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Research Article

Effect of Carboplatin Loaded Niosomal Nanoparticles on Ovarian Cancer Cells

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Abstract

Cancer is known as a major health problem and also as responsible for one in eight deaths world width. Chemotherapy considered as principal treatment for cancer, but its use is faced with major limitations because of drug resistance. Carboplatin is chemotherapy drug that is used against some forms of ovarian cancer. Nanoniosomal carboplatin was synthesized using the reverse phase evaporation method and characterized for shape morphology, particle size, zeta potential and drug-release properties. A2780CP ovarian cell line was used to determine the rate of nanoniosomal carboplatin cytotoxicity. In this research, the particle size and zeta potential of the niosomal nanoparticles (NPs) were measured 258.3 ± 11.5 nm and 27.1 ± 1.4 mV, respectively. The amount of encapsulated drug and the level of drug loading were determined 94.3 ± 1.5% and 4.4 ± 2.1%, respectively. The cytotoxic effect of this nanoniosome on A2780CP cell line was significantly increased when compared with free drug ($P < 0.05$). Our findings suggest that carboplatin niosomal nanocarriers could serve as a new chemotherapy modality for ovarian cancer therapy.

Keywords: *Carboplatin; Nanoniosome; Ovarian Cancer*

Introduction

There are many diseases in the world [1], but cancer has always been more important [2,3]. Due to ovarian cancer among the other cancer is the most lethal gynecologic malignancies and the seventh most common reason of cancer among women worldwide [4]. One of the most important anticancer drugs is carboplatin, which is used to treat many types of solid cancer, such as ovarian [4]. In recent years nanotechnology applied in several fields of medical sciences including clinical pharmacology to increase the efficacy of different therapeutic compounds and reduce its side effects [5]. NPs as a carrier in the drug delivery systems are due to the facts that, small size nanoparticles can penetrate the capillaries, and consequently efficient accumulation of drugs at target sites in the body. In addition, the use of biodegradable materials in the preparation of nanoparticles leads to a constant and uniform distribution of the drug at the target site for in long time [6,7]. Between the different drug carriers, noisomes and liposomes are well known for their efficacy. Niosomes or Non-ionic surfactant vesicles are a layered microscopic structure that is made up of a mixture of alkyl or di-alkyl nonionic surfactants of the polyglycerol ether and cholesterol, formed after hydration in aqueous environments. Since the noisomes are biodegradable and non-toxic, they are suitable carriers for delivering therapeutic agents to the target sites in the body [8-12]. The aim of presented study was to evaluate the anti-cancer properties of noisomal carboplatin extract in ovarian cancer, and also study the effect of noisomal nanoparticles, as carriers of carboplatin extract, to improve the therapeutics indices.

Methods and Materials

Products

Carboplatin, cholesterol, and polyethylene glycol 5000 from Sigma-Aldrich Co., UK; Span 60 from Acros Co, Belgium; and RPMI 1640 cell culture medium from Gibco Co., Germany, were obtained. Also, the cell line A2780CP was purchased from the cell bank of Pasteur Institute in Iran.

Nanoniosomal drug preparation

Niosomal nanoparticles were synthesized using the reverse phase evaporation method. Briefly, approximately 15 mg of carboplatin, 200 mg of span 60, 100 mg of cholesterol, and 110 mg of polyethylene glycol 5000 (with the molar ratio of 65: 50: 8) were dissolved in 120 ml of ethanol 96% by heating at 37°C and stirring for 1 hour at 160 rpm. After perfect dissolving, the solvent was separated using a rotary. The obtained thin film was dissolved in 30 cc phosphate buffer (pH 7.2), which was added two times. Finally, the formulations were sonicated for 5 minutes using an ultrasonic bath (Bandelin Sonorex Digitec, Germany). Light microscopy (S-4160 scanning microscope, Hitachi, Japan) was employed to determine the surface and shape morphology of the produced nanoniosomes. To determine the rate of the entrapped drug, 20 mg of the formulation was centrifuged for 1 hour at 4°C and at 15000 rpm. Then, optical absorbance of the supernatant of each formulation was measured at 240 nm using a spectrophotometer (UV1800, Shimadzu Co). Encapsulation efficiency and the rate of drug loading were calculated by using formulas 1 and 2 respectively.

$$Encapsulation\,percent = \frac{PC - CS}{PC} \times 100 \qquad (1)$$

In formula 1, PC: primary carboplatin and CS: carboplatin in supernatant in mg/ml

$$Drug\,loading\,percent = \frac{C}{W} \times 100 \qquad (2)$$

In formula 2, C: carboplatin content in the nanoniosome and W: weight of nanoniosome in mg/ml.

Results were analyzed by the SPSS software version 11. Data are expressed as the Mean ± SD from three separate tests that examined duplicates.

Particle size and zeta potential analysis

2 milligram of the formulation was dissolved in 5 ml of phosphate-buffered saline (PBS). After the determining of its absorption in 633 nm, the zeta potential and mean diameter of the nanoniosome were measured using a Zetasizer (Nano ZS3600, Malvern Instruments, UK).

Cytotoxicity assay

A2780CP cell line was cultured in RPMI 1640 containing 10% fetal bovine serum, 100 µg/ml streptomycin, and 100 U/ml penicillin. Cytotoxicity testing was performed using MTT assay [12]. After 48 hours of exposure, the supernatant was removed, and then 100 µl of a solution of MTT was added to the cells. After 1 hours of incubation, 100 µl of isopropanol solution was added to the culture medium. After 30 minutes, the optical absorbance of the formazan product was read at 570 nm using a plate reader (Synergy Multi-Mode Elisa Reader, Bio-Tek, USA). Finally, IC50 was calculated by using the pharm program.

Results

Particle size and zeta potential analysis

The mean size of nanoniosomal carboplatin and potential of zeta were determined as 258.3 ± 11.5 nm (Figure 1) and 27.1 ± 1.4 mV, respectively.

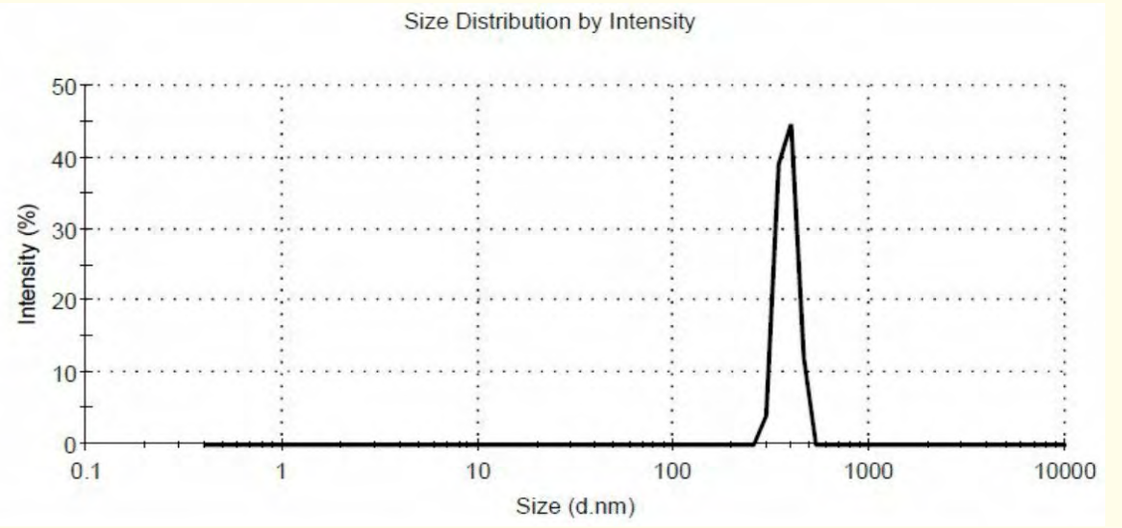

Figure 1: *The mean size of nanoniosomal carboplatin.*

Surface morphology

As shown in figure 2, Light microscopy images revealed that the carboplatin nanoniosomes had spherical and smooth surfaces.

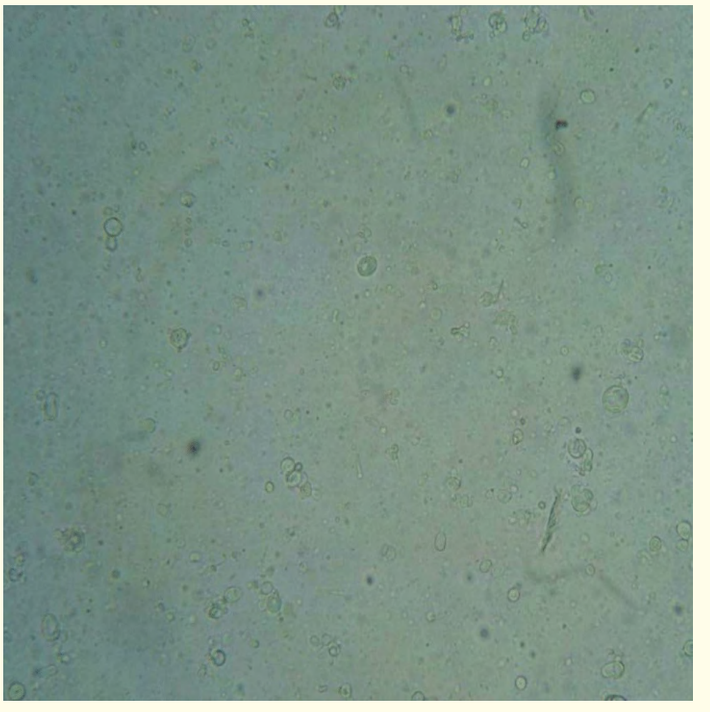

Figure 2: *Light microscopy of carboplatin loaded on PEGylated niosomal nanoparticles.*

Encapsulation efficiency and drug loading studies

According to formulas 1 and 2, the encapsulation efficiency and drug loading contents were calculated 94.3 ± 1.5% and 4.4 ± 2.1%, respectively.

In vitro drug release studies

As shown in figure 3, carboplatin released from the nanoniosome to PBS buffer was measured during time intervals of 1, 2, 4, 10, 23, 27, 31 and 48 hours using the standard curve of carboplatin. The results show the maximum amount of carboplatin released from nanoniosome during 48 hours at about 70%.

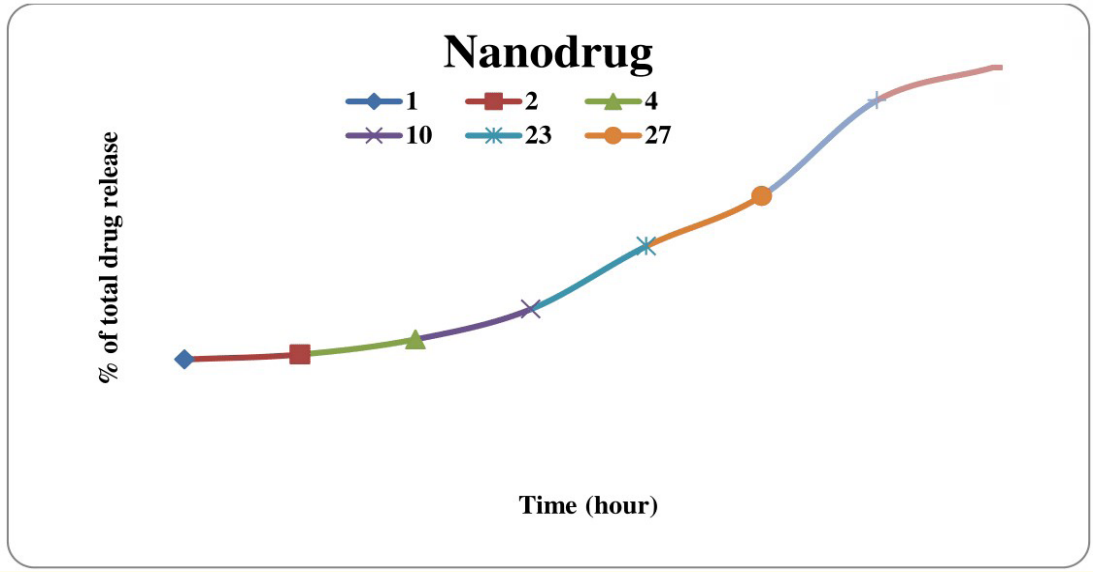

Figure 3: *Release of carboplatin from carboplatin Nano Niosome.*

Cytotoxicity assay

As shown in table 1, in comparison between this three treated cases, higher cytotoxic effects were obtained in all nanoniosomal carboplatin concentrations toward free carboplatin and nanoniosomal.

Ovarian ell Line	Nanoniosomal carboplatin	F-Carboplatin	Nanoniosomal	P value
A2780CP	40.8 ± 7.4	110. 4 ± 11.6	220.4 ± 9.9	P < 0.05

Table 1: *The cytotoxicity effects of Carboplatin in the standard form or encapsulated into Niosome nanoparticle. Results were expressed as mean ± 5% values of three independent experiments.*

Discussion

The aim of this study was to optimize and evaluate the effects of carboplatin loaded on noisome on ovarian cancer cells. The results indicated an increase in the cytotoxic effects of carboplatin loaded onto NPs compared to the standard drug. In general, NPs production methods have been proven to improve targeted drug delivery [9]. However, the nanonoisomal material used in drug delivery, its toxicity and physicochemical properties are a very important aspect that needs to be evaluated [11]. A drug delivery on tumor tissue is one of the main challenges of drug biotechnology. One of the most widely used noisome is neuromas, which can drive drugs to targeted cells. Leila Kanaani and colleagues in 2017 loaded cisplatin on the noisome to produce and optimize the formulation to improve its bioavailability. In this study, PEG and cholesterol were evaluated for retention percent, drug release, and size. They concluded that with the presence of surfactants, it increased the release rate of the drug from the NPs and also increased drug-trapping efficiency [9]. In this research, carboplatin was loaded onto noisomal nanoparticles by reverse phase evaporation method. After describing nanoparticles, the polyethylene glycol composition was used to optimize the formulation [4]. Although the loading rate in this study was low, however, since these nanoparticles were prepared in the presence of polyethylene glycol, they tend to remain intact. This results in longer nanoparticles remaining in the bloodstream, resulting in increased drug efficacy [4]. Mr. Zarei and his team in 2013 [11] examined the nano-noisomal paclitaxel in breast cancer category. In this study, the amount of drug release was calculated at 8% in 48 hours. Their results showed that the cytotoxicity of the paclitaxel nanonoisome was superior to that of the free drug. In the current study, drug release in 48 hours of carboplatin release from NPs was reported to be about 70%, which had an upward and slow release during 48 hours. Our research results suggest that nanonoisomal carboplatin has more cytotoxic effects than the standard drug on the ovarian cancer category, which will be a good alternative to chemotherapy in the near future.

Conclusions

Considering the preparation method, it seems that reverse phase evaporation is appropriate method to this method. It could be concluded that niosomes application in ovarian cancer is effective therapeutic strategy. The comparison between cytotoxicity effects of the Nano niosomal carboplatin with free drug shows the higher efficiency of nano niosomal carboplatin in destroying mention all cell line. Thus, this formulation may be an alternative chemotherapeutic candidate for ovarian cancer in the future.

Acknowledgment

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Conflict of Interest

The authors declare that there is no conflict of interest.

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