DOI:10.31557/APJCB.2024.9.4.479

RESEARCH ARTICLE

In vitro Assessment of Paclitaxel-loaded Niosome Nanoparticles and Their Cytotoxic Effects on the Ovarian Cancer Cell Line A2780CP

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Abstract

Background: One of the major concerns in contemporary medical science is the issue of cancer, with ovarian cancer being a significant contributor to cancer-related deaths. A key challenge in treating ovarian cancer is its initial responsiveness followed by resistance to paclitaxel therapy. However, recent advances in nanotechnology, particularly drug delivery systems like niosomes, offer promising solutions. **Methods:** Researchers fabricated nanoparticles via the ether injection approach and analyzed them for particle dimensions, surface charge, and medication release characteristics. Subsequently, they employed A2780CP ovarian cancer cell lines to evaluate the impact of nanodrug using an MTT assay. **Results:** The average particle size was reported at 190.3 ± 20.6 nm, with a zeta potential of -18.9 ± 2.7 mV. Notably, high encapsulation proficiency (87.6 ± 32%) verified the successfulness of the applied technique. Moreover, the cytotoxicity assessment demonstrated enhanced efficacy of nanodrug over free carboplatin when targeting A2780CP cell lines ($P < 0.05$). **Conclusion:** these findings suggest that pegylated liposomal nanocarriers could be effective carriers for delivering paclitaxel to A2780CP ovarian cancer cell lines.

Keywords: Nanoniosome- Paclitaxel- ovarian cancer

Asian Pac J Cancer Biol, **9 (4)**, 479-486 Submission Date: 07/17/2024 Acceptance Date: 09/07/2024

Introduction

Nanotechnology, bioinformatics, biomedical sciences, medicinal chemistry, mental health, and various engineering disciplines drive significant advancements in medicine and industry. Nanotechnology manipulates materials at the atomic or molecular scale, leading to innovations like nanoparticles. Bioinformatics merges computer technology with biological data analysis to understand complex processes. Biomedical sciences advance health through research and application, while medicinal chemistry focuses on drug design. Dental practices emphasize oral health and chemical and mechanical engineering create essential technologies for multiple industries. Foundational fields like analytical,organic, and inorganic chemistry provide insights into matter's composition, supporting discoveries. Biological studies explore the structures and mechanisms of living organisms, and pharmacology examines substance interactions with living beings for safer medications. These diverse fields and their interdisciplinary collaborations foster groundbreaking advancements and synergistic growth across sectors [1-23]. Cancer is a broad term for a group of diseases characterized by the uncontrolled growth and spread of abnormal cells. If not controlled, these cells can invade surrounding tissues and spread to other

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parts of the body through the blood and lymph systems [24-36]. Cancer arising from the ovary ranks as the fifth leading cause of death due to cancer among women. One of the challenges with this disease is that its symptoms can be vague, resulting in many women receiving a diagnosis only after the cancer has reached an advanced stage (stages 3 or 4) [37]. Common sites for ovarian cancer metastasis include the peritoneum, lymphatic system, and bloodstream. Advanced ovarian cancer is typically managed through surgical intervention followed by platimum-based chemotherapy. However, despite often initially responding well to chemotherapy, many patients experience recurrence and develop resistance to these drugs over time, which negatively impacts their prognosis. Specifically, for those diagnosed at an advanced stage, the five-year survival rate is only between 5-15%. Consequently, research aimed at discovering novel chemotherapeutic agents and investigating drug-resistance mechanisms holds great significance for improving outcomes in the management of ovarian cancer [38]. Paclitaxel, derived from the bark of the Taxus brevifolia tree, constitutes an efficacious chemotherapy drug. It sees widespread utilization in clinical settings specifically for treating malignant growths originating from the ovaries. Notably, paclitaxel functions by interfering with cell division processes within the tumorous tissues, thereby impeding their ability to multiply uncontrollably [39]. Lately, advancements in nanotechnology have facilitated the emergence of targeted therapies capable of minimizing undesirable side effects while simultaneously bolstering efficiency. These innovative techniques involve employing nanoscopic drug carriers designed to traverse biological obstacles and enable controlled release of medications. Among these cutting-edge vehicles are niosomes - versatile systems composed of non-ionic surfactants adept at transporting both hydrophobic and amphiphilic compounds. Crucially, because niosomes lack ionizable functional groups, they exhibit reduced cytotoxicity and elicit diminished reactions upon interaction with cells, thereby elevating the therapeutic index of entrapped pharmaceuticals. Regrettably, efforts thus far to engineer optimal nanoparticular constructs for paclitaxel administration have not yet yielded satisfactory results [40-41]. Despite various carrier types being explored for delivering paclitaxel, scientists continue searching for improved strategies to harness the full potential of this valuable antineoplastic agent.

Materials and Methods

Materials

Acquired from the Sigma Corporation Were Paclitaxel, Span 20, Cholesterol, Polyethylene Glycol 200, culture solution RPMI 16-40, Ethanol, Isopropanol, and Diethyl Ether. Additionally, the A2780CP cell line was supplied courtesy of the Cell Bank affiliated with the Iranian Pasteur Institute.

Preparation of nanoparticles containing drug

Initially, 180 milligrams of Span 20, 60 milligrams of Cholesterol, and 20 milligrams of Polyethylene Glycol 200 were combined in a solvent comprised of 20 milliliters of Diethyl Ether. Subsequently, two separate additions of Ethanol (96%) carrying 20 milligrams of Paclitaxel were made to the mixture, occurring gradually over time. Following complete mixing, achieved by agitating the concoction for an hour at 37 degrees Celsius and 300 rotations per minute, the resultant clear solution was introduced dropwise to 8 milliliters of Phosphate Buffer adjusted to pH 7.2 and maintained at 70 degrees Celsius under continuous stirring conditions. By slowly incorporating the lipid phase into the watery environment, rapid evaporation of the ether ensued, culminating in the spontaneous generation of Niosomes. Utilizing a sonicator operating at room temperature, the generated vesicles endured three minutes of processing to ensure adequate homogeneity. Further refinement was accomplished by subjecting the mixture to high-speed centrifugation at 10,000 revolutions per minute for four consecutive minutes, consequently achieving uniformity in the dimensions of the produced vesicles.

Determination of size of nanoniosomes

To ascertain the average particle size of the created niosomal formulation loaded with Paclitaxel, a dilution factor of 1:20 was applied utilizing Phosphate Buffered Saline set to pH 7.2. Post absorbance quantification at 633 nanometers wavelength, the particles' dimensions alongside surface charge characteristics were scrutinized with the assistance of a specialized Zetasizer instrument (model NANO ZS3600; manufactured by Malvern Instruments based in the United Kingdom).

Encapsulation efficiency

To determine the quantity of incorporated Paclitaxel, the freshly synthesized suspension underwent sequential centrifugation episodes lasting 30 minutes each at a temperature of 4 degrees Celsius and rotation speed equivalent to 45,000 revolutions per minute. Upon completion, the uppermost layer devoid of solid residues (supernatant) was carefully isolated following every round of centrifugation. Calculations regarding the degree of drug encapsulation and loading percentage were executed using established mathematical equations numbered 1 and 2 respectively post accomplishment of all necessary separation procedures.

Formulation 1:

EE% = [(Total Paclitaxel - Free Paclitaxel) / Total Paclitaxel] × 100

Formulation 2:

DLE% = [(Total Paclitaxel - Free Paclitaxel) / weight of nanoparticles] × 100

In Vitro Drug Release Study

A study was conducted to analyze the release of Paclitaxel from nanoparticles in a controlled lab setting using dialysis techniques. Samples of Paclitaxel nanoparticles were placed inside a dialysis bag with a molecular weight cutoff of 12 kilodaltons (Sigma). The samples were then immersed in 100 milliliters of

phosphate-buffered saline (PBS) at a pH level of 7.4 and temperature of 37 degrees Celsius with gentle stirring.

Every hour (1, 2, 4, 6, 8, 12, 24, 48, and 72 hours), 2 milliliters of the release medium were gathered and replaced with 2 milliliters of fresh PBS to maintain consistent conditions. The concentration of released Paclitaxel was quantified through high-performance liquid chromatography (HPLC) analysis. To evaluate the release pattern, cumulative amounts of released cisplatin over time were calculated and illustrated in a Table and graph.

MTT test

The MTT assay was utilized to determine the cytotoxicity of a formulation consisting of paclitaxel and compare it with that of the standard drug. Human ovarian cancer cells (A2780CP) were plated in a 96-well plate at a density of 10,000 cells per well in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum and 1% penicillin/streptomycin antibiotics. The cells were maintained at 37°C and 10% CO2 for 24 hours until they adhered to the surface. Following this period, the media was discarded, and treatment solutions including the nanoemulsion containing drugs, free drug, and untreated controls were applied at varying concentrations (40, 80, 160, 320, and 640 microMolar). The plates were incubated for an additional 48 hours before removing the drug-containing media. Then, 100 microliters of MTT solution (0.5 mg/ml prepared in PBS with pH 7.2) were introduced into each well, followed by one-hour incubation under similar conditions. Subsequently, the MTT solution was extracted, and 100% isopropanol was added to solubilize the purple formazan crystals produced due to mitochondrial reduction activity. Lastly, absorbance values were recorded at 570 nanometers utilizing an ELISA reader instrument (Bio Tek Instruments, USA).

Statistical analysis

The data obtained during the study underwent analysis using IBM SPSS Statistics Version 19 software. Statistical significance was determined at a p-value below 0.05.

Results

Characterization of nanoparticles

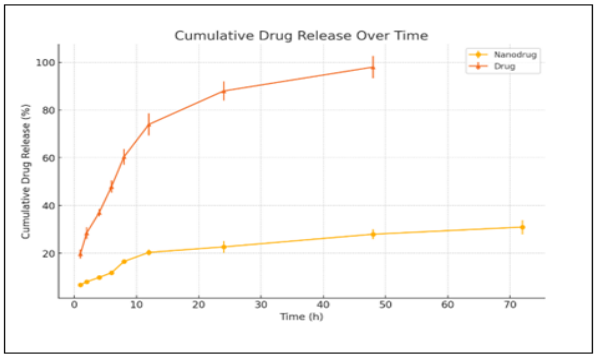

Figure 1. Cumulative Drug Release Over Time in both Standard and Encapsulated Forms. The results are presented as mean ± 5% values.

Table 1. The Percentage of Drug Released in PBS Was Measured for both the Encapsulated and Standard Drug Formulations. The results are expressed as mean ± 5% values.

	Cumulative drug release (%)	
Time (h)	Nanodrug	Drug
1	6.8±0.7	19.8±1.9
2	8.1±0.4	28.5±2.5
4	9.9±0.2	37±1.6
6	11.9±0.9	48±2.6
8	16.6±0.1	60.4±3.3
12	20.4±1.3	74±4.6
24	22.7±2.5	88±4.0
48	28±2.0	98±4.7
72	31±3.0	-

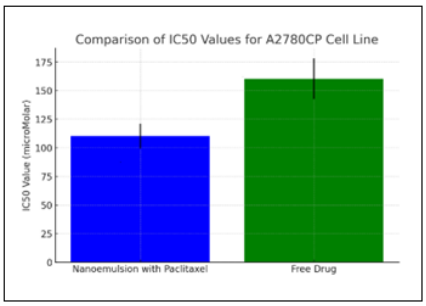

Figure 2. Diagram of Cytotoxicity on A2780CP Line

This study involved successfully preparing paclitaxel-loaded nanoemulsions using the ether injection technique. Key properties such as particle size and zeta potential were determined to be 190 nanometers and -18 millivolts, respectively. Furthermore, encapsulation efficiency and drug loading capacity were found to be 87% and 5.1%, respectively. These results demonstrate the successful development of stable and efficient nanoformulations of paclitaxel.

In Vitro Drug Release Study

During the experiment, a sustained drug release profile was observed throughout. Specifically, the highest release occurred during the first hour, however, only 31% of the total embedded drug was released even after reaching 72 hours, while the entire dose of the comparative drug was delivered within just 48 hours. Additionally, the controlled drug release demonstrated a gradual increase in a sustained manner compared to rapid depletion of the unregulated drug within 48 hours, but still, only 31% of the restricted drug was dispensed from the carrier throughout the trial (Table 1, Figure 1). Overall, the developed system showed promising extended-release characteristics suitable for long-term therapeutic applications.

Cytotoxicity and viability per cent

Based on the MTT test outcomes, the nanoemulsion containing paclitaxel displayed higher toxicity towards the specified A2780CP cell line when juxtaposed with the

free drug. More specifically, the half maximal inhibitory concentration (IC) value for the nanodrug stood at 110.3 ±10.8 microMolar whereas the value for the free drug reached 160.4±17.8 (Figure 2).

Discussion

This study aimed to enhance and analyze the toxic impact of Paclitaxel nano-niosomes on ovarian cancer cells. Research findings revealed that Paclitaxel enclosed in niosomes had greater cytotoxic effects compared to regular Paclitaxel. It can be inferred that creating nano-niosomes has been advantageous in enhancing the effectiveness of medical treatments. However, evaluating the toxicity and destiny of nano-niosomes is critical when they are utilized for pharmaceutical purposes [42-43]. In 2013, Zare et al. [44] researched the usage of niosomal nano-Paclitaxel in breast cancer cells and discovered that approximately 8% of the medication was released after 48 hours. They found that Paclitaxel combined with niosomes had higher cytotoxicity levels than the standalone drug. In comparison, this investigation reported a rapid release rate of roughly 31% over 72 hours. To prepare Paclitaxel niosome nanoparticles, the researchers employed the ether injection technique. By using polyethylene glycol, both drug-loaded and unloaded pegylated niosomes demonstrated improved stability and solubility of Paclitaxel. An MTT test was performed to examine the cytotoxicity effect in two pegylated formulations - one with the drug and another without. According to the results, the blank nanoparticles did not exhibit any toxicity, while those filled with drugs had lower IC50 values, indicating higher toxicity compared to the conventional drug. Therefore, utilizing drug nanocarriers could potentially improve drug efficacy, reduce dosage, and decrease side effects, making them a viable alternative to chemotherapy treatment.

Various fields are actively involved in treating different diseases and supporting other areas within medicine, psychology, biochemistry, dentistry, chemistry, pharmacology, and other disciplines [45-79]. For example, in medical studies, location-scale models are highly effective for evaluating the effectiveness of different treatments for particular diseases. These methods enhance the accuracy of data distribution assessments and enable precise comparisons of two treatment outcomes, even when dealing with censored data [80]. Pharmaceutical product quality is essential in healthcare, particularly in hospitals, as it directly impacts patient care, safety, and overall treatment effectiveness, ensuring better health outcomes and reducing risks [81], like a pharmaceutical product, Leuprolide, sold under the brand name LPR, is commonly prescribed for the treatment of uterine myoma and fibroids. Precise detection of lupron is crucial to ensure effective treatment and to monitor its presence in pharmaceutical waste and environmental sources, as it may pose risks to both human and environmental health [82]. Autism spectrum disorder is a neurodevelopmental condition characterized by significant difficulties in social interactions, impaired communication abilities, and repetitive behaviors [83]. Alzheimer's disease is a degenerative neurological condition marked by deficits in working memory, episodic memory, and executive function [84]. Persistent human papillomavirus infection is recognized as the primary cause of cervical cancer and other malignant tumors [85]. A qualitative study on the ethical challenges faced by Iranian nurses during the COVID-19 pandemic explores the moral dilemmas and pressures they encountered, such as resource scarcity, patient care prioritization, and balancing professional duties with personal safety. This research aims to provide insights that can inform future healthcare policies and support systems, ultimately improving the well-being of both patients and healthcare providers in crises [86]. Most deaths from breast cancer are caused by the spread of cancer cells to distant organs. Specifically, brain metastasis is highly aggressive and associated with a very low survival rate [87]. This innovative protocol for synthesizing iodine-containing compounds offers significant potential for developing targeted therapies in pharmaceutical applications, particularly due to its regiospecificity, high yields, and use of cost-effective reagents [88]. This innovative synthetic approach facilitates the development of new piperazine and piperidine compounds with dithiocarbamate functional groups, which hold promise for enhancing drug design and therapeutic applications [89]. Technology can have varying effects on educational outcomes depending on the context. For instance, during the COVID-19 pandemic, the shift to virtual learning environments sometimes led to a decrease in the effectiveness of education, as students faced challenges that impacted their performance [90]. In contrast, other studies have demonstrated that technology, when utilized effectively in educational settings, can significantly enhance learning outcomes and improve student performance [91]. Additionally, enjoying the learning process and adopting a positive attitude can provide effective solutions to problem-solving [92]. In conclusion, based on the findings of the study, the use of Paclitaxel nano-niosomes proves to be a promising approach in the optimization and assessment of its toxic effects on ovarian cancer cell lines. With enhanced cytotoxic effects observed in Paclitaxel encapsulated in niosomes compared to the traditional form of Paclitaxel, there is significant potential for improving therapeutic outcomes through the application of nano-niosomes synthesis techniques. Consequently, applying nanotechnology and niosome nanoparticles may lead to highly effective formulations of Paclitaxel drugs, thereby minimizing unwanted side effects and offering a valuable alternative to standard chemotherapy treatments. Further exploration and refinement of these methods will undoubtedly contribute to advancements in targeted cancer therapy.

Acknowledgements

None.

Data availability

Not applicable as we used information from previously published articles.

Approved by any scientific Body

Not applicable as the manuscript is not a part of any student thesis or study.

Ethical issue and approval

Not applicable as we used information from previously published articles.

Consent for publication

All authors have given consent for publication.

Conflict of interest

The authors declare no potential conflict of interest.

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