

Development of Nanoparticle-Based Drug Delivery Systems for Targeted Therapy

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Abstract

Drug delivery systems based on nanoparticles have been of great interest because of its capability to circumvent some of the key shortcomings of traditional drug therapies, such as low solubility, short half-life, and indifferent distribution. Both hydrophilic and hydrophobic drugs can be efficiently encapsulated and released through controlled release by their nanoscale, high surface area and tunable physicochemical properties. Animal-based studies have shown evidence of improved therapeutic performance in different disease models, including cancer, neurological disorders, chronic inflammation and wound infections. Polymeric nanoparticles, lipid-based nanoparticles, and metallic nanoparticles exhibit better biodistribution, have extended circulation and concentration at diseased locations due to passive targeting such as the Enhanced Permeation and Retention (EPR) effect and active targeting by ligand. Such systems help in decreased systemic toxicity and enhanced treatment outcomes. Nonetheless, there are still problems with long-term safety evaluation, organ build up, immunogenicity and mass production. The safety analyses that have been conducted in animal models emphasize this fact, namely that nanoparticle composition, size, biodegradability and surface properties should be optimized to reduce adverse effects. In general, nanoparticle-based drug delivery systems have a bright future ahead of them because they would provide better, safer, and disease-targeted treatment procedures.

Key Words:

Nanoparticles, Targeted Drug Delivery, Animal Models, Polymeric Nanoparticles, Lipid Nanoparticles, Metallic Nanoparticles, Controlled Release, Therapeutic Efficacy.

History:

Received: Aug,12,2025

Revised: Sep, 23,2025

Accepted: Oct, 23,2025

Published: Nov 04, 2025

DOI: <https://doi.org/10.64063/3049-1681.vol.2.issue11.1>

1. INTRODUCTION

Drug delivery systems through nanoparticles have come out as one of the most promising systems in contemporary therapeutics¹. Their peculiar physicochemical properties such as the mini size of nanoparticles, huge surface area and the capacity to encapsulate hydrophilic and hydrophobic drugs enable them to address significant drawbacks of the traditional drug delivery. Conventional formulations of drugs are characterized by low solubility, short half-life, tissue-invasive, and systemic side effects. Conversely, nanoparticles are designed to transport drugs in a direct and precise way to make sure that therapeutic molecules reach their target site of destruction by avoiding any exposure to normal tissues. Nanoparticles in preclinical experiments

Journal of Pharmaceutical Research and Integrated Medical Sciences (JPRIMS)

ISSN: 3049-1681 | Vol. 02 Issue 11, Nov-2025 | pp.-01-14

using animal models have been shown to have increased drug bioavailability and enhanced pharmacokinetics and selectivity in treatment in diseases like cancer, inflammation, neurological disorders as well as infectious diseases.

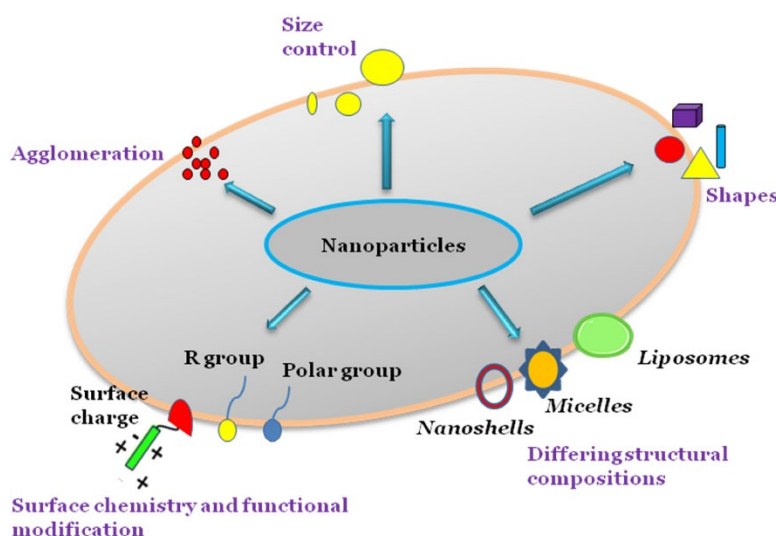


Figure 1: Nanoparticle-Based Drug Delivery²

Moreover, the technology of nanotechnology has facilitated the manufacture of several types of nanoparticles that are polymeric nanoparticles, lipid-based carriers, metallic nanoparticles, and bio-inspired Nanosystems. They may be functionalized with ligands, antibodies or peptides to achieve active targeting or may make use of physiological properties of these nanoparticles such as enhanced permeability and retention (EPR) effect to passively target them. Consequently, they have high therapeutic benefits such as lower dosing rate, an increased time of circulation and increased localization at the site of disease. Before advancing to the human trials; animal studies are considered to be an important phase towards the understanding of they safety, biodistribution, pharmacodynamic effects, and therapeutic efficacy. To make safe, effective, and translatable nanoparticle systems, therefore, it is important to review animal-based evidence.

1.1 Background Information and Context

Delivery of drugs through nanoparticle is a fast-developing area that aims at enhancing the efficacy and accuracy of therapeutic drugs use by altering materials at nanoparticle scale. Nanoparticles have demonstrated great potentials in animal studies in increasing targeted drug delivery, maintaining drug stability and decreasing systemic toxicity³.

1.2 Objectives of the Review

- To examine the development and types of nanoparticle systems used in targeted drug delivery.
- To summarize animal model-based evidence demonstrating the therapeutic potential of nanoparticles.
- To evaluate the benefits, challenges, and limitations of nanoparticle-based delivery approaches.

- To highlight knowledge gaps and suggest directions for future research⁴.

1.3 Importance of the Topic

Knowledge of nanoparticles performance and role in animal models is necessary to forecast how they will behave in the human system and to further proceed towards the clinical application of the nanoparticles. The review helps to make important comments about the way the nanoparticle drug delivery system can transform therapeutic approaches in the future offering more specific, effective, and less dangerous treatment models⁵.

2. PRECLINICAL EVALUATION OF NANOPARTICLE-BASED DRUG DELIVERY SYSTEMS IN ANIMAL MODELS

Nano-delivery of drugs has been shown to be a more targeted therapeutic effect, drug stability and low toxicity in cancer, inflammatory, neurological and wound-healing models, which is demonstrated by animal studies. Still, despite the positive aspects of controlled release and improved bioavailability, this is accompanied by a dilemma of long-term safety, difficulty in the production and accretion of nanoparticles on the organs⁶.

2.1 Overview of Key Animal-Based Research Studies

Nanoparticle-based drug delivery systems have proved to be useful in numerous therapeutic applications in several animal-based studies. PLGA nanoparticles were used on mice with tumors induced experimentally in the research on tumor-targeted drug release. The findings revealed significant nanoparticle concentration at the tumor location with low systemic toxicity, which is a better performance of targeting and a safer approach of drug delivery.

Chitosan nano-particles have been tested over a rat arthritis model in the field of anti-inflammatory drug therapy. These nanoparticles also significantly decreased the level of oxidative stress and joint inflammation which points at its possible applications in the treatment of chronic inflammatory disorders. Equally, liposomal nanoparticles in neurodegeneration neuroprotective drug delivery were also administered on a mouse model of neurodegeneration. The results exhibited better blood-brain barrier penetration and neuronal survival, an event that represents their potential as neurotherapy agents⁷.

Moreover, the antimicrobial effect of silver nanoparticles has been studied by use of the model of rabbit wound infection. Those findings demonstrated Hastened wound healing and significant decrease in bacterial load IN favor of the application of silver nanoparticles as effective antimicrobial agents in wound care. Taken together, these studies highlight the therapeutic flexibility and clinical prospects of nanoparticle drug delivery systems in the treatment of a broad spectrum of pathology.

2.2 Methodologies and Findings

A number of formulation methods have been developed to develop nanoparticle-based drug delivery systems with all the methods having their own advantages in order to maximize the size, the surface properties and the ability of loading the drug onto the particle. Techniques such as solvent evaporation, which involves dissolution of the polymer in organic solvents and then

emulsified into nanoparticles; ionic gelation, which involves using electric forces between the biopolymer molecules, nanoprecipitation, where the polymer and drug solutions rapidly combine, and self-assembly, where the amphiphilic molecules spontaneously form nanostructures, are common. These methods allow the packaging of a diverse range of therapeutic drugs⁸.

Nanoparticle systems have been identified to be very useful in targeting strategies to improve therapeutic outcomes. Passive targeting takes advantage of the effect of Enhanced Permeation and Retention (EPR) whereby nanoparticles are deposited in tissues during tumor or inflamed leak creating leaky vasculature. Active targeting, in its turn, is the functionalization of the surface of the nanoparticle with receptors on diseased cells that have been overexpressed with targeted ligands (e.g., folic acid, peptides, antibodies): an improved selectivity and reduced off-target effects.

Hydrophobic and hydrophilic drugs have been successfully encapsulated as nanoparticles into nanoparticle matrices which have had advantages of increased solubility, chemical stability, systemic retention and enzyme resistance. The results of preclinical animal experiments show various benefits: nanoparticles have the superior potential to extend the circulation time, achieve controlled and sustained delivery of drugs, and have an increased uptake in tumor, inflamed tissues, and infection sites. Also, it was shown that these systems exhibit decreased cytotoxicity over sensitized free drug forms because the controlled release minimizes intermittent drug concentrations and minimizes unfavorable systemic exposure.

2.3 Strengths and Weaknesses of Nanoparticle Approaches

- **Strengths:** Drug delivery systems based on nanoparticles have a number of important benefits, among which is the increase of the pharmacokinetic properties of drugs, since the bioavailability and half-life of drugs undergo an enhancement due to nanoparticles. Those have facilitated the targeted accumulation in disease tissues by both passive accumulation in disease tissues via the Enhanced Permeation and Retention (EPR) effect and active targeting solutions by ligand functionalization thus minimizing off-target distribution. Also, the nanoparticles play a role in the decreased toxicity in the systemic levels because regulated release produces sudden spikes in the concentration of drugs and restricts the exposures to normal tissues. In addition, they cause controlled and prolonged release, which enables therapeutic drug concentrations to remain at prolonged periods and enhance treatment effects⁹.
- **Weaknesses:** These advantages notwithstanding, there are a number of challenges impeding their extensive use in clinical practice. The problem of stability in the storing time can occur because of the aggregation or degradation of the particles, affecting the consistency and the efficacy. Long-term toxicity and food fate of nanoparticles in the body are not fully known, which gives questions associated with bioaccumulation and long-term exposure. Moreover, they are produced in a complicated and expensive manner and the technologies are used and the quality control is organized strictly. Finally, the biodegradation fates of nanoparticle materials in vivo are also poorly understood since some nanoparticle materials could be retained in organs, which affects

biocompatibility. In general, although nanoparticle-based drug delivery systems have a promising future in terms of therapy, current studies should focus on bettering the safety, scalability and regulatory frameworks in order to facilitate the translation of such systems into clinical action.

Table 1: Summary of Reviewed Literature on Nanoparticle-Based Drug Delivery Systems¹⁰

Author(s) & Year	Study Source	Focus Area	Methodology	Key Findings
Emeihe et al. (2024) ¹¹	Revolutionizing drug delivery systems: Nanotechnology-based approaches for targeted therapy	General advancements in nanotechnology-based targeted drug delivery	Narrative literature review synthesizing developments in nanoparticle design and application	Demonstrated that nanoscale carriers improved drug solubility, circulation time, and targeted tissue accumulation; highlighted benefits in reduced systemic toxicity; identified scalability and regulatory challenges.
Gao et al. (2024) ¹²	Nanoparticle-based drug delivery systems for inflammatory bowel disease treatment	Nanoparticle applications for treating Inflammatory Bowel Disease (IBD)	Review of experimental and preclinical research involving mucoadhesive and pH-responsive nanoparticles	Showed enhanced mucosal adhesion and targeted drug delivery to inflamed intestinal tissue; reduced systemic exposure and inflammatory cytokine levels; noted variability in animal models and need for long-term safety assessments.
Hong et al. (2023) ¹³	Nanoparticle-based drug delivery systems targeting cancer cell surfaces	Targeted cancer therapy using surface-functionalized nanoparticles	Analysis of ligand-based targeting strategies in cancer cellular environments	Found that ligand-modified nanoparticles improved receptor-mediated endocytosis and increased intratumoral drug uptake; limitations included receptor heterogeneity and complex tumor microenvironments.
Hong et al. (2020) ¹⁴	Protein-based nanoparticles as	Protein-derived nanoparticle	Compilation of research on	Reported high biocompatibility and

	drug delivery systems	carriers	albumin, ferritin, and other protein-based nanostructures	controlled release capabilities; surface functionalization enabled targeted delivery; concerns remained regarding immune reactions and reproducibility in large-scale production.
Hristova-Panusheva et al. (2024)¹⁵	Nanoparticle-mediated drug delivery systems for precision targeting in oncology	Precision and personalized nanomedicine in cancer therapy	Review of translational and preclinical oncology studies	Indicated that precision-designed nanoparticles enhanced tumor-specific therapeutic outcomes; highlighted gaps such as inconsistent clinical performance, incomplete biodistribution profiling, and regulatory complexity.

3. NANOPARTICLE CARRIERS AND THEIR TARGETING APPROACHES

Drug delivery systems based on nanoparticle employ polymeric, lipid-based, and metallic carriers to ensure drug stability, target, and therapy as well as minimize side effects. Passive gating can be realized by the inherent permeability of tissues, whereas active gating can be realized by surface modification by ligands with high specificity to diseased cells¹⁶.

3.1 Polymeric Nanoparticles

Polymeric nanoparticles are developed using biocompatible and biodegradable polymers like Poly (lactic-co-glycolic acid) (PLGA), chitosan, polycaprolactone, as well as other natural or synthetic polymeric materials. Their stable structure and controllable degradation rates make them perfect for controlled and sustained-release. The surface of the nanoparticles can also be modified with stabilizers or targeting ligands to improve their pharmacokinetic characteristics and biological compatibility. Polymeric nanoparticles have shown increased biodistribution and prolonged systemic circulation in different models of cancer in mice and were able to exploit the Enhanced Permeation and Retention (EPR) effect, which occurs when nanoparticles localize in tumor tissues due to the lack of vascular tight junctions and poor lymphatic drainage in tumors¹⁷.

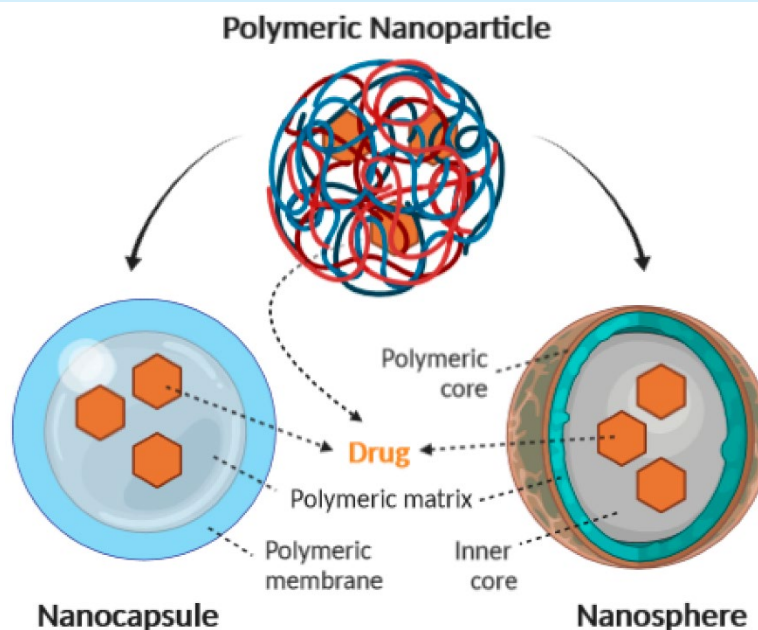


Figure 2: Polymeric Nanoparticles¹⁸

Increased drug concentration was observed in tumor tissues, leading to tumor volume shrinkage, reduced disease progression, and lower systemic side effects compared to traditional free drug treatments. These findings demonstrate the exciting potential of polymeric nanoparticles as delivery platforms for sustained and site-specific delivery of chemotherapy¹⁹.

3.2 Lipid-Based Nanoparticle

Nanoparticles developed from lipid sources, such as liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs), have advantages stemming from their structural similarity to natural cell membranes, inherent biocompatibility, and ability to incorporate both hydrophilic and hydrophobic therapeutic agents. The soft and flexible lipid bilayer enhances their stability and drug protection, leading to improved fusion/integration with biological membranes²⁰.

One application of particular interest is in the area of neurological drug delivery where crossing the 'blood-brain barrier (BBB) remains a primary therapeutic hurdle. In studies with rat brain models, lipid nanoparticles have demonstrated the ability to cross the BBB and provide therapeutically relevant drug concentrations to brain tissues. Recent findings are facilitating exciting developments in the treatment of neurodegenerative disorders such as Alzheimer's and Parkinson's disease alluding to the aptness of lipid nanoparticles as carriers that enhance bioavailability and provide increased therapeutic effect in drug delivery for central nervous system (CNS) targeting.

3.3 Metallic Nanoparticles

Metal-containing nanoparticles, particularly those made of gold and silver metal, are a great interest in therapeutic and diagnostic biomedical applications, in view of their unique physicochemical properties and functional talents. Silver nanoparticles are well known for their

powerful antimicrobial properties and their ability to modulate cellular responses associated with the promotion of wound healing. In rabbit wound healing models, silver nanoparticles were able to increase tissue regeneration, reduce microbial colonization, and increase the speed and quality of tissue healing, suggesting their use in the setting of injuries exposed to infection and in the treatment of chronic ulcers²¹.

Gold nanoparticles, on the other hand, demonstrate optical, thermal, and surface chemistry properties which allow their use in imaging, drug delivery, and photothermal therapy. The surfaces of gold nanoparticles are able to be modified with biological molecules that enhance selectivity and enable specific targeting. Gold nanoparticles can be especially useful in cancer therapy where absorbed light can be transformed to heat allowing specific destruction of tumor cells while sparing surrounding healthy tissue.

3.4 Targeting Mechanisms

Strategies targeting delivery mechanisms in drug delivery extending to nanoparticles are generally grouped into two categories: passive or active targeting mechanisms. Passive targeting establishes the use of physiological properties, often inherent, i.e. enhanced vascular permeability and retention in proliferated inflammatory or tumor microenvironments, where nanoparticles size allows preferential accumulation in pathologies without needing to use molecular recognition constituents. Passive or non-targeted drug delivery strategies are advantageous for delivery to tumor tissues where the EPR (enhanced permeability and retention) effect naturally promotes drug deposition²².

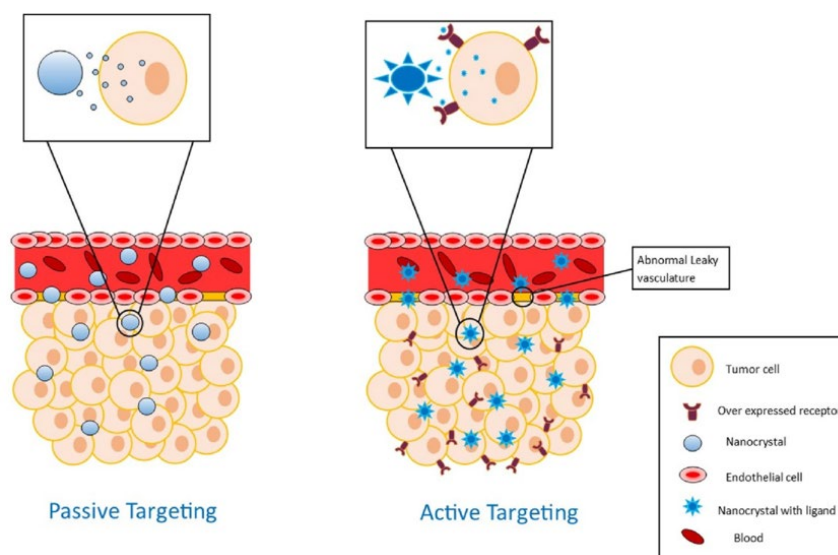


Figure 3: Targeting Mechanisms²³

Active targeting strategies, conversely, depend on surface modifying nanoparticles with biological ligands (e.g. antibodies, peptides, aptamers or receptor-specific agents i.e. folic acids) which may selectively bind to receptors that are overexpressed on diseased, or cancerous cells to enhance cellular uptake, and more generally increase the likelihood of therapeutic action. Studies evaluating treatment efficacy in various animal disease models or conditions have shown active nanoparticle delivery substantially increases intracellular drug delivery efficiencies and

decreased systemic toxicity contributing to improve overall efficacy (greater than if just passively delivered) by ensuring the drug is delivered to the intended site of action in a specific manner²⁴.

4. SAFETY AND TOXICITY EVALUATION IN ANIMAL MODELS

Before nanoparticle-based drug delivery systems can be translated into a clinical application, safety evaluation is essential²⁵. While animal models can provide the basis for understanding nanoparticle–host interactions — including potential toxicological effects, biodistribution, metabolic kinetics, and clearance pathways — these studies will aid in establishing whether nanoparticles are safe, tolerated, and effective for therapeutic purposes of long duration. Evaluation of safety typically involves parameters such as monitoring physiological variables, performing biochemical assays, conducting behavioral observation and at the organ level for adverse responses²⁶.

4.1 Acute and Chronic Toxicity Studies

Toxicity evaluations of animal models are typically done in two stages: acute (short-term) studies, and chronic (long-term) exposure studies²⁷.

- **Acute Toxicity:** The purpose of an acute toxicity study is to identify immediate adverse effects following exposure to nanoparticles. Various parameters are measured, including biomarkers of inflammation, oxidative stress (e.g., ROS), signs of tissue irritation, cardiovascular function, and respiratory function. Sudden changes in an animal's behaviour or ability to move can serve as indicators of neurological or systemic stress.
- **Chronic Toxicity:** Chronic studies evaluate the long-term safety of nanoparticles over a duration of weeks or even months and help to optimise dose and timing of exposure. Chronic studies assess the long-term health impact of nanoparticles (including organ accumulation effects), long term activation of immune and inflammatory response, and changes in metabolic processes or potential genotoxicity. For example, a chronic study evaluating gold nanoparticles showed no clinical signs of organ failure or mortality in following long-term exposure in a rat model; however, a modest increase in inflammatory-specific markers was observed, indicating a possible dependency between nanoparticles and safe biomarker/adverse reaction at exposure parameters, thus indicating possible dose-dependent safety of nanoparticles²⁸.

4.2 Biodistribution and Organ Accumulation

The distribution of nanoparticles through the body is subject to influence from physicochemical properties like size, surface charge, shape, and material composition²⁹.

- **Organ Accumulation:** Preclinical animal studies using polymeric nanoparticles in mice have all observed significant accumulation of particles in the liver, spleen, and kidneys, largely due to the clearance of the reticuloendothelial system (RES), as well as renal filtration. While these observations appear non-toxic for biodegradable nanoparticles, repeated doses may increase tissue burden and should be evaluated over time.

- **Clearance Pathways:** Nanoparticles smaller than ~10 nm could be filtered and cleared by renal processes, whereas particles larger than ~10 nm would be cleared using the process of hepatic metabolism, therefore it is important to consider size manipulations to minimize long term burden onto tissue.

4.3 Immunogenicity and Biocompatibility

The immune system is a key component determining whether nanoparticles are safe and result in systemic tolerance.

- **Biocompatible Nanoparticles:** Nanoparticles based on chitosan exhibited excellent biocompatibility in animals with minimal immune response as they are made from a natural polymer that resembles biological materials³⁰.
- **Metallic Nanoparticles:** In contrast, metallic nanoparticles, such as silver and copper nanoparticles, may elicit oxidative stress or inflammatory signaling at higher doses, as was seen in silver nanoparticles stimulating reactive oxygen species generation which could damage cellular components.
- **Surface Modifications:** Methods which include PEGylation (coating nanoparticles with polyethylene glycol) have shown to reduce reactivity from immune cells and significantly extended systemic circulation in rats, which increased the effectiveness of drug delivery systems by reducing premature clearance.

4.4 Hematological and Histopathological Effects

Comprehensive toxicology assessments often consist of hematology and histopathology assessment.

- **Hematological Evaluation:** Blood values such as red blood cell (RBC) count, white blood cell (WBC) count, hemoglobin, and platelet count provide a measurement of the potential systemic toxicity, anemia, immune dysfunction, or cell dysfunction. Biodegradable nanoparticles such as PLGA have demonstrated stable hematological values in mice, suggesting a high degree of systemic tolerance.
- **Histological Evaluation:** Sections of organs such as the liver, kidneys, lungs, and brain are obtained, stained, and analyzed microscopically for signs of structural damage, inflammation, fibrosis, or cell death.

While biodegradable nanoparticles generally do not lead to modified tissue structure, there can be mild tissue inflammation or cellular stress, if non-biodegradable metallic nanoparticles are given at high doses or over long exposure times³¹.

5. DISCUSSION

Drug delivery systems based on nanoparticles increase therapeutic efficacy by enhancing drug stability, targeting mechanism by minimizing systemic toxicity, and demonstrate general strong efficacy across disease models. Future studies must address long-term safety, organ accumulation, likelihood of immune-mediated reactions, and the challenges of multiphasic, complex manufacturing on large scales, in order to translate to clinical success³².

5.1 Interpret and Analyze the Findings

Animal studies that have been reviewed illustrate that drug delivery systems made of nanoparticles significantly facilitate improved therapeutic efficacy through improving drug stability, targeted distribution, and diminished toxic systemic exposure compared traditional drug forms³³. Polymeric, lipid-based, and metallic nanoparticles were able to reach the diseased tissue through passive targeting mechanisms like the EPR effect, as well as through active targeting possessing a ligand surface modification. These design qualities allow for prolonged drug release, sustained circulation, and higher biological uptake of the drug combination at the future site of use, thus enabling improved efficacy outcomes for therapy in cancer, inflammatory, neurological, and wound healing models³⁴.

5.2 Implications and Significance

The findings demonstrate the capacity of nanoparticles to solve major issues in contemporary therapeutics, such as drug solubility, off-target effects, and poor delivery into certain tissue types (e.g. brain)³⁵. The ability to encapsulate a wide range of drugs and their adaptability for multiple routes of delivery make nanoparticles exciting candidates for personalized and precision medicine. Additionally, nanoparticles have the potential to reduce dosing frequency and systemic toxicity, which can help promote patient compliance and improve overall treatment safety³⁶.

5.3 Gaps and Future Research Directions

While there is much promise, there are still many challenges to overcome before implementing it clinically³⁷. There are several important considerations, such as long-term toxicity, biodistribution of nanoparticles and potential accumulation in organs including the liver and spleen, immune system activation, and uncertainty about metabolic and clearance routes³⁸. In addition, the large-scale manufacture and quality assurance of the nanoparticles are complex and expensive³⁹. Future studies should emphasize long-term toxicity studies, modification of synthetic formulations for improved biodegradability, optimisation of surface modifications to reduce immune recognition, and development of scalable, inexpensive manufacturing approaches. Advancing all of these issues will be crucial in facilitating the transition of nanoparticle-based drug delivery systems from experimental animal studies to use as treatments for patients⁴⁰.

6. CONCLUSION

Drug delivery systems based on nanoparticles have offered a feasible option for a new era of therapeutic technology, providing better stability of drug agents, better bioavailability, and capability to target drugs effectively producing side effects in the body that resulted from the drug, and with possible therapeutic efficacy. While animal-based studies provide the flexibility of use in cancers, the treatment of neurological disorders, disease experience and the healing of wounds with mentioned superior therapeutic benefits compared to conventional drug formulations, long-term safety, organ accumulation, immune response, and complexities, still faces challenges for large scale translation from animal studies. Future research that continues to focus on improving the biocompatibility of nanoparticles, long term degradation, and cost of production will be vital to help aid these translational challenges from preclinical animal's

models to the clinic with efficacy and safety for patients. Drug delivery systems based on nanoparticles have promising potential to change targeted therapy and roles in the future of personalized medicine.

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