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Synthesis and Characterization of a Novel Niosome System Containing *Adiantum Capillus-Veneris* for Breast Cancer Therapy

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Abstract

Background: Due to the increase in cancer and side effects of common therapies, researchers are looking for treatments with the least side effects, which is why medicinal plants have become so important. Adiantum capillus-veneris L. plant commonly called southern maidenhair fern, and also named as "Pare-siavashan" in medical and pharmaceutical textbooks of Iranian Traditional Medicine, contains triterpenoid compounds that have anti-tumor properties. It is a perennial fern with narrow stems and small leaves that grows in hot and humid places. This study aims to make biocompatible nanosystems carrying Adiantum capillus-veneris extract with an appropriate loading rate and to compare the anti-tumor properties of the extract-carrying system with its free state.

Materials and Methods: After Extracting by Soxhlet, the resulting extract was loaded in the nano-niosome system by thin-film method and was subjected to physical, chemical, and cellular characterization.

Results: The results of this study showed that the loading rate of Adiantum capillus-veneris extract in niosomic formulation is 50.74% and the resulting particles are spherical with a size of 325.7nm and anionic. No chemical interactions were found between niosome and extract and the resulting system was chemically stable.

Conclusion: Based on acquired results, the designed system has acceptable anti-cancer properties on MCF7 cell line. It is notable that the cell survival rate was about 19 %.

Keywords: Adiantum capillus-veneris, Extract, Niosome, Breast cancer

Introduction

Iran with its special climate is the habitat for more than 7500 plant species, and it is estimated that there are more than 750 species of medicinal plants in the vegetation of Iran (1). In recent years, the use of medicinal plants has increased due to the belief in the safety and effectiveness of herbal products (2-4). Adiantum capillus veneris is a perennial herbaceous plant of the fern family, with a brown, slender, and knotted rhizome and playful and thin roots. This plant has three-part leaflets and very narrow branched petioles in brown or dark purple. One of the main characteristics of Adiantum capillus-veneris is the spores that are seen in the tip of the leaflets as protruding green or brown spots (5). Adiantum capillus-veneris belongs to the phylum Pteridophyyta, the family Filicina, and the class Polypodiaceae, whose class Polypodiaceae is divided into other genera. This plant belongs to the Adiantaceae and the genus Adiantum.

The plant grows in southern Europe, the Alps, and the Atlantic coast (6), as well as in northern Iran. The main ingredients of this plant are Sterols, tannins (tannic acid and gallic acid), bitter substances, gum, mucilage, quinic acid, chichemic acid (7-12). In traditional medicine, this plant is recommended as a tonic, diuretic, treatment of respiratory disorders, spleen tumors, liver, and internal organs. Anti-jaundice effects, hepatitis (13), antimicrobial (14-15), antioxidant (16), anti-inflammatory (17), and anti-diabetic (18-19) have been shown by this plant. This plant meanwhile has anti-tumor properties due to its flavonoids and phenols (20).

Based on statistics published by the Ministry of Health, cancers are an important and responsible factor in 29% of the mortality rate in the community.

Currently, breast cancer is the most common type of cancer among women living in developed countries. Unfortunately, 12% of breast cancers occur between the ages of 21 and 90. (21) In Iran, breast cancer accounts for 21.4% of all carcinogenic reports (22).Common therapies include surgery, hormone therapy, radiotherapy, and chemotherapy, from which the most important drawback is the non-selective function of these methods, regardless of their side effects; since these methods target both cancer and healthy cells (23).The increasing prevalence of mortality from various cancers and the lack of chemotherapy and radiation therapy require alternative therapies. Therefore, due to the problems of conventional drug delivery systems such as poor bioavailability, poor stability in the body, poor solubility, poor delivery and targeted delivery to the target site, today the use of nanocarriers to incorporate drug compounds and deliver it to the target tissues are of interest to researchers. Interior involvement means trapping the drug in drug carriers, which protects the drug from oxidation, isomerization, and decomposition, and also increases the half-life of the drug over a period of time and causes controlled and continuous delivery in the body. Drugs are delivered to target tissues (24). Niosomes are lipid carriers that are formed from the self-aggregation of surfactants in the aqueous medium to form an enclosed bilayer structure. Niosomic vesicles are bilayers composed of non-ionic active substances. The unique structure of the niosomes enables them to trap hydrophobic and hydrophilic materials, for which the niosome traps the hydrophobic material in its lipid part and the hydrophilic material inside the water nucleus (25). Easy design, biodegradability, biocompatibility, flexibility, and slow release of the drug are among the advantages of this drug nanocarrier (26-27). The purpose of this study was to construct and investigate nanosystems carrying Adantum capillus-veneris extract and to evaluate the system of this carrier in terms of embedded extract, release pattern from niosome system, nanosystem size, nanosystem surface load, nanosystem morphology and interaction between Adiantum capillus-veneris and nanosystems as well as the anti-cancer effect of the carrier system on MCF7 class cancer cells.

Materials and Methods

Extraction by Soxhlet apparatus

To this end, 50 grams of milled plant leaves were poured into the cartridge and placed in the machine compartment. Extraction was then performed with a hydroalcoholic solvent (70% ethanol) and then the ethanol solvent used was removed by a rotary apparatus (Heidolph, Germany).

Determining the maximum adsorption of *Adiantum capillus-veneris* extract and drawing the standard *Adiantum capillus-veneris* diagram in isopropyl and PBS (Phosphate Buffered Saline) buffer by UV / VIS spectrophotometry (T80 +, UK)

At this stage, different dilutions of *Adiantum capillus-veneris* in isopropyl solvent and different dilutions of the extract in PBS were prepared. Then, the absorbance of each dilution was measured using a spectrophotometer (T80 +, UK). The experiment was repeated three times at this stage. Then, using the absorption wavelengths obtained, the standard diagram of *Adiantum capillus-veneris* extract in isopropyl and the standard diagram in PBS were drawn (13).

Construction of a niosome system containing extracts

The thin-film hydration method was utilized to fabricate the extract-carrying nanosystem, so that the surfactant (Tween-60) and lipids (Cholesterol) used were weighed in a ratio of 70:30 and dissolved in chloroform. The balloon containing solvent to form a thin film at room temperature was placed on a rotary (Heidolph, Germany) at 40 °C for 150 rpm to form an evaporating organic phase and a thin, uniform film. Due

to the hydrophilicity of *Adiantum capillus-veneris*, a solution with a concentration of 1 mg/ml of the extract and saline phosphate buffer was prepared in a specific volume, and hydration was performed with this solution. To this end, a balloon containing a thin film and solution was placed on a rotary at 150 rpm for 30 minutes at 45 ° C. The result of this step was a milky solution. Particle size reduction from probe sonicate (PARSONIC 7500s, Iran) for 60 minutes, with a frequency of 28.5% KHz, and ultrasonic power 100 Watt was used and in order to separate particles larger than smaller ones, the solution was passed through the filter 0.022 micrometers. To separate the unencapsulated *Adiantum capillus-veneris* extract, the resulting milky solution was transferred to a dialysis bag and neutralized for 1 hr. at 4 °C in PBS medium (L50, Iran), where the buffer was changed every half hour.

Determining the percentage of *Adiantum capillus-veneris* extract loaded in Niosome system

In order to evaluate the amount of extract, a spectrophotometer (T80 +, UK) was used, so that the ultraviolet absorption of a niosomic solution mixed with isodopropanol was determined in certain proportions at the maximum wavelength. Afterward, the concentration of *Adiantum capillus-veneris* extract was obtained according to the standard formula:

(*Adiantum capillus-veneris* loading efficiency = (enclosed *Adiantum capillus-veneris* value) / (initial *Adiantum capillus-veneris* value) × 100).

Investigation of the process of extraction release from nanoniosome

For this purpose, the diffusion technique was used. One cc of Niosome suspension containing *Adiantum capillus-veneris* extract was poured into the bag. The dialysis bag was then immersed in a container containing 10 ccs of PBS buffer at pH = 7.4 at 37 °C (simulation of in vivo conditions). At intervals of 30 minutes to 72 hours, each time 1cc was removed from the buffer and replaced with the same amount of fresh buffer at the same temperature. The absorption of the samples at maximum wavelength was checked by spectrophotometer.

System characterization

In order to characterize the synthesized nanocarriers, Dynamic Light Scatting device was used to examine the size and surface charge of nanosystems carrying *Adiantum capillus-veneris* extract. Atomic Force Microscope was utilized to examine the structure of nanosystems carrying *Adiantum capillus-veneris* extract. Meanwhile, infrared spectroscopy was used to investigate the functional groups and the interaction of the nanosystem surface and *Adiantum capillus-veneris* extract.

MTT assay test

The MTT test has been used to assess cell viability and cytotoxicity of blank niosome. Besides, MTT assay method also been used to investigate the cytotoxic effect of drug compounds on the growth and proliferation of MCF7cancer cells. HFF cells have been seeded in 96-well plates and incubated for 24 hours and then treated with different concentrations of mere niosomes without extract to evaluate the toxicity after 48 hours. For study the anticancer activity of the prepared samples, MCF7 cells were seeded in 96-well plates and incubated for 24 hours. Cells were attached to the plate surface and were then treated with various concentrations of nanosystems carrying Adantum capillus-veneris**.** Cell viability has been evaluated using MTT assy. Briefly, MTT 10 **µ**L (5 mg/mL) was added to each well and the cells were incubated at 37°C for 2 hours. The formazan product was dissolved in 10% sodium dodecyl sulfate 100 **µ**L containing hydrochloric acid 15 mM. Color intensity has been quantified by an absorbance microplate reader at test and reference wavelengths of 570 nm**.**

Results

The absorption spectrum of *Adiantum capillus-veneris* extract in the wavelength range of 200 to 800 nm was plotted using a spectrophotometer. By examining the data of the diagram, the highest quercetin uptake was selected according to figure 1a at 315 nm.

In order to study the release process and the amount of extract load, the standard diagram of *Adiantum capillus-veneris* extract in isopropanol alcohol and PBS buffer was plotted for three times (figure 1 c and figure 1 d)

$y = 2.8835x + 0.0191$ $R = 0.9974$ (1)

$y = 4.6515 + 0.0273$ $R = 0.9999$ (2)

According to the linear formula of equation (2), the load of *Adiantum capillus-veneris* extract in the niosomic nanosystem is 50.75%. Also, the study of the release profile of *Adiantum capillus-veneris* extract from niosomic nanosystems showed that the release rate of *Adiantum capillus-veneris* at different times and at 37 °C temperature is slow release and has a continuous release process (figure 1 b). According to the obtained diagram, the highest slope of the diagram is related to the first ten hours, which indicates the intense release of *Adiantum capillus-veneris* extract in this period, which according to the concentration gradient between the dialysis bag and the surrounding PBS buffer seems normal and then the chart continues with an almost gentle and steady slope, and in 72 hours the release rate reaches its maximum value and from this time onward, we are faced with a slow slope of the release process.

Results of physicochemical characterization of nanosomic nanocarriers carrying *Adiantum capillus-veneris* extract

Specifications of Niosome nanosystems carrying *Adiantum capillus-veneris* extract was shown in Table I. Figure 2 a presents the 325.7 nm size of nanosomic nanosystems carrying *Adiantum capillus-veneris* extract and the Figure 2 b shows the zeta potential of -27.8 mV nanosomal nanosystems carrying *Adiantum capillus-veneris* extract. This results confirmed the proper size distribution and zeta potenials of current nanosystem. The image results obtained from photographing the nanocarrier by atomic force electron microscopy (AFM) to examine the surface and morphology of the spherical structure of the nanosystem (figure 2 c), show that the spherical structure of the system and the resulting particles are uniform and also indicate no accumulation and adhesion of particles.

In order to identify the functional groups and possible interactions between the compounds and to detect the encapsulation of the full-blown extract in the Noisome, the infrared spectroscopy is shown in Figure 3. According to the FTIR spectrum of *Adiantum capillus-veneris*, full extract (Figure 3 a), wide peak in the region of 3379.04 cm^{-1} characteristic of OH group, 2928.90 cm^{-1} characteristic of tensile vibration CH_3, tensile vibration C=O in wave-number 1608.21 cm^{-1} wavelength 1384.94 cm^{-1} characteristic of bending motion CH_3, peaks in the area 1000-1300 cm^{-1} belong to CO group, and wave number 995.13cm^{-1} is characteristic of P-OR. In the FTIR spectrum of the niosome without *Adiantum capillus-veneris* extract (Figure 3 b), the wide peak in the region of 3435.39 $cm^{-1,}$ characteristic of the OH group, the wave number of 1638.42 cm^{-1}, the characteristic of tensile vibration C=O, the peaks are in the region of 1000 -1300 cm^{-1} related to the tensile vibration of the CO group, which is transmitted to the peaks of 1638.44, 3436.69 cm^{-1} in the spectrum of liposomes containing the extract (Figure 3 c), which confirms the encapsulation of the full-blown extract in the niosome. No additional peaks were formed in the niosomic system containing the extract and no peaks were removed, indicating that no chemical interaction had taken place between the niosomic system and the extract. Also, the presence of the extract did not cause structural damage to the

nanosystem, and nature and chemical structure of the compounds in the nanocarrier was preserved.

MTT assay test results

HFF cells were treated with different concentrations of mere niosomes and without extract to evaluate the toxicity. According to the results of the treatment of cells with different concentrations of niosomes without extract after 48 hours, no toxicity was observed (figure 4). After ensuring non-toxicity, the breast cancer cells (MCF7 cell line) were exposed to the extract of *Adiantum capillus-veneris* for 48 hours. The results showed that the niosome carrier of *Adiantum capillus-veneris* extract compared to mere *Adiantum capillus-veneris* caused more cell death in both treatment time and the use of nanocarriers could increase the cell kill rate of the drug and it was also observed that the duration of treatment with cell death has been directly related (figure 5). Drug-free niosomic system had a survival rate of 97.5% in comparison to the control which was 100%, and was very low compared to the lowest concentration of niosomic system used, and it can be claimed that this toxicity is due to cell treatment with the empty system was insignificant and meant that the system was non-toxic. The anti-cancer function of niosome carrier of *Adiantum capillus-veneris* extract can be due to the slow release of the system, which reduces the amount of drug consumption.

Table I. Specifications of Niosome nanosystems carrying Adiantum capillus-veneris extract

Size (nm)	PDI (poly dispersion)	Zeta potential(mv)
325.7	0.462	-27.8

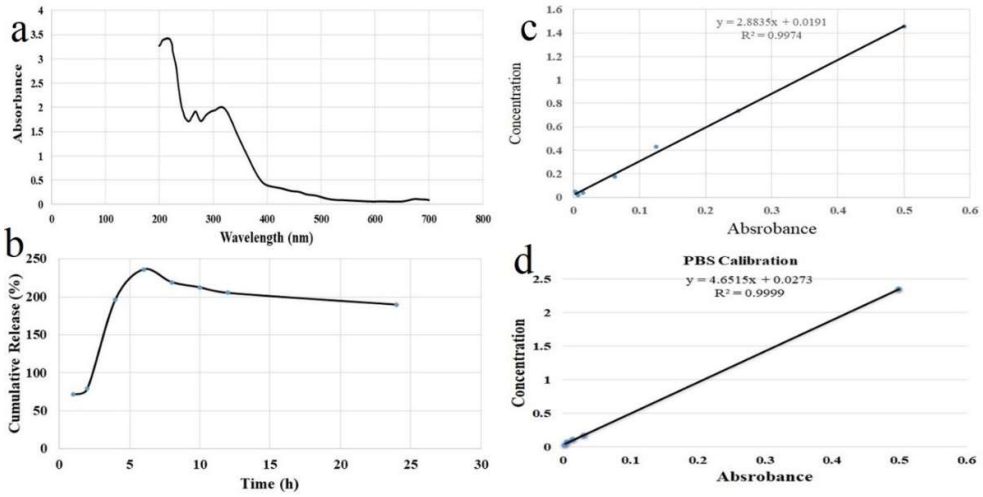

Figure 1. Diagram of the highest absorption of *Adiantum capillus-veneris* extract (a), Diagram of extraction release from Niosome system (b), Standard diagram of *Adiantum capillus-veneris* in isopropanol (c), and Standard diagram of *Adiantum capillus-veneris* in saline phosphate buffer (PBS) (d).

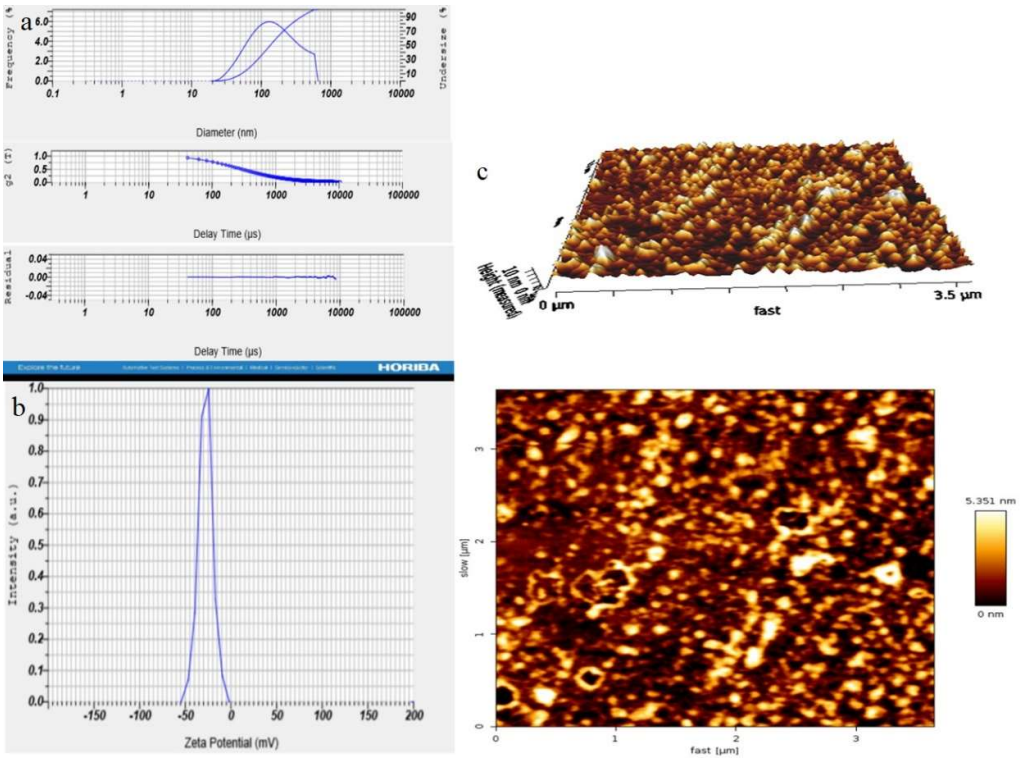

Figure 2. Size distribution of nanosomic nanosystems carrying Adiantum capillus-veneris extract (a), Zeta potential of nanosomal nanosystems carrying Adiantum capillus-veneris extract (b), and Particle morphology of the Niosome system carrying the Adiantum capillus-veneris extract.

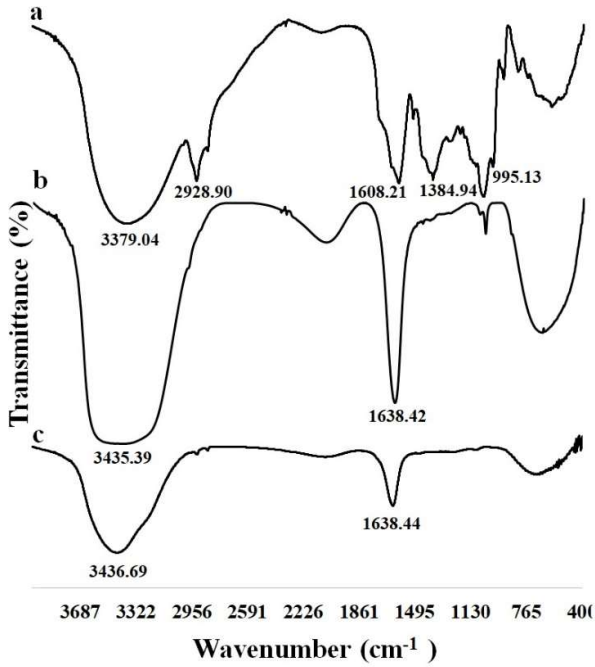

Figure 3. FTIR spectra of *Adiantum capillus-veneris* extract (a), a drug-free niosome system (b), and a niosome system containing *Adiantum capillus-veneris* extract (c)

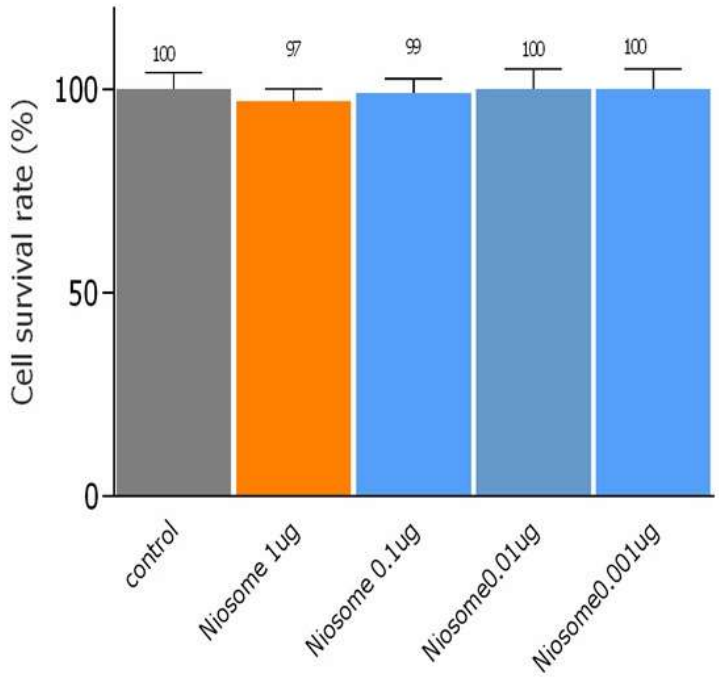

Figure 4. Chart of results from 48-hour MTT test of healthy HFF cell line.

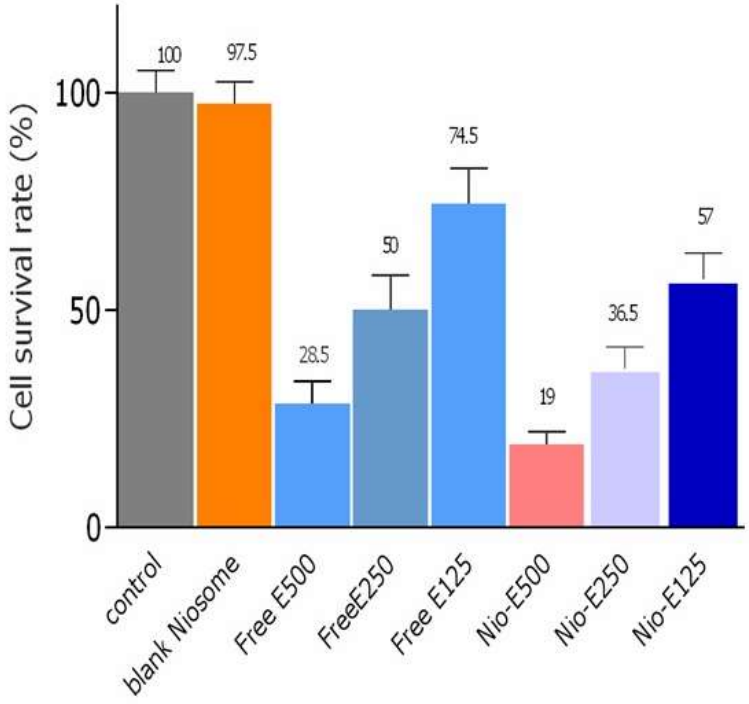

Figure 5. Results of MTT test for 48 hours of MCF7 cell line treatment.

Discussion

In designing and developing carriers of drug delivery systems, the goal is to achieve a system with proper drug loading and desired release properties along with a long half-life and low toxicity. Niosomes are among the carriers used in drug delivery. Due to the side effects of chemotherapy drugs, finding natural compounds and using dietary supplements in the production of drugs for diseases, especially cancer, has attracted the attention of researchers. Natural compounds can induce apoptosis in cancer cells by interfering with these signaling pathways, growth factors, transcription factors, protein kinases, inflammatory cytokines, and metastasis (28). The Niosomic system from the present study was physically and chemically evaluated and the results showed that the lipid nanosystem carrying *Adiantum capillus-veenris* extract has a load rate of 50.75%, a size of 325.7 nm and a zeta potential of -27.8 mV. Investigation of the release pattern of *Adiantum capillus-veneris* extract from Niosomic nanosystem in an indication of the slow release of the resulting system, which confirms the controlled release of the extract from the system. The constituent particles of the lipid system of suitable morphology and the lack of chemical interaction between the niosomic system and the *Adiantum capillus-veneris* extract are other suitable physicochemical properties of the niosomic system containing the *Adiantum capillus-veneris*. loading efficiency, which is calculated in the present study as 50.75%, is one of the most important characteristics of lipid systems, so that lipid systems with high interference efficiency are more desirable than systems with low interference efficiency. Research studies show that the loading efficiency of lipid systems depends on several factors such as the particle size of the nanosystem, the type of lipids used, and the molar percentage of each in the structure of the lipid system and the type of embedded material (29-30). In a study by Majdizadeh et al. for the construction of a lipid system containing Mentha piperita essential oil, the loading rate was reported to be 61.38% (13). The results are in line with the results of this research and are close to each other. Another important factor in the evaluation of lipid systems is the process of release of the drug-loaded from the system. The first hours (the first ten hours of release) were explosive, which could be due to the difference in the high concentration of saturated extract between the niosome system and saline phosphate buffer, and in the continuation of the release process by reducing the concentration difference. In addition, in the last hours, the release chart slopes are approaching zero.

Rapid advances in drug discovery methods have led to an exponential increase in new drugs. Due to the diversity of physical and chemical properties of various drugs, we need smarter drug delivery systems. One of the most important topics in the drug industry is the discussion of controlled drug delivery to the body.

Other studies on the loading of plant essential oils in nanosystems include the research of Haghir Al-Sadat et al. entitled "synthesis and characterization of phospholipid vesicles containing aloe vera essential oil, the results of which show 35.65±7.4% of embedded essential oil and its controlled release from the nanosystem (31) which in addition to confirming the results of this study, the amount of extract load in the niosomic system is significantly higher than that of Haghir Al-Sadat et al.'s study. Other studies conducted to load active plant materials in nanosystems include the study of Reza Nedainia and his colleagues on curcumin, the active ingredient in turmeric, which showed that the use of curcumin nanoparticles is an effective method in the treatment of cancer although curcumin nanoparticles have many therapeutic benefits (32) Hemmati et al., in a study, prepared several niosomic formulations containing quercetin, which reported the results of interference efficiency between 71% to 95%, particle

size below 100 nm and zeta potential between -6.5 to 35.2 mm (33).

Conclusion

In this study, the fabrication and characterization of niosomic nanosystems containing *Adiantum capillus extract* were performed. In addition to the acceptable physical and chemical properties of the nanosystem with the desired load, controlled release and spherical morphology, the results of MTT evaluation show significant anti-cancer properties of nanosomic nanosystems carrying *Adiantum capillus-veneris* extract on MCF7 cell line. Therefore, according to the results and evidence of the research, the niosomic nanosystem carrying *Adiantum capillus-veneris* extract can be used as a biocompatible and slow-release carrier to take advantage of *Adiantum capillus-veneris* medicinal properties and conduct more extensive research.

Conflict of interest

The authors declare no conflict of interest.

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