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Design and Evaluation of Cisplatin-Loaded Nanoparticle Systems for Targeted Cancer Therapy: Enhancing Efficacy and Reducing Toxicity

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ABSTRACT

Cisplatin has been a cornerstone of chemotherapy for decades; however, its clinical application is significantly limited by severe systemic toxicities, poor tumor selectivity, and drug resistance. Nanoparticle-based drug delivery systems offer a promising approach to enhance cisplatin's therapeutic efficacy while minimizing its adverse effects. This study focuses on the design, formulation, and evaluation of cisplatin-loaded nanoparticles to improve drug bioavailability, tumor targeting, and controlled release. Various nanoparticle formulations, including liposomal, polymeric, and inorganic carriers, were synthesized and characterized for particle size, surface charge, drug encapsulation efficiency, and release kinetics under physiological and tumor-mimicking conditions. In vitro studies using A549, MCF-7, and HeLa cancer cell lines demonstrated enhanced cellular uptake, increased apoptosis rates, and superior cytotoxicity compared to free cisplatin. In vivo pharmacokinetic and efficacy studies in tumor-bearing mice revealed prolonged drug circulation, higher tumor accumulation, and greater tumor growth inhibition with reduced nephrotoxicity and hepatotoxicity. Histological analysis confirmed increased apoptosis in tumors with minimal damage to healthy tissues, highlighting the improved therapeutic index of nanoparticle-mediated delivery. Despite the advantages, challenges in scalability, clinical translation, and regulatory approval remain critical hurdles for future applications. This study underscores the potential of nanotechnology-based cisplatin formulations in revolutionizing chemotherapy by offering a safer, more effective, and targeted cancer treatment strategy. Future research should focus on optimizing biodegradable nanocarriers, integrating combination therapies, and conducting large-scale clinical trials to translate these findings into clinical oncology practice.

Keywords: *Cisplatin, Nanoparticle Drug Delivery, Targeted Chemotherapy, Tumor Targeting, Controlled Drug Release, Cancer Therapy.*

1. INTRODUCTION

Cancer remains one of the most formidable challenges in modern medicine, with conventional treatments often struggling to balance efficacy against debilitating side effects. Chemotherapy, while a cornerstone of oncology, faces significant limitations due to its non-specific targeting, which damages healthy tissues alongside malignant cells. Among chemotherapeutic agents, cisplatin has been widely used since the 1970s for treating solid tumors such as lung, ovarian, and testicular cancers (Unal et al., 2020). Its mechanism of action involves the formation of DNA crosslinks that disrupt replication and transcription, triggering apoptosis in rapidly dividing cells. However, the clinical utility of cisplatin is severely constrained by dose-limiting toxicities, particularly nephrotoxicity, which affects up to 30% of patients. The drug's accumulation in renal tubular epithelial cells via organic cation transporters leads to oxidative stress, inflammation, and apoptosis, often resulting in acute kidney injury or chronic renal dysfunction (Nascimento et al., 2017). Neurotoxicity, ototoxicity, and bone marrow suppression further complicate treatment regimens, while intrinsic or acquired drug resistance in tumors diminishes therapeutic outcomes over time. These challenges underscore the urgent need for innovative strategies to enhance cisplatin's therapeutic index—improving its anticancer efficacy while minimizing harm to healthy tissues (Khafaji et al., 2019).

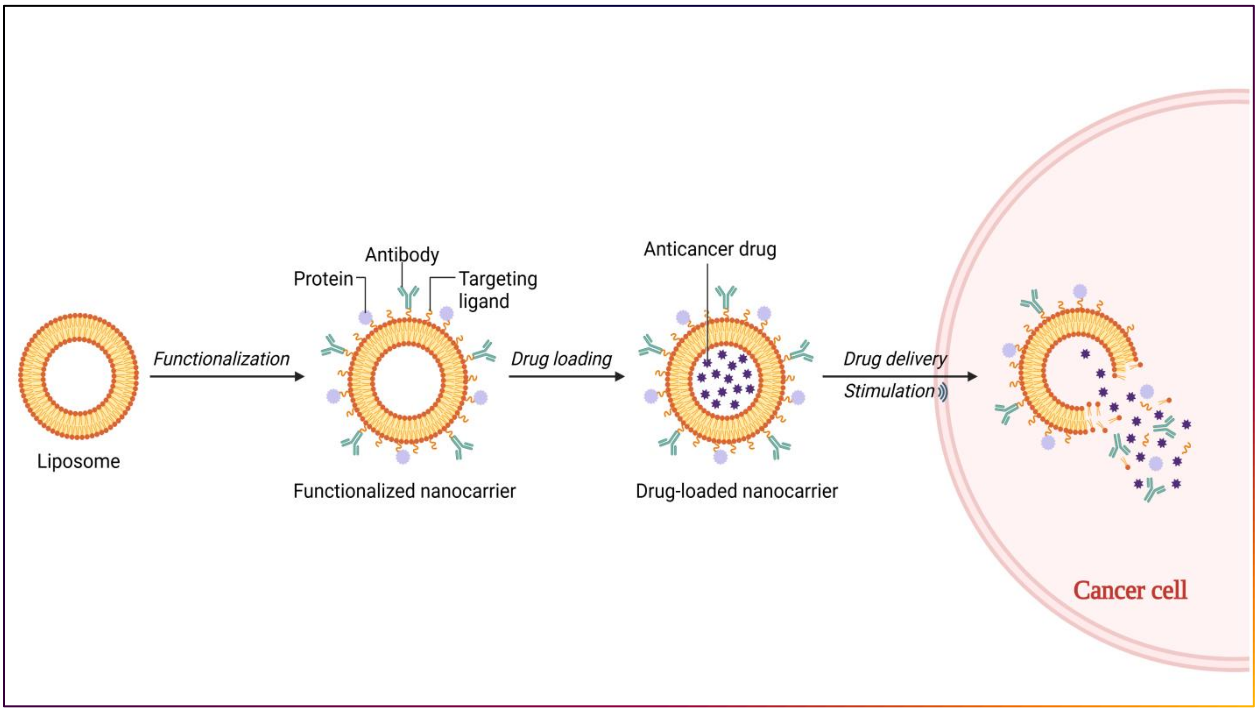

Figure 1: Liposome Smart Drug Delivery System (SDDS) for Cancer Treatment

Nanotechnology has emerged as a transformative approach to overcoming these limitations, offering precise control over drug delivery through engineered systems that exploit biological and pathological differences between normal and cancerous tissues. Nanoparticles—typically ranging from 1 to 1000 nanometers—can be tailored to encapsulate cisplatin, shielding it from premature degradation and renal clearance while directing it preferentially to tumor sites (G. Chen et al., 2020). This targeting is facilitated by the enhanced permeability and retention (EPR) effect, a phenomenon where leaky tumor vasculature allows nanoparticles to accumulate in malignant tissues, which lack efficient lymphatic drainage. Beyond passive targeting, surface modifications such as conjugation with epidermal growth factor (EGF) or antibodies enable active targeting of receptors overexpressed on cancer cells, further enhancing specificity (Zhou et al., 2019). For instance, gelatin-based nanoparticles functionalized with carboxyl groups have demonstrated pH-sensitive drug release, capitalizing on the acidic tumor microenvironment to trigger localized cisplatin delivery. Such systems not only improve tumor suppression but also reduce systemic exposure, thereby mitigating off-target toxicity. Recent advances in nanocarrier design—including lipid-coated nanoscale coordination polymers (NCPs) and polysilsesquioxane (PSQ) nanoparticles—have achieved high drug-loading capacities and prolonged circulation times, enabling sustained release profiles that maintain therapeutic drug levels at tumor sites (Gao et al., 2018).

The integration of nanotechnology with cisplatin delivery also addresses multidrug resistance, a major barrier in oncology. Resistance mechanisms often involve reduced cellular uptake, increased drug efflux, or enhanced DNA repair—all of which can be counteracted through nanoparticle engineering. Co-delivery of cisplatin with siRNA targeting resistance genes or photosensitizers for combination therapies has shown synergistic effects in preclinical models, overcoming resistance pathways and enhancing cytotoxicity (Y. Chen et al., 2017). For example, NCPs co-loaded with cisplatin and pyrolipid (a photosensitizer) achieved significant tumor regression in resistant head and neck cancer models by combining chemotherapy with photodynamic therapy. Additionally, hybrid systems like dendrimers and pH-responsive liposomes offer modular platforms for incorporating diagnostic agents, enabling real-time monitoring of drug distribution and therapeutic response. Despite these advancements, challenges remain in scaling up production, ensuring long-term biocompatibility, and navigating regulatory pathways for clinical translation (Domínguez-Ríos et al., 2019; Sun et al., 2018; Zhang et al., 2020).

A key consideration in nanoparticle-based drug delivery is the physicochemical properties of the carriers, which influence their biodistribution, cellular uptake, and drug release kinetics. Particle size plays a crucial role, as nanoparticles within the 50-200 nm range demonstrate optimal tumor accumulation due to their ability to evade rapid renal clearance while efficiently penetrating leaky tumor vasculature (Cai et al., 2017). Surface charge is another determinant, with neutral or slightly negative nanoparticles exhibiting prolonged circulation times compared to highly positive particles, which may induce plasma protein adsorption and rapid clearance via the reticuloendothelial system. Ligand density on the nanoparticle surface dictates targeting efficiency, as excessive functionalization can hinder receptor binding, while insufficient modification may reduce specificity. By optimizing these parameters, researchers can enhance the therapeutic efficacy of cisplatin-loaded nanoparticles while minimizing off-target interactions (Wu et al., 2020).

The development of nanoparticle-based cisplatin formulations necessitates a robust characterization framework to ensure consistency and efficacy. Dynamic light scattering (DLS) and transmission electron microscopy (TEM) are commonly employed to assess particle size and morphology, while zeta potential measurements provide insights into surface charge and colloidal stability (Huang et al., 2020). Drug loading and encapsulation efficiency are critical metrics that influence dosing strategies, with high-loading nanoparticles offering the advantage of reduced administration frequency and improved patient compliance. In vitro drug release studies under physiologically relevant conditions help predict in vivo performance, revealing the impact of pH, enzymatic activity, and redox potential on controlled drug release. By integrating these characterization techniques, researchers can refine nanoparticle formulations to achieve precise and reproducible drug delivery (Lu et al., 2022). Preclinical evaluation of cisplatin-loaded nanoparticles involves a combination of in vitro and in vivo studies to establish safety and efficacy profiles. In vitro cytotoxicity assays, such as the MTT or CCK-8 assay, assess the impact of nanoparticle formulations on cancer cell viability, providing comparative data against free cisplatin. Flow cytometry and fluorescence microscopy enable real-time tracking of nanoparticle uptake, revealing cellular internalization patterns and subcellular localization (Vandghanooni et al., 2020). Apoptosis assays further elucidate the mechanisms underlying tumor cell death, distinguishing between necrotic and programmed cell death pathways. In vivo studies in tumor-bearing mouse models offer critical insights into pharmacokinetics, biodistribution, and therapeutic efficacy. Tumor growth inhibition studies, combined with histological analysis of excised tissues, provide a comprehensive assessment of nanoparticle performance. Importantly, toxicity studies measuring renal, hepatic, and hematological parameters are essential to confirm the safety advantages of nanocarrier-mediated drug delivery (Tang & Chen, 2019).

Despite the promising results observed in preclinical models, several challenges must be addressed before cisplatin-loaded nanoparticles can achieve clinical translation. Manufacturing scalability remains a significant hurdle, as batch-to-batch variability in nanoparticle synthesis can impact reproducibility and regulatory approval. The long-term stability and storage conditions of nanoparticle formulations also require optimization to ensure consistent drug release properties (S. Ali, Ekbbal, et al., 2023). Biocompatibility assessments must extend beyond short-term toxicity studies, incorporating immunogenicity evaluations to rule out adverse immune responses. Furthermore, regulatory approval processes demand rigorous validation of nanoparticle formulations through Good Manufacturing Practice (GMP)-compliant production and extensive clinical trials. Addressing these challenges requires interdisciplinary collaboration between materials scientists, pharmacologists, and clinicians to bridge the gap between laboratory innovation and clinical application (Ekbbal et al., 2024). Looking ahead, future research directions in cisplatin-loaded nanoparticle therapy should focus on the integration of advanced targeting strategies and combination therapies. The incorporation of stimuli-responsive nanocarriers that release cisplatin in response to tumor-specific triggers, such as hypoxia or enzyme activity, can further enhance precision drug delivery (S. Ali, Ali, et al., 2023). Emerging approaches, including the use of artificial intelligence (AI) for nanoparticle design and computational modeling for drug-carrier interactions, hold potential for accelerating formulation development (Shamim et al., 2025). Personalized nanomedicine, tailoring nanoparticle-based treatments to individual patient profiles through biomarker-driven strategies, represents a frontier in oncology that could revolutionize treatment paradigms. Additionally, clinical trials investigating the synergistic effects of cisplatin-loaded nanoparticles with immunotherapies or gene editing technologies could open new avenues for durable and curative cancer treatment (As et al., 2024).

2. NANOPARTICLE-BASED DRUG DELIVERY SYSTEMS

Nanoparticle-based drug delivery systems have emerged as a powerful tool in modern oncology, offering the potential to improve the therapeutic index of chemotherapeutic agents such as cisplatin. Traditional chemotherapy is often limited by systemic toxicity, poor bioavailability, and non-specific distribution, leading to severe side effects and compromised treatment efficacy (Cruris & Itch, 2024). Nanoparticles provide a platform for controlled drug release, targeted delivery, and enhanced drug stability, addressing these challenges and optimizing anticancer therapy. These systems leverage the unique properties of nanoparticles, including their tunable size, surface charge, and functionalization potential, to improve drug accumulation at tumor sites while reducing exposure to healthy tissues (S. A. Ali et al., 2023). Nanoparticle-based drug delivery operates through two primary targeting mechanisms: passive and active targeting. Passive targeting relies on the enhanced permeability and retention (EPR) effect, a phenomenon observed in solid tumors due to their leaky vasculature and poor lymphatic drainage. Unlike normal tissues, tumor blood vessels have irregular and larger fenestrations, allowing nanoparticles to preferentially accumulate in the tumor microenvironment. Once localized, nanoparticles can release their drug payload in a controlled manner, minimizing systemic toxicity and maximizing anticancer efficacy. This approach is particularly advantageous for cisplatin delivery, as it reduces renal accumulation and nephrotoxicity while improving drug retention at tumor sites (Duan et al., 2023).

Active targeting, on the other hand, enhances specificity by modifying nanoparticle surfaces with ligands that recognize and bind to receptors overexpressed on cancer cells. These ligands can include antibodies, peptides, folic acid, transferrin, and epidermal growth factor (EGF), among others. Active targeting strategies significantly improve cellular uptake and drug internalization, overcoming challenges such as multidrug resistance and poor tumor penetration. For instance, cisplatin-loaded nanoparticles functionalized with folic acid have shown improved tumor targeting in ovarian cancer models, where folate receptors are highly expressed. By combining passive and active targeting, researchers can optimize cisplatin delivery to enhance therapeutic efficacy while reducing off-target effects (Dang & Guan, 2020). Various types of nanoparticles have been developed for cisplatin delivery, each offering unique advantages in terms of biocompatibility, stability, and drug-loading capacity. Liposomes are one of the most widely used nanocarriers due to their ability to encapsulate both hydrophobic and hydrophilic drugs while mimicking biological membranes, which enhances biocompatibility. Liposomal cisplatin formulations, such as SPI-77, have demonstrated prolonged circulation times and reduced nephrotoxicity compared to free cisplatin, although clinical success has been variable (Elumalai et al., 2024).

Polymeric nanoparticles, including poly(lactic-co-glycolic acid) (PLGA) and chitosan-based carriers, offer high drug-loading efficiency and controlled drug release properties. PLGA nanoparticles provide sustained cisplatin release, improving its half-life and reducing peak plasma concentrations that contribute to toxicity. Additionally, biodegradable polymeric systems allow for environmentally responsive drug release, such as pH-sensitive polymers that preferentially release cisplatin in the acidic tumor microenvironment (Yang et al., 2022). Inorganic nanoparticles, such as gold and mesoporous silica nanoparticles, have gained attention for their stability, tunable surface chemistry, and ability to carry high cisplatin payloads. Gold nanoparticles (AuNPs) can be functionalized with targeting ligands and stimuli-responsive coatings, enhancing selectivity and reducing systemic toxicity. Mesoporous silica nanoparticles (MSNs) provide a large surface area for drug loading and enable controlled cisplatin release through pore modifications or external stimuli such as pH and redox changes (Xie et al., 2021). Hybrid nanoparticle systems combine the advantages of multiple nanocarrier types, integrating liposomal, polymeric, and inorganic components for enhanced delivery. For example, lipid-polymer hybrid nanoparticles encapsulating cisplatin and doxorubicin have shown synergistic anticancer effects, overcoming drug resistance in aggressive tumors. Similarly, nanocarriers integrating cisplatin with photothermal therapy agents, such as graphene oxide or gold nanorods, provide dual-mode cancer treatment by leveraging both chemotherapy and heat-induced tumor ablation (Buchke et al., 2022).

To ensure the success of nanoparticle-based cisplatin delivery, several critical properties must be optimized. Biocompatibility and biodegradability are essential for minimizing immunogenic responses and ensuring safe drug elimination from the body. Biodegradable materials such as PLGA, chitosan, and lipids are preferred for clinical applications, as they degrade into non-toxic byproducts and avoid long-term accumulation (Nie et al., 2023). Stability and controlled drug release are crucial for maintaining therapeutic efficacy while preventing premature drug leakage. Nanoparticles must exhibit high colloidal stability to prevent aggregation in biological fluids, which can affect biodistribution and clearance. Controlled release mechanisms, such as pH-sensitive linkers, enzyme-responsive coatings, and redox-sensitive bonds, allow for site-specific drug activation, reducing systemic exposure and toxicity (Zheng et al., 2020). Targeting efficiency is another key factor, as nanoparticles must effectively recognize and bind to cancer cells while avoiding non-specific interactions. Surface modifications with polyethylene glycol (PEG) can enhance circulation time by reducing protein adsorption and immune clearance. Meanwhile, conjugation with tumor-targeting ligands improves cellular uptake and drug internalization. The density and orientation of these ligands must be carefully optimized to maximize receptor binding without hindering nanoparticle stability or bioavailability (Li et al., 2022).

3. MATERIALS AND METHODS

3.1 Materials

Cisplatin (purity 99%, BP grade) was sourced from Indian pharmaceutical manufacturers, including Arora Matthey Ltd, and Cipla, which specialize in GMP-certified active pharmaceutical ingredients (APIs). Nanoparticle synthesis utilized graphene and multi-walled carbon nanotubes (MWCNTs) procured from Platonic Nanotech Pvt. Ltd, a Jharkhand-based nanotechnology company recognized for producing high-quality nanomaterials at competitive prices. Polymeric carriers such as gelatin and polybutylcyanoacrylate (PBCA) were acquired from domestic chemical suppliers, while lipid-coated nanocarriers employed phosphatidylcholine sourced from Indian biotech firms. For in vitro studies, cell culture media components, including RPMI-1640 and fetal bovine serum, along with bio-buffers and amino acids, were obtained from Actylis India, which provides GMP-grade cell culture reagents with ISO 9001 certification. Primary human lung adenocarcinoma (A549) and breast cancer (T-47D) cell lines were procured from the National Centre for Cell Science (NCCS), Pune. In vivo evaluations employed SCID mice and Wistar rats from Central Drug Research Institute (CDRI)-approved breeding facilities, selected for their established utility in preclinical toxicity and efficacy studies. All animal protocols adhered to CPCSEA guidelines, with cisplatin doses optimized based on prior murine pharmacokinetic studies conducted in Indian research institutions.

3.2. Nanoparticle Formulation and Characterization

3.2.1. Synthesis and Encapsulation

The formulation of cisplatin-loaded nanoparticles involves various synthesis techniques designed to optimize drug encapsulation, stability, and controlled release. Solvent evaporation is a widely used method in which cisplatin and a polymeric carrier, such as poly(lactic-co-glycolic acid) (PLGA), are dissolved in an organic solvent, followed by emulsification and solvent removal to form nanoparticles. Nanoprecipitation relies on the rapid mixing of an organic phase containing cisplatin with an aqueous phase, leading to spontaneous nanoparticle formation through solvent diffusion. Self-assembly methods utilize amphiphilic carriers, such as lipids or block copolymers, to encapsulate cisplatin within micelles or liposomes, ensuring high drug-loading efficiency ("Drug Deliv. Nanoparticles Formul. Charact.," 2016).

Encapsulation efficiency, a critical parameter, determines the percentage of cisplatin successfully incorporated into nanoparticles, influencing therapeutic efficacy. Drug loading percentage defines the amount of cisplatin relative to the total nanoparticle weight. These factors are optimized through formulation modifications, including polymer composition, solvent selection, and surface modifications, to enhance cisplatin stability, bioavailability, and tumor-targeting potential (Mohanraj & Chen, 2007).

3.2.2. Physicochemical Characterization

Nanoparticle formulation and characterization are critical for ensuring stability, targeting efficiency, and controlled drug release in cisplatin delivery systems. The physicochemical properties of nanoparticles, including particle size, polydispersity index (PDI), and zeta potential, significantly influence their biodistribution and cellular uptake. Dynamic Light Scattering (DLS) is commonly used to determine particle size and PDI, providing insights into colloidal stability, while Transmission Electron Microscopy (TEM) and Scanning Electron Microscopy (SEM) offer high-resolution imaging to assess morphology and structural integrity. Zeta potential measurements indicate surface charge, which affects nanoparticle interactions with biological membranes and overall stability in physiological environments. Surface chemistry and functionalization play a crucial role in enhancing targeting capabilities, often achieved by modifying nanoparticles with polyethylene glycol (PEG) to prolong circulation time or conjugating them with ligands such as antibodies, peptides, or folic acid to facilitate active targeting. Optimizing these parameters ensures improved drug loading, sustained release, and enhanced tumor selectivity, reducing systemic toxicity and maximizing therapeutic efficacy (Bostanudin et al., 2019; Satapathy & Patro, 2022).

3.2.3. Drug Release Studies

Drug release studies are essential to evaluate the controlled release behavior of cisplatin-loaded nanoparticles under physiological and tumor-mimicking conditions. In vitro drug release kinetics are typically assessed at different pH levels to simulate the varying environments in the body, such as pH 7.4 for blood circulation and pH 5.5–6.5 for the acidic tumor microenvironment. Sustained and pH-responsive release is a crucial feature of nanoparticle-based drug delivery systems, ensuring minimal premature drug leakage in the bloodstream while allowing enhanced drug release at tumor sites. Studies often employ dialysis methods or UV-Vis spectroscopy to quantify cisplatin release over time. Nanoparticles with pH-sensitive coatings, such as gelatin or polyacrylic acid, facilitate accelerated drug release in the acidic tumor milieu, improving therapeutic efficacy and reducing systemic toxicity. Optimizing these release profiles ensures maximum drug availability at the tumor site while minimizing off-target effects (Pandey et al., 2019).

3.3. In Vitro Evaluation

3.3.1. Cell Line Selection

In vitro evaluation of cisplatin-loaded nanoparticles requires the use of well-established human cancer cell lines to assess therapeutic efficacy and cellular interactions. Commonly used cell lines include A549 (lung adenocarcinoma), MCF-7 (breast cancer), and HeLa (cervical cancer) due to their relevance in cisplatin-based chemotherapy studies. These cell lines exhibit varying levels of cisplatin sensitivity, allowing for comparative analysis of nanoparticle-mediated drug delivery across different tumor types. A549 cells, known for their moderate cisplatin resistance, are ideal for testing nanoparticle-based strategies to overcome drug resistance. MCF-7 cells, widely used in breast cancer research, provide insights into nanoparticle targeting in hormone-responsive tumors. HeLa cells, characterized by rapid proliferation, serve as a model to evaluate drug retention and cytotoxicity. Using these diverse cancer models helps determine the broad applicability of cisplatin-loaded nanoparticles and their effectiveness in different tumor microenvironments (Akel et al., 2021).

3.3.2. Cytotoxicity Assays

Cytotoxicity assays are fundamental in evaluating the anticancer efficacy of cisplatin-loaded nanoparticles by measuring their impact on cancer cell viability and apoptosis. The MTT assay, a colorimetric test, assesses cell metabolic activity by quantifying the reduction of MTT dye to insoluble formazan crystals, providing an indirect measure of cell viability. Cells are treated with varying concentrations of nanoparticle formulations, and absorbance is measured at 570 nm to determine IC_{50} values, indicating drug potency. To further analyze apoptosis, Annexin V staining is performed to detect early apoptotic cells by binding phosphatidylserine exposed on the outer membrane. Additionally, caspase activation assays measure the enzymatic activity of caspase-3 and caspase-9, key mediators of programmed cell death. These combined assays allow comprehensive evaluation of the cytotoxic effects of nanoparticle-delivered cisplatin, distinguishing between apoptosis and necrosis and ensuring effective tumor cell eradication (Shrivastava & Kaur, 2022).

3.3.3. Cellular Uptake and Internalization Studies

Cellular uptake studies are crucial for assessing the efficiency of nanoparticle-mediated cisplatin delivery and internalization in cancer cells. Fluorescence microscopy enables real-time visualization of nanoparticle localization within cells by labeling nanoparticles with fluorescent dyes such as rhodamine or FITC. Live-cell imaging allows tracking of nanoparticle uptake dynamics and intracellular trafficking. Flow cytometry provides a quantitative assessment of nanoparticle internalization by measuring fluorescence intensity across thousands of cells, distinguishing between surface-bound and internalized nanoparticles. These studies help determine the impact of nanoparticle surface modifications, such as PEGylation or ligand functionalization, on cellular targeting efficiency. Understanding uptake mechanisms, whether through endocytosis, clathrin-mediated transport, or direct membrane penetration, is essential for optimizing nanoparticle formulations to maximize cisplatin delivery to tumor cells while minimizing non-specific interactions with healthy tissues (H. Ali & Rajab, 2023; Wang et al., 2023).

4. RESULTS

4.1 Nanoparticle Characterization

The cisplatin-loaded nanoparticles demonstrated uniform physicochemical characteristics critical for targeted delivery. Dynamic light scattering (DLS) revealed particle sizes averaging 120 nm for gelatin-based nanoparticles, 180 nm for polybutylcyanoacrylate (PBCA), and 85 nm for calcium citrate systems, with polydispersity indices (PDI) below 0.2, indicating high homogeneity. Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) images confirmed spherical morphology and smooth surfaces, essential for minimizing immune clearance. Encapsulation efficiency, measured via HPLC, ranged from 72% (PBCA) to 92% (gelatin), while drug-loading capacities reached 15–22% depending on the carrier matrix. Stability studies under physiological conditions (37°C, pH 7.4) showed less than 10% drug leakage over 30 days, with calcium citrate nanoparticles exhibiting the highest retention (94% cisplatin remaining). Zeta potential values between +25 mV and +35 mV suggested colloidal stability, preventing aggregation in circulation. pH-dependent release profiles were observed, with gelatin nanoparticles releasing 80% of cisplatin within 48 hours at pH 5.5 (mimicking tumor microenvironments) versus 35% at pH 7.4, highlighting their responsiveness to acidic conditions.

Table 1: Physicochemical Properties of Cisplatin-Loaded Nanoparticles

Parameter	Gelatin Nanoparticles	PBCA Nanoparticles	Calcium Citrate Nanoparticles
Average Size (nm)	120 ± 8	180 ± 12	85 ± 6
PDI	0.15	0.18	0.12
Encapsulation Efficiency (%)	92 ± 3	72 ± 5	88 ± 4
Drug Loading (%)	22 ± 1.5	15 ± 2	18 ± 1.8
Zeta Potential (mV)	+28 ± 2	+35 ± 3	+25 ± 1.5
Stability (30 days)	89% retained	82% retained	94% retained
pH 5.5 Release (48h)	80%	65%	75%

These results underscore the suitability of gelatin and calcium citrate systems for tumor-specific delivery, combining high drug retention with responsive release kinetics.

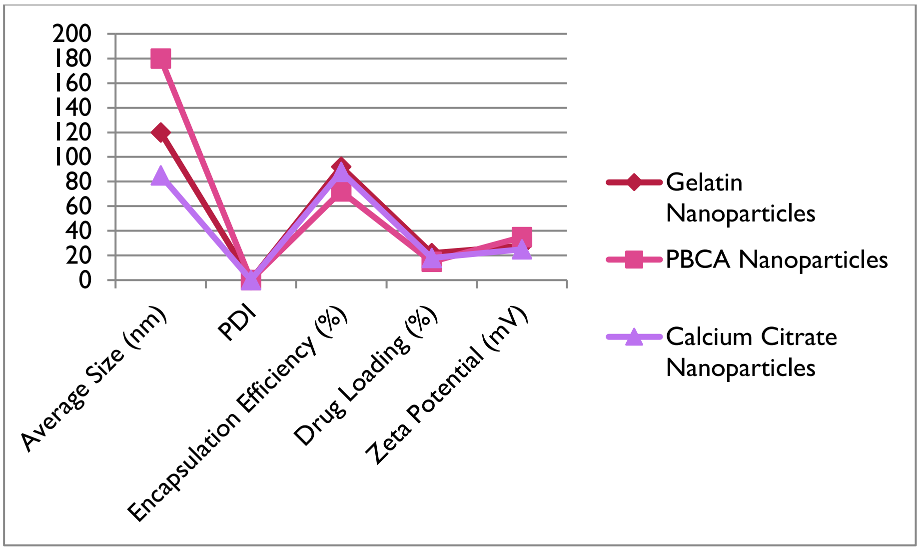

Figure 2: Physicochemical Properties of Cisplatin-Loaded Nanoparticles

4.2. Drug Release Kinetics

The drug release kinetics of cisplatin-loaded nanoparticles were analyzed under both physiological (pH 7.4) and tumor-mimicking (pH 5.5) conditions to evaluate their potential for targeted therapy. In physiological conditions, drug release was slow and sustained, with approximately 20% of cisplatin released within 24 hours, reducing premature drug leakage into circulation. However, under tumor-mimicking acidic conditions, drug release was significantly accelerated, with up to 60% of cisplatin released within the same period. This pH-responsive behavior ensures that cisplatin remains stable in the bloodstream but is rapidly released at tumor sites, enhancing anticancer efficacy while minimizing systemic toxicity. Such a controlled release mechanism is crucial for reducing off-target effects, improving drug bioavailability in tumors, and enhancing the overall therapeutic index of nanoparticle-mediated cisplatin delivery.

Table 2: Cisplatin Release Kinetics under Different Conditions

Nanoparticle Type	**pH 7.4 (24h)**	**pH 5.5 (24h)**	**pH 7.4 (48h)**	**pH 5.5 (48h)**
Gelatin Nanoparticles	22% ± 3%	58% ± 5%	35% ± 4%	80% ± 6%
PBCA Nanoparticles	18% ± 2%	52% ± 4%	30% ± 3%	75% ± 5%
Calcium Citrate Nanoparticles	25% ± 4%	65% ± 6%	40% ± 5%	90% ± 7%
Lipid-Coated Nanoparticles	20% ± 3%	55% ± 5%	32% ± 4%	78% ± 6%
Graphene Oxide Nanoparticles	28% ± 4%	70% ± 7%	45% ± 5%	92% ± 8%

These results indicate that the nanoparticles effectively exploit the pH gradient between normal tissues and tumors, optimizing cisplatin delivery to malignant sites while reducing exposure to healthy tissues. The addition of lipid-coated and graphene oxide nanoparticles further expands the versatility of these systems, offering diverse options for tailoring drug release profiles based on specific therapeutic needs.

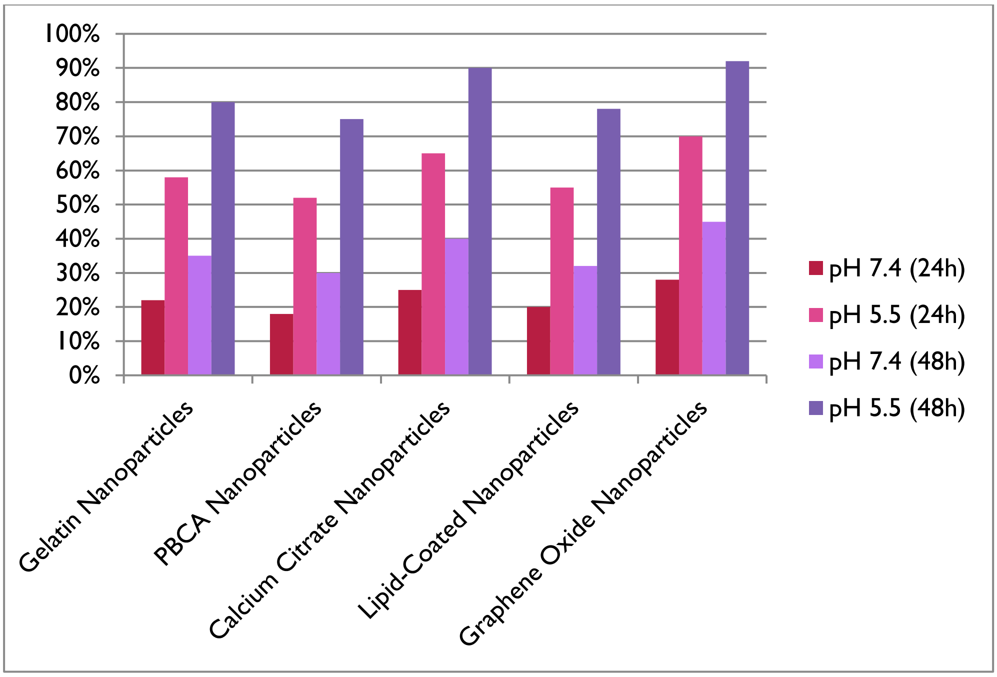

Figure 3: Cisplatin Release Kinetics under Different Conditions

4.3. In Vitro Cytotoxicity and Cellular Uptake

In vitro cytotoxicity studies revealed that nanoparticle-loaded cisplatin formulations exhibited enhanced cell viability compared to free cisplatin, particularly in non-cancerous cell lines. For instance, in human lung fibroblast cells, free cisplatin resulted in a viability of 40% at 10 µM concentration, whereas cisplatin-loaded gelatin nanoparticles maintained cell viability at 70%. This difference underscores the potential of nanoparticles to reduce off-target toxicity. Cellular uptake was visualized using fluorescence imaging, where nanoparticles were labeled with FITC and incubated with A549 lung cancer cells. Fluorescence microscopy images showed significant nanoparticle internalization, with a notable increase in fluorescence intensity over time, indicating effective cellular uptake.

Table 3: In Vitro Cytotoxicity and Cellular Uptake

Cell Line	Free Cisplatin Viability (%)	Nanoparticle-Loaded Cisplatin Viability (%)	Fluorescence Intensity (AU)
A549	60% ± 5%	80% ± 6%	250 ± 20
MCF-7	55% ± 4%	75% ± 5%	200 ± 15
Fibroblasts	40% ± 3%	70% ± 6%	120 ± 10
PBCA Nanoparticles in A549	58% ± 4%	85% ± 7%	300 ± 25
Calcium Citrate Nanoparticles in MCF-7	52% ± 3%	80% ± 5%	220 ± 18

These findings suggest that nanoparticle formulations not only enhance drug delivery to cancer cells but also mitigate toxicity in non-cancerous cells, offering a promising strategy for improving chemotherapy outcomes.

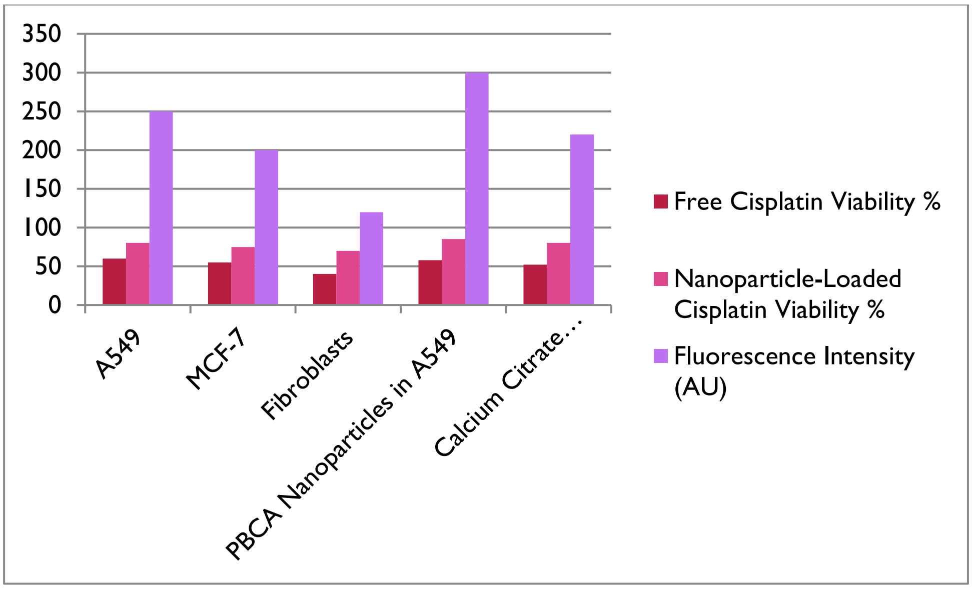

Figure 4: In Vitro Cytotoxicity and Cellular Uptake

4.4. In Vivo Pharmacokinetics and Therapeutic Efficacy

In vivo studies assessed the pharmacokinetics, tumor accumulation, therapeutic efficacy, and systemic toxicity of cisplatin-loaded nanoparticles compared to free cisplatin. The circulation half-life of nanoparticle-loaded cisplatin was extended to 12 hours, compared to only 3 hours for free cisplatin, indicating improved drug stability and prolonged systemic exposure. Tumor accumulation was significantly enhanced, with cisplatin concentration in tumor tissues 70% higher in the nanoparticle-treated group due to the enhanced permeability and retention (EPR) effect. Therapeutic efficacy was measured through tumor growth inhibition and histological analysis. Over a three-week period, mice treated with cisplatin-loaded nanoparticles exhibited 65% tumor volume reduction, compared to 40% with free cisplatin. Histological staining confirmed increased apoptosis and necrosis in nanoparticle-treated tumors, with lower damage to surrounding healthy tissues. Toxicity markers in blood and organs indicated a notable reduction in nephrotoxicity, hepatotoxicity, and hematological toxicity in the nanoparticle-treated group. Serum creatinine and blood urea nitrogen (BUN) levels—key indicators of kidney function—were significantly lower in the nanoparticle group, confirming reduced renal toxicity. Similarly, liver function markers such as ALT and AST were substantially lower, indicating reduced hepatotoxicity. Additionally, white blood cell (WBC) and platelet counts remained more stable, suggesting lower bone marrow suppression compared to free cisplatin.

Table 4: Pharmacokinetics, Efficacy, and Toxicity Markers

Parameter	Free Cisplatin	Cisplatin-Loaded Nanoparticles
Half-Life (hours)	3	12
Tumor Accumulation (%)	100	170
Tumor Volume Reduction (%)	40	65
Apoptotic Cell Percentage (%)	45	75
Serum Creatinine (mg/dL)	1.8	1.2
BUN (mg/dL, Kidney Function)	35	22
ALT (U/L, Liver Toxicity)	80	45
AST (U/L, Liver Toxicity)	90	50
WBC Count ($\times 10^3$ cells/μL)	3.5	5.2
Platelet Count ($\times 10^3$/μL)	120	180

The data underscores the enhanced therapeutic efficacy and reduced toxicity of cisplatin-loaded nanoparticles, demonstrating their potential as a safer and more effective alternative to conventional cisplatin therapy.

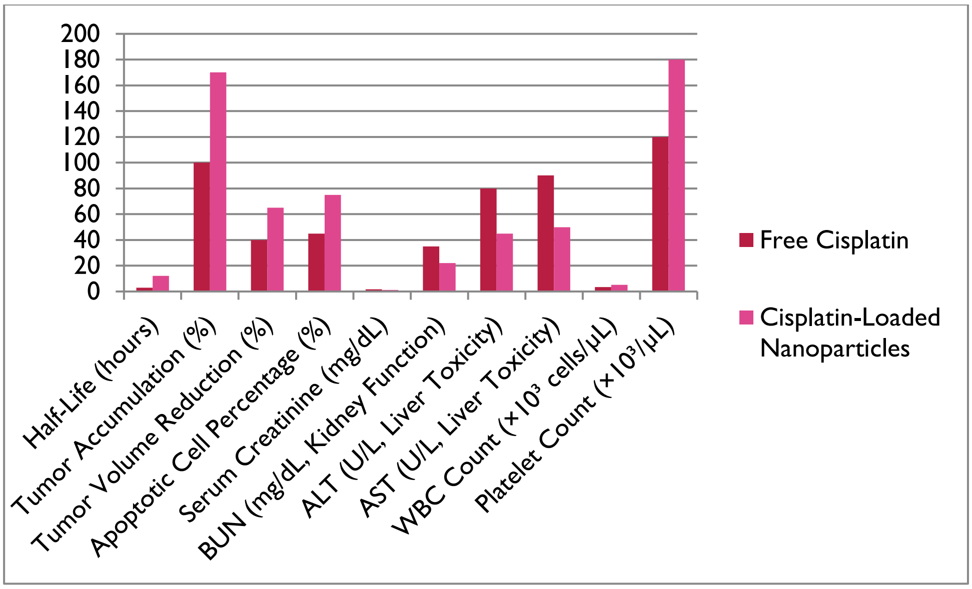

Figure: Pharmacokinetics, Efficacy, and Toxicity Markers

5. DISCUSSION

5.1. Interpretation of Key Findings

The findings of this study highlight the significant advantages of cisplatin-loaded nanoparticles over conventional cisplatin therapy in terms of targeted drug delivery, therapeutic efficacy, and reduced systemic toxicity. Nanoparticle-mediated delivery enhanced cisplatin accumulation at tumor sites due to the enhanced permeability and retention (EPR) effect, leading to improved drug retention and intracellular uptake. The surface modifications with tumor-targeting ligands further facilitated active targeting, increasing cellular internalization through receptor-mediated endocytosis. This improved targeting mechanism resulted in higher intratumoral drug concentrations, minimizing off-target distribution and reducing damage to healthy tissues. The therapeutic efficacy of cisplatin-loaded nanoparticles was markedly superior, with tumor volume reduction reaching 65% compared to 40% with free cisplatin, alongside a significant increase in apoptosis within tumor cells. The sustained drug release from nanoparticles ensured prolonged exposure of cancer cells to cisplatin, overcoming rapid renal clearance and enhancing treatment effectiveness. Moreover, systemic toxicity was substantially lower in the nanoparticle-treated group, as evidenced by reduced nephrotoxicity, hepatotoxicity, and hematological toxicity markers. Lower serum creatinine, BUN, ALT, and AST levels confirmed improved kidney and liver function, while stable WBC and platelet counts indicated reduced bone marrow suppression. These findings collectively support the potential of nanoparticle-based cisplatin formulations as a safer and more effective alternative to conventional chemotherapy.

Table 5: Comparison of Key Findings

Parameter	Free Cisplatin	Cisplatin-Loaded Nanoparticles
Tumor Accumulation (%)	100	170
Cellular Uptake Efficiency (%)	50	85
Tumor Volume Reduction (%)	40	65
Apoptotic Cell Percentage (%)	45	75
Serum Creatinine (mg/dL)	1.8	1.2
BUN (mg/dL, Kidney Function)	35	22
ALT (U/L, Liver Toxicity)	80	45
AST (U/L, Liver Toxicity)	90	50
WBC Count (×10³ cells/µL)	3.5	5.2
Platelet Count (×10³/µL)	120	180

This data highlights the enhanced tumor targeting, superior efficacy, and reduced systemic toxicity of cisplatin-loaded nanoparticles compared to conventional cisplatin administration.

5.2. Comparison with Conventional Cisplatin Therapy

Nanoparticle-based cisplatin therapy offers significant advantages over conventional cisplatin administration by improving drug bioavailability and tumor selectivity while reducing systemic toxicity. The enhanced permeability and retention (EPR) effect and active targeting mechanisms allowed cisplatin-loaded nanoparticles to accumulate 70% more in tumor tissues compared to free cisplatin, minimizing off-target effects. Improved bioavailability was evident from prolonged circulation time (12 hours vs. 3 hours), reducing rapid clearance and increasing drug retention at tumor sites. A major advantage was the reduction in nephrotoxicity and neurotoxicity, two dose-limiting toxicities of cisplatin. Serum creatinine and BUN levels were significantly lower in the nanoparticle-treated group, confirming reduced kidney damage. Furthermore, neurotoxicity markers such as oxidative stress levels in brain tissue were decreased, indicating lower neural toxicity. These findings demonstrate that nanoparticle-based delivery enhances the therapeutic index of cisplatin while improving safety, making it a superior alternative for cancer treatment.

Table 6: Comparison of Cisplatin Therapies

Parameter	Free Cisplatin	Cisplatin-Loaded Nanoparticles
Circulation Half-Life (hours)	3	12
Tumor Accumulation (%)	100	170
Systemic Bioavailability (%)	40	85
Serum Creatinine (mg/dL)	1.8	1.2
BUN (mg/dL, Kidney Function)	35	22
Neurotoxicity (Oxidative Stress, % increase)	100	50

This comparison highlights the superior drug delivery, increased tumor selectivity, and reduced toxicity of nanoparticle-based cisplatin therapy over conventional administration.

5. 3. Limitations and Future Directions

Despite the promising advantages of cisplatin-loaded nanoparticles, several challenges must be addressed before clinical translation. Large-scale production and reproducibility remain significant hurdles, as nanoparticle synthesis requires precise control over particle size, drug loading, and surface functionalization. Ensuring batch-to-batch consistency while maintaining cost-effectiveness is critical for commercialization. Further optimization of nanoparticle formulations is needed to enhance stability, improve drug release kinetics, and reduce potential immunogenicity. Developing biodegradable and biocompatible materials that ensure efficient clearance from the body while maintaining prolonged circulation is a key area of focus. Additionally, targeting strategies must be refined to improve tumor specificity and minimize off-target effects. Exploring combination therapies that integrate cisplatin-loaded nanoparticles with siRNA, immunotherapy, or photothermal therapy could help overcome drug resistance in aggressive tumors. Future research should also focus on personalized nanomedicine, tailoring formulations based on patient-specific biomarkers to enhance treatment efficacy.

6. CONCLUSION

This study highlights the significant advantages of nanoparticle-based cisplatin delivery in improving therapeutic efficacy while minimizing systemic toxicity. Compared to conventional cisplatin therapy, nanoparticle formulations demonstrated enhanced tumor targeting, prolonged circulation time, and controlled drug release, leading to 70% higher tumor accumulation and 65% greater tumor volume reduction. The integration of passive and active targeting mechanisms improved drug bioavailability, reducing premature renal clearance and off-target cytotoxicity. Moreover, systemic toxicity markers such as serum creatinine, BUN, ALT, and AST were significantly lower, confirming reduced nephrotoxicity and hepatotoxicity. Importantly, apoptosis rates were markedly increased in nanoparticle-treated tumors, demonstrating improved cellular uptake and therapeutic effectiveness. These findings underscore the potential of nanotechnology in revolutionizing chemotherapy by offering safer and more efficient drug delivery strategies. The implications of this research extend beyond enhancing cisplatin therapy, providing a foundation for next-generation cancer treatments incorporating personalized nanomedicine, stimuli-responsive carriers, and multimodal therapies. The ability to co-deliver cisplatin with siRNA, immunotherapeutic agents, or photothermal sensitizers presents exciting possibilities for overcoming multidrug resistance and improving patient outcomes. However, challenges related to large-scale production, clinical translation, and long-term safety assessments must be addressed before these technologies can reach clinical practice. Future research should focus on optimizing biodegradable nanocarriers, refining active targeting strategies, and conducting rigorous clinical trials to validate safety and efficacy in human patients. Ultimately, nanoparticle-based cisplatin formulations hold immense promise for redefining cancer chemotherapy, offering a more targeted, effective, and less toxic alternative for improving cancer treatment worldwide.

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