Journal of Pharmaceutical Research and Integrated Medical Sciences (JPRIMS)
ISSN: 3049-1681 | Vol. 03, Issue-07, July-2026 | pp.-51-78

ORIGINALARTICLE https://jprims.in/

Nanocarrier-Based Drug Delivery Systems: Advances in Design, Targeting Strategies, and Clinical Translation

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Abstract:

Poor aqueous solubility is a major limitation in pharmaceutical development, affecting nearly 40% of approved drugs and up to 90% of drug candidates in the discovery pipeline. Low solubility directly compromises oral bioavailability, therapeutic effectiveness, dose proportionality, and clinical reproducibility, particularly for drugs classified under Biopharmaceutical Classification System (BCS) Classes II and IV. To address these challenges, formulation science has advanced significantly over the past two decades. This review critically evaluates recent progress from 2022 to 2025 in three major technological approaches: solid dispersions, lipid-based formulations, and nanotechnology-enabled drug delivery systems. Emphasis is placed on mechanistic principles governing solubility enhancement, formulation design strategies, in vivo performance outcomes, and translational considerations. Emerging hybrid platforms that integrate polymers, lipids, and nanocarriers are also discussed, as they demonstrate synergistic improvements in dissolution rate, permeability, and systemic exposure, often achieving 3–7 fold enhancement in oral bioavailability. In addition, the evolving regulatory landscape for complex and nanotechnology-based formulations is examined, highlighting current expectations for characterization, stability, and safety evaluation. Overall, this review provides an updated and integrated perspective on formulation strategies for poorly soluble drugs, offering practical insights for both academic research and industrial development.

Keywords

Poor aqueous solubility; Oral bioavailability; Solid dispersions; Lipid-based drug delivery; Nanotechnology; BCS Class II and IV drugs; Hybrid formulations; Regulatory considerations

Received: March. 28, 2026 **Revised: April 30, 2026** **Accepted: June 27, 2026** **Published: July 09, 2026**

DOI: https://doi.org/10.64063/3049-1681.vol3.issue7.000283

1. Introduction

Significant progress in medicine and pharmaceuticals relies on the ability to deliver drugs effectively to specific targets within the body. Although many medications possess substantial therapeutic potential, conventional delivery methods such as tablets, capsules, injections, and syrups often lack the precision required for optimal absorption and distribution [1-2]. Consequently, only a limited proportion of the administered drug reaches the intended site,

diminishing therapeutic efficacy and increasing the risk of side effects and toxicity in non-target tissues. For example, demonstrated that doxorubicin-loaded lipid-polymer hybrid nanoparticles enhanced tumour targeting and reduced systemic toxicity in breast cancer models, illustrating the superior precision of nanocarrier-based approaches compared to traditional formulations. The demand for precise drug delivery underscores the potential of nanocarriers as a transformative solution to improve treatment administration and patient outcomes [3-4].

Conventional drug delivery systems also lack control over drug release, often resulting in rapid increases in blood drug concentration. This can lead to toxicity in about 30% of patients undergoing chemotherapy due to high systemic exposure. To maintain effective concentrations, frequent dosing is required, often every 4 to 6 hours, as seen with certain antibiotics, which decreases patient comfort and adherence. Biological barriers, such as enzymatic degradation, limited membrane permeability, rapid metabolism, and immune clearance, further limit the amount of drug that reaches the target site. These issues highlight the need for improved approaches that protect drugs, enhance targeting, and allow controlled and sustained release [5-6].

Nanocarrier-based drug delivery systems offer a promising solution to these challenges. Nanocarriers, microscopic materials in the nanometer size range, can encapsulate or bind drugs, protecting them from degradation and preserving their activity. Studies such as those by Wang et al. (2023) have shown that nanocarriers not only protect drug molecules but also enhance their interactions with biological systems. Their small size and large surface area improve tissue penetration and prolong circulation time, increasing the chance of effective drug accumulation at target tissues [7-8].

Surface modification improves nanocarrier performance by facilitating site-specific drug delivery. The attachment of targeting molecules enables nanocarriers to recognise diseased cells and concentrate the drug at the affected site, thereby minimising exposure to healthy tissues. Additionally, nanocarriers can be engineered to release drugs in response to specific biological cues, such as pH or enzyme concentrations, offering enhanced control over drug delivery [9]. Figure 1

Nanocarrier-based drug delivery systems have become integral to the treatment of complex diseases in contemporary medicine. These systems enhance drug stability, targeting specificity, side effect profiles, and patient adherence, representing substantial progress in pharmaceutical research. This review examines the fundamental principles of nanocarrier systems, their design considerations, targeting strategies, clinical translation, and expanding significance in medical practice. By elucidating how nanocarriers address the limitations of conventional methods and improve therapeutic outcomes, this review underscores the necessity for advanced delivery systems and highlights their critical role in modern healthcare [10].

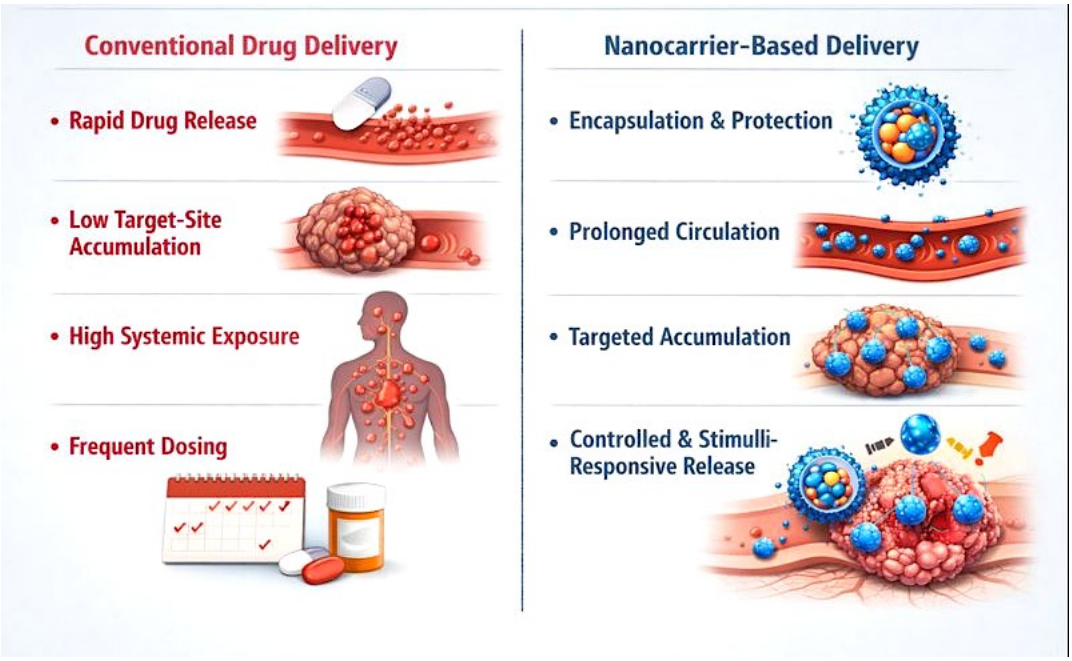

Figure 1. Limitations of Conventional Drug Delivery vs Advantages of Nanocarrier-Based Systems

2. Basics of Nanocarrier Drug Delivery

To understand how these improvements are achieved, it is essential to examine the basics of nanocarrier drug delivery systems. These systems represent a significant advancement in pharmaceutical science and medicine. They use minimal materials, known as nanocarriers, to transport drugs inside the body in a controlled and efficient manner. Nanocarriers are generally defined as particles with sizes ranging from about 1 to 1000 nanometers. At this tiny size, materials behave differently from larger particles. These differences allow nanocarriers to interact more effectively with biological systems, making them suitable for improving drug delivery.

The main goal of nanocarrier drug delivery is to enhance drug efficacy while reducing unwanted side effects. Many drugs that perform well in laboratory testing do not perform as well clinically because they cannot reach the target tissue in sufficient amounts or are broken down too quickly in the body. Nanocarriers act as protective vehicles that deliver drug molecules through the bloodstream and release them at the intended site. This helps overcome many limitations of traditional drug delivery systems [11-12.]

A key advantage of nanocarriers is their ability to improve drug stability. Many drugs are sensitive to heat, light, enzymes, or acidic conditions and may lose activity before reaching the target site. When loaded into nanocarriers, drugs are shielded from these harsh environments. This protection helps maintain drug activity longer and increases the chance the drug will reach diseased tissue in its active form.

Nanocarriers also improve drug absorption. Poor absorption is a problem for many drugs, especially those with low water solubility. Nanocarriers can increase the solubility of these drugs and enhance their absorption across biological membranes. As a result, more drug enters the bloodstream and becomes available for therapeutic action. Improved absorption can reduce the required dose and lower the risk of side effects [13-14].

2.1 Size, Shape, and Surface Characteristics of Nanocarriers

Nanocarrier size strongly impacts their behaviour in the body, affecting circulation duration, tissue penetration, and cellular uptake. Smaller nanocarriers can pass through narrow blood vessels and biological barriers more easily, but may be cleared by the kidneys more quickly. Larger nanocarriers circulate longer but have more difficulty penetrating tissues. Selecting the optimal size requires balancing circulation time and tissue interaction for each application.

Nanocarrier size also affects immune system clearance. Particles that are too large are more likely to be recognised and cleared by immune cells, such as macrophages. Proper size control helps nanocarriers stay in circulation long enough to reach the target site. A longer circulation time increases the risk of drug accumulation in diseased tissues, especially in cancer and inflammation [15-16].

Nanocarrier shape also affects their interaction with biological systems. Spherical nanocarriers are most commonly used because they are easier to prepare and generally stable. They interact predictably with cells and tissues. Non-spherical shapes, such as rods, discs, and elongated particles, have attracted attention for their distinct circulation and cell-uptake patterns. For example, rod-shaped particles may attach to cell surfaces more effectively in some cases. The choice of shape depends on the drug-delivery goal and the disease.

Surface characteristics of nanocarriers are also important. Surface charge affects interactions with blood components and cell membranes. Positively charged nanocarriers may interact strongly with negatively charged cell membranes, enhancing cell uptake but also increasing toxicity and immune response. Neutral or slightly negative surfaces are often preferred to reduce unwanted interactions and prolong circulation time [17-18].

Surface composition and chemical groups influence protein binding and immune recognition. When nanocarriers enter the bloodstream, proteins may bind to their surfaces, forming a layer that can lead to rapid clearance by immune cells. Surface modification techniques, such as coating with suitable materials, help reduce protein binding, improve stability, and increase circulation time [19].

2.3 Surface Modification and Functionalisation

Surface modification is a key strategy for improving nanocarrier performance. By modifying the surface, researchers can control how nanocarriers interact with biological systems. One common approach is to coat nanocarriers with polymers to create a protective layer. This layer reduces immune recognition and prolongs nanocarrier circulation in the blood.

Another essential surface modification approach is the attachment of targeting molecules. These molecules allow nanocarriers to recognise and bind to specific cells or tissues, enhancing the precision of drug delivery. Targeting improves drug concentration at the disease site and reduces exposure to healthy tissues. An example is ligands, such as folic acid. By targeting receptors on specific cancer cells, folic acid can direct the nanocarrier to the disease site more effectively. Surface modification can also improve stability during storage and prevent particle aggregation [20-21].

In addition to targeting, surface modification can be used to control drug release. Certain surface materials respond to biological conditions such as pH or enzyme levels. When nanocarriers reach the target site, changes in the local environment trigger drug release. This approach improves treatment accuracy and reduces side effects.

2.4 Drug Loading and Drug Transport Mechanisms

Nanocarriers can load and deliver drugs via different mechanisms, depending on their structure and composition. One standard method is drug encapsulation, in which the drug is entrapped within the nanocarrier's core. Encapsulation protects the drug from degradation and prevents early release. This method is beneficial for sensitive drugs that degrade easily in biological fluids [22].

Another approach is embedding the drug within the nanocarrier matrix. Here, the drug is distributed throughout the carrier material. As the carrier slowly breaks down or allows diffusion, the drug is released over time. This method supports sustained drug release and helps maintain stable drug levels in the body [23].

Drugs can also be attached to nanocarrier surfaces via physical or chemical interactions. Surface attachment allows faster drug release and is useful when rapid action is needed. Chemical attachment can provide stronger binding and more controlled release. The choice of drug loading method depends on drug properties such as solubility, stability, and required release profile [24].

Nanocarriers are highly versatile and can deliver a wide range of therapeutic agents. These include small drug molecules, proteins, peptides, and genetic materials such as DNA and RNA. This flexibility makes nanocarriers suitable for treating various diseases and supporting advanced therapies.

2.5 Drug Release Control

Controlled drug release is one of the most essential advantages of nanocarrier-based drug delivery systems. Traditional drug delivery often results in rapid drug release, leading to fluctuating drug levels in the body. Nanocarriers allow drugs to be released slowly over time, maintaining effective drug concentration for more extended periods.

Drug release from nanocarriers can occur through several mechanisms. Diffusion-based release involves the gradual release of drug molecules from the nanocarrier. Degradation-based release occurs when the carrier material breaks down in the body, releasing the drug. Many nanocarriers use a combination of these mechanisms [25-26].

Advanced nanocarriers are designed to respond to specific biological signals. For example, some nanocarriers release drugs in response to acidic environments, which are common in diseased tissues. Others respond to enzymes that are present at higher levels in certain conditions. Temperature-sensitive systems release drugs when heated. These trigger-based systems provide better control and improve treatment precision.

2.6 Advantages of Nanocarrier Drug Delivery Systems

Nanocarrier drug delivery systems offer several significant advantages over traditional delivery methods. They improve drug stability, enhance absorption, and allow targeted delivery. By concentrating drugs at the disease site, nanocarriers reduce damage to healthy tissues and lower the risk of side effects. Figure 2

Nanocarriers also enable reduced dosing frequency through controlled drug release, which enhances patient comfort and treatment adherence. Studies indicate that patients receiving sustained-release nanocarrier formulations demonstrate higher adherence compared to those on conventional dosing schedules. The versatility of nanocarriers in delivering various drugs makes them applicable to a broad spectrum of medical conditions. Furthermore, nanocarriers facilitate the development of advanced therapies, including combination treatments and personalised

medicine. By tailoring nanocarrier design, therapies can be customised to address specific disease conditions and individual patient requirements [27-28].

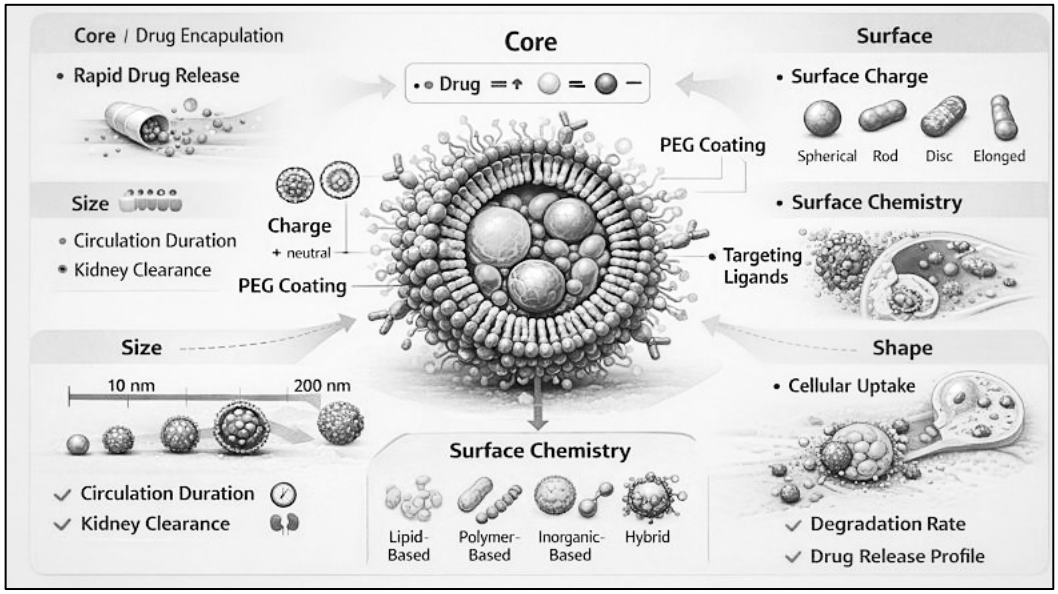

Figure 2. Fundamental Components and Design Parameters of Nanocarriers

2.7 Importance in Modern Drug Delivery Research

Nanocarrier-based drug delivery systems have become a primary focus of modern pharmaceutical research. Their ability to address key challenges in drug delivery has led to rapid growth in this field. Ongoing research aims to improve safety, increase effectiveness, and support clinical translation.

Understanding the basic principles of nanocarrier drug delivery is essential for designing better systems and improving treatment outcomes. As research continues, nanocarriers are expected to play an increasingly important role in the future of medicine [29-30].

3. Types of Nanocarriers

Nanocarriers are classified primarily by the materials used in their preparation. The choice of material is critical because it directly affects drug loading capacity, release behaviour, stability, safety, circulation time, and overall clinical usefulness. Different materials interact with drugs and biological systems in other ways, which determines how effective a nanocarrier system will be. Among the various nanocarriers developed to date, lipid-, polymer-, inorganic-, and hybrid-based nanocarriers are the most widely studied and applied in drug delivery research.

Each type of nanocarrier has its own advantages and limitations. Some systems offer high biocompatibility and safety, while others provide better stability or additional functions such as imaging or heat response. Understanding the basic features of each nanocarrier type helps in selecting the most suitable system for a specific drug and disease condition [31-32].

3.1 Lipid-Based Nanocarriers

Lipid-based nanocarriers are among the most well-established and clinically accepted drug delivery systems. They are prepared using natural or synthetic lipids that closely resemble the structure of biological cell membranes. Due to this similarity, lipid-based nanocarriers show excellent biocompatibility and low toxicity. Their ability to interact easily with cell membranes makes them highly effective in drug delivery applications.

Common types of lipid-based nanocarriers include liposomes, solid lipid nanoparticles, and nanostructured lipid carriers. Liposomes consist of one or more lipid layers surrounding an aqueous core. This structure allows them to carry both water-soluble and poorly water-soluble drugs. Hydrophilic drugs can be trapped inside the aqueous core, while hydrophobic drugs can be embedded within the lipid layer. This dual loading capacity makes liposomes highly versatile [33-34].

Solid lipid nanoparticles and nanostructured lipid carriers are newer lipid-based systems designed to improve stability and drug loading. In these systems, drugs are incorporated into a solid or semi-solid lipid matrix. This structure protects drugs from degradation and enables controlled, sustained release. Compared to liposomes, solid lipid-based systems often show better physical stability during storage.

Lipid-based nanocarriers are particularly useful for delivering drugs with poor water solubility. Many essential drugs fail in clinical use because they cannot dissolve properly in body fluids. Lipid-based systems improve solubility and absorption, thereby enhancing bioavailability. These nanocarriers also protect drugs from enzymatic degradation and reduce drug loss during circulation.

Another essential advantage of lipid-based nanocarriers is their reduced toxicity compared to many conventional delivery systems. Since lipids are naturally present in the body, these substances are generally well-tolerated. Their ability to fuse with cell membranes further enhances drug uptake by target cells. Because of these properties, lipid-based nanocarriers are widely used in cancer therapy, vaccine delivery, gene delivery, and the treatment of infectious diseases. Several lipid-based formulations have already been approved for clinical use, demonstrating their strong potential for real-world applications [35-36].

Figure 3. Classification of Nanocarrier Types with Key Features

3.2 Polymer-Based Nanocarriers

Polymer-based nanocarriers represent another primary class of drug delivery systems and offer great flexibility in design and function. These nanocarriers are made from natural polymers such as chitosan, alginate, gelatin, and starch, or synthetic polymers such as PLGA, PEG, and polycaprolactone. The wide variety of available polymers enables researchers to design nanocarriers with specific properties tailored to different drugs and diseases [37-38].

One of the most essential advantages of polymer-based nanocarriers is their ability to provide precise control over particle size, drug loading, and drug release rate. By adjusting polymer composition and structure, nanocarriers can be designed to release drugs over hours, days, or even weeks. For example, PLGA (poly(lactic-co-glycolic acid)) depots release drugs continuously over a 4-week period, demonstrating their controlled-release properties. This controlled-release behaviour is beneficial for chronic diseases that require long-term treatment.

Common polymer-based nanocarriers include polymeric nanoparticles, polymeric micelles, and dendrimers. Polymeric nanoparticles are solid particles in which the drug is either embedded in the polymer matrix or attached to the surface. Polymeric micelles formed by self-assembly of amphiphilic polymers are particularly effective for delivering poorly water-soluble drugs. Dendrimers are highly branched polymers with a well-defined structure, offering multiple attachment sites for drugs [39-40].

Biodegradability is a key advantage of polymer-based nanocarriers. Many polymers used in these systems break down into non-toxic by-products that are safely eliminated from the body. This property reduces the risk of long-term accumulation and toxicity. Biodegradable polymer-based systems are therefore preferred for repeated or long-term drug administration.

Polymer-based nanocarriers are highly versatile and can deliver a wide range of therapeutic agents. These include small drug molecules, proteins, peptides, and genetic materials such as DNA and RNA. Their surfaces can be easily modified with targeting molecules, thereby improving site-specific delivery and reducing damage to healthy tissues. Due to these advantages, polymer-based nanocarriers are widely studied for cancer treatment, gene therapy, vaccine delivery, and treatment of inflammatory and infectious diseases [41-42].

3.3 Inorganic Nanocarriers

Inorganic nanocarriers are prepared from mineral- or metallic-based materials, such as gold, silica, iron oxide, calcium phosphate, and quantum dots. These nanocarriers are known for their strong structural stability and unique physical properties. Unlike lipid and polymer systems, inorganic nanocarriers often provide additional functions beyond drug delivery.

One significant advantage of inorganic nanocarriers is their ability to support combined therapeutic and diagnostic applications. Many inorganic materials exhibit optical, magnetic, or imaging properties that enable tracking and visualisation within the body. For example, iron oxide nanoparticles are widely used in imaging and can also be guided using magnetic fields for targeted drug delivery. Gold nanoparticles are explored for controlled drug release and heat-based therapies, in which heat is applied to trigger drug release or damage diseased cells [43-44].

Despite these promising applications, clinical translation of inorganic nanocarriers remains limited, with few examples achieving FDA approval. This limited progress primarily reflects persistent regulatory and safety challenges, such as concerns over long-term toxicity and the absence of standardised testing protocols. Furthermore, complex product classification issues can arise, as inorganic nanocarriers may overlap with categories for drugs, devices, or combination products. The resulting lack of harmonised guidelines and fragmented regulatory requirements across regions further complicates approval. Addressing these obstacles will require streamlined regulatory pathways and standardised assessment protocols to ensure the safety, quality, and efficacy of inorganic nanocarriers [45-46].

Silica-based nanocarriers are another important inorganic system. They offer high surface area and pore volume, allowing high drug loading. Drugs can be stored inside pores and released slowly over time. Calcium phosphate nanocarriers are especially useful for bone-related applications due to their similarity to natural bone minerals.

Despite these advantages, inorganic nanocarriers face significant safety challenges. Many inorganic materials are not biodegradable and may accumulate in organs such as the liver and spleen. Long-term accumulation raises concerns about chronic toxicity and delayed side effects. In addition, clearance of inorganic nanocarriers from the body is often slow, which limits their widespread clinical use.

Because of these concerns, careful safety evaluation is required before inorganic nanocarriers can be used in humans. Research effort focused on improving their biocompatibility, reducing toxicity, and developing biodegradable inorganic systems. While their clinical use is currently

limited, inorganic nanocarriers remain valuable tools in research and specialised medical applications [47-48].

3.4 Hybrid Nanocarriers

Hybrid nanocarriers are advanced drug delivery systems that combine two or more materials into a single structure. These materials often include combinations of lipids, polymers, and inorganic components. The main goal of hybrid nanocarriers is to integrate the advantages of each material while minimising their individual limitations.

For example, a hybrid system may combine the biocompatibility of lipids with the stability and controlled release properties of polymers. In other cases, inorganic materials are added to provide imaging or heat-response capabilities. By carefully designing hybrid systems, researchers can achieve improved drug loading, greater stability, precise control over drug release, and enhanced targeting [49-50].

Hybrid nanocarriers are particularly useful for complex treatments that require multiple functions. These systems can be designed to deliver drugs while also allowing imaging or monitoring of treatment progress. Some hybrid nanocarriers can carry various medicines, enabling combination therapy. It is essential for diseases such as cancer, where multiple drugs are often needed to improve treatment outcomes and reduce resistance.

Another significant advantage of hybrid nanocarriers is their flexibility. The composition and structure of these systems can be adjusted according to specific treatment requirements. Surface modification further enhances targeting capabilities and circulation time. Owing to their multifunctional properties, hybrid nanocarriers are garnering considerable interest in advanced therapies and personalised medicine [51-52].

Although hybrid systems offer many benefits, they also present challenges. Their complex structure can make large-scale production difficult. Quality control and reproducibility are critical issues that must be addressed before clinical use. Despite these challenges, hybrid nanocarriers represent a promising direction for future drug delivery research.

3.4 Comparative Importance of Different Nanocarrier Types

Each type of nanocarrier plays a vital role in drug delivery research. Lipid-based systems are widely used due to their safety and clinical success. Polymer-based systems offer high design flexibility and controlled release. Inorganic nanocarriers provide unique physical functions, while hybrid systems combine multiple advantages into a single platform.

The choice of nanocarrier depends on several factors, including the nature of the drug, the disease type, the route of administration, and the required release behaviour. No single nanocarrier system is ideal for all applications. Instead, careful selection and design are needed to match the nanocarrier system with therapeutic goals [53-54].

4. Design of Nanocarriers

The design of nanocarriers is a critical step in developing effective nanocarrier-based drug delivery systems. An optimally designed nanocarrier maintains drug stability during circulation, achieves sufficient concentration at the target site, and enables controlled release over a specified period. Inadequate design may result in premature drug loss, reduced targeting efficiency, instability, or increased toxicity. Consequently, comprehensive planning and evaluation of multiple design parameters are vital for therapeutic success. A reflective checklist encompassing

key criteria such as biocompatibility, degradability, and scalability can facilitate this process. Major criteria include:

1. Biocompatibility, as it ensures that the nanocarrier does not evoke adverse body reactions.
2. Degradability, focusing on how the nanocarrier can safely decompose into non-toxic by-products.
3. Scalability, highlighting the ease of transitioning the nanocarrier system from lab-scale production to large-scale manufacturing while maintaining consistent quality and performance.

This checklist can serve as a practical decision-making framework, inviting researchers to score and evaluate the prospective materials based on these critical factors, thereby turning theoretical considerations into actionable design insights.

Several aspects must be considered during nanocarrier design, including material selection, drug-loading strategy, drug-release behaviour, and the stability and safety profile. Each of these factors is closely connected and together determines how the nanocarrier performs in biological systems. A balance between effectiveness and safety is required to ensure clinical usefulness [55].

4.1 Material Selection

Material selection is the foundation of nanocarrier design and strongly influences the system's other properties. The chosen material must be biocompatible, meaning it should not cause harmful reactions when introduced into the body. Biodegradable materials are preferred whenever possible because they can break down into by-products and be cleared from the body, reducing the risk of long-term accumulation and toxicity [56].

The nature of the drug plays a significant role in deciding which material is most suitable. Drugs with poor water solubility are often loaded into lipid-based nanocarriers because lipids can easily dissolve and protect hydrophobic drugs. Lipid materials also interact well with cell membranes, thereby improving drug uptake. Polymeric materials are commonly selected when long-term and controlled drug release is required. Polymers allow precise control over degradation rate, particle size, and drug release profile. Inorganic materials are sometimes used when high structural strength or additional functions, such as imaging or heat response, are needed [57].

In addition to drug compatibility, the selected material should support surface modification. Surface modification helps improve blood circulation time, reduce recognition by the immune system, and enable targeting to specific tissues or cells. Materials that allow easy chemical modification are therefore highly valuable for nanocarrier design.

4.2 Drug Loading Methods

Drug loading is the process by which the therapeutic agent is incorporated into the nanocarrier system. The drug-loading method strongly influences drug stability, loading efficiency, release behaviour, and overall treatment effectiveness. An ideal loading method should protect the drug, prevent early release, and maintain drug activity.

Drugs can be loaded into nanocarriers using several approaches. Physical entrapment is one of the most common methods, in which the drug is entrapped within the core or matrix of the nanocarrier during its formation. This approach is beneficial for protecting sensitive drugs from enzymatic breakdown and harsh biological conditions. Chemical attachment involves binding the drug to the carrier via chemical bonds, enabling strong attachment and controlled release. Adsorption onto the carrier surface is another method, often used when faster drug release is required [58.]

The choice of drug-loading method depends on drug properties, such as solubility, molecular size, and stability. High drug loading efficiency is essential because it reduces the amount of carrier material required and ensures that a sufficient dose reaches the target site. Poor loading efficiency can lead to higher costs and an increased risk of side effects from excess carrier material [59].

4.3 Drug Release Control

Controlled drug release is a key advantage of nanocarrier-based drug delivery systems. Traditional drug delivery methods often release drugs rapidly after administration, leading to sudden peaks in drug concentration followed by rapid decline. Nanocarriers are designed to release drugs slowly and in a controlled manner, maintaining stable drug levels in the body for extended periods. This controlled release can align with specific dosing schedules, such as enabling once-monthly injections, which significantly enhances patient adherence and convenience. By linking release kinetics directly to real-world dosing intervals, nanocarrier systems offer practical benefits for patients, potentially reducing the frequency of drug administration and improving overall treatment outcomes [60].

Drug release from nanocarriers can occur through diffusion, carrier material degradation, or a combination of both. Diffusion-based release involves the gradual movement of drug molecules from the nanocarrier into the surrounding environment. Degradation-based release occurs when the carrier material breaks down over time, releasing the drug. By controlling material properties, researchers can adjust the release rate to match therapeutic needs.

Advanced nanocarriers are often designed to respond to specific biological conditions present at the disease site. For example, some nanocarriers release drugs in acidic environments, which are common in tumours and infected tissues. Others respond to enzymes that are present at higher levels in diseased areas. Temperature-sensitive systems release drugs when exposed to increased temperature. These responsive systems help ensure that drugs are released mainly at the target site, reducing damage to healthy tissues [61].

Controlled drug release reduces dosing frequency, improves patient comfort, and lowers the risk of toxic side effects caused by sudden drug release.

4.4 Stability and Safety Considerations

Stability and safety are essential for the successful clinical use of nanocarriers. Nanocarriers must remain physically and chemically stable during storage, transportation, and after administration. Instability can lead to particle aggregation, drug leakage, changes in size, or loss of therapeutic effectiveness. Factors such as particle size, surface charge, formulation method, and storage conditions strongly affect stability.

Safety evaluation is equally essential and includes assessing short-term toxicity, long-term effects, immune system response, and potential organ accumulation. Nanocarriers may interact with blood components or immune cells, leading to inflammation or rapid clearance. Using biocompatible and biodegradable materials helps reduce these risks [62].

The use of non-toxic solvents, mild preparation techniques, and well-controlled formulation processes further improves safety. A careful balance between stability, controlled drug release, and biodegradability is necessary. Highly stable systems may persist in the body for too long, while highly biodegradable systems may release drugs too quickly. Optimising this balance is a key challenge in nanocarrier design.

5. Targeting Strategies

Targeting strategies are a key feature of nanocarrier-based drug delivery systems. The main goal of targeting is to deliver the drug mainly to the diseased site while reducing exposure to healthy tissues. These improve treatment effectiveness and lower side effects. Targeting strategies are generally divided into passive, active, and stimulus-based targeting. Each approach works differently and is selected based on the disease condition and treatment needs.

Passive targeting relies on the natural differences between healthy tissues and diseased tissues. This approach does not require any special targeting molecules on the nanocarrier surface. Instead, it takes advantage of the abnormal blood vessel structure and poor lymphatic drainage often found in diseased tissues, such as tumours and inflamed areas. Under these conditions, nanocarriers tend to accumulate more in diseased tissue than in normal tissue. Passive targeting is mainly influenced by nanocarrier size, shape, and surface properties. Properly designed nanocarriers can circulate in the bloodstream for extended periods, increasing the chance of reaching and accumulating at the target site. Passive targeting is simple and widely used, especially in cancer therapy, but it offers limited control over exact cell-level targeting [63-64].

Active targeting involves modifying the surface of nanocarriers with specific molecules that can bind directly to receptors present on target cells. These molecules may include ligands, antibodies, peptides, or sugars. Active targeting improves the selectivity of drug delivery by allowing nanocarriers to recognise and bind to specific cells. Once attached to the target cell, the nanocarrier is taken up by cellular processes, resulting in higher drug concentration within the diseased cells. This approach reduces drug loss and minimises damage to healthy tissues. Active targeting is beneficial for diseases where specific receptors are overexpressed, such as cancer and certain infections. However, careful design is required to maintain stability and avoid immune reactions [65-66].

Stimuli-based targeting is an advanced strategy that allows drug release in response to specific internal or external conditions. These systems are designed to remain stable during circulation and release the drug only when they encounter a particular stimulus at the target site. Stimuli-based targeting provides high control over drug release and improves treatment precision.

pH-sensitive systems are designed to respond to changes in acidity. Many diseased tissues, such as tumours and infected areas, have a slightly acidic environment compared to normal tissues. pH-sensitive nanocarriers remain stable at normal body pH but release the drug when exposed to acidic conditions. This helps ensure that the drug is released primarily at the disease site rather than during circulation.

Temperature-sensitive systems respond to changes in temperature. These nanocarriers are designed to release drugs when the temperature rises above normal body temperature. This strategy is often used in combination with localised heating techniques. When heat is applied to the target area, the nanocarrier structure changes, leading to controlled drug release. Temperature-sensitive systems offer precise control but require careful temperature management to avoid tissue damage [67-68]. Figure 4

Enzyme-sensitive systems are designed to release drugs in the presence of specific enzymes that are overexpressed in diseased tissues. Certain enzymes are found in higher amounts in cancer, inflammation, and infections. Enzyme-sensitive nanocarriers use materials that break

down in response to these enzymes, triggering drug release only at the target site. This approach provides high selectivity and reduces unwanted drug release in healthy tissues.

Overall, targeting strategies greatly enhance the effectiveness of nanocarrier-based drug delivery systems by improving drug concentration at the disease site, reducing side effects, and supporting more precise and controlled treatment outcomes [69].

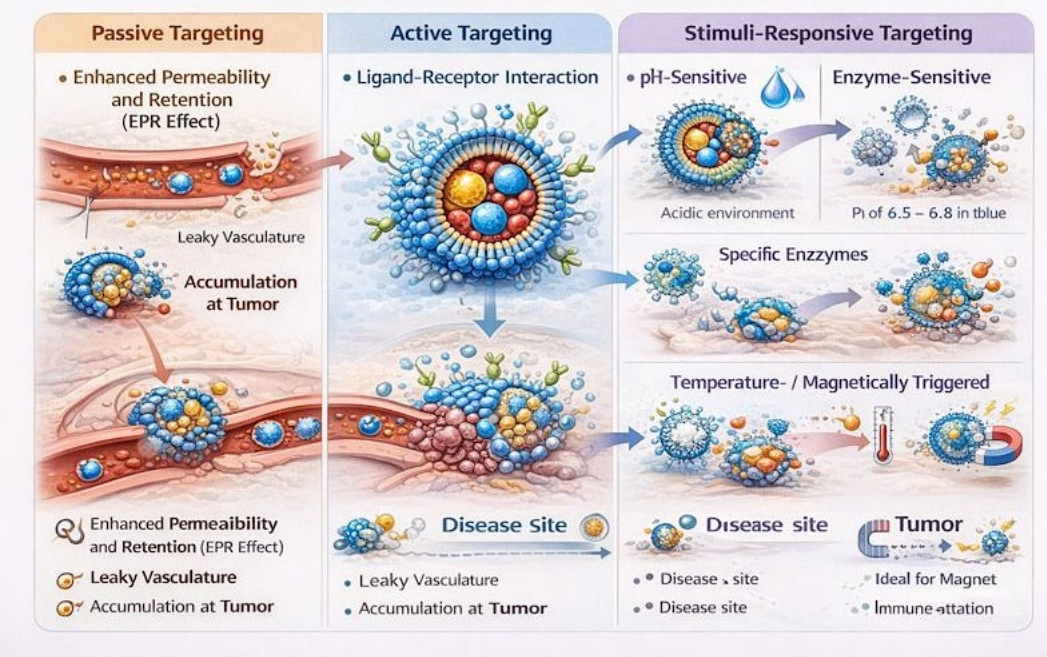

Figure 4. Targeting Strategies in Nanocarrier Drug Delivery

6. Interaction with Biological Systems

Once nanocarriers are administered into the body, they immediately begin to interact with various biological systems. These interactions strongly influence how long the nanocarriers remain in circulation, how efficiently they enter target cells, how they distribute across tissues, and how they are finally removed from the body. Understanding these interactions is essential for designing safe and effective nanocarrier-based drug delivery systems.

Blood circulation behaviour determines how long nanocarriers stay in the bloodstream and how effectively they can reach the target site. After entering the blood, nanocarriers interact with plasma proteins, which may bind to their surface. This process can lead to rapid recognition and removal by the immune system. Nanocarriers with an appropriate size, surface charge, and surface coating can avoid rapid clearance and circulate for longer periods. A longer circulation time increases the likelihood that nanocarriers reach diseased tissues. Surface modification techniques, such as polymer coating, are commonly used to reduce protein binding and improve blood stability [70].

Cell uptake mechanisms describe how nanocarriers enter cells after reaching the target tissue. Most nanocarriers are taken up by cells through energy-dependent processes such as endocytosis. The efficiency of cell uptake depends on factors such as nanocarrier size, shape, surface charge, and the presence of targeting molecules. Positively charged nanocarriers often exhibit higher cell uptake due to interactions with negatively charged cell membranes, but they may also exhibit greater toxicity. Active targeting strategies further enhance uptake by allowing

nanocarriers to bind specific receptors on the cell surface. Efficient cell uptake ensures that the drug reaches its site of action inside the cell.

Distribution in tissues refers to how nanocarriers spread throughout the body's organs and tissues. After leaving the bloodstream, nanocarriers may accumulate in specific tissues depending on blood flow, vessel permeability, and tissue structure. Diseased tissues with leaky blood vessels often show higher nanocarrier accumulation. However, non-target tissues such as the liver and spleen may also accumulate nanocarriers due to their role in filtering blood. Proper control of nanocarrier size and surface properties is necessary to improve selective tissue distribution and reduce unwanted accumulation [71-72].

Clearance from the body is the final stage of nanocarrier interaction with biological systems. After delivering the drug, nanocarriers must be safely removed to avoid long-term toxicity. Clearance mainly occurs through organs such as the liver, kidneys, and spleen. Biodegradable nanocarriers break down into smaller, non-toxic components that can be easily excreted. Non-biodegradable nanocarriers may remain in the body for extended periods, raising safety concerns. Therefore, designing nanocarriers with efficient and safe clearance pathways is essential for their successful clinical use.

Overall, the interaction of nanocarriers with biological systems plays a critical role in determining their safety, effectiveness, and suitability for clinical applications [73].

7. Applications in Disease Treatment

Nanocarrier-based drug delivery systems have shown wide application in the treatment of many diseases. By improving drug targeting, stability, and controlled release, nanocarriers help increase treatment effectiveness while reducing side effects. Their use has expanded across several major disease areas, including cancer, infectious diseases, neurological disorders, and cardiovascular diseases.

Cancer therapy is one of the most important and well-studied applications of nanocarriers. Conventional anticancer drugs often damage healthy cells along with cancer cells, leading to serious side effects. Nanocarriers help overcome this problem by delivering anticancer drugs more selectively to tumour tissues. Due to abnormal blood vessels in tumours, nanocarriers can accumulate more easily at the tumour site. Targeted nanocarriers further enhance drug uptake by cancer cells, increasing drug concentration within tumours while reducing harm to normal tissues. Controlled drug release from nanocarriers also helps maintain adequate drug levels for more extended periods, reducing the need for frequent dosing and improving patient comfort.

Infectious diseases also benefit significantly from nanocarrier-based drug delivery [74-75]. Many antimicrobial drugs face challenges, including poor solubility, rapid degradation, and limited penetration into infected tissues. Nanocarriers protect these drugs from early degradation and improve their delivery to infection sites. They can enhance drug penetration into bacteria-infected cells and tissues, thereby improving treatment outcomes. In addition, nanocarriers can help reduce drug resistance by maintaining effective drug concentrations and supporting combination therapy. Their use is for bacterial, viral, and fungal infections [76].

Neurological disorders present significant challenges for drug delivery due to the presence of substantial protective barriers in the brain. Many drugs are unable to reach the brain in sufficient amounts using traditional delivery methods. Nanocarriers offer a promising solution by improving drug transport across these barriers. Properly designed nanocarriers can protect drugs

and enhance their movement into brain tissues. Approaches studied for the treatment of conditions such as brain tumours, neurodegenerative diseases, and central nervous system infections. By improving brain drug delivery, nanocarriers help increase treatment effectiveness and reduce systemic side effects [77].

Cardiovascular diseases are another critical area where nanocarrier-based drug delivery shows strong potential. Drugs used to treat heart and blood vessel diseases often require precise dosing and targeted delivery to avoid unwanted effects. Nanocarriers can deliver drugs directly to diseased blood vessels or heart tissues, improving therapeutic efficiency. They can also provide controlled drug release, which helps maintain stable drug levels and reduces dosing frequency. Nanocarrier systems are being explored for the treatment of conditions such as atherosclerosis, hypertension, and clot-related disorders [78].

Overall, the application of nanocarrier-based drug delivery systems across multiple disease areas highlights their importance in modern medicine. Their ability to improve targeting, enhance drug effectiveness, and reduce side effects makes them a valuable tool for advancing disease treatment [79].

8. Safety and Toxicity Issues

Safety and toxicity are critical factors in the development and clinical use of nanocarrier-based drug delivery systems. Although nanocarriers offer many advantages in drug delivery, their small size and unique properties can also lead to unwanted biological effects. Careful evaluation of short-term toxicity, long-term safety, and immune system response is necessary to ensure that these systems are safe for patient use [80].

Short-term toxicity refers to the immediate harmful effects that may occur soon after nanocarrier administration. These effects can include irritation at the injection site, damage to blood cells, or toxicity to organs such as the liver and kidneys. Short-term toxicity often depends on factors such as nanocarrier size, surface charge, material type, and dose. Highly reactive or positively charged nanocarriers may interact strongly with cell membranes, leading to cell damage. Using biocompatible materials, proper surface modification, and controlled dosing can significantly reduce short-term toxic effects [81].

Long-term safety is a significant concern, especially for nanocarriers intended for repeated or long-term use. Some nanocarriers may accumulate in organs over time if they are not easily broken down or removed from the body. This accumulation can cause chronic inflammation, organ dysfunction, or delayed toxic effects. Biodegradable nanocarriers are preferred because they can be safely broken down into non-toxic components and cleared from the body [82].

Long-term safety studies are essential for understanding how nanocarriers behave in the body over extended periods and for identifying potential risks associated with prolonged exposure.

Immune system response plays a significant role in the safety of nanocarrier systems. The immune system may recognise nanocarriers as foreign particles and trigger immune reactions such as inflammation or allergic responses. In some cases, rapid clearance by immune cells can reduce treatment effectiveness. Surface properties of nanocarriers strongly influence immune recognition. Surface coating techniques are commonly used to reduce immune system activation and prolong circulation time. A balanced design that minimises immune response while maintaining effective drug delivery is essential for the safe clinical use of nanocarrier-based systems [83-84].

Overall, addressing safety and toxicity issues is essential for the successful translation of nanocarrier drug delivery systems from research to clinical practice.

9. Clinical Translation of Nanocarriers

Clinical translation refers to the process of moving nanocarrier-based drug delivery systems from laboratory research to real use in patients. Although many nanocarriers show excellent results in laboratory and animal studies, only a limited number successfully reach clinical use. For instance, out of hundreds of preclinical nanocarrier candidates reported in the literature, estimated clinical development progression rates indicate that only about 10% manage to advance to Phase I clinical trials, and even fewer, approximately 1%, reach Phase III trials (data summarised from recent nanomedicine pipeline reviews; see Park et al., 2016; Anselmo & Mitragotri, 2019). This stark attrition highlights the crucial bottleneck in the process and underscores the importance of developing robust regulatory strategies as part of the translation pathway [85-86]. This transition requires careful testing, large-scale production, and strict safety evaluation to ensure that the nanocarrier system is effective, safe, and reliable for human use. Some successful examples include Doxil, a liposomal formulation of doxorubicin, which was one of the first nanocarrier-based drugs approved and is noted for its improved drug delivery to cancer tissues, reducing the side effects associated with conventional formulations. Another example is Abraxane, a nanoparticle albumin-bound paclitaxel used in cancer therapy, which enhances drug solubility and bioavailability, thereby improving treatment outcomes. These successes often owe to factors like improved target specificity, controlled drug release, and enhanced safety profiles [87-88] .

The journey from lab to clinic is long and complex. In the laboratory, nanocarriers are first designed and tested for drug loading, release behaviour, and basic safety. After this, studies are conducted in cell and animal models to evaluate effectiveness, toxicity, and body distribution. Only systems that show clear benefits and acceptable safety profiles move forward to human clinical trials. Clinical trials are conducted in multiple phases to test safety, proper dose, and treatment effectiveness in patients. Many nanocarrier systems fail at this stage due to unexpected toxicity, poor performance in humans, or a lack of clear improvement over existing treatments [89].

Approved nanocarrier-based drugs demonstrate that clinical translation is possible when careful design and testing are used. These approved systems primarily use well-established, biocompatible materials, especially lipid-based nanocarriers. Their success has encouraged further research and investment in nanocarrier drug delivery. However, approval usually requires extensive testing and strong evidence that the nanocarrier system offers clear advantages over conventional drug-delivery methods in terms of safety and effectiveness.

Challenges in large-scale production are a significant barrier to clinical translation. Nanocarriers that are easy to prepare in small laboratory batches may be difficult to produce consistently on a large scale. Problems such as batch-to-batch variation, particle size control, drug loading consistency, and storage stability can affect product quality. Large-scale production also requires cost-effective and reproducible manufacturing methods. Any variation in nanocarrier properties can influence safety and treatment outcome, making strict quality control essential [90-91].

Regulatory concerns play a critical role in the approval of nanocarrier-based drug delivery systems. Regulatory authorities require detailed information on material composition, manufacturing process, safety, toxicity, and long-term effects. Because nanocarriers behave differently from traditional drugs, standard testing methods may not be sufficient, creating uncertainty and potentially delaying approvals. While efforts are underway to develop more straightforward guidelines specifically for nanomedicine, these standards are still in development across many regions. Strong communication between researchers, manufacturers, and regulatory agencies is necessary to ensure that nanocarrier systems meet all safety and quality requirements [92-94].

Overall, while nanocarrier-based drug delivery systems show strong promise, their clinical translation requires careful design, thorough testing, reliable manufacturing, and clear regulatory approval pathways.

10. Current Challenges and Limitations

Although nanocarrier-based drug delivery systems offer many advantages over traditional methods, several challenges and limitations still limit their widespread clinical application. These challenges relate to stability, cost and manufacturing, and differences among patients. Addressing these issues is essential to ensure that nanocarrier systems can move successfully from research laboratories to routine clinical use.

One significant challenge is stability. Nanocarriers must remain physically and chemically stable during storage, transportation, and after administration. Instability can lead to serious problems such as particle aggregation, drug leakage, or changes in particle size and structure. When nanocarriers aggregate, they may lose their ability to circulate properly in the bloodstream or reach the target site. Drug leakage during storage or circulation can reduce the effective dose and increase the risk of side effects. Environmental factors such as temperature, light, humidity, and pH can further affect nanocarrier stability. Maintaining a long shelf life while preserving drug activity and nanocarrier structure remains a significant technical challenge. Special storage conditions are often required, which can increase cost and limit practical use [95-96].

Cost and manufacturing issues also pose significant barriers to the large-scale production of nanocarrier systems. Many nanocarriers require complex preparation techniques, specialised equipment, and strict control of processing conditions. These requirements make production expensive and time-consuming. Scaling up nanocarrier production from laboratory scale to industrial scale is particularly difficult. Minor variations during manufacturing can lead to differences in particle size, drug loading, and release behaviour. Ensuring uniformity and batch-to-batch reproducibility is technically demanding but essential for safety and regulatory approval. High production costs can limit accessibility, especially in low- and middle-income regions, reducing the potential impact of nanocarrier-based therapies in global healthcare.

Another significant limitation is patient-to-patient variation [97]. Biological differences among patients can strongly influence how nanocarriers behave inside the body. Factors such as age, genetic background, disease type and stage, immune system activity, and organ function can affect nanocarrier distribution, drug release, and clearance. For example, differences in immune response may lead to faster clearance of nanocarriers in some patients, reducing treatment effectiveness. Similarly, variations in enzyme levels or tissue structure can alter drug release

behaviour. As a result, a nanocarrier system that performs well in one patient may show reduced benefit or increased side effects in another. This variability makes it challenging to design a single nanocarrier system that works equally well for all patients [98].

To address these challenges, emerging approaches like biomarker-driven design and adaptive dosing are being explored. Biomarker-driven design involves customising nanocarrier characteristics based on specific biological markers found in individual patients, aiming for more precise targeting and improved efficacy. Adaptive dosing strategies, which adjust drug dosage dynamically based on real-time feedback from patients' physiological responses, offer a sophisticated mechanism for optimising therapeutic outcomes and minimising side effects. Unlike conventional fixed-dose regimens, adaptive dosing enables clinicians to respond to fluctuations in patient metabolism, drug clearance, or emerging adverse effects, continually refining dosage to reflect the individual's physiological state. This iterative approach can help maintain therapeutic concentrations within an optimal range, particularly in populations characterised by high pharmacokinetic or pharmacodynamic variability [99-100]. By integrating adaptive dosing into nanocarrier-based therapies, treatment regimens can be tailored more precisely, overcoming challenges associated with patient heterogeneity. These personalised strategies, therefore, hold significant promise for enhancing both the safety and efficacy of nanocarrier-based treatments.

In addition, regulatory and clinical testing challenges further limit the translation of nanocarrier systems. Standard testing methods used for conventional drugs are not always suitable for nanocarriers, due to their complex structure and behaviour. Long-term safety data are often limited, and regulatory guidelines specific to nanocarrier-based systems are still evolving. These uncertainties can delay approval and increase development costs.

Overall, while nanocarrier-based drug delivery systems hold great promise, overcoming challenges related to stability, manufacturing cost, and patient variability is essential for their broader clinical adoption. Continued research focused on improving formulation stability, simplifying manufacturing processes, reducing cost, and developing patient-specific approaches is necessary to fully realise the potential of nanocarrier drug delivery in modern medicine [101-102].

11. Future Directions

The future of nanocarrier-based drug delivery systems centres on enhancing precision, safety, and therapeutic outcomes, with innovation at the forefront of ongoing research. An important area of development is the emergence of smart nanocarriers that can respond to specific biological signals or external stimuli, enabling drug release only when and where needed. These systems hold promise for improving targeting accuracy, minimising drug loss, and further reducing adverse effects. Advances in material science and nanotechnology continue to drive these innovations, making nanocarriers more responsive and efficient [103]. Among recent developments, significant focus has been on self-regulating nanoparticles that release drugs in response to disease-associated biomarkers. For example, reported ROS-responsive polymeric nanoparticles that detect elevated reactive oxygen species in inflamed tissues and selectively release anti-inflammatory agents, thereby enhancing therapeutic outcomes while minimising off-target effects. Other examples include pH-sensitive micelles, which release drugs in acidic tumour microenvironments, and magnetically modulated nanocarriers, which provide precisely controlled release through external magnetic fields [104-105]. Despite these advances, several

critical questions remain for future research. It will be essential to investigate how these smart nanocarriers interact with highly dynamic and heterogeneous disease microenvironments and how robustly they adapt to patient-specific physiological cues. Moreover, translating such advanced systems into universal nanocarrier platforms capable of tailoring drug delivery to individual patient biomarkers represents a significant challenge and a transformative opportunity. Addressing these questions will require interdisciplinary collaboration and the development of new evaluation models that reflect complex in vivo conditions. Ultimately, future research must not only focus on technological breakthroughs but also critically assess the translational and practical implications of these innovations to redefine the boundaries of precision medicine [105].

Personalised nanomedicine is another important future direction. Instead of using the same treatment for all patients, nanocarrier systems can be tailored to individual patient characteristics, such as disease type, genetic profile, and treatment response. Personalised approaches aim to improve treatment effectiveness and reduce unwanted reactions by matching the drug delivery system to the patient's specific needs [106].

Combination therapy approaches using nanocarriers are also gaining attention. Nanocarriers can be designed to carry more than one drug at the same time, allowing combined treatment strategies. This approach is beneficial for complex diseases such as cancer and infections, where multiple drugs are often required. Combination therapy using nanocarriers can improve treatment efficiency, reduce drug resistance, and enhance overall therapeutic outcomes.

Together, these future directions highlight the strong potential of nanocarrier-based drug delivery systems to transform modern medicine and improve patient care [107-108].

12. Conclusion

Nanocarrier-based drug delivery systems represent a significant advancement in modern pharmaceutical and biomedical research. Throughout this chapter, key aspects of nanocarrier drug delivery have been discussed, including their basic principles, different types, design strategies, targeting methods, interactions with biological systems, applications in disease treatment, safety concerns, and challenges in clinical translation. Nanocarriers address many limitations of traditional drug delivery systems by improving drug stability, enhancing targeting, enabling controlled drug release, and reducing side effects. Their ability to deliver drugs more effectively to specific disease sites makes them especially valuable in the treatment of complex conditions such as cancer, infections, neurological disorders, and cardiovascular diseases.

Despite their apparent advantages, several challenges remain, including stability issues, high production costs, manufacturing difficulties, patient-to-patient variation, and regulatory barriers. Addressing these challenges is essential for wider clinical acceptance. Continued research focusing on safer materials, better design approaches, and improved manufacturing methods is necessary to ensure consistent performance and long-term safety.

Looking ahead, the future of nanocarrier drug delivery promises dynamic innovation. Anticipated advances include the emergence of next-generation smart nanocarriers capable of real-time responsiveness to complex physiological cues, allowing for even greater precision in therapeutic delivery. Integration of artificial intelligence and machine learning may enable personalised nanomedicine platforms that adapt to individual patient biology in unprecedented ways. Furthermore, innovative combination therapy approaches using multifunctional

nanocarriers have the potential to address multidrug resistance and target complex disease networks. As interdisciplinary research continues to bridge gaps between nanomaterial science, computational biology, and clinical medicine, nanocarrier-based drug delivery will likely redefine treatment paradigms, establishing new standards for safety, efficacy, and customisation in future healthcare.

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