GSC Advanced Research and Reviews
eISSN: 2582-4597 CODEN (USA): GARRC2
Cross Ref DOI: 10.30574/gscarr
Journal homepage: https://gsconlinepress.com/journals/gscarr/

(REVIEW ARTICLE)

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Development of cisplatin as an anti-cancer drug

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GSC Advanced Research and Reviews, 2025, 23(01), 005-011

Publication history: Received on 17 February 2025; revised on 25 March 2025; accepted on 27 March 2025

Article DOI: https://doi.org/10.30574/gscarr.2025.23.1.0101

Abstract

Cisplatin, a platinum-based chemotherapeutic agent, has been a cornerstone in the treatment of various cancers since its FDA approval in 1978. It is particularly effective against cancers such as ovarian, colorectal, prostate, bladder, and non-small cell lung cancer (NSCLC). Cisplatin exerts its anticancer effects by forming platinum-DNA adducts that inhibit DNA replication and transcription, leading to cell cycle arrest and apoptosis. However, its clinical application is limited by severe side effects, including renal toxicity, nausea, vomiting, and the development of drug resistance. To mitigate these challenges, there has been increasing interest in encapsulating cisplatin in nanocarriers, particularly liposomes. Liposomal formulations, such as Lipoplatin™, enhance cisplatin's accumulation in tumors through the enhanced permeability and retention (EPR) effect while reducing toxicity to healthy tissues. Further innovations, including cisplatin encapsulated in PLGA-coated liposomes and co-encapsulation with other therapeutic agents, have shown promise in improving drug release profiles and therapeutic efficacy. This review examines the molecular mechanisms of cisplatin action, its therapeutic challenges, and advancements in its nanostructured formulations. Emphasis is placed on liposomal delivery systems, which offer significant potential to improve cisplatin's effectiveness, reduce systemic toxicity, and overcome resistance, paving the way for more efficient and targeted cancer treatments.

Keywords: Cisplatin; Anti-cancer treatment; Nanoparticles; Combination Therapy; Lipoplatin™

1. Introduction

Cisplatin, a platinum-based chemotherapeutic agent, has become a cornerstone in the treatment of various cancers since its discovery in the 1960s and subsequent approval by the FDA in 1978. It is widely used for treating cancers such as ovarian, colorectal, prostate, bladder, and non-small cell lung cancer (NSCLC), among others. Cisplatin exerts its anticancer effects through its ability to bind to DNA, forming platinum-DNA adducts that inhibit DNA replication and transcription, leading to cell cycle arrest and induction of apoptosis in cancer cells. Despite its significant therapeutic benefits, cisplatin is associated with several challenges, including severe side effects such as renal toxicity, nausea, vomiting, and the development of drug resistance in cancer cells.

To address these limitations, researchers have increasingly focused on enhancing the efficacy and reducing the toxicity of cisplatin by encapsulating it in various nanocarriers. One promising approach is the use of liposomes—nano-sized lipid vesicles that can encapsulate cisplatin and improve its targeted delivery to cancer cells. Liposomal formulations such as Lipoplatin™ have shown promise by enhancing the drug's accumulation in tumors through the enhanced permeability and retention (EPR) effect, while minimizing toxicity to normal tissues. Additionally, alternative formulations such as cisplatin encapsulated in PLGA-coated liposomes or co-encapsulation with other agents, have demonstrated improvements in drug release profiles, targeting, and therapeutic efficacy.

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This review explores the mechanisms of cisplatin's action in cancer therapy, its challenges, and the advancements in its formulation into nanostructures to improve its therapeutic potential. Emphasis will be placed on liposomal formulations and their ability to enhance drug delivery, reduce systemic toxicity, and overcome resistance mechanisms, highlighting the prospects of nanotechnology in improving the outcomes of cisplatin-based cancer therapy.

2. Mechanism of action: Cisplatin in cancer therapy (Dasari & Tchounwou, 2014)

Several membrane transporters involved in the transport of platinum compounds, similar to MDR1, have been identified, including efflux ATPases like MRPs and ATP7A/B, and solute carrier importers such as CTR1, the SLCs, AQP2, and AQP9. MDR1, a well-known ATP-binding cassette transporter, has been recognized for years as P-glycoprotein. In human cells, cisplatin induces rapid degradation of the CTR1 transporter, reducing cisplatin influx and contributing to drug resistance. Genetic knockout of CTR1 results in cellular resistance to cisplatin, whereas cells with increased CTR1 expression show greater platinum accumulation and, in most cases, heightened sensitivity to cisplatin. The protein TMEM205, associated with cellular resistance to cisplatin, is expressed at higher levels in tissues such as the liver, pancreas, and adrenal glands. Overexpression of TMEM205 in CP-r cells may contribute to platinum resistance, making it a potential biomarker or target for cancer chemotherapy. Additionally, although Glucose Transporter 1 (Glut1) does not directly transport cisplatin, its mis localization can exacerbate cisplatin resistance.

Cisplatin becomes activated upon entering the cell, where its chloride atoms are replaced by water molecules, creating a hydrolyzed product that acts as a potent electrophile. This product reacts with nucleophiles, including the sulfhydryl groups of proteins and nitrogen donor atoms of nucleic acids. Cisplatin primarily binds to the N7 position of purine residues, causing DNA damage in cancer cells by blocking cell division, leading to apoptosis. The formation of 1,2-intrastrand cross-links between purine bases is the most prominent DNA modification, with d(GpG) adducts accounting for around 90% and d(ApG) adducts about 10%. Other adducts, such as 1,3-intrastrand d(GpXpG) cross-links, interstrand cross-links, and nonfunctional adducts, also contribute to cisplatin's toxicity. DNA is widely considered a critical target for cisplatin-induced cytotoxicity, with evidence supporting this from studies showing hypersensitivity to cisplatin in prokaryotic and eukaryotic cells deficient in DNA repair mechanisms. As illustrated in various studies, multiple molecular pathways are involved in the induction of apoptosis following cisplatin treatment.

The following are the various molecular mechanisms leading to apoptosis:

2.1. Cisplatin-Induced Oxidative Stress

Cisplatin-induced oxidative stress plays a key role in its toxicity, as it generates reactive oxygen species (ROS) that damage cellular components like proteins, lipids, and DNA. Cancer cells, which experience higher ROS levels, are particularly vulnerable. Cisplatin affects mitochondria, causing loss of protein sulfhydryl groups, calcium uptake inhibition, and reduced membrane potential. ROS-induced cell death occurs through apoptosis, either via the extrinsic pathway (Fas activation) or the intrinsic pathway (cytochrome c release). High ROS levels can also trigger autophagy, leading to further cell death.

2.2. Cisplatin Modulation of Calcium Signaling

Cisplatin hydrolyzes into more reactive species under low chloride conditions, increasing its toxicity by inhibiting mitochondrial respiration and disrupting calcium homeostasis. This leads to mitochondrial dysfunction, reduced glutathione (GSH) levels, and oxidative stress, which damages cells through lipid peroxidation and enzyme inhibition. These effects contribute to apoptosis and tissue necrosis. Calcium supplementation may offer cytoprotection by competing with cisplatin and reducing toxicity. Thus, it seems that elevated calcium levels, via calcium supplementation, may act as another means of cytoprotection, by competing for binding sites with cisplatin and prevent various toxicities associated with it.

2.3. Cisplatin-Induced Cell Apoptosis

Apoptosis is a controlled, energy-dependent cell death process involving caspase activation, leading to cell shrinkage, chromatin condensation, and DNA fragmentation. Cisplatin induces apoptosis through two main pathways: the extrinsic pathway (via death receptors and caspase 8 activation) and the intrinsic pathway (via mitochondrial dysfunction and caspase 9 activation). Bcl-2 family proteins regulate the release of cytochrome c in response to DNA damage. Defects in apoptotic signaling can lead to cisplatin resistance.

2.4. Cisplatin and Protein Kinase C

Protein kinase C (PKC) is a family of enzymes involved in signal transduction and cell regulation. The role of PKC in cisplatin sensitivity or resistance is complex, with contrasting reports indicating that the effect depends on the specific PKC isozymes and cellular context.

2.5. Cisplatin and Signaling for DNA Damage

Mutations are caused by several signals associated with stress. DNA damage triggers the activation of cell cycle checkpoints, delaying progression to allow for repair or to induce cell death if the damage is irreparable. The cell's response to cisplatin-induced DNA damage ultimately determines whether the cell survives or undergoes apoptosis (cell death).

2.6. Liposomes formulation of Cisplatin

The primary components of lipid nanoparticles (LNPs) include four key lipid ingredients: phospholipids and cholesterol, which are essential for the formation and stability of the particles; cationic or ionizable lipids, which facilitate the binding of negatively charged nucleic acids and enhance drug loading; and PEGylated lipids, which help improve the stability of the particles and extend their circulation time in the body.

3. Challenges of Cisplatin anti-cancer activity

A major challenge in cisplatin therapy is the development of resistance in cancer cells. Tumors can adapt through pathways like translesion DNA synthesis, which helps them tolerate cisplatin-induced DNA damage. Mechanism of action is thus necessary to develop strategies to overcome resistance. Various side-effects have also been associated with cisplatin treatment such as nephrotoxicity, neurotoxicity, and ototoxicity, that's why careful management and less toxic approach is necessary. While cisplatin continues to be a crucial component of cancer treatment, its future success depends on addressing the challenges of resistance and toxicity. By utilizing combination therapies, personalized medicine, and novel compounds, the therapeutic potential of cisplatin can be enhanced, offering hope for improved patient outcomes in the fight against cancer. The paper will further explore Cisplatin various formulations and different approaches to reduce the toxicity. (Elmorsy et al., 2024)

4. Formulation of Cisplatin as a Nanoformulation

Lipoplatin™ is a prominent liposomal formulation of cisplatin, created using liposomal particles composed of soy phosphatidylcholine (SPC-3), cholesterol, dipalmitoyl phosphatidylglycerol (DPPG), and methoxy-polyethylene glycol-distearoyl phosphatidylethanolamine (DSPE-mPEG (2000)). liposomes are formed via the subsequent addition of neutral lipids. Lipoplatin has displayed promising results in both in vitro and in vivo studies, inhibiting tumour growth and cell proliferation in both cisplatin-resistant and cisplatin-sensitive cells in a comparable way through an apoptosis induction-dependent mechanism while exhibiting lower toxicity to normal cells. Clinical trials have confirmed the promising results, including a long circulation time (up to 117 hours), a feature that facilitates drug accumulation in the tumor via the enhanced permeability and retention (EPR) effect, a hallmark of many solid tumors.

SPI-077, another liposomal cisplatin formulation, was found to be less effective due to poor drug release within the tumor. This latter consists of HSPC (hydro soy phosphatidylcholine), cholesterol, and DSPE-mPEG(2000) in a 55:45:5 ratio, but while showing good incorporation of the drug and high stability, it has proven poor therapeutic activity. In this respect, studies on cisplatin-based liposomes with different lipid compositions have further confirmed that both excessively fast and excessively slow-release rates of the drug can be responsible for poor efficacy. In this respect, studies on cisplatin-based liposomes with different lipid compositions have further confirmed that both excessively fast and excessively slow-release rates of the drug can be responsible for poor efficacy.

4.1. Reverse-phase evaporation method

Using the reverse-phase evaporation method, the researchers successfully encapsulated the platinum drug in two distinct formulations, which differed only in the inclusion of PEG(2000). Both formulations displayed spherical unilamellar vesicles with an average diameter ranging from 250 to 300 nm and a negative zeta potential, which slightly increased with the addition of PEG(2000). Both formulations exhibited sustained drug release over 48 hours in PBS, although the PEGylated formulation released a lower amount of cisplatin compared to the non-PEGylated one. In vitro tests on the HTB-9 bladder carcinoma cell line showed approximately a 2-fold increase in cytotoxicity when the drug was encapsulated in PEGylated liposomes. These findings were supported by in vivo studies, which demonstrated a

significant enhancement in drug efficacy, with tumor growth inhibition reaching 91% for the PEGylated formulation compared to 59% for free cisplatin, along with a reduction in side effects.

4.2. Cisplatin Encapsulation in PLGA-Coated Liposomes (Saengkrit et al.)

A method was developed where cisplatin is encapsulated inside PLGA (Poly-lactic-co-glycolic acid) nanoparticles and coated with a liposomal bilayer to improve cellular uptake. The liposomes were further functionalized with Avastin® (anti-VEGF antibody) for active targeting of tumor cells, specifically those overexpressing VEGF. This formulation showed better accumulation and efficacy in vitro and in vivo, with enhanced targeting and reduced collateral damage.

Other innovative strategies for improving the delivery and efficacy of platinum-based chemotherapeutic drugs like carboplatin, and oxaliplatin are also widely researched.

4.3. Carboplatin and Oxaliplatin in Liposomes

Notable innovations include the co-encapsulation of oxaliplatin with Ylang-Ylang oil into niosomes, leading to improved cytotoxicity and drug release in acidic conditions. After the extraction of the essential oil through hydro distillation and the determination of its composition, niosomes were prepared via the thin film hydration method. The two drugs were encapsulated singularly and then together, obtaining niosomes with an average diameter of lower than 200 nm and a ζ-potential between −10 mV and −15 mV. (Botter et al., 2024).

4.4. Pt(IV) Prodrugs

Pt(IV) complexes, such as picoplatin, offer the advantage of being more inert and less toxic until reduced into their active Pt(II) form within the tumors. For instance, the complex Pt-4 combines picoplatin with cantharidin and is encapsulated in liposomes, with a controlled release profile that improves bioavailability, reduces systemic toxicity, and enhances tumors accumulation.

4.5. Cisplatin; Cubosomes formulation

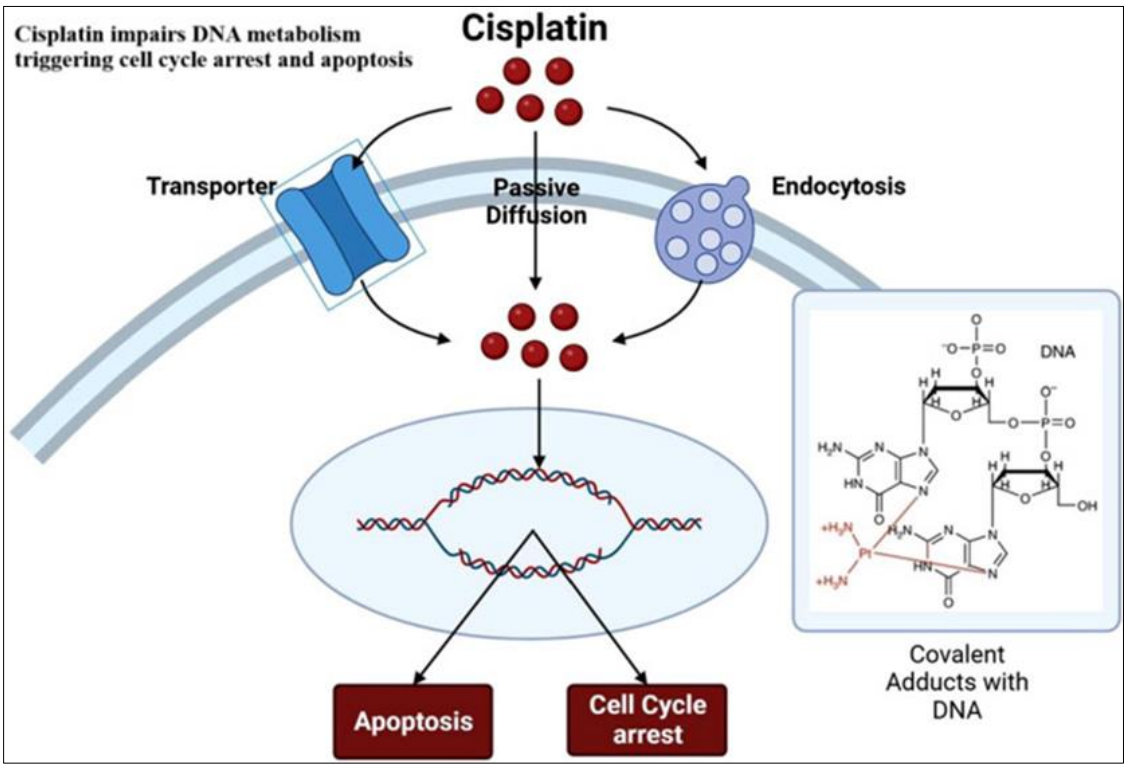

Figure 1 Cisplatin Mechanism of Action for Cell cycle arrest and Apoptosis (Elmorsy et al., 2024)

Cubosomes, as advanced nanocarriers, offer significant potential for enhancing the delivery of traditional chemotherapeutic agents like alkylating compounds. Drugs such as cisplatin, an alkylating agent widely used in cancer treatment, can benefit from cubosomes encapsulation by improving their stability, bioavailability, and targeted delivery.

Cisplatin exerts its anticancer effects through DNA crosslinking and apoptosis induction, but its conventional use is often associated with systemic toxicity and side effects. By incorporating cisplatin into cubosomes, it is possible to achieve controlled release, reduce toxicity, and enhance the drug's effectiveness by delivering it directly to tumor cells. This approach not only maximizes the therapeutic potential of alkylating agents but also aligns with the goal of cubosomes-based drug.

5. Uses of Cisplatin in Cancer Treatment

Here is a comparison table summarizing the use of cisplatin across various cancer types:

Table 1 Use of cisplatin across various cancer types (Dasari & Tchounwou, 2014)

Cancer Type	Primary Use of Cisplatin	Effectiveness	Challenges/Side Effects
Lung Cancer (SCLC & NSCLC	Used in chemotherapy for small cell lung cancer (SCLC) and as adjuvant therapy for non-small cell lung cancer (NSCLC)	Effective in SCLC and NSCLC, providing a 5-year survival benefit of 5.3%	Renal toxicity, nausea, and vomiting. Aggressive hydration needed. Carboplatin is a substitute to avoid toxicity.
Ovarian Cancer	First-line treatment with platinum/taxane combination chemotherapy. Used for both sensitive and resistant cell lines	Effective in both initial and recurrent ovarian cancer, but resistance develops in 75% of patients	Severe side effects, including resistance. Cisplatin often combined with other agents (e.g., honey venom, withaferin) to overcome resistance.
Head and Neck Carcinoma	Not effective as monotherapy. Often combined with other drugs like methotrexate, vinblastine, or gemcitabine	Limited effectiveness as monotherapy. Survival rate remains around 50%	Cisplatin alone is not effective in head and neck cancer. Requires combination therapy for better outcomes.
Breast Cancer	Used in chemotherapy for various cancers, including breast cancer. Targets rapidly dividing cells	Effective in increasing patient lifespan, often as part of a combination therapy	Cytotoxic effects targeting dividing cells. Can lead to side effects due to targeting both cancerous and healthy dividing cells
Brain Cancer (GBM)	Part of treatment regimen for recurrent childhood brain tumors and other cancers like gastric and anal cancer	Median survival increase by only 2.5 months in GBM; limited effectiveness	Generally, poor survival outcomes; cisplatin provides limited advantage. Side effects common in brain cancer treatments.

6. Combination Therapy of Cisplatin (Dasari & Tchounwou, 2014)

Cisplatin combination chemotherapy forms the foundation of treatment for various cancers. While cisplatin initially shows high effectiveness, many patients eventually experience relapse with cisplatin-resistant disease. Drug resistance has been observed in numerous patients following cisplatin treatment relapse. The proposed mechanisms of cisplatin resistance include alterations in the cellular uptake and efflux of cisplatin, enhanced biotransformation and detoxification in the liver, and increased DNA repair and anti-apoptotic pathways (Gottesman, et al., 2002). To combat resistance, cisplatin is often used in combination with other drugs for treating cancers such as ovarian cancer, biliary tract cancer, diffuse malignant pleural mesothelioma, gastric cancer, salivary gland carcinoma, breast cancer, colon cancer, lung cancer, prostate cancer, melanoma, pancreatic cancer, squamous cell carcinoma of the male genital tract, urothelial bladder cancer, and cervical cancer.

6.1. Cisplatin and Paclitaxel

Paclitaxel is a mitotic agent that binds preferentially to microtubules. The combination chemotherapy of paclitaxel, cisplatin, and fluorouracil has been reported to be an effective and well-tolerated first-line and second-line treatment for Chinese patients with advanced gastric and esophagogastric junction adenocarcinoma, demonstrating improved tolerance.

6.2. Cisplatin and Doxorubicin

The combination of doxorubicin and cisplatin is both effective and well-tolerated, making it a potential option for palliative treatment in symptomatic patients with diffuse malignant pleural mesothelioma.

6.3. Cisplatin and Gemcitabine

Compared to gemcitabine alone, the combination of cisplatin and gemcitabine offers a significant survival benefit without causing substantial additional toxicity. This combination is a suitable treatment option for patients with advanced biliary cancer.

6.4. Cisplatin and Curcumin

Niosomes co-loaded with Cisplatin and Curcumin, as well as separate niosomes for each drug, were formulated using a mixture of Span 60, Chol, and PEG200. The release rates throughout the period were consistent, suggesting that the encapsulation allowed for a sustained and simultaneous release of both drugs, supporting their synergistic potential.

7. Conclusion

Cisplatin has long been a mainstay in cancer therapy, offering potent anticancer effects through its ability to induce DNA damage and apoptosis in cancer cells. It has been extensively used for the cure of different types of neoplasms including head and neck, lung, ovarian, leukemia, breast, brain, kidney and testicular cancers However, its clinical application is limited by significant side effects, including renal toxicity and the development of drug resistance. The encapsulation of cisplatin in advanced nanocarriers, particularly liposomes, has shown promise in addressing these challenges. Liposomal formulations, such as Lipoplatin™, exploit the enhanced permeability and retention (EPR) effect to enhance drug accumulation at tumor sites while minimizing toxicity to healthy tissues. Innovations in cisplatin encapsulation, including the use of PLGA-coated liposomes, co-encapsulation with other therapeutic agents, and the use of alternative nanocarriers like cubosomes, have further improved the controlled release and efficacy of cisplatin.

The molecular mechanisms of cisplatin's action, including its ability to bind DNA, induce oxidative stress, and modulate calcium signaling, are well-documented and contribute significantly to its cytotoxicity. However, resistance mechanisms, including alterations in drug uptake and efflux, overexpression of resistance-associated proteins like TMEM205, and defects in apoptotic pathways, present ongoing hurdles in treatment efficacy. Nanotechnology-based strategies, such as PEGylation and functionalization with targeting agents like Avastin®, offer new avenues for overcoming these resistance mechanisms and improving cisplatin's therapeutic index.

Moreover, the combination of cisplatin with other chemotherapeutic agents, such as paclitaxel, doxorubicin, and gemcitabine, has shown increased effectiveness, providing further opportunities for enhancing cancer treatment regimens. These combination therapies help address the issue of cisplatin resistance while potentially reducing side effects by delivering synergistic treatment at optimal doses.

In summary, the encapsulation of cisplatin in nanocarriers, especially liposomes, presents a promising strategy to overcome the limitations of conventional cisplatin therapy. Advances in nanomedicine, including modifications to drug release profiles and targeted delivery systems, offer significant potential in improving the clinical outcomes of cisplatin-based treatments. The continued development of these innovative formulations holds the key to enhancing the effectiveness, safety, and precision of cisplatin therapy in cancer treatment.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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