug, surface properties like charge and permeability, biodegradability, and the intended route of administration. Among various nanocarriers, gold nanoparticles are frequently employed in cancer treatment, while solid lipid nanoparticles have shown potential in both antiviral and anticancer therapies. Other nanotechnological tools, such as nanofibers and nanosuspensions, are also being utilized. Overall, nanotechnology has significantly advanced the capability to deliver drugs in a controlled, targeted, and efficient manner.(2)

Nanotechnology-based approaches for drug delivery and in vivo imaging represent a rapidly evolving area of biomedical research. This review focuses on both the physical characteristics of nanocarriers used for therapeutic and diagnostic purposes, and the biological mechanisms that enable their selective accumulation in damaged or diseased tissues. Key strategies for targeted delivery, including passive targeting through enhanced vascular permeability in inflamed or tumor tissues, as well as active targeting via ligand-receptor interactions with overexpressed biomarkers, are explored. The review also examines how these nanoscale systems—such as liposomes, micelles, nanoemulsions, and dendrimer-based nanocomposites—are engineered and the methods used for their preparation. Additionally, their physicochemical properties and current clinical applications in the treatment and diagnosis of various conditions are discussed.(3)

Over the past few decades, the emergence of nanotechnology has played a pivotal role in advancing numerous scientific disciplines, especially in medicine and pharmaceuticals. One of the most notably impacted areas is the design and formulation of injectable parenteral products. The increasing number of nanotechnology-driven injectable therapies, both on the market and in development, highlights the depth of this influence. Nanomaterials not only enhance the precision of drug delivery to specific targets but also contribute to a wide range of formulation improvements. These include boosting the solubility of poorly water-soluble drugs, enabling sustained drug release for both localized and systemic effects, and introducing mechanisms for stimulus-responsive release. Additionally, nanotechnology has proven valuable in immunological applications, enhancing vaccine efficacy and supporting immunotherapeutic strategies.(4)

We have examined the evolution of nanotechnology in pharmaceutical science, particularly focusing on its applications in both oral and injectable drug delivery systems, and explored how we can adapt our strategies to more effectively harness nanoparticles for immuno-oncology. Departing from the traditional approach of using nanoparticles solely for localized tumor targeting, we introduce an alternative paradigm: utilizing nanoparticles to initiate T cell priming that leads to tumor eradication. Due to their inherently uneven distribution throughout the body, nanoparticles are well-suited to engage immune cells across multiple sites, enabling a systemic—or "global"—immune activation. When combined with appropriate therapeutic agents, this strategy has the potential to continuously expose tumor antigens to the immune system, sustain immune memory, and ultimately drive effective and lasting tumor destruction.(5)

## 2. Physiological barrier to the parentral drug delivery

Despite bypassing the gastrointestinal tract, parenteral drug delivery faces several physiological barriers that can limit drug efficacy, distribution, and safety. One of the major barriers is the **reticuloendothelial system (RES)**, also known as the mononuclear phagocyte system. This system, primarily located in the liver, spleen, and lungs, rapidly identifies and clears foreign substances such as nanoparticles from the bloodstream. This rapid clearance can significantly reduce the amount of drug reaching the target site. Surface modifications like **PEGylation** (attaching polyethylene glycol chains) are often used to create "stealth" nanoparticles that can evade immune detection and extend circulation time.(6)

Another critical barrier is the **blood-brain barrier (BBB)**, a highly selective membrane that restricts most drugs from entering the brain due to tight endothelial junctions and efflux transporters. This presents a major challenge for treating neurological conditions. Nanocarriers designed to cross the BBB use strategies like **receptor-mediated transport** or increased lipophilicity to facilitate drug delivery to the brain.(7)

**Endothelial barriers** throughout the body also play a key role in regulating drug movement from the bloodstream into tissues. Large or hydrophilic drugs often struggle to cross these barriers. Nanoparticles can overcome this through **passive targeting** (using the enhanced permeability and retention, or EPR effect in tumors) or **active targeting** (functionalizing the surface with ligands that bind to specific receptors on target cells.[6]

Additionally, **enzymatic degradation** in the bloodstream can break down labile drugs such as proteins, peptides, and nucleic acids before they reach their site of action. To address this, drugs can be encapsulated in **liposomes, polymeric nanoparticles, or lipid-based carriers**, which protect them from enzymatic attack and improve their stability. [7]

**Renal clearance** is another factor affecting parenteral drug delivery. Drugs or nanoparticles smaller than 5–10 nanometers are often quickly filtered out by the kidneys, leading to a short half-life. Increasing particle size above the renal threshold or using PEGylation can slow this filtration process and prolong drug availability. [7]

Lastly, the **tumor microenvironment (TME)** presents unique barriers in cancer therapy. The dense extracellular matrix, abnormal vasculature, and high interstitial pressure in solid tumors can limit the penetration and uniform distribution of therapeutic agents. To overcome this, researchers have developed **stimuli-responsive nanoparticles** that release drugs in response to pH changes or specific enzymes within the tumor, improving drug accumulation and therapeutic outcomes.

In summary, while parenteral drug delivery bypasses some external barriers, internal physiological defenses like the RES, BBB, and enzymatic systems pose significant challenges. Nanotechnology-based strategies offer promising solutions to overcome these barriers, enhancing the delivery, targeting, and effectiveness of therapeutic agents.[8]

## 3. Traditional routes of drug administration

Parenteral drug delivery encompasses the administration of medications via injection, bypassing the gastrointestinal tract to ensure rapid and direct systemic absorption. Traditional routes include intravenous (IV), intramuscular (IM), subcutaneous (SC), and intradermal (ID) injections, each selected based on the drug's properties and therapeutic requirements.

**3.1 Intravenous (IV) administration** delivers drugs directly into the bloodstream, providing immediate therapeutic effects and 100% bioavailability. This route is particularly advantageous for emergency situations and for drugs requiring precise dosage control. However, it necessitates skilled administration and carries risks such as infection and thrombosis.[9]

**3.2 Intramuscular (IM) injections** involve delivering medication into muscle tissue, allowing for slower absorption compared to IV administration. This route is commonly used for vaccines and depot formulations, offering a balance between rapid onset and sustained release. Nonetheless, it may cause discomfort and carries a risk of tissue damage.

**3.3 Subcutaneous (SC) injections** administer drugs into the tissue layer between the skin and muscle, facilitating slower absorption suitable for medications like insulin and certain monoclonal antibodies. While SC injections can be self-administered and are less invasive, they are limited by the volume of medication that can be administered and may result in variable absorption rates.[9]

**3.4 Intradermal (ID) injections** are administered into the dermis layer of the skin and are primarily used for diagnostic purposes, such as allergy testing and tuberculosis screening. This route allows for localized drug delivery but is limited by the small volume that can be injected and requires precise technique.[9]

While traditional parenteral routes offer rapid and reliable drug delivery, they also present challenges, including the need for sterile techniques, potential for patient discomfort, and risks associated with invasive procedures. Advances in formulation technologies, such as the development of long-acting injectables and nanoparticle-based systems, aim to address these limitations by enhancing drug stability, targeting, and patient compliance.

## 4. Types of Nanocarriers used in Parentral Drug Delivery

### 4.1 Liposomes

Liposomes are spherical nanocarriers composed of lipid bilayers that encapsulate an aqueous core, making them suitable for delivering therapeutic agents such as drugs. Their fabrication, drug loading, and purification steps can be streamlined using continuous-flow microfluidic platforms. Despite their promise as drug delivery vehicles, conventional liposomes often lack the capability for controlled, on-demand release of their contents. To address this limitation, researchers have developed X-ray-responsive liposomes by integrating verteporfin and gold nanoparticles. In one study, exposure to 6 MeV X-rays activated the photosensitizer verteporfin, generating singlet oxygen that disrupted the liposomal membrane and facilitated drug release. In a separate investigation, thermosensitive liposomes were shown to improve drug accumulation and efficacy at tumor sites. This was achieved by applying ultrasound to locally increase tumor temperature, thereby triggering the release of the encapsulated drug. (11)

### 4.2 Polymeric nanoparticles

Polymeric nanoparticles are colloidal carriers made from biodegradable polymers and typically appear in two main structural forms: nanocapsules and nanospheres. Nanocapsules consist of a liquid core—either aqueous or oily—enclosed by a polymeric shell, in which the drug is either dissolved or dispersed. In contrast, nanospheres involve the uniform entrapment of the therapeutic agent within a solid polymeric matrix. Due to the complexity associated with nanocapsule fabrication, a one-step self-assembly method has been introduced as a simplified alternative. In one application, this method was employed to encapsulate doxorubicin hydrochloride along with $NaYF_4$:Yb,Er@$NaGdF_4$ using poly(DL-lactic-co-glycolic acid), demonstrating a pH-responsive release—35.7 wt% at pH 5.0 and 14.58 wt% at pH 7.4. Another study reported the formulation of hyaluronic acid-based nanocapsules containing docetaxel, which exhibited sustained drug release over a 24-hour period. Additionally, Das and co-researchers developed a nanosphere composed of poly-L-glutamic acid embedded within mesoporous bioactive glass. When loaded with daunomycin, the system showed enhanced drug release under mildly acidic conditions (pH 5.5) compared to physiological pH (7.4), indicating its potential for site-specific drug delivery in acidic tumor microenvironments..(15)

### 4.3 Lipid nanoparticle

Lipid nanoparticles have demonstrated strong potential for delivering therapeutic agents via parenteral routes. The development of transferrin-conjugated solid lipid nanoparticles (SLNs) represents a significant advancement in achieving active targeting, although further in-depth research is necessary to fully validate this approach. One of the primary obstacles to the commercial success of SLNs lies in the biocompatibility of the lipids and surfactants used, especially for injectable applications. To address this, it is feasible to utilize glycerides derived from fatty acids commonly found in approved parenteral fat emulsions—such as those containing C14-C18 or C22 fatty acids—which may enhance the biocompatibility of SLNs. Nonetheless, comprehensive in vivo evaluations are essential to confirm their suitability for parenteral use. On the other hand, technical parameters such as sterilization methods, lyophilization processes, product stability, and scalability for industrial manufacturing have reached considerable maturity. Although no SLN-based injectable drug has yet reached the market, current advancements suggest that commercial products may emerge in the near future.(12)

### 4.4 Dendrimer

Dendrimers are innovative, three-dimensional nanopolymers characterized by their hyperbranched, globular architecture. Their distinctive features—including nanoscale dimensions, low polydispersity, precise structural control, numerous surface functional groups, and internal cavities—set them apart from conventional polymeric systems. These unique attributes have enabled their investigation across a broad spectrum of applications. In the field of drug delivery, dendrimers have garnered significant interest due to their potential as versatile carriers. The terminal functional groups offer opportunities for drug conjugation and the attachment of targeting ligands. Moreover, these surface functionalities can be chemically modified to fine-tune the physical and chemical properties of dendrimers, further broadening their applicability.(10)

### 4.5 Inorganic Nanomaterials

In the last ten years, nanotechnology has emerged as a critical component in advancing drug delivery systems. A variety of nanostructured inorganic materials are under development as promising drug carriers, thanks to their distinct architectures, functional capabilities, and ability to regulate drug release. These nanoscale inorganic carriers have shown strong potential for improving the delivery and sustained release of poorly water-soluble drugs, as well as biomacromolecules like proteins, DNA, and RNA. Their functional attributes—including mesoporosity, luminescence, magnetic behavior, and tunable surface characteristics—grant them unique physical and chemical properties that depend on size, shape, and composition. These qualities make them highly suitable for both therapeutic and diagnostic uses. The application of such nanomaterials in medical treatments and diagnostics, known as "nanomedicine," has seen significant growth in recent years. [13]

### 4.6 Exosomes

Exosomes present several unique advantages that make them exceptionally promising as drug delivery vehicles. Derived from cellular membranes and equipped with surface proteins that facilitate adhesion, exosomes naturally function in intercellular communication and offer a distinctive method for delivering therapeutic molecules directly to target cells. They can also be engineered via their parent cells to display specific targeting ligands or to possess tailored biological activities. This review centers on the advancement and assessment of exosome-based drug delivery platforms. It explores various methods for isolating and characterizing exosomes, techniques for loading therapeutic agents, and their implementation in both preclinical models and clinical settings. Exosome-mediated therapies hold potential across a broad spectrum of diseases, including cancer, infectious diseases, cardiovascular conditions, and neurodegenerative disorders. Ultimately, exosomes combine the advantages of synthetic nanocarriers and biologically derived delivery systems while mitigating many of their associated drawbacks.[14]

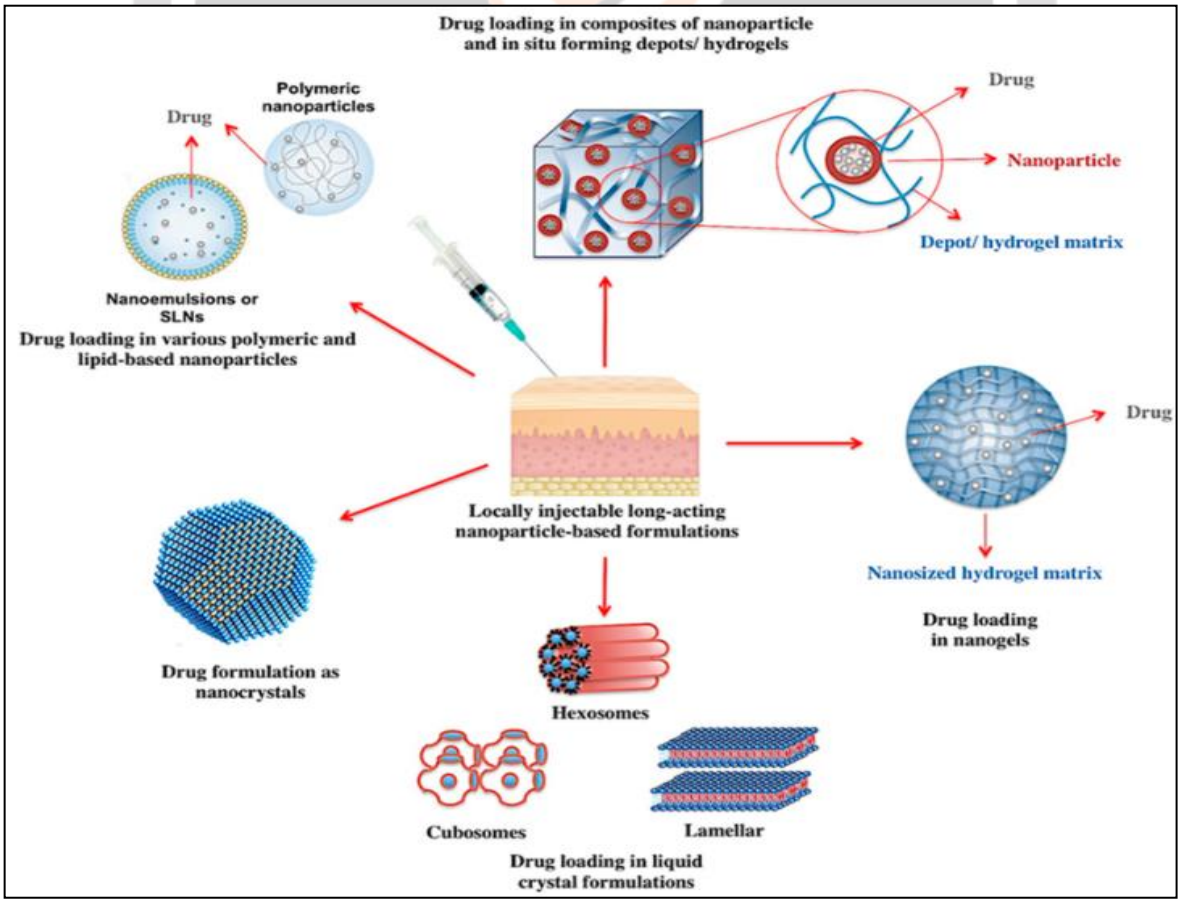


**Fig no.1-Schematic Of Injectable Nanocarrier for Parenteral Drug Delivery**

## 5. Mechanism of Nanoparticle -based drug delivery

### 5.1 Passive targeting

In the field of nanomedicine, the concept of "passive targeting" is commonly used to describe the tendency of nanoparticles to accumulate in solid tumors. This phenomenon was first highlighted by Matsumura and Maeda in 1986, who made two foundational observations following intravenous administration of macromolecular drug carriers. The first was the preferential accumulation of these carriers in tumor regions characterized by leaky blood vessels. The second was the prolonged retention of nanoparticles within tumor tissue, attributed to the tumor's impaired lymphatic drainage. These findings collectively led to the formulation of the "enhanced permeability and retention (EPR) effect," a principle central to passive targeting strategies. To understand how passive targeting operates, it is essential to explore the abnormal features of tumor vasculature that contribute to increased vascular permeability. Additionally, nanoparticle retention in tumors is largely influenced by inadequate lymphatic clearance. In healthy tissues, the lymphatic system plays a crucial role in draining interstitial fluids to preserve fluid homeostasis—an ability that is markedly diminished in solid tumors.[16]

### 5.2 Active targeting

Active targeting involves modifying nanoparticles (NPs) with specific ligands—such as antibodies, peptides, aptamers, carbohydrates, or small molecules—to facilitate selective binding to target cells or tissues. Some of these ligand-drug conjugates have progressed into clinical trials or have already been integrated into therapeutic practice. Despite these advancements, their success has primarily been observed with direct ligand-drug conjugates. To improve therapeutic efficacy, efforts have shifted toward encapsulating drugs within targeted nanoparticles. A wide range of nanocarrier systems has been developed for this purpose, including biodegradable polymers, dendrimers, nanoshells, nucleic acid-based nanoparticles, and liposomes. Among these, biodegradable polymeric nanoparticles have received significant attention in oncology. These systems often achieve extended circulation times in the bloodstream by surface modification with hydrophilic polymers like polyethylene glycol (PEG), through grafting, adsorption, or covalent attachment. Moreover, polymeric nanoparticles can be engineered to carry both hydrophilic and hydrophobic drugs, as well as larger biomolecules such as proteins and nucleic acids.[17]

### 5.3 Controlled and sustained drug release

Nanoparticle-based drug delivery systems facilitate controlled and sustained release of therapeutic agents through a variety of mechanisms. In diffusion-based release, the drug gradually migrates out of the nanoparticle matrix. Degradation-controlled systems rely on the breakdown of carrier materials—such as PLGA or PLA polymers—to release their payload. In hydrogel-based systems, drug release is triggered by the swelling of the matrix upon water absorption. Additionally, stimuli-responsive nanoparticles can release drugs in response to environmental cues such as pH shifts, temperature changes, enzymatic activity, or external stimuli like magnetic or electric fields. Osmotically driven release systems operate by drawing in water to maintain a consistent drug release rate. These release strategies can be used individually or in combination to improve drug targeting, extend systemic circulation, and reduce adverse effects, underscoring their potential in advancing precision medicine. [18]

### 5.4 Overcoming biological barriers

Advancing technologies that target the blood–brain barrier (BBB) is a highly active area of research, particularly for delivering therapeutics to the central nervous system via systemic administration. Overcoming the BBB remains one of the greatest challenges in drug development. This physiological barrier serves as a selective interface that shields the brain from direct exposure to circulating blood, thereby preserving the brain's internal environment. However, this same protective function restricts the entry of many diagnostic and therapeutic agents into brain tissue. One promising approach to circumvent this obstacle involves the use of nanoparticle-based delivery systems specifically engineered to interact with BBB-forming cells at the molecular level. These nanocarriers can facilitate the transport of drugs, nucleic acids, proteins, or imaging agents into the brain without disrupting its normal physiological functions.[19]

## 6. Advantages of Nanotechnology in Parenteral Drug Delivery

### 6.1 Improved Bioavailability & Solubility

Nanotechnology enhances the solubility and absorption of poorly water-soluble drugs by using nanoscale carriers (e.g., liposomes, polymeric nanoparticles, and micelles). This allows for better drug dispersion in the bloodstream, leading to improved therapeutic effects. [20]

### 6.2 Prolonged Circulation Time & Reduced Dosing Frequency

Nanoparticles can be engineered to evade rapid clearance by the immune system, extending their half-life in circulation. Encapsulation in PEGylated liposomes or polymeric nanoparticles helps in controlled and sustained drug release, reducing the need for frequent dosing and improving patient compliance. [20]

### 6.3 Targeted drug delivery & Reduced systemic toxicity

Functionalized nanoparticles can be designed with targeting ligands (e.g., antibodies, peptides) that bind to specific receptors on diseased cells. This precision reduces drug accumulation in healthy tissues, minimizing systemic side effects and enhancing treatment efficacy, especially in cancer therapy. [25]

### 6.4 Enhanced stability of liable drug

Biopharmaceuticals like proteins, peptides, and nucleic acids are highly unstable in physiological conditions. Nanocarriers provide a protective environment that prevents degradation from enzymes and pH changes, ensuring higher drug stability and potency. [25]

### 6.5 Potential for combination therapy.

Nanotechnology enables the co-delivery of multiple therapeutic agents in a single carrier, allowing for synergistic effects in treatment. This is particularly beneficial in diseases requiring combination therapy, such as cancer and infectious diseases, as it can enhance efficacy while reducing drug resistance. [26]

## 7. Safety and Toxicological Concerns

### 7.1 Immunogenicity and Hypersensitivity

Nanoparticles (NPs) can inadvertently activate the immune system, leading to hypersensitivity reactions and altered pharmacokinetics. This activation often results from complement system engagement and opsonization, which can accelerate NP clearance and provoke immune responses. Antibodies may form against the NP carrier, the therapeutic agent, or targeting ligands, compromising efficacy and safety. Platelet activation has also been implicated in NP-induced immunogenicity.[4]

### 7.2 Biodistribution and Accumulation

The distribution of NPs within the body is influenced by their size, surface charge, and hydrophobicity. These properties affect their interaction with biological barriers and subsequent accumulation in organs such as the liver, spleen, and lungs. Understanding these interactions is vital for predicting therapeutic outcomes and potential toxicity.[20]

### 7.3 Cytotoxicity and Genotoxicity

NPs can induce cytotoxic effects through oxidative stress, leading to DNA damage and potential carcinogenicity. Mechanisms include the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which can cause strand breaks and chromosomal aberrations. Standard assays like the comet assay and micronucleus test are employed to assess these genotoxic effects.[21]

### 7.4 Interaction with Blood Components

Upon entering the bloodstream, NPs interact with plasma proteins, forming a "protein corona" that alters their biological identity. This corona can affect NP stability, circulation time, and targeting ability. Additionally, NPs may activate the complement system, leading to inflammation, or interact with blood cells, causing hemolysis or platelet aggregation. (22)

### 7.5 Long-Term Effects and Clearance Mechanisms

The long-term fate of NPs in the body remains a significant concern. Some NPs may persist in tissues, leading to chronic toxicity. Clearance mechanisms vary depending on NP composition and size, with some being metabolized and others excreted unchanged. Understanding these pathways is essential for assessing long-term safety. (23)

## 8. Challenges in Nanotechnology for Parenteral Drug Delivery

Nanotechnology has significantly advanced parenteral drug delivery, yet several biological and physiological challenges remain, particularly concerning immune system interactions, toxicity, and biodistribution.

### 8.1 Biological and Physiological Challenges

#### 1. Immune System Recognition and Clearance

One of the primary challenges in nanotechnology-based drug delivery is the immune system's recognition and subsequent clearance of nanoparticles. Upon entering the bloodstream, nanoparticles (NPs) are rapidly coated by plasma proteins in a process known as opsonization. This tagging facilitates recognition and uptake by the mononuclear phagocyte system (MPS), especially macrophages in the liver and spleen, leading to swift clearance from circulation and diminished therapeutic efficacy. To mitigate this, surface modifications such as polyethylene glycol (PEG) coating have been employed to reduce protein adsorption and enhance circulation time. Additionally, disguising NPs with leukocyte or platelet membranes can help them evade immune detection.(9)

#### 2.Toxicity and Biocompatibility Concerns

The interaction of NPs with the immune system can result in either immunosuppression or immunostimulation, potentially leading to adverse effects. Factors such as particle size, surface charge, and hdrophobicity significantly influence these interactions. For instance, cationic and hydrophobic NPs are more prone to opsonization and subsequent phagocytosis, which can trigger inflammatory responses. Ensuring biocompatibility necessitates careful selection of NP characteristics and thorough preclinical evaluations to assess potential toxicities. (10)

#### 3. Unpredictable Biodistribution and Accumulation

NPs often exhibit unintended accumulation in organs like the liver, spleen, and kidneys due to MPS uptake. This sequestration can lead to off-target effects and organ-specific toxicities. Design parameters such as size, shape, and surface properties critically affect biodistribution. For example, NPs smaller than 5 nm may undergo renal clearance, whereas those around 30–100 nm tend to evade both renal excretion and MPS clearance, prolonging circulation time. However, achieving precise control over NP distribution remains challenging. (11)

### 8.2 Formulation and Manufacturing Challenges

#### 1.Scalability and Reproducibility Issues

Transitioning nanotechnology-based drug delivery systems from laboratory settings to large-scale industrial production poses considerable difficulties. Ensuring uniformity in particle size, surface properties, and drug loading across production batches is essential for maintaining reproducibility and therapeutic consistency. Even slight deviations in synthesis conditions can significantly impact the safety and efficacy of the final product. To overcome these obstacles, advanced manufacturing methods—including microfluidic systems and continuous processing technologies—are being investigated to enhance scalability and process control.(18)

**2. Stability During Storage and Transport Challenges**

Nanoparticle-based drug formulations often face stability issues, including aggregation, degradation, and loss of functional properties over time. Environmental factors such as temperature, humidity, and mechanical stress during transport can further compromise stability. Strategies like lyophilization, incorporation of stabilizing agents, and optimized storage conditions are critical to extending shelf life and ensuring therapeutic effectiveness upon administration.(4)

**3. High Production Costs and Complex Synthesis Methods**

The high cost of production remains a major barrier to the widespread adoption of nanotechnology in drug delivery. The complexity of nanoparticle synthesis, purification, and quality control contributes to increased manufacturing expenses. Additionally, regulatory challenges add to the cost burden, requiring extensive testing and compliance with stringent guidelines. Developing cost-effective, scalable, and simplified fabrication techniques while maintaining quality standards is essential to making these technologies more accessible.(4)

**8.3 Regulatory and Clinical Challenges**

**1.Stringent Approval Processes and Regulatory Guidelines**

Nanomedicines often encounter complex regulatory pathways due to their intricate structures and multifunctional characteristics. Regulatory bodies like the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) evaluate these products on a case-by-case basis, lacking standardized guidelines specific to nanotechnology-based therapeutics. This individualized assessment can lead to prolonged approval timelines and increased development costs. The absence of harmonized international standards further complicates the global approval process. (27)

**2. Limited Understanding of Long-Term Safety and Pharmacokinetics**

The long-term safety profiles and pharmacokinetic behaviors of nanomedicines are not yet fully elucidated. Nanoparticles may exhibit unique interactions within biological systems, leading to unforeseen toxicities or prolonged retention in organs such as the liver and spleen. Comprehensive, long-term studies are essential to assess potential cumulative effects and ensure patient safety. (28)

**3. Variability in Clinical Translation from Preclinical Studies**

Translating nanomedicines from preclinical models to clinical applications presents notable challenges. Discrepancies often arise due to differences in disease models, physiological variations between animal models and humans, and scaling complexities in manufacturing processes. Ensuring reproducibility and consistency in large-scale production while maintaining the therapeutic efficacy observed in preclinical studies remains a significant hurdle.(29)

## 9. Opportunities and Future Perspectives

Nanotechnology has significantly advanced parenteral drug delivery by enabling the development of sophisticated nanocarriers that enhance therapeutic efficacy and minimize side effects. These advancements encompass personalized nanomedicine, precision drug delivery, smart nanocarriers, surface engineering, integration with emerging technologies, and applications in gene therapy, cancer therapy, and infectious diseases.

**9.1 Personalized Nanomedicine and Precision Drug Delivery**

Nanomedicine facilitates personalized treatment by tailoring therapies to individual patient profiles. Nanocarriers can be engineered to deliver drugs specifically to targeted cells or tissues, improving therapeutic outcomes and reducing adverse effects. This approach allows for the customization of drug formulations based on a patient's genetic makeup, disease characteristics, and treatment responses.(4)

### 9.2 Development of Smart Nanocarriers

Smart nanocarriers are engineered to release drugs in a controlled and targeted manner by responding to specific stimuli. These stimuli can originate from within the body—such as pH changes, enzymatic activity, or redox imbalances—or be externally applied, including heat, light, or magnetic fields. For example, enzyme-sensitive nanocarriers can release therapeutic agents specifically in tumor environments where certain enzymes are overexpressed, thereby enhancing site-specific drug delivery. Moreover, theranostic nanocarriers integrate both therapeutic and diagnostic capabilities, enabling real-time tracking of treatment progress and response.[30])

### 9.3 Advances in Nanomaterials and Surface Engineering for Better Targeting

Surface engineering of nanocarriers enhances their targeting capabilities and biocompatibility. Functionalizing nanoparticle surfaces with ligands such as antibodies, peptides, or aptamers enables active targeting of specific cell receptors, facilitating precise drug delivery to diseased cells while sparing healthy tissues. Hybrid membranes, combining different cell membranes, have also been developed to create unique biological properties that improve targeting efficiency.[31]

### 9.4 Integration with Emerging Technologies

The integration of artificial intelligence (AI) and machine learning with nanotechnology is revolutionizing drug design and delivery. AI algorithms assist in optimizing nanoparticle design by predicting interactions with biological systems, enhancing drug encapsulation efficiency, and improving targeting accuracy. This synergy accelerates the development of intelligent nanoparticles capable of navigating complex biological environments and delivering therapeutics more effectively.[32]

## 10.Applications in Disease Areas

### 10.1 Cancer

Nanocarriers like liposomes (e.g., Doxil®) enhance chemotherapy by targeting tumors via the EPR effect, reducing systemic toxicity. Recent innovations include dual peptide-functionalized nanoparticles that cross the blood-brain barrier (BBB**)** to treat cancer cachexia, with potential for other neuro-oncology applications.[33]

### 10.2 Infectious Diseases

**Tuberculosis(TB):**
Nanocarriers (e.g., lipid-polymer hybrids) improve the delivery of drugs like isoniazid and rifampicin, enhancing lung targeting, drug stability, and patient compliance.[31]

**HIV:**
Nanoformulations using cell-penetrating peptides for siRNA or antiretroviral drugs show promise in protecting immune cells and suppressing viral replication.([33])

### 10.3 Neurological Disorders

Crossing the BBB remains a major hurdle. Functionalized polymeric nanoparticles and liposomes can deliver drugs or genes to the brain, targeting diseases like Alzheimer's, Parkinson's, and multiple sclerosis.[28]

### 10.4 Autoimmune/Inflammatory Diseases

Nanocarriers allow targeted delivery of immunosuppressants (e.g., methotrexate) and siRNA to inflamed tissues in diseases like rheumatoid arthritis, minimizing side effects and enhancing efficacy.[29]

**10.5 Gene Therapy (siRNA, mRNA)**Nanoparticles (lipid-based or polymeric) protect and deliver nucleic acids like siRNA/mRNA, overcoming barriers like enzymatic degradation and enabling gene silencing or protein expression. Applications include cancer, genetic disorders, and viral infections.[27]

### 11. Conclusion

Nanotechnology has revolutionized parenteral drug delivery, offering unprecedented opportunities for targeted, efficient, and personalized therapies. By harnessing the power of nanoscale engineering, we've overcome traditional barriers in drug administration, enhancing bioavailability, reducing toxicity, and improving patient outcomes. From smart nanocarriers that respond to specific stimuli to surface-engineered particles that navigate complex biological environments, the field continues to push the boundaries of what's possible in medicine. However, challenges remain. Immune system interactions, long-term safety concerns, and regulatory hurdles must be addressed to fully realize the potential of nanomedicine. The integration of artificial intelligence and advanced manufacturing techniques promises to accelerate progress, paving the way for more sophisticated and effective drug delivery systems. As we look to the future, the convergence of nanotechnology with personalized medicine, gene therapy, and cutting-edge diagnostic tools holds immense promise. From combating cancer to treating neurological disorders and infectious diseases, nanoparticle-based drug delivery stands at the forefront of medical innovation. While obstacles persist, the transformative potential of nanotechnology in healthcare is undeniable, offering hope for more effective treatments and improved quality of life for patients worldwide.

## Reference

[1]. Gulati N, Gupta H. Parenteral drug delivery: a review. Recent patents on drug delivery & formulation. 2011 May 1;5(2):133-45.

[2]. Lata S, Sharma G, Joshi M, Kanwar P, Mishra T. Role of nanotechnology in drug delivery. Int J Nanotechnol Nanosci. 2017;5:1-29.

[3]. Koo OM, Rubinstein I, Onyuksel H. Role of nanotechnology in targeted drug delivery and imaging: a concise review. Nanomedicine: nanotechnology, biology and medicine. 2005 Sep 1;1(3):193-212

[4]. Shetab Boushehri MA, Dietrich D, Lamprecht A. Nanotechnology as a platform for the development of injectable parenteral formulations: a comprehensive review of the know-hows and state of the art. Pharmaceutics. 2020 Jun 3;12(6):510.

[5]. Tyagi P, Subramony JA. Nanotherapeutics in oral and parenteral drug delivery: Key learnings and future outlooks as we think small. Journal of Controlled Release. 2018 Feb 28;272:159-68.

[6]. Muro S, editor. Drug delivery across physiological barriers. CRC press; 2016 Apr 27.

[7] .Hu M, Li X, You Z, Cai R, Chen C. Physiological barriers and strategies of lipid-based nanoparticles for nucleic acid drug delivery. Advanced Materials. 2024 May;36(22):2303266.

[8]. Sun W, Hu Q, Ji W, Wright G, Gu Z. Leveraging physiology for precision drug delivery. Physiological reviews. 2017 Jan;97(1):189-225.

[9]. Bhattacharjee H, Loveless V, Thoma LA. Parenteral drug administration: routes of administration and devices. InParenteral Medications, Fourth Edition 2019 Jul 19 (pp. 11-26). CRC Press.

[10]. Kesharwani P, Jain K, Jain NK. Dendrimer as nanocarrier for drug delivery. Progress in Polymer Science. 2014 Feb 1;39(2):268-307.

[11]. Weiner N, Martin F, Riaz M. Liposomes as a drug delivery system. Drug Development and Industrial Pharmacy. 1989 Jan 1;15(10):1523-54.

[12]. Joshi MD, Müller RH. Lipid nanoparticles for parenteral delivery of actives. European journal of pharmaceutics and biopharmaceutics. 2009 Feb 1;71(2):161-72.

[13]. Chen S, Hao X, Liang X, Zhang Q, Zhang C, Zhou G, Shen S, Jia G, Zhang J. Inorganic nanomaterials as carriers for drug delivery. Journal of biomedical nanotechnology. 2016 Jan 1;12(1):1-27.

[14]. Batrakova EV, Kim MS. Using exosomes, naturally-equipped nanocarriers, for drug delivery. Journal of Controlled Release. 2015 Dec 10;219:396-405.

[15]. Chan JM, Valencia PM, Zhang L, Langer R, Farokhzad OC. Polymeric nanoparticles for drug delivery. Cancer nanotechnology: Methods and protocols. 2010:163-75.

[16]. Clemons TD, Singh R, Sorolla A, Chaudhari N, Hubbard A, Iyer KS. Distinction between active and passive targeting of nanoparticles dictate their overall therapeutic efficacy. Langmuir. 2018 Nov 15;34(50):15343-9.

[17]. Anarjan FS. Active targeting drug delivery nanocarriers: Ligands. Nano-Structures & Nano-Objects. 2019 Jul 1;19:100370.

[18]. Kamaly N, Yameen B, Wu J, Farokhzad OC. Degradable controlled-release polymers and polymeric nanoparticles: mechanisms of controlling drug release. Chemical reviews. 2016 Feb 24;116(4):2602-63.

[19]. Paliwal R, Babu RJ, Palakurthi S. Nanomedicine scale-up technologies: feasibilities and challenges. Aaps Pharmscitech. 2014 Dec;15(6):1527-34.

[20]. Hamidi M, Azadi A, Rafiei P, Ashrafi H. A pharmacokinetic overview of nanotechnology-based drug delivery systems: an ADME-oriented approach. Critical Reviews™ in Therapeutic Drug Carrier Systems. 2013;30(5).

[21]. Jain K, Kumar Mehra N, K Jain N. Nanotechnology in drug delivery: safety and toxicity issues. Current pharmaceutical design. 2015 Sep 1;21(29):4252-61.

[22]. Guo S, Shi Y, Liang Y, Liu L, Sun K, Li Y. Relationship and improvement strategies between drug nanocarrier characteristics and hemocompatibility: what can we learn from the literature. Asian journal of pharmaceutical sciences. 2021 Sep 1;16(5):551-76.

[23]. Patel P, Shah J. Safety and toxicological considerations of nanomedicines: the future directions. Current Clinical Pharmacology. 2017 May 1;12(2):73-82.

[24]. Patra JK, Das G, Fraceto LF, Campos EV, Rodriguez-Torres MD, Acosta-Torres LS, Diaz-Torres LA, Grillo R, Swamy MK, Sharma S, Habtemariam S. Nano based drug delivery systems: recent developments and future prospects. Journal of nanobiotechnology. 2018 Dec;16:1-33.

[25]. Arafat M, Sakkal M, Beiram R, AbuRuz S. Nanomedicines: Emerging platforms in smart chemotherapy treatment—a recent review. Pharmaceuticals. 2024 Feb 28;17(3):315.

[26]. Dobrovolskaia MA. Lessons learned from immunological characterization of nanomaterials at the Nanotechnology Characterization Laboratory. Frontiers in Immunology. 2022 Oct 10;13:984252.

[27]. Dobrovolskaia MA. Pre-clinical immunotoxicity studies of nanotechnology-formulated drugs: Challenges, considerations and strategy. Journal of Controlled Release. 2015 Dec 28;220:571-83.

[28]. Desai N. Challenges in development of nanoparticle-based therapeutics. The AAPS journal. 2012 Jun;14(2):282-95.

[29]. Min Y, Caster JM, Eblan MJ, Wang AZ. Clinical translation of nanomedicine. Chemical reviews. 2015 Oct 14;115(19):11147-90.

[30]. .Đorđević S, Gonzalez MM, Conejos-Sánchez I, Carreira B, Pozzi S, Acúrcio RC, Satchi-Fainaro R, Florindo HF, Vicent MJ. Current hurdles to the translation of nanomedicines from bench to the clinic. Drug delivery and translational research. 2022 Mar:1-26.

[31]. Younis MA, Tawfeek HM, Abdellatif AA, Abdel-Aleem JA, Harashima H. Clinical translation of nanomedicines: Challenges, opportunities, and keys. Advanced drug delivery reviews. 2022 Feb 1;181:114083.

[32]. Bhange M, Telange D. Convergence of nanotechnology and artificial intelligence in the fight against liver cancer: a comprehensive review. Discover Oncology. 2025 Dec;16(1):1-20.

[33[. Huang Y, Guo X, Wu Y, Chen X, Feng L, Xie N, Shen G. Nanotechnology's frontier in combatting infectious and inflammatory diseases: prevention and treatment. Signal Transduction and Targeted Therapy. 2024 Feb 21;9(1):34.