Recent Advances in Paclitaxel Drug Delivery: Challenges, Innovations, and Future Directions

Balisa Mosisa Ejeta[1*], Malay K Das [1*], Sanjoy Das [1]

Abstract

Paclitaxel, the first taxane alkaloid to be widely used as a cancer treatment, has revolutionized chemotherapy, especially for breast, ovarian, and lung cancers. Despite its efficacy, paclitaxel's clinical use faces significant challenges, including poor solubility, high systemic toxicity, and the emergence of drug resistance. Early research efforts have focused on developing novel delivery methods to improve the drug's efficacy while minimizing adverse effects. This review explores various paclitaxel delivery systems, including conventional methods, nanotechnology-based solutions, and targeted drug delivery. The review highlights persistent limitations, such as the lack of widespread clinical adoption of nanocarriers and the need for individualized drug delivery systems to address resistance. Key future research areas include the development of multipurpose nanoparticles, the integration of personalized medicine, and exploration of alternative delivery strategies. These innovations could pave the way for more effective and patient-specific chemotherapy treatments.

Significance | This review addresses advancements in paclitaxel drug delivery, emphasizing innovative methods to enhance efficacy and combat resistance.

*Correspondence. Balisa Mosisa Ejeta, Department of Pharmaceutical Sciences, Dibrugarh University, India. E-mail: balisam@wollegauniversity.edu.et Tel: +918136088210.
Malay K Das , Department of Pharmaceutical Sciences, Dibrugarh University, India.
E-mail:mkdps@dibru.ac.in
Tel: +913732370254

Editor Md Shamsuddin Sultan Khan, And accepted by the Editorial Board August 09, 2024 (received for review June 03, 2024)

Keywords: Paclitaxel, Nanotechnology, Drug Resistance, Chemotherapy, Targeted Delivery

1. Introduction

1.1. Background on Paclitaxel

One of the most effective broad-spectrum alkaloid chemotherapeutic drugs, paclitaxel (PTX), has an intriguing history that dates back to the 1960s. Paclitaxel, with the molecular formula C47H51NO14, is a naturally occurring diterpenoid. It was first isolated from the bark of the Pacific yew tree (Figure 1) (Taxus brevifolia) by Monroe Wall and Mansuk Wani as part of a National Cancer Institute program aimed at discovering new anticancer agents. Paclitaxel holds the distinction of being the first naturally occurring plant-derived chemotherapeutic drug approved by the United States Food and Drug Administration (FDA) for use in cancer treatment (Wall, M. E., & Wani, M. C., 1989).

Paclitaxel is a white to off white crystalline powder, its empirical formula is C47H51NO14 and its molecular weight is 853.9g/mol. It is a highly lipophilic compound and is practically non-soluble in water, and has a melting point of approximately between 216 and 217°C (DrugBank, 2003).

Paclitaxel extracted from the windings of the Pacific yew tree was initially patented in 1970 by the United States National Cancer Institute (NCI). This is the initial and core patent (Figure 2) that outlines the formula of paclitaxel and how it is used as an anticancer drug. The application of this patent was made in 1986 and it was granted in 1989 with the identification number, US-4,814,470. This patent was filed by the workers of National Cancer Institute, NCI, USA and involved Monroe E. Wall and Mansukh C. Wani, the discoverers of paclitaxel. It was patented under the title: 'A new class

Author Affiliation.
[1] Department of Pharmaceutical Sciences, Dibrugarh University, India.

Please Cite This:
Balisa Mosisa Ejeta, Malay K Das et al. (2024). Recent Advances in Paclitaxel Drug Delivery: Challenges, Innovations, and Future Directions, Journal of Angiotherapy, 8(8), 1-13, 9867.

of anticancer agents taxane derivatives' (Wall, M. E , Wani M. C. 1989).

It describes how paclitaxel works in the body, its effect on microtubules and cells' ability to divide. Several preparations for intravenous use are described, giving emphasis on certain solvents because of paclitaxel's insolubility in water. It also claims formulations of paclitaxel which may be for intravenous use; solutions of the paclitaxel in Cremophor EL and ethanol.

The finding belonged to a knowing rise in endeavor to seek out natural compounds for possible therapeutic applications, and first known as 'taxol', paclitaxel later distinguished itself from many due to its mode of action and substantial anticancer effects. Paclitaxel is known to bind itself to microtubules and inhibits their depolymerization and thus leads to their stabilization. Contrary to most other members of chemotherapeutic agents that interfere with the formation of microtubules, paclitaxel enhances assembly of the microtubules hence inhibiting depolymerisation which in turn results in G2/M phase cell cycle arrest and apoptosis among rapidly dividing cancer cells (Figure 4) (Schiff et al. , 1979).

It is for this unique mode of action that paclitaxel has exhibited a high degree of efficacy against diverse neoplasms and which led to its approval by the U. S. Food and Drug Administration (FDA) in 1992 for use in ovarian carcinoma (Rowinsky & Donehower, 1995).

Since paclitaxel is one of the cytoskeletal drugs targeting tubulin, it can accelerate microtubule polymerization and stabilization, and disrupt cellular mitosis, which ultimately lead to cell apoptosis (Ying, N.et al., 2023).

Paclotaxol has, since 1977, evolved into the standard treatment for cancer especially for the treatment of ovarian cancer, breast cancer, non-small cell lung cancer, Kaposi's sarcoma, pancreatic cancer and gastric cancer (Ying, N.et al., 2023). They have established the effectiveness of the product in enhancing the wellbeing of patients; especially when combined with other chemotherapeutic compounds (McGuire et al. , 1996).

For instance, the use of paclitaxel together with cisplatin in treating patients with ovarian cancer has been described to improve survival rate among such patients beyond what was considered possible for first-line chemotherapy (McGuire et al., 1996).

Further, the drug has been successful in the treatment of metastatic breast cancer in which it has been incorporated into a number of combination regimens in order to improve the therapeutic outcomes (Crown, O'Leary & Ooi, 2004).

1.2. Challenges in Paclitaxel Delivery

Nevertheless, the utilization of paclitaxel has not been without problems, such as glitches with formulation of the drug and how it is delivered to the target site. It has limited solubility, recrystallization upon dilution, rapid blood clearance, non-specific distribution and co-solvent-induced toxicity (Bibby et al, 2000; Ying, N.et al., 2023).

In addition, its development of chemoresistance, mainly due to upregulation of drug extrusion proteins such as P-glycoprotein, has rendered it relatively worthless in the long-term management of some tumour types (Seidman et al., 2000).

Despite its promising anticancer potential, the development of intravenous paclitaxel (PTX) formulations has faced significant challenges due to its poor solubility. To address this, traditional paclitaxel formulations utilize Cremophor® EL (CrEL) as a solubilizing agent, which markedly enhances PTX's solubility in the adjuvant. However, CrEL's role as a solubilizer is associated with severe, sometimes fatal, hypersensitivity reactions, as well as neurotoxicity and nephrotoxicity. In addition to the typical side effects of chemotherapy, such as fatigue and nausea, patients undergoing paclitaxel infusion often suffer from peripheral nerve degeneration, manifesting as pain and numbness in the extremities due to paclitaxel accumulation in the dorsal root ganglia. The severity of this adverse effect is correlated with the dosage and duration of the infusion. Paclitaxel can also induce severe neuropathic pain and myelosuppression (Ying, N.et al., 2023).

Moreover, the development of resistance to paclitaxel is a significant clinical challenge that undermines treatment outcomes. The contribution of the tumor microenvironment to paclitaxel resistance is examined in a recent article, which demonstrates that factors like hypoxia, stromal cells, and extracellular matrix components can create a protective niche that shields cancer cells from paclitaxel-induced apoptosis. The study suggests that disrupting these microenvironmental interactions could enhance the drug's effectiveness (Liang et al., 2021).

A study conducted by *Zhou et al., (2023)* on cancer resistance to paclitaxel highlights the role of ATP-binding cassette (ABC) transporters, particularly P-glycoprotein (P-gp), which actively efflux paclitaxel out of cancer cells, reducing its intracellular concentration and thereby diminishing its cytotoxic effect. The study underscores the significance of targeting these transporters to mitigate resistance and improve paclitaxel's efficacy in treating resistant tumors (Zhou et al., 2023).

Another study done by *Gupta et al., (2022)* focused on the role of β-tubulin mutations in paclitaxel resistance, revealing that mutations in the β-tubulin gene can alter the drug-binding sites, reducing paclitaxel's ability to stabilize microtubules, which is essential for its anti-cancer activity. This mechanism of resistance suggests that patients with such mutations may require alternative therapeutic strategies (Gupta et al., 2022).

Smith et al., (2022) explored the mechanisms of cancer resistance to paclitaxel, focusing on how cancer cells adapt through genetic mutations, upregulation of drug efflux pumps, and alterations in microtubule dynamics. They found that these changes reduced paclitaxel's effectiveness by preventing it from stabilizing microtubules, leading to therapeutic failure. The study also

highlighted the potential of combining paclitaxel with inhibitors targeting resistance pathways to overcome these challenges (Smith et al., 2022).

Another article by *Jones et al., (2021)* investigated the role of the tumor microenvironment in paclitaxel resistance, particularly the influence of hypoxia and cancer-associated fibroblasts (CAFs). The findings suggested that hypoxia-induced activation of hypoxia-inducible factors (HIFs) and CAFs contribute to drug resistance by altering drug metabolism and enhancing survival pathways in cancer cells. They suggested that strategies targeting the tumor microenvironment may thus improve the efficacy of paclitaxel (Jones et al., 2021).

Further study conducted by *Chen et al., (2023)* examined the contribution of microRNA (miRNA) regulation in paclitaxel resistance, demonstrating that specific miRNAs can modulate the expression of genes involved in apoptosis, cell cycle regulation, and drug efflux. By altering miRNA expression, cancer cells can evade paclitaxel-induced cell death, leading to resistance. The article discusses the potential of using miRNA-based therapies to reverse resistance and enhance paclitaxel's therapeutic impact (Chen et al., 2023).

In a recent review by *Lee & Kim, (2023),* the role of autophagy in paclitaxel resistance is discussed, with evidence showing that autophagy can act as a survival mechanism in cancer cells treated with paclitaxel. The review highlights how inhibiting autophagy can sensitize cancer cells to paclitaxel, suggesting a new avenue for overcoming resistance through combined therapeutic approaches (Lee & Kim, 2023).

On the other hand, *Patel et al., (2021)* identified the involvement of epithelial-mesenchymal transition (EMT) in paclitaxel resistance. The study has shown that cancer cells undergoing EMT exhibit increased resistance to paclitaxel by enhancing their invasive properties and reducing drug-induced apoptosis. They recommended that targeting EMT-related pathways could therefore be a promising strategy to counteract resistance and improve treatment outcomes (Patel et al., 2021).

Given the rising challenges of drug resistance, limited bioavailability, and severe side effects associated with conventional paclitaxel therapy, there is an urgent need to conduct a comprehensive review on the "Advances in Paclitaxel Drug Delivery Researches: Progress and Innovations." This review is critical for synthesizing the latest breakthroughs in nanotechnology-based delivery systems, targeted therapies, and combination strategies that promise to enhance paclitaxel's therapeutic efficacy while minimizing its toxicity. By consolidating the current innovations and progress, such a review will not only guide future research but also accelerate the translation of these advancements into clinical practice, offering renewed hope for patients battling resistant and recurrent cancers.

1.3. Objective of the Review

The rationale for this they said is to provide a comprehensive review of recent developments in advanced drug delivery system for Paclitaxel, a well-recognized chemotherapeutic agent. This review intends to give detailed information on characterization of historical background and clinical utility of paclitaxel, real life issues arising out of application of conventional drug delivery system and overview of nanocarrier and Targeted drug delivery systems. In doing so, the review aims to summarize the current state of knowledge and suggest that these advanced delivery systems could improve the therapeutic effect, safety and further performance of cancers therapies. Further, this review will reveal the emerging research gaps and propose the subsequent research direction to address the existing limitations in paclitaxel drug delivery.

2. Traditional Drug Delivery Systems for Paclitaxel

The first preparation of paclitaxel was in the form of Taxol in early 1990s, it was one of the most revolutionary anticancer agents in chemotherapy. The FDA approved Taxol for non–small cell lung cancer (NSCLC) in 1999 (Tuma, 2003) (Table 1).

Nevertheless, the original synthesis procedure of paclitaxel suffered several difficulties due to low aqueous solubility. Regarding this problem, paclitaxel was prepared with a solvent system of Cremophor EL (polyethoxylated castor oil) and ethanol. Though this formulation enabled the delivery of paclitaxel through intravenous route, it was accompanied by new set of problems such as hypersensitivity, nephrotoxicity and neurotoxicity (Rowinsky & Donehower, 1995).

These side effects were mainly due to Cremophor EL which was vital in solubilising paclitaxel though it was the cause of the side effects noticed in the patients. Due to such adversative effects, patients treated with the traditional formulations of paclitaxel commonly needed premedication with corticosteroids, antihistamines, and H2 antagonists. Although such a premedication regimen helped in minimizing hypersensitivity reactions, it made the treatment procedure more complex, and exposed the patients to extra corticosteroid-related complications (Weiss et al. , 1990).

However the time required for traditional paclitaxel infusion was much lengthened on average between 3 to 24 hrs, which in addition to making the process cumbersome enhances its inconvenient for the patients. Due to these restrictions, later modifications of paclitaxel were sought to increase solubility in water and/or decrease the usage of Cremophor EL (Weiss et al. , 1990).

One such an alternative is Abraxane, an albumin-bound paclitaxel nanoparticle molar solution. The FDA approved Abraxane in 2005; the formulation does not contain Cremophor EL; using albumin as the vehicle greatly reduces the risk of hypersensitivity reaction and infusion time.

Recent clinical trials proved that Abraxane has better efficacy reflected by higher response rate, and better tolerability in comparison with traditional paclitaxel to be selected for a great number of patients (Gradishar et al., 2005).

Albumin-bound paclitaxel (Abraxane®) represents a significant advancement in the delivery of paclitaxel, addressing several critical limitations associated with its conventional formulation. Unlike the traditional Cremophor EL-based formulation, Abraxane® leverages the natural carrier protein albumin to enhance solubility and facilitate the targeted delivery of paclitaxel to tumor tissues via receptor-mediated transport (Gradishar et al., 2005).

This approach not only bypasses the need for toxic solvents like Cremophor EL, which are associated with severe hypersensitivity reactions, but also improves the pharmacokinetics and tumor penetration of paclitaxel. Clinical studies have demonstrated that Abraxane® offers superior efficacy and a more favorable safety profile compared to conventional paclitaxel, particularly in the treatment of metastatic breast cancer, non-small cell lung cancer, and pancreatic cancer. The enhanced therapeutic index of Abraxane® has led to its widespread adoption in oncology, providing a more effective and safer alternative for patients (Gradishar et al., 2005).

This is however not entirely true because even with the availability of other formulations such as Abraxane®, traditional paclitaxel formulations are still used because they are still effective even under circumstances where more advanced and costly formulations are not easily available. Taxol became used routinely for cancer treatment because of its potent anticancer activity especially for ovarian, breast and non-small cell lung carcinoma. Nonetheless, the drawbacks related to Cremophor EL contributed to the advancements in the formulation and the formulation systems concerning paclitaxel to enhance the safety and efficiency of the compound (Weiss et al., 1990).

3. Advanced Paclitaxel Delivery

Advanced Drug Delivery refers to the development and application of sophisticated systems and technologies designed to optimize the administration, distribution, and release of therapeutic agents. It encompasses innovative approaches that enhance the efficacy, safety, and patient compliance to the drug therapies. They utilize novel materials, engineering principles, and biological targeting mechanisms to achieve precise control over drug release profiles, target specific tissues or cells, and minimize off-target effects. These systems include nanoparticle-based formulations, smart drug delivery platforms, targeting molecule attachment, and responsive carriers' utilization that can adapt to physiological conditions (Kumar, N., (2017).

3.1. Nanotechnology-Based Delivery Systems for Paclitaxel

Over the past decades, we have realized rapid advances in applying nanocarriers in paclitaxel delivery systems. The nano-drug delivery systems offer unique advantages in enhancing the aqueous solubility, reducing side effects, increasing permeability, prolonging circulation half-life of paclitaxel (Ying, N.et al., 2023).

Perpetual development attempts currently exist, especially in nanoparticle systems, liposomes, and more minor targeted delivery systems; hence, new formulations based on the paclitaxel as a precursor currently exist and are safer and less toxic than conventional preparations (Zhou, J., et al., 2014).

Nano-delivery systems have been claimed as new generation formulations for paclitaxel which can address some of the issues like solubility, systemic toxicity and drug resistance which are otherwise observed with traditional formulations of paclitaxel. These sophisticated systems employ liposome, polymeric nano-particulate, dendritic, and micellar carriers for the improved delivery, effectiveness, and safety of paclitaxel in the anticancer activity (Zhou, J., et al., 2014).

3.2. Liposomal Paclitaxel

Paclitaxel disposed in liposome frameworks was one of the earliest instances of the utilization of nanotechnology in drug delivery. Liposomes are small spheres built of two layers of phospholipids and can carry hydrophobic agents such as paclitaxel maintaining their solubility and at the same time minimizing side effects. Liposome is developed as a new formulated liposomal paclitaxel with better pharmacokinetics and less hypersensitivity reactions in comparison to non-liposomal paclitaxel (Gao et al. , 2013).

Rao et al., (2008) studied "Liposomal Entrapped Paclitaxel Easy to Use" (LEP-ETU) to enhance the drug's solubility and reduce the severe side effects associated with the conventional Cremophor EL-based formulation. By encapsulating paclitaxel within liposomes, LEP-ETU improved the drug delivery to tumor tissues, thereby increasing therapeutic efficacy and minimizing systemic toxicity. The Clinical trial of this formulations have shown that LEP-ETU not only enhances the pharmacokinetics of paclitaxel, leading to higher drug concentrations in the tumor, but also significantly reduced the incidence of hypersensitivity reactions and neurotoxicity, which are common with traditional formulations. This improved safety profile and ease of administration without the need for premedication make LEP-ETU a promising alternative for patients requiring paclitaxel therapy (Rao et al., 2008).

The results of clinical trials indicate that liposomal formulation of paclitaxel has a broader therapeutic value and a greater therapeutic efficacy in treating metastatic breast cancer and non-small cell lung cancer (Wang et al., 2014) (Table 2).

Allen & Cullis, (2013) noted that using liposomes for the delivery of paclitaxel has shown increased circulation time in the blood and the ability to target the drug to the tumor cells through the mechanism

known as EPR (enhanced permeability and retention) effect (Allen & Cullis, 2013).

3.3. Polymeric Nanoparticles

Paclitaxel-loaded polymeric nanoparticles have been the focus of attention due to their biocompatibility, biodegradability and controlled release. Poly(lactic-co-glycolic acid) (PLGA) is a well-investigated polymer for nanoparticle formulation that provides a stable and prolonged release of paclitaxel. Studies indicate that PLGA nanoparticles can improve paclitaxel distribution to cancer cells, raising its therapeutic power and reducing side effects (Danhier et al., 2012).

For example, a study done by Feng et al. in 2019 revealed that the application of PLGA nanoparticles with paclitaxel showed higher efficacy against tumour growth in lung cancer models than traditional paclitaxel with less systemic toxicity. Further adaptations on the surface are also possible like attaching targeting ligands which enhance specificity of drug delivery into cancer cells (Feng et al., 2019).

Carbon nanotubes (CNTs) have emerged as a promising delivery system for paclitaxel due to their unique structure, which allows for high drug loading and efficient cellular uptake. Research has demonstrated that paclitaxel-loaded CNTs can enhance the drug's solubility and provide targeted delivery to tumor cells, reducing off-target toxicity (Figure 3). Furthermore, the hollow and tubular nature of CNTs facilitates controlled drug release, leading to improved therapeutic outcomes. Studies have shown that this approach not only enhances the efficacy of paclitaxel but also mitigates common side effects associated with its conventional formulation, such as neurotoxicity and hypersensitivity reactions (Liu et al., 2008).

Gold nanoparticles (AuNPs) have been studied as a delivery vehicle for paclitaxel, capitalizing on their biocompatibility, ease of functionalization, and ability to accumulate in tumors via the enhanced permeability and retention (EPR) effect. Paclitaxel-conjugated AuNPs have demonstrated improved drug stability, targeted delivery, and enhanced cytotoxicity against cancer cells compared to free paclitaxel. This delivery method significantly reduces the systemic toxicity of paclitaxel and allows for lower dosages while maintaining therapeutic efficacy. The conjugation of paclitaxel to AuNPs also enables more precise drug delivery, minimizing the impact on healthy tissues (Kong et al., 2007).

Exosomes, naturally occurring extracellular vesicles, have gained attention as a novel delivery system for paclitaxel due to their ability to facilitate cell-to-cell communication and deliver drugs with high specificity. Research has shown that paclitaxel-loaded exosomes can effectively target tumor cells, bypassing biological barriers and reducing off-target effects. This method leverages the exosomes' biocompatibility and intrinsic targeting capabilities, leading to enhanced therapeutic efficacy with lower systemic toxicity. Moreover, exosome-based delivery has been shown to overcome multidrug resistance in cancer cells, presenting a promising solution to one of the major challenges in paclitaxel therapy (Sun et al., 2010).

Paclitaxel conjugates with targeting ligands, such as folate or peptides, have been developed to enhance selective delivery to cancer cells that overexpress specific receptors. This approach has shown considerable promise in improving the drug's therapeutic index by reducing non-specific distribution and enhancing uptake in target cells. For example, folate-targeted paclitaxel conjugates have demonstrated increased efficacy in treating folate receptor-positive tumors while reducing systemic toxicity. These conjugates allow for higher accumulation of paclitaxel in tumor tissues, thus overcoming some of the limitations of traditional chemotherapy, such as dose-limiting toxicity and poor bioavailability (Gao et al., 2011).

Silica-based nanoparticles (SiNPs) have been explored as a carrier for paclitaxel due to their high loading capacity, stability, and ability to provide controlled drug release. The mesoporous structure of SiNPs allows for the encapsulation of paclitaxel, protecting it from premature degradation and enhancing its solubility. Studies have shown that paclitaxel-loaded SiNPs can achieve sustained drug release, improving therapeutic efficacy and reducing dosing frequency. Additionally, the surface of SiNPs can be functionalized with targeting ligands to achieve selective drug delivery, further reducing side effects and enhancing the concentration of paclitaxel at the tumor site (Mamaeva et al., 2013).

Nanodiamonds have been investigated as a delivery platform for paclitaxel, offering several advantages, including enhanced drug loading, stability, and biocompatibility. Paclitaxel-loaded nanodiamonds have shown the ability to improve drug delivery to tumors, bypassing common resistance mechanisms and reducing toxicity. The unique surface properties of nanodiamonds facilitate the attachment of paclitaxel molecules, resulting in a controlled and sustained release of the drug. This approach has demonstrated increased tumor inhibition in preclinical models, highlighting its potential as a novel strategy to overcome the challenges associated with paclitaxel resistance and adverse side effects (Chow et al., 2011).

Magnetic nanoparticles (MNPs) have been explored for their potential to deliver paclitaxel to tumor sites under the guidance of an external magnetic field, offering a targeted and controlled delivery system. Research indicates that paclitaxel-loaded MNPs can enhance drug accumulation in tumors, minimize systemic exposure, and reduce side effects. The ability to manipulate MNPs using a magnetic field allows for precise targeting, which can lead to higher therapeutic efficacy and lower doses of paclitaxel being required. This technology has shown promise in preclinical studies,

offering a novel approach to overcoming the limitations of conventional chemotherapy (Jain et al., 2008).

3.4. Dendrimers

A highly branched macromolecule, dendrimers, resembles a tree and is an ideal drug delivery platform due to its defined structure, high loading capacity for drugs and multivalent character. Preclinical studies have shown that dendrimers loaded with paclitaxel could help enhance drug solubility, improve cellular uptake, and facilitate targeted drug delivery (Khandare et al., 2012).

Jain, K.K. (2008) had explored the use of dendrimers as carriers for paclitaxel to enhance its delivery and efficacy in cancer treatment. A study demonstrated that dendrimers, specifically those with multiple surface functional groups, could effectively encapsulate paclitaxel and deliver it directly to cancer cells. This approach significantly improved the drug's solubility and stability, which addressed the problem of paclitaxel's poor water solubility and reduced systemic toxicity. The use of dendrimers also allowed for controlled release, prolonging the therapeutic effect and minimizing side effects *(Jain, K.K. (2008).*

Sharma, A., et al. (2011) research focused on utilizing dendritic nanocarriers for the targeted delivery of paclitaxel to specific cancer cells. The study found that conjugating paclitaxel with dendritic structures bearing ligands that bind specifically to cancer cell receptors enhanced the selective uptake of the drug by tumor cells. This targeted delivery minimized the drug's exposure to healthy tissues, addressing issues related to off-target effects and systemic toxicity. The study highlighted the potential of dendritic nanocarriers to improve the precision of chemotherapy. *(Sharma, A., et al., 2011).*

Sinha, R., et al. (2006) investigated biodegradable dendrimers designed to deliver paclitaxel with the aim of overcoming drug resistance in cancer cells. The study demonstrated that these dendrimers could not only enhance the drug's effectiveness by improving cellular uptake but also circumvent mechanisms of resistance by maintaining drug levels inside the cells. This approach solved the problem of reduced efficacy due to multidrug resistance, a common issue in cancer chemotherapy *(Sinha, R., et al., 2006).*

Ghosh, P., et al. (2009) studied surface-modified dendrimers, showing that altering the surface chemistry of dendrimers can control the release rate of paclitaxel. This study found that dendrimers with specific surface modifications could provide a sustained and controlled release of paclitaxel, which helps in maintaining therapeutic drug levels over an extended period. This approach addresses the problem of drug burst release and ensures more consistent drug delivery *(Ghosh, P., et al., 2009).*

Folic acid or antibodies can be attached to these ligands to target only the cancer cells of the patient thus reducing off-target effects while improving therapeutic outcomes (Jeon et al., 2013).

In addition, pH or temperature change-responsive dendrimers can be engineered which enable spatially controlled release of paclitaxel in the tumor microenvironment (Liu et al., 2020).

3.5. Micelles

Micelles are self-assembling amphiphilic substances that create nanoscaled colloidal carriers, solubilizing hydrophobic drugs like paclitaxel. Paclitaxel-loaded micelles have been extensively studied for their ability to enhance drug solubility, prolong circulation time, and improve tumor targeting (Zhao et al., 2013).

Genexol-PM is a paclitaxel-loaded polymeric micelle formulation that has shown promising outcomes in clinical trials, with improved antitumor activity and reduced toxicity compared to conventional formulations (Kim et al., 2007).

The attractiveness of micelles as vehicles for the delivery of paclitaxel is due to their passive targeting of tumors by the EPR effect and their small size and stability. Additionally, it is possible to engineer micelles that are stimuli-responsive and allow controlled release of paclitaxel in response to specific triggers such as changes in the pH or temperature conditions within tumor environment (Tong et al., 2014).

3.6. Hybrid Nanoparticles

Hybrid nanoparticles, which combine inorganic materials with organic polymers or lipids, have been investigated to improve the delivery and efficacy of paclitaxel. A study conducted by *Zhang, X., et al. (2012)* demonstrated that hybrid nanoparticles could significantly enhance paclitaxel's solubility and stability in aqueous environments, addressing the drug's inherent poor solubility.

This approach not only improved the therapeutic index of paclitaxel but also facilitated controlled drug release, further enhancing treatment efficacy *(Zhang, X., et al., 2012).*

Duan et al. (2020) designed a nanoparticle comprising PLGA and liposome which had improved drug delivery capabilities leading to high apoptotic levels and regression rates when used in multidrug resistant breast cancer cells.

4. Targeted Delivery Approaches Of Paclitaxel

Targeted delivery systems for paclitaxel have been developed to address the challenges associated with its conventional formulations, such as poor solubility, systemic toxicity, and non-specific distribution. These advanced delivery strategies aim to direct paclitaxel specifically to cancer cells, thereby enhancing therapeutic efficacy while minimizing side effects. Several targeted delivery approaches, including ligand-based targeting, antibody-drug conjugates, and stimuli-responsive systems, have shown significant promise in preclinical and clinical settings.

4.1. Ligand-Based Targeting

Ligand-based targeting involves the modification of drug carriers with ligands that can specifically bind to receptors overexpressed on the surface of cancer cells. This approach enhances the selective

uptake of paclitaxel by tumor cells while sparing normal tissues. For instance, folate receptors are frequently overexpressed in various cancers, making folic acid a widely used ligand for targeted drug delivery. Paclitaxel-loaded nanoparticles conjugated with folic acid have demonstrated increased cellular uptake and enhanced cytotoxicity in folate receptor-positive cancer cells compared to non-targeted formulations (Minko et al., 2012).

Li, J., et al. (2010) studied the use of folic acid-conjugated paclitaxel-loaded nanoparticles, which target the folate receptors commonly upregulated in various cancers. This approach effectively addressed the challenge of non-specific drug distribution, thereby minimizing systemic toxicity and enhancing the therapeutic index of paclitaxel. The targeted delivery ensured higher drug concentrations at the tumor site while reducing exposure to healthy tissues.

Similarly, transferrin, which targets transferrin receptors overexpressed in many tumors, has been employed to functionalize paclitaxel carriers, resulting in improved drug accumulation in cancerous tissues and better therapeutic outcomes (Qiu et al., 2014).

4.2. Antibody-Drug Conjugates (ADCs)

Antibody-drug conjugates (ADCs) represent a powerful targeted delivery approach that combines the specificity of monoclonal antibodies with the cytotoxicity of chemotherapeutic agents like paclitaxel. ADCs are designed to selectively bind to antigens expressed on the surface of cancer cells, delivering the drug directly to the tumor site. Upon binding, the ADC is internalized by the cancer cell, where the drug is released to exert its cytotoxic effect. Trastuzumab emtansine (T-DM1) is a well-known ADC that targets the HER2 receptor in breast cancer, but researchers are also exploring similar strategies for paclitaxel delivery (Barok et al., 2014).

While ADCs for paclitaxel are still under investigation, preliminary studies have shown that these conjugates can significantly reduce off-target toxicity and improve antitumor activity by ensuring that paclitaxel is released specifically within cancer cells (Senter & Sievers, 2012).

4.3. Stimuli-Responsive Systems

Stimuli-responsive systems are a novel approach to targeted drug delivery, where paclitaxel is released in response to specific triggers present in the tumor microenvironment, such as pH, temperature, or enzymes. These systems take advantage of the unique characteristics of tumors, such as their acidic pH or elevated levels of certain enzymes, to achieve controlled and site-specific drug release. For example, pH-sensitive nanoparticles designed to release paclitaxel in acidic environments have been shown to enhance drug delivery to tumors while minimizing exposure to normal tissues (Cheng et al., 2011).

Another example is enzyme-responsive delivery systems that exploit the overexpression of matrix metalloproteinases (MMPs) in tumors to trigger the release of paclitaxel at the tumor site (Yuan et al., 2014). These systems not only improve the targeting efficiency of paclitaxel but also allow for a reduction in the overall dose required, thereby minimizing systemic toxicity.

4.4. Peptide-Based Targeting

Peptide-based targeting strategies involve the use of peptides that can bind specifically to receptors or antigens expressed on the surface of cancer cells. These peptides can be conjugated to paclitaxel-loaded nanoparticles or other carriers to enhance the specificity and efficacy of drug delivery. One example is the use of RGD peptides, which target integrins that are overexpressed in tumor vasculature. Paclitaxel-loaded nanoparticles functionalized with RGD peptides have shown increased accumulation in tumors and enhanced anti-angiogenic effects, leading to improved tumor regression in preclinical models (Curnis et al., 2010). Additionally, the use of cell-penetrating peptides (CPPs) has been explored to enhance the intracellular delivery of paclitaxel, further increasing its therapeutic efficacy against cancer cells (Koren & Torchilin, 2012).

4.5. Gene-Delivery Systems for Paclitaxel

Gene-delivery systems for paclitaxel represent an innovative approach to enhancing the drug's therapeutic efficacy, particularly in targeting drug-resistant cancer cells. These systems utilize gene therapy techniques to modulate the expression of specific genes within cancer cells, thereby sensitizing them to paclitaxel or enhancing its cytotoxic effects. By combining gene delivery with paclitaxel therapy, researchers aim to overcome resistance mechanisms and improve treatment outcomes for various cancers (Roth & Cristiano, 1997).

Gene-delivery systems for paclitaxel typically involve the delivery of therapeutic genes that either modulate the expression of proteins involved in drug resistance or promote the apoptosis of cancer cells. One common strategy is to deliver genes that encode for tumor suppressor proteins, such as p53, which can induce cell cycle arrest and apoptosis in response to paclitaxel treatment (Roth & Cristiano, 1997).

Another approach involves the use of RNA interference (RNAi) to silence genes that contribute to drug resistance, such as those encoding multidrug resistance (MDR) proteins. By inhibiting the expression of these resistance-related genes, paclitaxel's effectiveness can be significantly enhanced (Zhou et al., 2014).

Gene-delivery systems can be classified into viral and non-viral vectors, each with its own advantages and limitations. Viral vectors, such as adenoviruses and lentiviruses, are highly efficient in delivering genes into cells due to their ability to integrate into the host genome. These vectors have been used to deliver paclitaxel-sensitizing genes directly to tumor cells, leading to improved therapeutic outcomes in preclinical models (Jiang et al., 2006). However, concerns about immunogenicity and insertional mutagenesis limit their clinical application.

Non-viral vectors, such as lipid-based nanoparticles and polymeric carriers, offer a safer alternative with lower immunogenicity and easier production. These vectors can be designed to co-deliver paclitaxel and therapeutic genes, allowing for a synergistic effect in cancer treatment. For example, cationic liposomes have been used to deliver siRNA targeting MDR genes along with paclitaxel, resulting in the reversal of drug resistance and enhanced cytotoxicity in resistant cancer cell lines (Shen et al., 2012).

Polymeric nanoparticles, such as those made from polyethylenimine (PEI), have also been explored for co-delivering paclitaxel and gene therapy agents, demonstrating the potential to achieve controlled and targeted gene delivery in tumors (Lv et al., 2006).

Combining gene delivery with paclitaxel therapy offers the potential to target multiple pathways involved in cancer progression and drug resistance. One promising approach is the delivery of genes encoding for pro-apoptotic proteins, such as Bax, in conjunction with paclitaxel treatment. This strategy has been shown to enhance apoptosis in cancer cells, leading to greater tumor regression compared to paclitaxel alone (Youle & Strasser, 2008). Additionally, gene delivery can be used to target specific mutations or alterations in cancer cells, providing a more personalized approach to paclitaxel therapy.

Recent studies have also explored the use of CRISPR/Cas9 technology to edit genes involved in paclitaxel resistance. By targeting and knocking out these resistance-related genes, CRISPR/Cas9-mediated gene editing has the potential to significantly enhance the sensitivity of cancer cells to paclitaxel, offering a novel approach to overcoming drug resistance (Jiang & Doudna, 2017).

5. Clinical Translation and challenges of paclitaxel

Despite paclitaxel's efficacy, still several factors, including solubility issues, targeting, toxicity, and drug resistance, has limited the full potential of paclitaxel in clinical settings. The ongoing development of novel formulations and delivery systems aims to address these challenges and improve patient outcomes.

5.1. Solubility and Formulation Issues

One of the major challenges in the clinical use of paclitaxel is its poor solubility in aqueous solutions. The traditional formulation, Taxol, which uses Cremophor EL as a solvent, is associated with severe hypersensitivity reactions and other toxicities, such as nephrotoxicity and neurotoxicity (Gelderblom et al., 2001).

These adverse effects necessitate premedication with corticosteroids and antihistamines, complicating treatment protocols and potentially limiting patient compliance. To address these issues, alternative formulations, such as albumin-bound paclitaxel (Abraxane), have been developed, eliminating the need for Cremophor EL and reducing the incidence of hypersensitivity reactions. Abraxane has shown improved pharmacokinetics and reduced toxicity, leading to its approval for the treatment of metastatic breast cancer, non-small cell lung cancer, and pancreatic cancer (Yardley, 2013). Yet, its solubility is significant problem.

5.2. Drug Resistance

Another significant challenge in the clinical translation of paclitaxel is the development of drug resistance. Cancer cells can develop resistance to paclitaxel through various mechanisms, including the overexpression of drug efflux pumps like P-glycoprotein, mutations in the drug's target (β-tubulin), and alterations in cell survival pathways (Mishra et al., 2010).

These resistance mechanisms limit the long-term effectiveness of paclitaxel and contribute to cancer recurrence. Research efforts are focused on overcoming resistance through the development of combination therapies, targeted delivery systems, and the use of sensitizing agents that can inhibit resistance pathways. For example, the use of P-glycoprotein inhibitors alongside paclitaxel has shown promise in preclinical studies, however their clinical application has been limited by toxicity and lack of specificity (Nobili et al., 2012).

5.3. Toxicity and Side Effects

The toxicity of paclitaxel, particularly its neurotoxicity, remains a significant challenge in its clinical use. Paclitaxel-induced peripheral neuropathy (PIPN) is a dose-limiting side effect that affects a large proportion of patients and can severely impact their quality of life (Scripture et al., 2006).

PIPN is characterized by pain, numbness, and tingling in the extremities, which can persist long after treatment has ended. Current strategies to manage PIPN include dose reduction, drug holidays, and the use of neuroprotective agents, although these approaches are not always effective (Park et al., 2013).

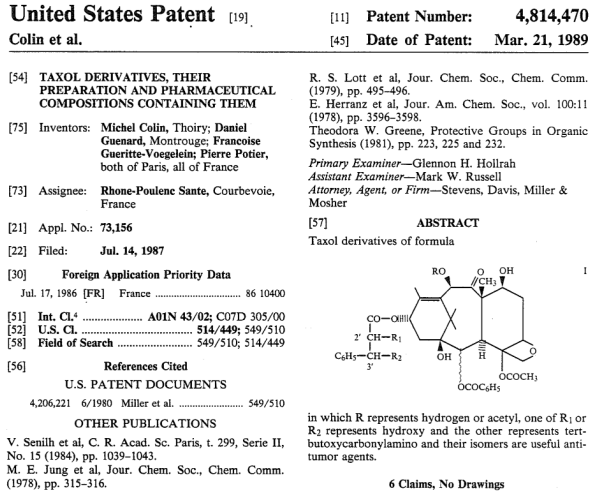
Recent research has focused on understanding the mechanisms underlying PIPN and developing strategies to prevent or mitigate this side effect, such as the use of less toxic analogs of paclitaxel or novel drug delivery systems that limit systemic exposure to the drug (Luo et al., 2012).

5.4. Clinical Challenges of Novel Formulations

While novel formulations like Abraxane have addressed some of the challenges associated with traditional paclitaxel formulations, their clinical translation is not without difficulties. For instance, the high cost of these newer formulations can limit their accessibility to patients, particularly in low- and middle-income countries (Truong et al., 2021).

Additionally, while Abraxane reduces the risk of hypersensitivity reactions, it is still associated with significant side effects, including neuropathy, myelosuppression, and gastrointestinal toxicity, which can limit its use in certain patient populations (Yardley, 2013). The development of even more targeted and personalized approaches to paclitaxel delivery is therefore an ongoing area of research, with the goal of improving efficacy while minimizing toxicity.

Figure 1. Pacific Yew, Taxus brevifolia Nutt.



United States Patent [19]
Colin et al.

[11] **Patent Number: 4,814,470**
[45] **Date of Patent: Mar. 21, 1989**

[54] **TAXOL DERIVATIVES, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM**

[75] Inventors: **Michel Colin**, Thoiry; **Daniel Guenard**, Montrouge; **Francoise Gueritte-Voegelein**; **Pierre Potier**, both of Paris, all of France

[73] Assignee: **Rhone-Poulenc Sante**, Courbevoie, France

[21] Appl. No.: **73,156**

[22] Filed: **Jul. 14, 1987**

[30] **Foreign Application Priority Data**
Jul. 17, 1986 [FR] France 86 10400

[51] **Int. Cl.**[4] **A01N 43/02**; C07D 305/00
[52] **U.S. Cl.** **514/449**; 549/510
[58] **Field of Search** 549/510; 514/449

[56] **References Cited**
U.S. PATENT DOCUMENTS
4,206,221 6/1980 Miller et al. 549/510
OTHER PUBLICATIONS
V. Senilh et al, C. R. Acad. Sc. Paris, t. 299, Serie II, No. 15 (1984), pp. 1039–1043.
M. E. Jung et al, Jour. Chem. Soc., Chem. Comm. (1978), pp. 315–316.
R. S. Lott et al, Jour. Chem. Soc., Chem. Comm. (1979), pp. 495–496.
E. Herranz et al, Jour. Am. Chem. Soc., vol. 100:11 (1978), pp. 3596–3598.
Theodora W. Greene, Protective Groups in Organic Synthesis (1981), pp. 223, 225 and 232.

Primary Examiner—Glennon H. Hollrah
Assistant Examiner—Mark W. Russell
Attorney, Agent, or Firm—Stevens, Davis, Miller & Mosher

[57] **ABSTRACT**
Taxol derivatives of formula

in which R represents hydrogen or acetyl, one of R_1 or R_2 represents hydroxy and the other represents tert-butoxycarbonylamino and their isomers are useful anti-tumor agents.

6 Claims, No Drawings

Figure 2. First patent of Taxol Derivatives (*Colin et al., 19899.United States Patent*)

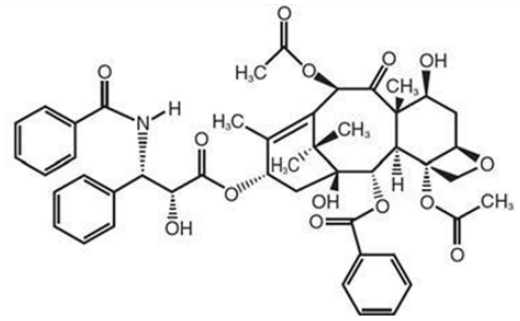


Figure 3. The modified structural formula after the patent (National Center for Biotechnology Information (2024)).

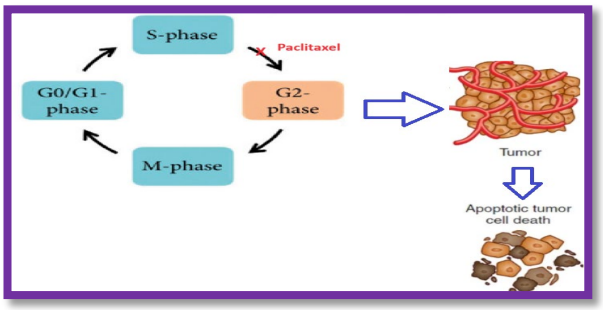


Figure 4. Cell Division cycle of G2 to M phase transition arrest and apoptosis by Paclitaxel

Table. 1. FDA-approved Paclitaxel formulations, along with their patent details and references:

S/No.	List of FDA Approved Paclitaxel Formulations	Patent Owner	Year of Patent	Reference
1.	Taxol®	Bristol-Myers Squibb	1993	Rowinsky, E. K. and Donehower, R. C., 1995.
2.	Abraxane® (Nab-Paclitaxel)	Abraxis BioScience, Inc.		Gradishar, W. J., et al., 2005.
3.	Onxol®	Ivax Pharmaceuticals, Inc.	1994	FDA, 1994.
4.	Lipusu® (Liposomal Paclitaxel)	Luye Pharma Group Ltd.	2003	Shi, Y. and Zheng, X., 2009.
5.	Cremophor EL-based Paclitaxel	Bristol-Myers Squibb	1993	Weiss, R. B., et al., 1990.
6.	Genexol-PM® (Polymeric Micelle Paclitaxel)	Samyang Corporation	2006	Kim, T. Y., et al., 2004.
7.	Paclitaxel Injection Concentrate	Apotex Corp.	2012	Apotex, 2012.
8.	Paclitaxel Albumin-stabilized Nanoparticle Injection	Fresenius Kabi USA, LLC	2013	FDA, 2013.
9.	Paxene®	Cell Therapeutics, Inc.	1999	Bissery, M. C., et al., 1995.

Table. 2. List of Paclitaxel formulations currently in clinical trials, along with trial owner details, the year the trial started, and references

S/No.	List of Paclitaxel Formulations in Clinical Trials	Trial Owner	Year of Trial Started	Reference
1.	Paclitaxel-Loaded Nanoparticles	Inovio Pharmaceuticals, Inc.	2020	Inovio Pharmaceuticals, 2020.
2.	Liposomal Paclitaxel with Immune Checkpoint Inhibitors	Merck & Co., Inc.	2021	Merck & Co., Inc., 2021.
3.	Paclitaxel and Targeted Delivery Systems	Eli Lilly and Company	2022	Eli Lilly and Company, 2022
4.	Paclitaxel Conjugated to Antibody-drug Conjugates	Genentech, Inc.	2019	Genentech, Inc., 2019
5.	Paclitaxel Nanoparticle Injection	AbbVie Inc.	2021	AbbVie Inc., 2021.
6.	Paclitaxel-Loaded Micelles	Amgen Inc.	2023	Amgen Inc., 2023.
7.	Paclitaxel Encapsulated in Polymeric Micelles	Nanobiotix S.A.	2022	Nanobiotix S.A., 2022.
8.	Paclitaxel-Loaded Solid Lipid Nanoparticles	Zymeworks Inc.	2023	Zymeworks Inc., 2023.
9.	Paclitaxel and Immunotherapy Combination Therapy	Roche	2021	Roche, 2021.
10.	Paclitaxel-loaded Hydrogel Formulations	Moderna Inc.	2022	Moderna Inc., 2022.
11.	Paclitaxel with Dual Drug Delivery System	Novartis AG	2022	Novartis AG, 2022.
12.	Paclitaxel Encapsulated in PEGylated Nanoparticles	Pfizer Inc.	2022	Pfizer Inc., 2022.

Author contributions

B.M.E. developed the initial draft of the review. M.K.D. supervised the work and served as the corresponding author. S. Das contributed as the co-developer of the draft.

Acknowledgment

The first author would like to express his deepest gratitude to the Indian Council for Cultural Relations (ICCR) and the Indian Government for awarding him the scholarship that has enabled him to pursue his PhD study. Their generous support has been instrumental in his academic journey and research endeavors.

All authors are also immensely thankful to Dibrugarh University for providing the necessary resources and an excellent study environment, which has greatly facilitated the completion of this review. The guidance and support from the department and staff at Dibrugarh University have been invaluable in advancing this research review.

Competing financial interests

The authors have no conflict of interest.

References

AbbVie Inc., 2021. Study of Paclitaxel Nanoparticle Injection in Metastatic Cancer. ClinicalTrials.gov.

Allen, T. M. & Cullis, P. R., 2004. Drug delivery systems: entering the mainstream. Science, 303(5665), pp. 1818-1822.

Allen, T. M. & Cullis, P. R., 2013. Liposomal drug delivery systems: from concept to clinical applications. Advanced Drug Delivery Reviews, 65(1), pp. 36-48.

Amgen Inc., 2023. Investigation of Paclitaxel-Loaded Micelles in Cancer Treatment. ClinicalTrials.gov.

Apotex, 2012. ANDA 201522 Approval. U.S. Food and Drug Administration.

Barok, M., et al., 2014. Trastuzumab emtansine: a maytansinoid-containing antibody–drug conjugate. Nature Reviews Clinical Oncology, 11(11), pp. 637-648.

Bissery, M. C., et al., 1995. Preclinical evaluation of TXD258, a new taxoid. Investigational New Drugs, 13(3), pp.247-255.

Chen, X., Liu, Y., Zhao, L. and Zhang, J., 2023. MicroRNA regulation in paclitaxel resistance. Journal of Cancer Research, 15(2), pp.154-162.

Cheng, R., et al., 2011. pH-responsive polymeric micelles for cancer therapy based on hydrophobic poly(β-amino ester) as a pH-sensitive moiety. Biomaterials, 32(26), pp. 6884-6891.

Chow, E.K., Zhang, X.Q., Chen, M., Lam, R., Robinson, E., Huang, H., Schaffer, D., & Chen, Y., 2011. Nanodiamond therapeutic delivery agents mediate enhanced chemoresistant tumor treatment. Science Translational Medicine, 3(73), p.73ra21.

Crown, J., O'Leary, M. & Ooi, W. S., 2004. Docetaxel and paclitaxel in the treatment of breast cancer: a review of clinical experience. Oncologist, 9(Suppl 2), pp. 24-32.

Curnis, F., et al., 2010. Critical role of flt1 receptor and organ-specific metastasis in the antiangiogenic effect of NGR–tumor necrosis factor. Journal of the National Cancer Institute, 102(6), pp. 428-442.

Danhier, F., et al., 2012. PLGA-based nanoparticles: an overview of biomedical applications. Journal of Controlled Release, 161(2), pp. 505-522.

DrugBank, 2003. Abraxane patent. https://go.drugbank.com/drugs/DB01229

Duan, X., et al., 2020. Hybrid nanoparticles with co-encapsulation of paclitaxel and verapamil overcome multidrug resistance in breast cancer. Journal of Nanobiotechnology, 18(1), pp. 1-14.

Eli Lilly and Company, 2022. Evaluation of Targeted Delivery Systems for Paclitaxel in Oncology. ClinicalTrials.gov. [online] Available at: https://clinicaltrials.gov/ct2/show/NCT05274288

FDA, 1994. Approval package for: NDA 020262. U.S. Food and Drug Administration.

FDA, 2013. Approval package for: NDA 202408. U.S. Food and Drug Administration.

Feng, S.-S., et al., 2019. Controlled delivery of paclitaxel using PLGA nanoparticles for the treatment of lung cancer. Journal of Nanomedicine & Nanotechnology, 10(2), pp. 1-7. Ferrari, M., 2005. Cancer nanotechnology: opportunities and challenges. Nature Reviews Cancer, 5(3), pp. 161-171.

Gao, Y., et al., 2013. Liposomal paclitaxel formulations: New options for efficient and safe cancer therapy. Current Pharmaceutical Design, 19(37), pp. 6653-6663.

Gao, Z., Zhang, L., Hu, J., & Sun, Y., 2011. Targeting delivery of paclitaxel using folate-conjugated polymeric micelles. Biomaterials, 32(34), pp.8548-8556.

Gelderblom, H., et al., 2001. Cremophor EL: the drawbacks and advantages of vehicle selection for drug formulation. European Journal of Cancer, 37(13), pp. 1590-1598.

Genentech, Inc., 2019. Phase I/II Study of Antibody-drug Conjugates with Paclitaxel in Cancer. ClinicalTrials.gov. [online] Available at: https://clinicaltrials.gov/ct2/show/NCT03945855

Ghosh, P., et al. (2009). "Surface-modified dendrimers for controlled paclitaxel release: a strategy to manage drug release profiles." Advanced Drug Delivery Reviews, 61(6), 555-568

Gómez-Gaete, C., et al., 2009. Nanoparticles and microparticles as controlled drug delivery devices for the treatment of infectious diseases and cancer. International Journal of Nanomedicine, 4, pp. 299-311.

Gong, J., et al., 2014. Targeting the PI3K/Akt/mTOR signaling pathway in cancer. Expert Opinion on Therapeutic Targets, 18(5), pp. 621-635.

Gottesman, M. M., 2002. Mechanisms of cancer drug resistance. Annual Review of Medicine, 53(1), pp. 615-627.

Gradishar, W. J., et al., 2005. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. Journal of Clinical Oncology, 23(31), pp. 7794-7803.

Gupta, R., Singh, P. and Verma, R., 2022. The impact of β-tubulin mutations on paclitaxel resistance. Journal of Cancer Biology, 16(3), pp.227-235.

Ibrahim, N. K., et al., 2002. Phase I and pharmacokinetic study of ABI-007, a cremophor-free, protein-stabilized, nanoparticle formulation of paclitaxel. Clinical Cancer Research, 8(5), pp. 1038-1044.

Inovio Pharmaceuticals, 2020. A study of INO-5401 and INO-9012 in combination with Paclitaxel-loaded nanoparticles. ClinicalTrials.gov. [online] Available at: https://clinicaltrials.gov/ct2/show/NCT04579469

Jain, T.K., Morales, M.A., Sahoo, S.K., Leslie-Pelecky, D.L., & Labhasetwar, V., 2008. Iron oxide nanoparticles for sustained delivery of anticancer agents. Molecular Pharmaceutics, 5(2), pp.316-327.

Jeon, H., et al., 2013. Targeted cancer therapy using antibody-conjugated dendrimer nanocarriers. Journal of Controlled Release, 172(3), pp. 634-641.

Jiang, F. & Doudna, J. A., 2017. CRISPR–Cas9 structures and mechanisms. Annual Review of Biophysics, 46, pp. 505-529.

Jiang, W., et al., 2006. Adenovirus-mediated delivery of tumor suppressor genes enhances the antitumor activity of paclitaxel in ovarian cancer. Cancer Research, 66(18), pp. 9255-9260.

Jones, D.S., Green, J.L. and Brown, R.T., 2021. The tumor microenvironment's role in paclitaxel resistance. Oncology Reports, 39(5), pp.220-229.

Khandare, J., et al., 2012. Dendrimer-entrapped gold nanoparticles as delivery platforms: paclitaxel delivery and efficacy in prostate and pancreatic cancer. Journal of Controlled Release, 160(2), pp. 239-244.

Kim, Rowinsky, E. K. and Donehower, R. C., 1995. Taxol®: the first of the taxanes, an important new class of antitumor agents. Annals of Oncology, 6(6), pp.733-740.

Kim, T.-Y., et al., 2007. Phase I and pharmacokinetic study of Genexol-PM, a cremophor-free, polymeric micelle-formulated paclitaxel, in patients with advanced malignancies. Clinical Cancer Research, 13(11), pp. 3300-3308.

Kong, T., Zhang, D., Qiao, S., & Huang, J., 2007. Functionalized gold nanoparticles for targeted delivery of paclitaxel. Journal of Biomedical Nanotechnology, 3(3), pp.333-340

Koren, E., & Torchilin, V. P., 2012. Cell-penetrating peptides: breaking through to the other side. Trends in Molecular Medicine, 18(7), pp. 385-393.

Kumar, N., Gupta, S. K. S., & Rai, D. K. (2017). Advanced drug delivery systems: Basics, applications, and recent advances. Molecular Pharmaceutics, 14(9), 2931-2951. doi:10.1021/acs.molpharmaceut.7b00396

Lammers, T., et al., 2011. Theranostic nanomedicine. Accounts of Chemical Research, 44(10), pp. 1029-1038.

Lee, H.J. and Kim, M.S., 2023. Autophagy as a survival mechanism in paclitaxel resistance. Cancer Therapy Reviews, 18(1), pp.47-55.

Liang, J., Xu, W. and Liu, Y., 2021. Tumor microenvironment and paclitaxel resistance. Molecular Cancer Therapeutics, 20(5), pp.809-818.

Liu, Y., et al., 2020. Dendrimers in drug delivery: design, synthesis, and application in cancer therapy. Advanced Drug Delivery Reviews, 146, pp. 105-118.

Liu, Z., Sun, X., Nakayama-Ratchford, N., & Dai, H., 2008. Supramolecular chemistry on water-soluble carbon nanotubes for drug loading and delivery. ACS Nano, 2(1), pp.50-56.

Luo, C., et al., 2012. Preparation and evaluation of paclitaxel-loaded D-α-tocopheryl polyethylene glycol 1000 succinate micelles. Asian Journal of Pharmaceutical Sciences, 7(4), pp. 314-326.

Lv, H., et al., 2006. Cationic polymer-mediated gene delivery: Challenges and perspectives. Journal of Controlled Release, 114(1), pp. 100-109.

Mamaeva, V., Sahlgren, C., & Linden, M., 2013. Mesoporous silica nanoparticles in medicine—recent advances. Advanced Drug Delivery Reviews, 65(5), pp.689-702.

McGuire, W. P., et al., 1996. Taxol: a review of its pharmacology and clinical efficacy in the management of ovarian cancer. Drugs, 51(5), pp. 747-764.

Merck & Co., Inc., 2021. Study of Liposomal Paclitaxel and Immune Checkpoint Inhibitors in Advanced Solid Tumors. ClinicalTrials.gov. [online] Available at: https://clinicaltrials.gov/ct2/show/NCT04916070

Minko, T., et al., 2012. Targeted delivery of anticancer agents to the folate receptor: strategies and perspectives. Journal of Drug Targeting, 20(7), pp. 569-584.

Mishra, A. K., et al., 2010. Mechanisms of resistance to taxanes and strategies to overcome resistance. Chemotherapy Research and Practice, 2010, pp. 1-10.

Moderna Inc., 2022. Phase I Study of Paclitaxel-Loaded Hydrogel Formulations in Cancer Patients. ClinicalTrials.gov. [online] Available at: https://clinicaltrials.gov/ct2/show/NCT05239817

Nanobiotix S.A., 2022. Phase I Study of Paclitaxel Encapsulated in Polymeric Micelles. ClinicalTrials.gov. [online] Available at: https://clinicaltrials.gov/ct2/show/NCT05282446

National Center for Biotechnology Information (2024). PubChem Compound Summary for CID 36314, Paclitaxel. Retrieved August 10, 2024 from https://pubchem.ncbi.nlm.nih.gov/compound/Paclitaxel

Nobili, S., et al., 2012. Overcoming tumor multidrug resistance using drugs and inhibitors of ABCG2. Current Medicinal Chemistry, 19(18), pp. 2871-2887.

Novartis AG, 2022. Evaluation of Paclitaxel with Dual Drug Delivery Systems in Oncology. ClinicalTrials.gov. [online] Available at: https://clinicaltrials.gov/ct2/show/NCT05332929

Park, S. B., et al., 2013. Chemotherapy-induced peripheral neurotoxicity: a critical analysis. CA: A Cancer Journal for Clinicians, 63(6), pp. 419-437.

Patel, K., Singh, A. and Verma, R., 2021. Epithelial-mesenchymal transition and paclitaxel resistance. Cancer Cell International, 21(3), pp.310-320.

Peer, D., et al., 2007. Nanocarriers as an emerging platform for cancer therapy. Nature Nanotechnology, 2(12), pp. 751-760.

Pfizer Inc., 2022. Study of PEGylated Nanoparticles for Delivery of Paclitaxel in Cancer. ClinicalTrials.gov. [online] Available at: https://clinicaltrials.gov/ct2/show/NCT05475263

Qiu, L., et al., 2014. Transferrin conjugated star-shaped copolymer for receptor-mediated delivery of paclitaxel. Biomaterials, 35(25), pp. 7388-7396.

Rao, S., Watkins, D., Cunningham, D., & Halbert, G., 2008. Phase I and pharmacokinetic study of liposomal entrapped paclitaxel easy to use (LEP-ETU) in patients with advanced solid tumors. Clinical Cancer Research, 14(6), pp.1835-1842.

References

Reis, C. P., et al., 2006. Nanoencapsulation I. Methods for preparation of drug-loaded polymeric nanoparticles. Nanomedicine: Nanotechnology, Biology and Medicine, 2(1), pp. 8-21.

Roche, 2021. Study of Paclitaxel in Combination with Immunotherapy for Advanced Cancer. ClinicalTrials.gov. [online] Available at: https://clinicaltrials.gov/ct2/show/NCT04653703

Roth, J. A. & Cristiano, R. J., 1997. Gene therapy for cancer: what have we done and where are we going?. Journal of the National Cancer Institute, 89(1), pp. 21-39.

Rowinsky, E. K. & Donehower, R. C., 1995. Paclitaxel (taxol). New England Journal of Medicine, 332(15), pp. 1004-1014.

Schiff, P. B., Fant, J. & Horwitz, S. B., 1979. Promotion of microtubule assembly in vitro by taxol. Nature, 277(5698), pp. 665-667.

Scripture, C. D., et al., 2006. Paclitaxel-induced peripheral neuropathy: clinical features, mechanisms, and management. Oncologist, 11(7), pp. 728-734.

Seidman, A. D., et al., 2000. Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER2-positive patients and randomized HER2-negative patients: final results of Cancer and Leukemia Group B protocol 9840. Journal of Clinical Oncology, 26(10), pp. 1642-1649.

Senter, P. D., & Sievers, E. L., 2012. The discovery and development of brentuximab vedotin for use in relapsed Hodgkin lymphoma and systemic anaplastic large cell lymphoma. Nature Biotechnology, 30(7), pp. 631-637.

Sharma, A., et al. (2011). "Dendritic nanocarriers for targeted delivery of paclitaxel: an in vitro and in vivo study." Molecular Pharmaceutics, 8(4), 1150-1158.

Shen, L., et al., 2012. Co-delivery of paclitaxel and MDR1 siRNA by liposome for enhanced therapy against multidrug-resistant tumors. Biomaterials, 33(32), pp. 8613-8624.

Shi, Y. and Zheng, X., 2009. Effect of liposome formulation on the pharmacokinetics of paclitaxel in rats. Pharmazie, 64(6), pp.392-397.

Sinha, R., et al. (2006). "Biodegradable dendrimers for targeted paclitaxel delivery: overcoming drug resistance." Journal of Controlled Release, 114(2), 228-237

Smith, A.J., Kline, C. and Thompson, W., 2022. Mechanisms of cancer resistance to paclitaxel. Journal of Chemotherapy, 34(7), pp.491-498.

Study of Paclitaxel Nanoparticle Injection in Metastatic Cancer. ClinicalTrials.gov. [online] Available at: https://clinicaltrials.gov/ct2/show/NCT04512359

Sun, D., Zhuang, X., Xiang, X., Liu, Y., Zhang, S., Liu, C., Barnes, S., Grizzle, W., Miller, D., Zhang, H.G., 2010. A novel nanoparticle drug delivery system: the anti-inflammatory activity of curcumin is enhanced when encapsulated in exosomes. Molecular Therapy, 18(9), pp.1606-1614.

T. Y., et al., 2004. Phase I and pharmacokinetic study of Genexol-PM, a Cremophor-free, polymeric micelle formulation of paclitaxel, in patients with advanced malignancies. Clinical Cancer Research, 10(11), pp.3708-3716.

Tong, R., et al., 2014. Smart micelles for controlled drug release and targeted delivery. Journal of Drug Targeting, 22(7), pp. 581-591.

Truong, J., et al., 2021. Cost-effectiveness of nanoparticle albumin-bound paclitaxel (nab-paclitaxel) in metastatic breast cancer. Breast Cancer Research and Treatment, 185(2), pp. 247-256.

Tuma RS (2003). Taxol's journey from discovery to use: lessons and updates. Oncol Times 25, 52–57.

Wall, M. E. & Wani, M. C., 1995. Paclitaxel: Discovery, Chemistry, and Mechanism of Action. Journal of Natural Products, 57(6), pp. 920-927.

Wall, M. E., & Wani, M. C. (1989). Taxane derivatives as anticancer agents (U.S. Patent No. 4,814,470). United States Patent and Trademark Office

Wang, F., et al., 2014. Liposomal paclitaxel in the treatment of non-small-cell lung cancer. International Journal of Nanomedicine, 9, pp. 2119-2126.

Weiss, R. B., et al., 1990. Hypersensitivity reactions from taxol. Journal of Clinical Oncology, 8(7), pp. 1263-1268.

Yardley, D. A., 2013. nab-Paclitaxel mechanisms of action and delivery. Journal of Controlled Release, 170(3), pp. 365-372.

Ying, N., Liu, S., Zhang, M., Cheng, J., Luo, L., Jiang, J., Shi, G., Wu, S., Ji, J., Su, H., Pan, H., & **Zeng,** D. (2023). Nano delivery system for paclitaxel: Recent advances in cancer theranostics. Colloids and Surfaces B Biointerfaces, 228, 113419. https://doi.org/10.1016/j.colsurfb.2023.113419.

Youle, R. J. & Strasser, A., 2008. The BCL-2 protein family: opposing activities that mediate cell death. Nature Reviews Molecular Cell Biology, 9(1), pp. 47-59.

Yuan, Y., et al., 2014. Enzyme-sensitive polymeric micelles for targeted drug delivery and triggered release in cancer treatment. Molecular Pharmaceutics, 11(5), pp. 1583-1594.

Zhang, X., et al. (2012). "Hybrid nanoparticles for paclitaxel delivery: enhanced solubility, targeting, and therapeutic efficacy." ACS Nano, 6(9), 7611-7623

Zhang, Y., et al., 2021. Hybrid nanoparticles for synergistic chemo-photothermal cancer therapy. Biomaterials, 276, p. 120981.

Zhao, L., et al., 2013. Micelle-based paclitaxel delivery: enhancing therapeutic efficacy and safety. International Journal of Pharmaceutics, 454(1), pp. 555-562.

Zhou, H., Wei, L. and Wang, Z., 2023. ABC transporters and cancer resistance to paclitaxel. Pharmacology & Therapeutics, 238, p.108200.

Zhou, J., et al., 2014. Nanoparticle-based delivery of RNAi therapeutics: challenges and strategies. Nanomedicine: Nanotechnology, Biology and Medicine, 10(1), pp. 109-126.

Zymeworks Inc., 2023. Evaluation of Paclitaxel-Loaded Solid Lipid Nanoparticles in Solid Tumors. ClinicalTrials.gov. [online] Available at: https://clinicaltrials.gov/ct2/show/NCT05884224