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Role of Nanoparticles in Targeted Drug Delivery Systems

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ABSTRACT

Nanoparticles have become a game changer and the multifunctional system in delivery of drugs to be used in addressing the shortfalls of traditional therapeutic i.e. low solubility, systemic clearance and lack of targeting that tends to diminish effect and increase side effects. To date, preclinical animal models have shown that varying platforms of nanoparticles, including polymeric nanoparticles, liposomes, solid lipid nanoparticles, metallic nanoparticles, dendrimers, and quantum dots, have the potential to improve therapeutic outcome by determining the accumulation of drugs within the body, by controlling and prolonging their release, and by improving bioavailability as well as selective deposition in target tissues. These systems have demonstrated to have potential in a vast field of applications including oncology, neurodegenerative disorders, antimicrobial therapy and anti-inflammatory treatment. The safety and biocompatibility of polymeric and lipid-based nanoparticles are typically favorable, and with metallic nanoparticles, although these types of nanoparticles are multifunctional and have theranostic potential, there is a risk of accumulation or toxicity over time. The animal research has also emphasized the key role of particle size, surface functionalization and composition in determining pharmacokinetics, biodistribution and therapeutic efficacy. However, interspecies variability, large-scale synthesis that can be reproduced and reproducible, standard toxicity tests and optimization of targeting strategies are still critical barriers to clinical translation. Further research on biodegradable nanoparticle substitutes, long-term safety analysis, and comparative studies done systematically are necessary to ensure full utilization of the potential of nanoparticle-based drug delivery system and develop it to a safe, effective, and clinically viable drug delivery system.

Key Words:

Keywords: Nanoparticles, Targeted Drug Delivery, Polymeric Nanoparticles, Liposomes, Metallic Nanoparticles, Dendrimers, Quantum Dots, Preclinical Studies

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1. INTRODUCTION

Nanotechnology has become a revolution in the biomedical field especially in drug delivery. Traditional therapeutic agents are usually restricted by insolubility, quick clearance by the body, and random distribution, which may lower the effectiveness and augment the danger of adverse side effects. The nanoparticles can be considered a versatile solution, as they provide the possibility to encapsulate drugs precisely, provide targeted delivery, and regulate the release kinetics[1]. These characteristics allow increasing the concentration of therapeutic agents in the disease area and reducing the off-target exposure. The animal model preclinical research has

also been valuable to assess the pharmacokinetics, biodistribution, and therapeutic potential of different nanoparticle platforms and have yielded important information about their safety, efficacy, and translational plausibility.

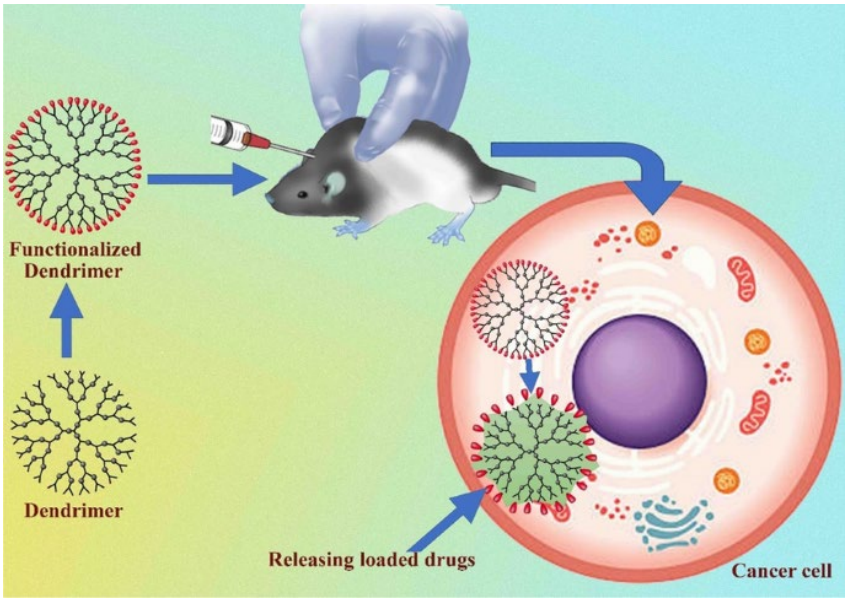

Figure 1: Targeted Drug delivery System[2]

The proposed review will compose a synthesis of existing evidence on the use of nanoparticles in targeted drug delivery systems in animal studies. The emphasis is made in discussing various nanoparticle vectors such as polymer nanoparticles, liposomes, metallic nanoparticles, dendrimers, and quantum dots and their methodology, treatment use, and the results experienced. Also, strengths and limitations of the mentioned platforms have been critically assessed with a special focus on the willingness of preclinical strategies that may bridge the gap between the laboratory justice and clinical translation. This topic is of importance because it can guide the development of nanotherapeutics of the next generation, and hasten the process of flipping new knowledge of experimental research into the process of safe and effective application in the clinic[3].

1.1 Background Information and Context

Nanosystems have become a groundbreaking technology in drug delivery covering most of the drawbacks of traditional therapeutics. Side effects of the treatments are usually undesirable, traditional drugs usually lack solubility as well as rapid clearance, non-specific targeting, and clearance, thus affecting efficacy and side effects of the used treatment. Nanoparticle systems avoid these problems by allowing passive and sustained delivery of drug, enhancing solubility of poorly water-soluble drugs, and through surface functionalization to actively target a tissue or cell. This directed technique does not only increase the therapeutic efficacy, but also avoids off-target toxicity[4]. Animal research is an important one in determining these nanoscale systems, they offer information that is valuable on animal pharmacokinetics, biodistribution, metabolism, and clearance. Using in vivo models, researchers are able to evaluate the effect of particle size, surface charge, composition, and function alteration(s) on circulation time, tissue retention, and general therapeutic efficacy. These types of preclinical studies are the basis of the development of safe and effective nanoparticles-based therapies that will have a statistically significant clinical translation.

1.2 Objectives of the Review

- To evaluate the role of various nanoparticle platforms (polymeric, lipid-based, metallic, dendrimers, and quantum dots) in enhancing targeted drug delivery in animal models.
- To analyze the pharmacokinetics, biodistribution, and clearance patterns of nanoparticles and their impact on therapeutic efficacy and safety.
- To assess the therapeutic applications of nanoparticles in oncology, neurodegenerative disorders, antimicrobial, and anti-inflammatory conditions.
- To critically examine the strengths, limitations, and safety profiles of different nanoparticle systems for preclinical and potential clinical translation.
- To identify research gaps, including standardization of toxicity assessments, long-term safety studies, and optimization strategies for improved targeting and biodegradability.

1.3 Importance of the Topic

Nanoparticle research in drug delivery is important as it contributes greatly in providing critical connection between preclinical and clinical practice. Nanoparticles can relieve all the challenges of the traditional therapy and ensure the efficacy of the drugs at the point of action emphasizing minimal levels of systemic exposure and negative side effects, thus increasing the efficacy of the therapeutic agents in the whole body. They are versatile and can be adapted to different mezzanine sizes, surface characteristics, and ligand bounded or to stimuli-responsive units, enabling the generation of precision medicine approaches that are specific to particular diseases or groups of patients[5]. In addition, pharmacokinetic, biodistribution, and safety profile of results obtained during animal studies at least present critical information to form the guide determining clinical trial design, dose optimization and regulatory evaluation. On the whole, the future of nanoparticle-based drug delivery can radically transform therapeutics such that disease-specific, safer, and not to mention more effective cures are offered not only in oncology treatment, but also in infectious disease treatment, and even treatment of neurodegenerative disorders.

2. NANOPARTICLE PLATFORMS AND THEIR APPLICATIONS IN ANIMAL MODELS

Various platforms have been investigated to use in animal models on the targeted delivery of drugs, and they include polymeric nanoparticles, liposomes, solid lipid nanoparticles, metallic nanoparticles, dendrimers, and quantum dots. Polymeric carriers like PLGA and chitosan enhance location to tumors and oral accessibility and liposomes and SLN increase the duration of circulation and allow the brain delivery. Metallic nanoparticles such as gold, silver, and iron oxide bring many possibilities through multifunctionality in terms of therapy and imaging, however, there are concerns on toxicity and accumulation in the long-term. Dendrimers identify an increase in solvency and controlled delivery, and the quantum dots offer an excellent aspect in imaging and theranostics, whereas the challenges faced by these two technologies are safety concerns. Together, all these systems show high potential in therapeutic response although it needs to be streamlined to achieve reproducibility, safety, and the large-scale applicability[6].

2.1 Polymeric Nanoparticles

- **Key Research Studies:** There is a great number of preclinical studies demonstrating the potential of biodegradable materials e.g. poly (lactic-co-glycolic acid) (PLGA) and chitosan in targeted drug delivery. PLGA nanoparticles loaded with anticancer drugs

were tested in murine tumor model, this type reported an improved capacity of tumor targeting through the use of enhanced permeability and retention (EPR) effect resulting in better therapeutic effects, higher survival rates as well as minimized systemic side effects in opposition to free drugs. Chitosan nanoparticles have obtained a lot of attention in the field of gastrointestinal models where their mucoadhesiveness allows residence in the gut longer, and more advantageous to the administration of orally active therapeutic drugs as well as bioavailability.

- **Methodologies and Findings:** Methods of administration involved intravenous (IV) administration to deliver the administration to tumors and oral delivery to administer to the gastrointestinal tract. Fluorescence imaging and radiolabeling methods were used to measure biodistribution and give an accurate location of nanoparticles in tissues. In both methods, high-tumor accumulation was always observed at the instances of PLGA formulations whereas intestinal permeability was enhanced at the instances of chitosan nanoparticles. The findings demonstrate the versatility of polymeric systems in different therapeutic processes[7].
- **Strengths and Weaknesses:** Polymeric nanoparticles have the significant excellence of high levels of biocompatibility, predetermined biodegradation to innocent metabolites and also adaptability in encasing both hydrophilic and hydrophobic drugs. They are also enabled to functionalize their surface in order to achieve active targeting. Nevertheless, there are still difficulties in relation to high-scale reproducibility, between-lots variability, and the immunogenicity. The duration of complex processes involved during manufacturing can also negatively affect fast clinical translation.

2.2 Liposomes and Solid Lipid Nanoparticles (SLNs)

- **Key Research Studies:** Liposomes because of the phospholipid forms have been widely investigated in rodent during cancer and infectious illnesses research. They were shown to have an extended circulation time, decreased systemic toxicity and increased tumor retention in xenografted mice. SLN composed of physiological lipids was observed to effectively transplant through the blood-brain barrier in rats and deliver neuroprotective factors to the brain with good prospects in neurodegenerative diseases[8].
- **Methodologies and Findings:** In xenograft tumor-bearing mice, liposomal preparations were the main research, and the efficacy of the treatment was determined by tumor regression and tumor survival. Brain distribution studies of the SLNs in rat models were conducted more frequently with radiolabeled or green fluorescent tracers as a treatment to verify the central nervous system (CNS) penetration. Both delivery systems were allied with the enhanced state of the drugs, increased systemic circulation and accumulating diseased tissues selectively.
- **Strengths and Weaknesses:** Liposomes are known to be safe and biocompatible in addition to their capacity to encapsulate both hydrophilic and lipophilic agents with a number of FDA-approved formulations appearing (e.g., Doxil). Rapid dissolution by the reticuloendothelial system (RES), however, and excessive cost of production continues to be major disadvantages. SLNs are more stable and offer resistance to degradation in sensitive drugs, but suffer comparatively low drug-loading capacity, rather there is the possibility of gelation in storage, as well as scalability.

2.3 Metallic Nanoparticles (Gold, Silver, Iron Oxide)

- **Key Research Studies:** The interest in metallic nanoparticles is connected with their exceptional physicochemical features. Tumor-targeted nanoparticles One type of nanoparticles are the gold nanoparticles (AuNPs) functionalized with tumor-targeting ligands (antibodies or peptides). These particulate systems exhibit selective uptake in the tumor and can enhance treatment of animals with photothermal therapy. Silver nanoparticles (AgNPs) had shown strong antimicrobial properties in bacterial infection models by reducing the bacteria count, and improving survivability, although their clinical application was limited due to dose related lethality. In rodent models, iron oxide nanoparticles have been used in the delivery of a drug into the body by a magnetic mechanism and has the dual therapeutic and diagnostic (theranostic) advantages.
- **Methodologies and Findings:** Research assumed a rigorous organ distribution monitoring with the imaging modalities and pathophologic studies. Gold nanoparticles enabled therapy and imaging which improved precision medicine. Silver nanoparticles demonstrated the balance strategy between antimicrobial activity and cytotoxicity adding weight to the need to optimize dosing. Nanoparticles made of iron oxide allowed external targeting of the accumulation sites and the magnetic property additionally allowed their use in the MRI scanning as well as the therapy.
- **Strengths and Weaknesses:** The main appealing aspects of the metallic nanoparticles are the high surface reactivity, dual emission as well as theranostic employment ability. They are flexible systems to single imaging and therapy. Nevertheless, one of the key issues is toxicity, in which case silver nanoparticles are in particular danger whereas the fact that silver oxide nanoparticles turn out to accumulate over time and lead to possible oxidative stress. There is also impediment of the high cost of the manufacturing of the gold nanoparticle as an element towards large scale application.

2.4 Dendrimers and Quantum Dots

- **Key Research Studies:** Dendrimers which are highly branched synthetic polymers have shown promise in rodent models to enhance solubility and controlled release of poorly soluble drugs such as anticancer drug and anti-inflammatory drugs. Targeting ligands and therapeutic agents can be conjugated to their tunable surface groups. Quantum dots (QDs) are the nanocrystals of semiconductors that have been commonly studied as imaging agents, but are also undergoing research in the field of theranostic agents, including conjugation to drugs or biomolecules to perform diagnostic and therapeutic functions in mice[9].
- **Methodologies and Findings:** Tracking of the in vivo studies of dendrimers have indicated increased drug solubility, regulated release profile, and pharmacokinetics leading to optimum therapeutic effects. Animal imaging applications of quantum dots have been demonstrated where the dots demonstrated long-term cellular and tissue localization due to their strong photostability and high intensity as fluorescents. QDs allowed therapeutic and diagnostic effects when used in combination with therapeutic agents.
- **Strengths and Weaknesses:** Dendrimers possess excellent control over drug delivery, high encapsulation rates, and it is able to be surface functionalized. Nevertheless, increasing generation of dendrimers can lead to toxicity as a result of a higher cationic charge density. Quantum dots have attractive properties as they are bright and stable and those associated with safety (e.g., heavy metal cores, e.g., cadmium, lead), render

these dots difficult to translate to clinical use. Biodegradability and toxicity also continue to be main limitations to dendrimers and quantum dots.

Table 1: Summary of Key Studies on Nanoparticle-Based Drug Delivery Systems[10]

Author(s) & Year	Study	Focus Area	Methodologies	Key Findings
Hong et al., (2020)[11]	Protein-based nanoparticles as drug delivery systems	Protein nanoparticles for drug delivery	Review of protein-based nanoparticle design using albumin and gelatin	Protein nanoparticles improved drug stability and bioavailability, were biocompatible and biodegradable, and enabled controlled drug release while minimizing systemic toxicity
Hu et al., (2018)[12]	DNA nanotechnology-enabled drug delivery systems	DNA nanostructures for targeted drug delivery	Review of DNA-based nanostructures for drug encapsulation and transport	DNA nanostructures allowed precise, stimuli-responsive drug release and selective targeting, showing promise for oncology applications
Huang & Huang, (2018)[13]	Hyaluronic acid-based biopharmaceutical and tumor-targeted drug delivery	Hyaluronic acid-functionalized nanoparticles for tumor targeting	Literature review on HA receptor-mediated targeting	HA-functionalized nanoparticles enhanced drug accumulation in tumors via CD44 receptor interaction, improving therapeutic index and reducing off-target effects
Jacob et al., (2021)[14]	Emerging role of hydrogels in drug delivery, tissue engineering, and wound management	Hydrogel-based drug delivery systems	Review of hydrogel applications in drug encapsulation, tissue	Hydrogels provided tunable, biocompatible platforms for controlled drug release and tissue regeneration,

			engineering, and wound healing	adaptable for various biomedical applications
Karami et al., (2024)[15]	Metal nanoparticles in drug delivery systems: A comprehensive review	Metal nanoparticles (Au, Ag, Fe3O4) for targeted drug delivery	Review of physicochemical properties, surface modifications, and biomedical applications	Metal nanoparticles enhanced targeting and therapeutic efficacy but posed challenges in cytotoxicity and long-term biocompatibility
Kianfar, (2021)[16]	Magnetic nanoparticles in targeted drug delivery	Magnetic nanoparticle-based drug delivery	Review of magnetic nanoparticle applications for site-specific targeting	Magnetic nanoparticles allowed precise localization using external fields, useful in cancer therapy, hyperthermia, and controlled drug release; optimization of magnetic properties and biocompatibility was critical

3. THERAPEUTIC APPLICATIONS AND SAFETY OF NANOPARTICLES IN ANIMAL MODELS

Animal experiments point to therapeutic and safety issues of nanoparticles in different applications. Nanoparticles in mouse xenografts with tumor targeting showed a higher rate of tumor accumulation through passive and active targeting and inhibited tumor progression, extended life and decreased systemic toxicity. In models of neurodegenerative diseases, polymeric and solid lipid nanoparticles enhanced the penetration of the blood brain barrier to relieve symptoms in models of Parkinson and Alzheimer. Nanoparticles were also reported to have antimicrobial and anti-inflammatory advantages in wound-healing and arthritis models because optimization of doses is essential to prevent cytotoxicity[17]. It has been demonstrated that biodegradable nanoparticles such as PLGA and chitosan are non-toxic, but metallic nanoparticles can cause organ toxicity; hence, toxicological screening and standardized safety measures are necessary.

3.1 Tumor-Targeted Nanoparticles in Animal Models

It has been well demonstrated in mouse xenograft models that nanoparticles are effective in treating cancer. The accumulation into tumors can be done through passive method of exploiting the increased permeability and retention, or EPR, effect or through active method using surface-functionalized ligands like antibodies or peptides. In these experiments, drug preparations using nanoparticles had an important role in inhibiting the tumor growth, increasing the survival rate, and reducing the systemic side effects as opposed to the use of free drugs[18]. Notably, higher drug concentration in tumors was proved using fluorescence and radiolabeling methods, which makes them potentially useful in precision medicine. Nonetheless, even with these developments, the heterogeneity of tumor vasculature and possible clearance by the mononuclear phagocyte system are a hindrance to general effectiveness.

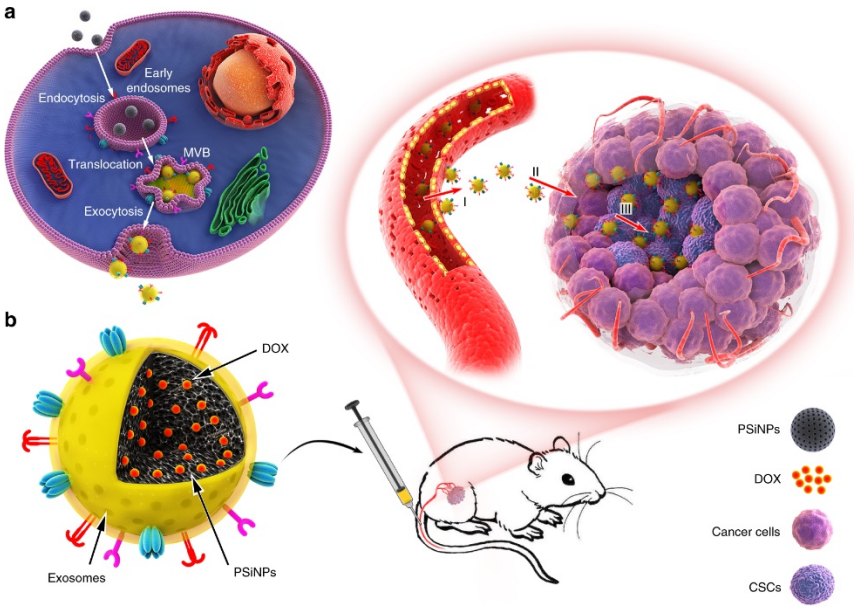

Figure 2: Tumor-Targeted Nanoparticles in Animal Models[19]

3.2 Nanoparticles for Neurodegenerative Disorders

Solid lipid nanoparticles (SLNs) and polymeric nanoparticles used as central nervous system delivery systems have exhibited encouraging findings in rodent models of Parkinson and Alzheimer disease[20]. Such systems increased the ability of drugs to get across the blood-brain barrier, a significant shortcoming of traditional treatments. Nanoparticle-loaded drugs have been shown to improve motor performance and restore dopaminergic activity in models of PD, and limit amyloid plaque deposition and neuronal degeneration in models of AD. Their potential was proved by imaging studies that revealed brain distribution of these carriers. These, however, have not been studied in long-term so their safety, biodistribution and clearance under chronic neurodegenerative conditions are yet to be fully understood[21].

3.3 Antimicrobial and Anti-inflammatory Applications

The therapeutic action of nanoparticles in the body is dual, as was shown in animal models of both infectious and inflammatory pathologies[22]. Silver nanoparticles and chitosan nanoparticles, which have been used in rat wound-healing models, have hastened the rate of tissue regeneration, decreased the growth of microbes, and decreased the healing duration. On the same note, polymeric nanoparticles containing anti-inflammatory drugs had improved

retention at inflamed areas leading to increased symptomatology and decreased systemic toxicity in mice with arthritis. These results indicate the synergistic effect of nanoparticles as antimicrobial dressings and anti-inflammatory agents. Nonetheless, the key point is dose optimization because metallic nanoparticles can cause cytotoxic effects at more significant concentrations because of which their long-term use is limited[23].

3.4 Safety and Toxicological Evaluations

Preclinical investigation supports the need to examine therapeutic efficiency and safety[24]. A repeated-dose viability of rats showed dependent dose changes of the liver and its kidney functionality using metallic nanoparticles more so, silver and iron oxide. On the other hand, biodegradable polymeric nanoparticles PLGA and chitosan were shown to have preferable safety profiles and in long-term research showed little or no systemic toxicity. However, there is still the issue of immunogenicity of some surface modifications (e.g. PEGylation) and random biodistribution profiles. These data indicate that biodegradable platforms have more potential to be translated into clinical practice, but thorough toxicological screening and a standardized safety plan should be followed before these therapies can be widely used[25].

4. PHARMACOKINETICS AND BIODISTRIBUTION IN ANIMAL MODELS

Pharmacokinetics and biodistribution of nanoparticles are essential in determining therapy and toxicity of nanoparticle therapeutics. Controlled Animal experiments offer good avenue to study the absorption, distribution metabolism and excretion (ADME) of nanoparticles following administration[26]. As an example, the injected intravenously in the rodent murine models, polymeric nanoparticles, especially those based on PLGA and chitosan, exhibited a longer period of presence in the blood vessels. This led to prolonged circulation leading to preferential accumulation in tumor tissues by enhancing permeability and retention (EPR) effect and consequently improved targeted drug delivery and reduced the systemic exposure. These works highlight that polymeric nanoparticles have a great potential in being used in accurately treating cancer[27].

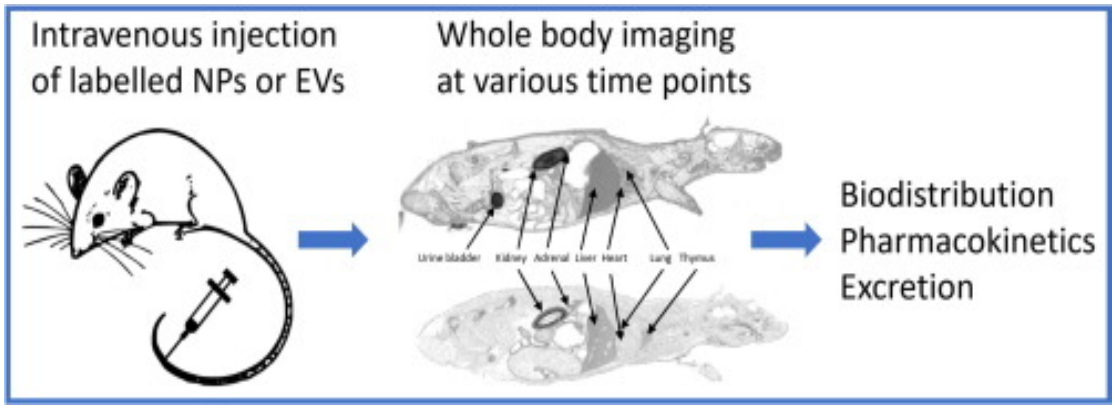

Figure 3: Pharmacokinetics And Biodistribution in Animal Models[28]

Nanoparticles based on lipids (such as liposomes and solid lipid nanoparticles SLNs), have quite different pharmacokinetic behavior[29]. Rodent experiments have demonstrated these carriers to be quickly endocytosed by the reticulo endothelial system (RES) especially in the liver and spleen, after being administered into the system. This rapid uptake makes this not only an opportunity but also a limitation in that whilst it can be used to specifically target organs

that contain high levels of RES it is also possible that bioavailability to non-RES tissues could be lost unless PEGylation or attaching some type of surface ligand is done. These results highlight the relevance of maximizing the size of particles, surface chemistry and composition to balance the circulation time and tissue targeting[30].

Other biodistribution profiles such as those of metallic nanoparticles including gold and iron oxide show a different profile[31]. These nanoparticles are typically retentive in various body organs (such as liver, spleen, and kidneys), and in the long term, in mouse and rat models. Although imaging or localized therapy may be beneficial with this retainment, there are great safety issues associated with this retainment such as possible organ toxicity and substance retention of non- biodegradable materials. Therefore, preclinical studies need to be conducted over time, which would evaluate the chronic impact of metallic nanoparticles and inform the safe dose by communicating safe dose translations into clinical[32].

Analysis tools used to examine the pharmacokinetics of nanoparticles in animals can be categorized as fluorescence imaging, radiolabeling, and histological tissue due to the simultaneous ability to assess the distribution patterns with both quantitative and qualitative analysis[33]. These methods have shown that the monolith size, surface charge, hydrophobicity and composition of material play an important role in influencing circulation time, organ diffusion and clearance rates. Interspecies differences in metabolism and immune response do not ensure lack of understanding of animal-to-human pharmacometabolism predictions and comparative studies and close extrapolation in the planning of clinical trials are warranted[34].

5. DISCUSSION

Animal research results are strong indicators that nanoparticles play a major role in improving the therapeutic effect by enhancing drugs targeting, increasing bioavailability enhancement and reducing the systemic toxicity[35]. These papers show that different nanoparticle platforms can penetrate across the biological barriers, including blood-brain barrier, to treat some of the hard-to-treat illnesses like neurodegenerative diseases and solid tumors. The data however meet significant difficulty as well with variability of biodistribution in various animal models, scaling up production of nanoparticles and lack of knowledge of long-term safety and accumulation among others. The absence of standard toxicity assessment procedures and the dearth of comparative study in the types of nanoparticles also underscores the current gaps[36]. The simulations given across these areas are important in the translation of preclinical results into safe and effective clinical applications and long-term safety studies, maximization of targeting approaches and investigation of biodegradable substitutes to metallic nanoparticles is vital.

5.1 Interpret and Analyze the Findings

Nanoparticles formulations demonstrated initiate targeted delivery, extend the blood stream and increase pharmacologic activity on animal's studies, with known beneficial effects on tissues and cancer treatment mono- and combination therapy[37]. Polymeric nanoparticles, liposomes and SLNs have shown better bioavailability and lower off-target toxicity and metallic nanoparticles multifunctional contribution towards therapy and imaging. All of the results underscore the possibilities of nanotechnology to overcome the drawbacks of implementing traditional drug delivery systems[38].

5.2 Discuss Implications and Significance

Nanoparticles have the potential of being an effective tool in treating diseases that are difficult to treat due to their capacity to cross through complex biological barriers such as the blood brain barrier. Controlled drug release and improved targeting can lower the number of side effects that are systemic, positively change patient outcomes, and increase precision medicine. This highlights their importance towards linking the preclinical research with possible clinical translation[39].

5.3 Highlight Gaps and Suggest Future Research Directions

While these are promising, there are considerable gaps such as variability in the biodistribution, missing long-term safety information and absence of standardized toxicity measures. The future studies targeted should be on the long-term preclinical safety studies, biodegradable nanoparticle substitutes, targeting ligand optimization, and comparative evaluations done systematically across the various nanoparticle platforms in order to support credible clinical translation[40].

6. CONCLUSION

Nanoparticles denote a disruptive method in directed drug delivery in terms of improving therapeutic potential, elevating bioavailability, and reducing systemic toxicity as opposed to the traditional therapy. The animal studies evidence shows that they are capable of crossing biological barriers, accumulating selectively in the target tissues and provide controlled drug release in various applications, such as oncology, neurodegenerative disorders, and antimicrobial or anti-inflamic applications among various others. Although the large molecule nanoparticles, such as polymeric and lipid-based nanoparticles, display good safety profiles, the intake of metallic nanoparticles in the event of accumulation and toxicity are alarming which explain the effective consideration of green particles. In spite of their promise, there are still challenges in the standardization of toxicity tests, optimization of approaches to targeting and reproducible and scalable manufacture. Further preclinical studies with emphasis on biodegradable options, long-term safety and comparative analysis of variations among the nanoparticle platforms are necessary to convert such innovations into safe, efficacious and clinically feasible nanotherapeutic.

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