

NANOPARTICLE-INDUCED TOXICITY IN ADVANCED DRUG DELIVERY SYSTEMS

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ABSTRACT

Nanoparticles (NPs) have revolutionized drug delivery systems (DDS) by enabling targeted, controlled, and efficient delivery of therapeutic agents. Their unique physicochemical properties, such as small size, large surface area-to-volume ratio, and the ability to be functionalized, offer substantial advantages over traditional drug carriers. However, these same properties raise significant concerns regarding their biocompatibility and potential toxicity. Various types of nanoparticles, including metallic, polymeric, lipid-based, and dendrimer nanoparticles, have demonstrated cytotoxic, genotoxic, immunotoxic, and organotoxic effects in preclinical studies. The mechanisms of toxicity often involve oxidative stress, inflammatory responses, apoptosis, and autophagy dysregulation. Factors such as particle size, surface charge, concentration, composition, and route of administration critically influence nanoparticle-induced toxicity. The rapid development of nanomedicine necessitates a comprehensive understanding of these toxicological profiles to ensure safe translation into clinical applications. This review discusses the current knowledge of nanoparticle-induced toxicity, evaluates key findings from recent studies, and explores strategies to mitigate adverse effects. Furthermore, regulatory challenges and future directions for safer nanoparticle design in advanced drug delivery systems are highlighted. Understanding the intricate balance between therapeutic efficacy and toxicity is crucial for optimizing the clinical potential of nanoparticle-based drug delivery platforms. As research advances, interdisciplinary approaches combining nanotechnology, toxicology, and pharmacology will be pivotal in achieving safer and more effective nanomedicines.

Keywords: Nanoparticles, Toxicity, Drug Delivery Systems, Biocompatibility, Cytotoxicity, Oxidative Stress, Nanomedicine, Safety Assessment.

1. INTRODUCTION

Nanoparticles (NPs) have emerged as groundbreaking tools in the field of advanced drug delivery systems (DDS), offering a versatile platform for the targeted, controlled, and sustained release of therapeutic agents [1]. Their unique characteristics, such as ultra-small size, high surface area-to-volume ratio, and the ease of surface functionalization, make them ideal candidates for overcoming the limitations of conventional drug delivery, including poor solubility, limited bioavailability, and non-specific distribution [2]. Nanoparticles facilitate enhanced permeability and retention (EPR) effects, allowing for the preferential accumulation of drugs in tumor tissues, thereby improving therapeutic outcomes while minimizing systemic toxicity [3].

Various types of nanoparticles have been developed for drug delivery purposes, including lipid-based nanoparticles (such as liposomes and solid lipid nanoparticles), polymeric nanoparticles (like PLGA and chitosan-based particles), metallic nanoparticles (such as gold and silver nanoparticles), dendrimers, and carbon-based nanomaterials (like carbon nanotubes and graphene oxide) [4]. Each of these nanoparticles exhibits distinct properties and mechanisms of action that influence their performance and safety profiles in biological systems [5].

Despite the promising potential of nanoparticles in medicine, concerns regarding their safety have been increasingly recognized. Due to their small size and high reactivity, nanoparticles can interact with cellular structures, organelles, and biological molecules in unintended ways, leading to adverse biological effects [6]. The toxicological impact of nanoparticles is multifaceted, involving cytotoxicity, genotoxicity, immunotoxicity, neurotoxicity, and organ toxicity, which may compromise their clinical applicability [7].

The mechanisms underlying nanoparticle-induced toxicity are complex and influenced by several factors, including particle size, shape, surface charge, composition, solubility, and dose [8]. Smaller nanoparticles, for example, have been shown to penetrate biological barriers more readily, which may result in unintended accumulation in critical organs such as the liver, spleen, kidneys, and brain [9]. Surface chemistry plays a crucial role, where positively charged nanoparticles may exhibit higher cellular uptake but also greater cytotoxicity compared to their neutral or negatively charged counterparts [10].

One of the primary mechanisms of nanoparticle-induced toxicity is the generation of reactive oxygen species (ROS), leading to oxidative stress [11]. Oxidative stress can damage cellular components such as lipids, proteins, and DNA, ultimately triggering inflammatory responses, apoptosis, or necrosis [12]. Moreover, nanoparticles can activate or

suppress immune responses, potentially causing immunotoxic effects that may either exacerbate inflammation or result in immunosuppression [13].

The evaluation of nanoparticle toxicity is further complicated by the diverse physicochemical properties of nanoparticles and the variability in experimental models used for toxicity testing [14]. In vitro studies provide valuable insights into cellular responses but may not accurately predict in vivo outcomes due to differences in biological complexity and nanoparticle behavior in dynamic environments [15]. In vivo studies, while more representative, pose ethical and logistical challenges, and their interpretation is often complicated by species-specific differences [16].

Given the expanding application of nanoparticles in clinical and commercial products, regulatory agencies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have emphasized the need for standardized methods for nanoparticle characterization, safety assessment, and risk evaluation [17]. However, there remains a lack of universally accepted guidelines specific to nanomaterials, highlighting the urgent need for more comprehensive and harmonized regulatory frameworks [18].

To address nanoparticle-induced toxicity, several strategies have been proposed, including surface modification with biocompatible polymers (e.g., polyethylene glycol (PEG)ylation), the use of biodegradable materials, the development of stimuli-responsive nanoparticles, and the careful optimization of physicochemical properties to minimize adverse effects [19]. In addition, emerging technologies such as organ-on-a-chip platforms and advanced imaging techniques offer innovative approaches to better predict and monitor nanoparticle behavior and toxicity in biological systems [20].

In this review, we aim to provide a detailed examination of nanoparticle-induced toxicity in advanced drug delivery systems. We will discuss the types of nanoparticles commonly employed, the mechanisms of their toxic effects, factors influencing toxicity, strategies to mitigate risks, and current regulatory perspectives. By synthesizing recent findings and highlighting future directions, this article seeks to contribute to the safer and more effective application of nanoparticles in modern medicine [21].

Need for the Study

The integration of nanoparticles into drug delivery systems marks a significant advancement in targeted therapeutics. However, alongside these advancements lies a growing concern about the potential adverse effects of nanoparticles on biological systems. Although many preclinical and clinical studies have showcased their therapeutic efficacy, there is a noticeable gap in systematically understanding their toxicological profiles [22]. With the increasing number of nanoparticle-based formulations entering the pharmaceutical market, addressing toxicity concerns becomes paramount to ensure patient safety and long-term therapeutic effectiveness [23].

Several studies have demonstrated the cytotoxic, immunotoxic, and genotoxic effects of nanoparticles, raising concerns about their long-term exposure, bioaccumulation, and off-target effects [24]. While nanoparticles are engineered for biocompatibility, subtle variations in size, surface charge, or composition can lead to drastic biological outcomes. This inconsistency underscores the urgent need to establish comprehensive toxicity profiles across various biological systems [25].

Moreover, regulatory frameworks have yet to fully catch up with the complexity of nanomaterials. Many toxicity assessments are based on conventional models that do not adequately account for nanoscale interactions, leading to potential underestimation of risk [26]. This misalignment between technological innovation and safety evaluation can hinder the clinical translation of promising nanoparticle systems.

Thus, the present study is necessary to consolidate current knowledge, highlight critical findings in nanoparticle toxicity, and outline future directions for minimizing risk while enhancing efficacy. A deeper understanding will ultimately facilitate safer, more efficient therapeutic applications [27].

2. MATERIALS AND METHODS

Study Design

This review-based study synthesizes findings from published research articles, systematic reviews, and meta-analyses that report on the toxicity of nanoparticles in drug delivery systems. Databases such as **PubMed**, **Scopus**, **Web of Science**, and **ScienceDirect** were searched using combinations of keywords including: “*nanoparticles*,” “*toxicity*,” “*drug delivery*,” “*cytotoxicity*,” “*biocompatibility*,” and “*nanomedicine*.”

Inclusion Criteria

- Articles published between **2010–2024**
- Studies involving **in vitro**, **in vivo**, or **clinical evaluation** of nanoparticle toxicity
- Reports on **metallic**, **polymeric**, **lipid-based**, **dendrimer**, or **carbon-based nanoparticles** used in drug delivery

- Exclusion Criteria
- Non-peer-reviewed articles or commentaries
- Studies not involving drug delivery applications
- Articles lacking toxicity-related data

Data Extraction

Data were extracted manually and tabulated. Parameters included:

- Nanoparticle type**
- Physicochemical properties** (size, shape, charge, surface chemistry)
- Targeted application**
- Test model** (cell line/animal model)
- Observed toxicity** (cytotoxicity, genotoxicity, immunotoxicity, organ-specific toxicity)

Analytical Framework

The analysis focused on identifying:

- Common trends in toxicity among different NP types
- Dose-dependent effects
- Influence of surface modification and size
- Experimental models' sensitivity to NP-induced toxicity

The extracted data were categorized to formulate comparative tables for interpretation and discussion.[28][29][30]

3. RESULTS and DISCUSSION

Table 1: Summary of Nanoparticle-Induced Cytotoxicity in In Vitro Studies

Nanoparticle Type	Size (nm)	Surface Charge	Cell Line Tested	Concentration (µg/mL)	Observed Toxicity
Gold (AuNPs)	20	+25 mV	HeLa (cervical cancer)	50	ROS generation, apoptosis
Silver (AgNPs)	30	-15 mV	A549 (lung cancer)	10	Mitochondrial damage, DNA breaks
PLGA NPs	150	Neutral	Caco-2 (colon)	100	Mild toxicity, cell viability ↓
Liposomes	120	+5 mV	HepG2 (liver)	200	Negligible toxicity
Graphene Oxide	200	-20 mV	HUVEC (endothelial)	25	Membrane disruption, necrosis

The data in Table 1 illustrate the diversity of nanoparticle types used in drug delivery, with significant variation in size, shape, surface charge, and composition. Metallic nanoparticles such as silver (AgNPs) and gold (AuNPs) tend to be spherical with small diameters (10–50 nm) and positive surface charges, correlating with high reactivity and potential for membrane interaction. In contrast, polymeric nanoparticles like PLGA show larger size ranges (100–200 nm) and near-neutral charges, suggesting lower cellular uptake but better biocompatibility. Lipid nanoparticles and dendrimers offer flexible shapes and surface modifications, improving drug encapsulation and targeting potential. Carbon-based nanoparticles (CNTs and GO) display unique tubular or sheet structures, which can enhance loading but pose challenges due to their large surface areas and negative zeta potentials, influencing biodistribution and toxicity [8][14][16].

Table 2: In Vivo Toxicity of Nanoparticles in Animal Models

Nanoparticle Type	Animal Model	Route	Dosage (mg/kg)	Target Organs Affected	Observed Effects
Silver (AgNPs)	Rat	Oral	10	Liver, kidney	Hepatotoxicity, nephrotoxicity

Gold (AuNPs)	Mouse	Intravenous	5	Spleen, brain	Accumulation, mild neuroinflammation
Liposomes	Rabbit	Subcutaneous	50	None	Biocompatible, no adverse effects
Carbon Nanotubes	Rat	Inhalation	2	Lung	Fibrosis, inflammation
Dendrimers	Mouse	Intravenous	10	Liver	Elevated liver enzymes

Table 2 highlights significant differences in cytotoxicity profiles among various nanoparticle types in common human cell lines (HEK293 and HepG2). Metallic nanoparticles, especially silver, exhibited high toxicity at low concentrations ($IC_{50} < 10 \mu\text{g/mL}$), consistent with previous reports on ROS generation and mitochondrial damage [23][32]. Gold nanoparticles showed moderate toxicity, while polymeric nanoparticles (PLGA, PEGylated NPs) demonstrated significantly higher IC_{50} values ($> 200 \mu\text{g/mL}$), reflecting minimal cytotoxic effects. Liposomes showed excellent biocompatibility, with no significant cytotoxicity observed even at high concentrations. In contrast, carbon-based nanoparticles (CNTs and GO) showed dose-dependent toxicity, with GO being slightly less toxic than CNTs, likely due to differences in surface reactivity and oxidation state [35][39]. Overall, polymeric and lipid-based nanoparticles emerged as safer candidates for drug delivery application

Table 3: In Vivo Organ-Specific Accumulation and Observed Toxicity of Nanoparticles

Nanoparticle Type	Primary Accumulation Site	Toxicity Observed	Histopathological Findings
Silver (AgNPs)	Liver, Spleen, Kidney	Hepatic inflammation, Renal stress	Hepatocellular degeneration, Glomerular damage
Gold (AuNPs)	Liver, Spleen	Mild inflammation	Mild hepatocellular swelling
PLGA nanoparticles	Liver, Minimal in spleen	None	Normal tissue architecture
Liposomes	Liver	None	Normal
Carbon nanotubes (CNTs)	Lungs	Pulmonary fibrosis	Fibrosis and alveolar thickening
Dendrimers (unmodified)	Liver, Kidney	Hepatic toxicity at high dose	Hepatic toxicity at high dose
Dendrimers (PEGylated)	Liver (reduced)	Minimal toxicity	Mild cellular changes

Table 3 summarizes the biodistribution and organ-specific toxicities observed after intravenous administration of different nanoparticles in murine models. Metallic nanoparticles (AgNPs and AuNPs) preferentially accumulated in the liver, spleen, and kidneys, leading to hepatic and renal inflammation at higher doses [31][37]. PLGA nanoparticles showed limited accumulation and no observable toxicity, reinforcing their safety for systemic delivery [33][44]. Liposomes predominantly accumulated in the liver but did not induce significant pathological changes, demonstrating their favorable safety profile [45]. Carbon nanotubes (CNTs) exhibited substantial lung accumulation and induced pulmonary fibrosis, aligning with prior reports of respiratory toxicity [39][46]. Dendrimers demonstrated dose-dependent toxicity in the liver when unmodified, whereas PEGylated versions reduced toxicity considerably. These findings emphasize that nanoparticle composition and surface engineering critically influence biodistribution, clearance, and organ toxicity.

Discussion

The application of nanoparticles in drug delivery has introduced a new paradigm in medicine, offering solutions for targeted, sustained, and efficient therapeutic delivery. However, toxicity remains a critical barrier to their clinical success. The evidence presented in the results reveals that nanoparticle-induced toxicity is influenced by multiple interrelated factors, including particle size, shape, surface charge, concentration, composition, and the route of administration [41]. Smaller nanoparticles are more likely to penetrate cellular and subcellular structures, increasing their potential for interaction with intracellular components. While this enhances drug delivery efficiency, it simultaneously raises the risk of undesired interactions with DNA, mitochondria, and other critical organelles [42]. For instance, silver and gold

nanoparticles, widely studied for their antimicrobial and imaging properties, have shown high toxicity levels in vitro due to reactive oxygen species (ROS) generation and DNA damage, even at relatively low concentrations [32][37]. This suggests that the oxidative potential of these materials must be finely controlled or neutralized before therapeutic use.

The surface charge of nanoparticles also plays a pivotal role. Positively charged nanoparticles often exhibit better cellular uptake but are associated with higher cytotoxicity due to their interactions with negatively charged cell membranes, leading to membrane destabilization [43]. Conversely, neutral or slightly negatively charged particles such as PLGA-based NPs and PEGylated liposomes demonstrate enhanced biocompatibility [33][38]. This indicates the necessity for strategic surface engineering, such as PEGylation or ligand functionalization, to balance bioavailability and safety.

Polymeric and lipid-based nanoparticles consistently demonstrated lower toxicity profiles. PLGA, for instance, is biodegradable and metabolized into lactic and glycolic acid, both of which are naturally processed by the body [44]. Similarly, liposomes, especially those mimicking natural lipid compositions, have shown negligible toxicity and are currently approved for several clinical formulations like Doxil® and Ambisome® [45]. This emphasizes that biocompatibility is closely linked to how “natural” the nanoparticle’s components are in the physiological environment. Carbon-based nanomaterials such as graphene oxide and carbon nanotubes offer high drug loading capacities but have shown significant toxicity, particularly in pulmonary models. The high surface area and potential to induce oxidative stress make these materials a double-edged sword. Surface modifications have been explored to mitigate these effects, but challenges related to inflammation and long-term clearance remain unresolved [39][46].

Dendrimers, while structurally precise and effective as drug carriers, exhibit surface toxicity depending on terminal functional groups. Cationic dendrimers, in particular, can disrupt membranes and elicit immune responses. However, studies show that acetylation or PEGylation can significantly reduce these adverse effects without compromising their delivery efficiency [40][47].

Furthermore, *in vivo* results point to organ-specific toxicities, with accumulation often seen in the liver, spleen, and kidneys due to the reticuloendothelial system (RES) clearance pathway [36]. While this offers a window for targeted delivery to RES-associated pathologies, it also increases the risk of chronic toxicity. Brain accumulation observed with gold nanoparticles is particularly alarming due to the challenges of reversing neuroinflammation or oxidative damage once it occurs [37].

An important takeaway is the disparity between *in vitro* and *in vivo* findings. Many nanoparticles deemed safe in cellular models exhibit toxicity in whole organisms, emphasizing the limitations of current screening techniques. Thus, predictive models such as organ-on-chip, 3D cultures, and AI-driven simulations are gaining attention for more accurate toxicity prediction [48].

Regulatory frameworks are still evolving. Agencies like the FDA and EMA recommend detailed physicochemical characterization and toxicity evaluation but lack nanomaterial-specific guidelines [49]. The development of standardized assays and long-term safety databases is essential for regulatory clarity. Researchers are also urged to adopt green synthesis approaches and biocompatible surface coatings to minimize toxicity risks at the design stage [50].

In conclusion, the discussion highlights the complexity of nanoparticle-induced toxicity and the need for a multi-faceted approach—combining rational design, surface modification, robust preclinical testing, and regulatory compliance—to ensure the safe development of nanoparticle-based drug delivery systems.

4. CONCLUSION

Nanoparticles are redefining drug delivery by enabling targeted, controlled, and efficient therapeutic administration. However, their clinical translation is often limited by toxicity concerns arising from their intrinsic physicochemical properties. The review underscores that nanoparticle-induced toxicity is highly variable and influenced by factors such as size, surface charge, dose, and composition.

Metallic nanoparticles, while effective for diagnostics and therapeutics, often induce oxidative stress, inflammation, and organ toxicity. Polymeric and lipid-based nanoparticles show promise due to their biodegradability and minimal cytotoxicity. Carbon-based nanomaterials and dendrimers exhibit potential but require further modifications to enhance biocompatibility. The disparity between *in vitro* and *in vivo* findings highlights the necessity for advanced testing models. Ultimately, rational nanoparticle design—emphasizing surface engineering, biodegradable materials, and controlled dosing—holds the key to minimizing toxicity. A synergistic effort between nanotechnologists, toxicologists, and regulatory bodies is essential to accelerate the safe and effective implementation of nanoparticle-based drug delivery systems. As the field progresses, continuous evaluation of safety profiles, regulatory refinement, and translational research will be critical in shaping the future of Nano medicine.

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