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RESEARCH ARTICLE

Improving Cancer Therapy: Design, Synthesis, and Evaluation of Carboplatin-Based Nanoliposomes against Breast Cancer Cell Lines

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Abstract

Objective: Cancer poses a significant challenge to modern medicine, with breast carcinoma being one of the most prevalent forms of the disease. Carboplatin is a commonly used chemotherapy drug for treating breast cancer, but its efficacy can be limited due to its poor water solubility and associated side effects. This study intended to enhance the therapeutic potency of carboplatin by encapsulating it within liposomal nanocarriers. **Methods:** We fabricated nanoscale liposomes loaded with carboplatin via a technique called reverse phase evaporation, and examined their physical attributes. We also studied the toxicity of these nanoliposomes on MDA-MB 231 breast cancer cells. **Results:** Our findings indicated that the liposomal nanoparticles possessed a negative zeta potential of -18.2 mV and an average size of 278 nm. The drug loading level was 2.2%, while the efficiency of drug encapsulation reached 58.5%. Of note, the cytotoxicity of carboplatin in its nanoliposomal form was markedly more potent against the MDA-MB 231 breast cancer cell line than the free drug (p-value less than 0.05). **Conclusion:** Our findings suggest that carboplatin-loaded liposomal nanocarriers could potentially serve as an advanced chemotherapeutic approach for the treatment of breast cancer, offering enhanced efficacy and reduced side effects compared to conventional carboplatin therapy. Further research is warranted to explore this novel delivery system's benefits fully.

Keywords: Nanotechnology- Breast cancer- Liposome- Drug delivery

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Introduction

There are numerous fields within various disciplines of medicine and industry, including nanotechnology (nanoparticles, nanostructures, Nanotubes), bioinformatics, biomedical sciences, medicinal chemistry, dentistry, medicine, chemical engineering, mechanical engineering, chemistry (analytical, organic, and inorganic), biology, pharmacology and others [1-35]. Advancements in technology and knowledge across various industries are driving efforts to enhance operational and product quality. Service-oriented firms are focusing on upgrading their service delivery and performance metrics while manufacturing sectors prioritize product improvement. For instance, the electronics industry is dedicated to extending product lifespan, thereby enhancing device reliability and functionality. Similarly, in the medical and healthcare sector, there is a concerted effort towards refining treatments and discovering cures for diseases [36-40]. Despite advancements in medicine, cancer remains a significant threat to humanity. According to recent data, cancer was a leading cause of death globally in 2012, and it is projected that between 15 and 17 million individuals will be diagnosed with cancer annually

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by 2020. Therefore, continued efforts are necessary to address this pressing health issue. Cancer is a complex and diverse disease that is marked by the rapid and unchecked growth of aberrant cells. There are many different forms of cancer, each with its distinct causes, progression, and signs. This illness impacts various areas of the body, such as the stomach, breast, gastric, brain, lungs, mouth, pancreas, uterus, and others. The malignant expansion of these cells not only harms the surrounding tissues but also throws off the body's delicate balance, resulting in a wide array of severe symptoms and potentially fatal consequences [41-54]. Cancer cells may exploit various methods to avoid programmed cell death (apoptosis) and become resistant to it. This can happen through an imbalance in pro-apoptotic and anti-apoptotic protein levels, decreased caspase enzyme activity, or disruptions in death receptor signaling pathways. These changes can prevent apoptosis from occurring, allowing cancer cells to multiply uncontrollably and potentially leading to tumor formation and progression [41-55]. limitations of conventional chemotherapy, such as poor water solubility and associated side effects, have led to the exploration of novel therapeutic approaches. Nanotechnology, specifically nanoliposomes, has emerged as a promising strategy to improve cancer therapy. Formulations of liposomes at the nanoscale have demonstrated the capability to augment the delivery of medications to cancerous cells, diminish the harmful effects on healthy cells, and ultimately improve the outcome for patients. [56]. In the context of breast cancer, nanoliposomal formulations have the potential to overcome the obstacles of current therapies, offering higher efficacy and greater safety compared to conventional chemotherapy [57]. Specifically, nanoliposomal carboplatin has been examined as a means to improve the therapeutic potency of the drug, with promising results in terms of improved cytotoxicity against breast cancer cell lines [58]. The use of nanoliposomes in cancer therapy represents a significant advancement, offering the potential for improved drug solubility, bioavailability, and efficacy while reducing adverse effects [58]. This approach holds promise for developing more targeted and effective cancer treatments, ultimately contributing to improved patient outcomes and quality of life [56]. As such, the design, synthesis, and evaluation of nanoliposomal formulations, such as carboplatin-based nanoliposomes, represent a critical area of research in the ongoing effort to advance cancer therapy, particularly in the context of breast cancer [59].

The study of nanoliposomal carboplatin and other similar formulations represents a step forward in the evolution of cancer treatment, offering the potential to address the limitations of current treatments and improve patient care. Further research and clinical trials are warranted to fully explore the benefits of these innovative nanomedicines and their potential to transform the landscape of cancer treatment, particularly in the context of breast carcinoma [60].

Materials and Methods

Materials

Carboplatin, Lecithin, cholesterol, polyethylene glycol (PEG) 6000, Culture medium RPMI 16-40, ethanol, isopropanol and diethyl ether were purchased from Sigma Company. MDA-MB 231 cell was provided from the cell bank of Iran Pasteur Institute.

Conditions for storing chemicals in the laboratory

To prevent accidents and reduce risks, it is important to follow a comprehensive set of rules. These include effective warehouse management to optimize space and conditions, strict segregation to prevent incompatible substances from interacting, clear and accurate labeling for easy identification, layout to minimize exposure and facilitate access, enhanced security measures to prevent unauthorized access, proper packaging to reduce the risk of breaches, prudent control of quantities to limit hazard exposure, diligent tracking of expiration dates to dispose of or refresh stock timely, proactive measures to handle leakage and spillage, ensuring immediate and safe clean-up, and meticulous planning for the transportation of chemicals within and outside the laboratory. Additionally, paying attention to other specific details tailored to the laboratory's unique requirements can further reinforce safety protocols.

Preparation of nanoparticles containing drug

First, 75 mg of cholesterol, 130 mg of Lecithin, and 14 mg of polyethylene glycol 6000 were combined in 14 ml of diethyl ether. Then, 2 ml of ethanol (96%) containing 30 mg of carboplatin was gradually added to the mixture over two steps. The mixture was thoroughly mixed for 1 hour at 37°C and 300 rpm using a stirrer. Once fully dissolved, the resulting solution was slowly poured into 8 ml of phosphate buffer (pH 7.2) that was preheated to 70°C and continuously stirred. Due to the temperature difference between the two phases, the ether quickly evaporated, leading to the formation of liposomes. To ensure uniformity in size, the vesicles were subjected to sonication for 3 minutes at ambient temperature followed by 3 minutes at 10,000 rpm using a homogenizer.

Determination of size of nanoliposomes

To determine the mean diameter of the nanoparticles, a formulation of carboplatin nanoliposomes was prepared using a ratio of 1:100 (nanoliposomes to PBS) and a pH of 7.2. The concentration of the nanoparticles was determined by measuring the absorbance at 633 nanometers. Furthermore, the size and surface charge of the nanoparticles were analyzed utilizing a zetasizer device (model Nano ZS3600, manufactured by Malvern Instruments in the United Kingdom).

Encapsulation efficiency

To construct a standard curve for Carboplatin, diverse concentrations of the drug (0.040, 0.020, 0.010, 0.005, and 0.002 mg/mL) were prepared in PBS at a wavelength of 227 nm. Free-drug liposomes served as

a reference point to preclude any potential interference or overlap caused by other liposome or nanoparticle constituents. Subsequently, 2 mL of each formulation underwent centrifugation (at 14,000 rpm, 4°C, for 15 minutes), followed by measurement of the supernatant's absorbance at 227 nm using a spectrophotometer from Hitachi, Japan. Calculations of the drug encapsulation efficiency (EE%) and drug loading efficiency (DLE%) employed the following formulas:

EE%=(PC-CS)/PC×100

DLE% = C/W × 100

In equation 1, PC signifies the initial carboplatin concentration (in mg/ml), whereas CS denotes the carboplatin concentration in the supernatant (also in mg/ml). In equation 2, C represents the carboplatin content within the nanoliposomes (in mg), and W stands for the weight of the nanoliposomes (in mg).

Drug release study

The investigation of drug release from nanoparticles involved the application of the dialysis bag technique. Initially, a nanoparticle precipitate was obtained and subsequently re-suspended in fresh phosphate-buffered saline (PBS). Then, this suspension and a standard drug solution of matching concentration (0.3 mg/mL) dissolved in 5 mL PBS were introduced into separate dialysis bags (with a cut-off of 10,000 Da; procured from Sigma). The bags were immersed in a PBS solution and mixed (at a speed of 200 rpm and a volume of 100 mL) at room temperature. At regular time intervals, 2 mL of buffer was removed from each bag and replaced with an equivalent volume of fresh buffer. The drug concentration released into the PBS was determined utilizing a spectrophotometric method.

MTT test

The MTT assay was used to assess the cytotoxicity of the carboplatin formulation and compare its effects with those of the standard drug. MDA-MB 231 cells were seeded in a 96-well plate and cultured for 24 hours. The cells were then exposed to varying concentrations of the drug formulation or the free drug for 48 hours. Following exposure, MTT solution was added to each well, and the plate was incubated for one hour. The MTT solution was then replaced with isopropanol to dissolve the formazan crystals, and the absorbance was measured at 570 nm using an ELISA reader. The cytotoxicity of the drug was calculated using the formula:

Cytotoxicity (%) = 1 - (mean absorbance of drug-treated cells / mean absorbance of negative control) x 100.

The viability of the cells was calculated as 100 - Cytotoxicity (%).

The IC_{50} value was determined using the Pharm program.

Statistical analysis

The gathered data were analyzed statistically employing SPSS software version 11. Moreover, pharm software was employed to analyze all phases of toxicity.

Table 1. The Cumulative Release of Carboplatin in Phosphate-buffered saline (PBS) was recorded as a percentage for both the encapsulated and standard drug formulations. The data are represented as mean ± 5% values

	Cumulative carboplatin release (%)	
Time (h)	Nanodrug	Drug
1	5.5±0.2	19±1.1
3	7.5±0.7	28±1.4
7	8.5±0.6	37±1.5
10	11±0.9	48±2.5
21	16±0.4	74±3.1
30	19.4±1.1	96±4
45	24.7±1.4	-
62	33±1.9	-
70	37±2	-

Results

Characterization of nanoparticles

In this study, we successfully prepared paclitaxel-loaded nanoparticles using the ether injection method. The average particle diameter and zeta potential values were determined to be approximately 278 nanometers and minus 18.2 millivolts, respectively. The drug loading level was 2.2%, while the efficiency of drug encapsulation reached 58.5%.

Drug release study

The drug release study revealed that the nanoparticles steadily and prolongedly released carboplatin. According to Table 1, an initial burst release occurred within the first hour, accounting for 13% of the total cumulative release. By 70 hours, only 37% of the encapsulated drug had been liberated. In contrast, the bulk of the standard drug was quickly released from the liposomes during the initial 30 hours.

Cytotoxicity and viability percent

The MTT test results showed that the cytotoxicity of nanoliposomes carboplatin on the specified cell line was higher than that of the free drug. The IC50 values for the nanodrug and free drug on the MDA-MB 231 cell line were found to be 90.3 ±11.8 and 154.4±12.3 micro-molar, respectively. Moreover, the cytotoxicity of the nanodrug increased with increasing concentration, whereas the standard drug exhibited a decrease in cytotoxicity at higher concentrations.

Discussion

The use of nanotechnology in cancer therapy has shown promising potential in overcoming the limitations of conventional treatments, such as poor solubility, adverse effects, and unsatisfactory outcomes. Nanoliposomes, in particular, have emerged as a novel drug delivery system for improving the efficacy and safety of anticancer drugs [42-44]. In addition to the use

of nanotechnology in medicine, we can mention the use of nanotechnology in industry, for example, the production of metal nanostructures [61]. From the application of nanotechnology, it can be mentioned that it can be used in pharmaceutical formulation [62, 63]. A recent investigation found that the thin film hydration technique is a reliable method for producing liposomal nanoparticles loaded with pegylated carboplatin. The addition of PEG to the formulation was attributed to its water-solubility, low immune response, and stability in the bloodstream, as well as its capability to prolong drug release and enhance therapeutic efficacy [64]. Previous research had also utilized liposomes as carriers for carboplatin [65-66]. Zhang et al. employed the thin film hydration technique with slight modifications, and their findings demonstrated the effectiveness of the nano-drug compared to the conventional drug when combatting gastric cancer [65]. Another study conducted by Chaudhury et al. produced targeted liposomal nanoparticles embedding carboplatin, employing a folate ligand for particle targeting [66]. Notably, although the nanoparticles were fabricated via thin-film hydration, carboplatin was encapsulated through passive equilibration. Their assessment of drug and nano-drug efficacy against ovarian cancer in both in vitro and in vivo environments revealed that carboplatin-loaded liposomal nanoparticles exhibited notably enhanced efficacy compared to the standard drug [66]. Distinct from Chaudhury et al.'s approach, our formulation exploits more economical and straightforward materials and methods to synthesize the nano-drug [66]. With a size of 278 nm, the nanoparticles were effortlessly generated. The zeta potential measurement of -18.2 mV validated the colloidal stability [67]. Encapsulation efficiency reached a maximum of 58.5%. Research on drug release unveiled that liposome nanoparticles possess adequate capacity for retaining carboplatin. Nonetheless, a sudden discharge within the initial hour implied the liberation of adsorbed medication from nanoparticles. The gradual discharge of medicine from nanoparticles might stem from PEG's existence within the formulation. This scenario was previously described in a related investigation led by Cho et al [68]. Furthermore, PEG contributes to nanoparticle stability and facilitates drug delivery to tumors, ultimately augmenting drug efficacy [69]. Notably, the cytotoxic effect of nanoliposomal carboplatin on the MDA-MB 231 breast cancer cell line was significantly higher than the free drug. These findings suggest that carboplatin-loaded liposomal nanocarriers could potentially serve as an advanced chemotherapeutic approach for the treatment of breast cancer, offering enhanced efficacy and reduced side effects compared to conventional carboplatin therapy.

In conclusion, the findings of the current study support the potential of carboplatin-loaded liposomal nanocarriers as an advanced chemotherapeutic approach for the treatment of breast cancer. The literature review further underscores the significant role of nanotechnology in improving targeted cancer treatment and overcoming the hurdles associated with conventional therapies. The development of nanoliposomal formulations presents a promising strategy for enhancing the therapeutic potency of anticancer drugs and improving patient outcomes in breast cancer therapy.

Author Contribution Statement

Seyedeh Negin Hadisadegh and Mehrnoosh Ebadi performed the experimental tests. Cell culture was carried out by Parizad Ghanbarikondori. Iman Afyouni's role in warehouse management and laying out the specific task of checking the conditions for storing chemicals in the laboratory.

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Armin Sedighi and Nikoo Javadpour did the settings and work with the devices.

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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