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FULL PAPER

PEGylated cationic nano-niosomes formulation containing herbal medicine curcumin for drug delivery to MCF-7 breast cancer cells

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This study aimed to PEGylated cationic nano-niosomes formulation containing curcumin (CUR) for drug delivery to MCF-7 breast cancer cell lines and slow release of encapsulated CUR to reduce drug side effects on other healthy cells and increase drug effect on cancer cells. In this applied/*in vitro* study, PEGylated cationic nano-niosomes containing curcumin as herbal anticancer drug in MCF-7 cell line were prepared in laboratory through lipid phase mixing, phosphate buffer addition to a lipid thin film, and the production of nano-niosomes by sonication and dialysis process. Curcumin-containing niosomes were produced using the lipid phase by thin film fabrication method and reduced to a nanometer size by sonication. The average diameter (85.4 nm) of drug-carrying nano-niosomes was determined using a nano-sizer. Our results includes acquisition of technical knowledge of fabricating nano-niosomes containing a herbal bioactive ingredient as a nanosystem with the herbal medicine curcumin, proper loading of curcumin (with anticancer effect) at > 95% inside nano-niosomes with a size of < 100 nm to intensify the effectiveness of this medicine in cancer treatment, and preparation of PEGylated cationic nano-niosomes containing a body-compatible herbal bioactive substance with a slow release curve and good stability in terms of size and surface loading after 2 months of production. The produced curcumin-carrying liposomal nano-carrier has a slow-release curve and body biocompatibility that can be used in preparation of drug delivery systems containing similar hydrophobic drugs as an effective approach in treatment of various cancers, and agriculture, as well as in various pharmaceutical, medical, health, and environmental industries.

KEYWORDS

Curcumin; breast cancer cell; bioactive; nano-niosomes; PEGylated; MCF-7 cancer cell; drug delivery.

Introduction

Turmeric is the common name for *Curcuma longa* Linn belonging to the Zingiberaceae (ginger) family [1]. Medicinal properties of turmeric are associated with the active ingredient (i.e. curcumin) in its rhizome [2]. Curcumin has been used in traditional Chinese and Iranian medicine for thousands of years [3,4]. Traditional treatment with turmeric to overcome inflammation, infectious diseases, and autoimmunity dates back to about 5000 years ago [5]. Curcumin has immense therapeutic potential against human diseases

such as metabolic and infectious diseases, diabetes, psoriasis, rheumatoid arthritis, neurodegenerative diseases, arthritis, atherosclerosis, Parkinson's, Alzheimer's, heart diseases, digestive disorders (e.g., indigestion, bloating, stomach ulcers, duodenal ulcers, etc.), and cancer [6-10].

Curcumin has chemical inhibitory, induction of sensitivity to cancer cells against chemotherapy, anti-inflammatory, antioxidant, anti-aging, anti-tumor, and anti-metastatic effects. The importance of anticancer effects of curcumin is because high doses of this substance prevent the proliferation of cancer cells but do not damage healthy cells [11-14].

Research on curcumin as an anticancer agent has actually accelerated since 1990 after the recognition of its ability to suppress transcription factors and nuclear factors [15]. Several phase I and phase II trials are currently ongoing for treatment of various cancers and Alzheimer's disease [16].

Chemotherapy is the standard treatment for various types of cancers. However, chemotherapy is associated with high systemic toxicity and low therapeutic efectiveness [17].

Nanotechnology has revolutionized cancer diagnosis and treatment [18]. A nano-sized drug delivery system (DDS), or nanocarrier, is designed to deliver therapeutic and/or diagnostic agents to their target sites [19].

Over recent decades, drug delivery systems using vesicular carriers have attracted great interest because these carriers provide high encapsulation efciency, control drug release, enhance drug solubility, carry both hydrophilic and hydrophobic drugs, reduce side efects, prolong circulation in blood, and possess the ability to target a specifc area [20].

Vesicles made of natural or synthetic phospholipids are called liposomes, while transferosomes are modifed liposomal systems that, in addition to phospholipids, contain a single chain surfactant as an edge activator; ethosomes contain ethanol as an edge activator instead of a single chain surfactant. Despite having some advantages over conventional dosage forms, vesicular carriers present many problems in practical applications, such as high cost, the use of organic solvents for preparation, and a limited shelf life due to lipid rancidifcation [21]. Terefore, a continuous endeavor has been made to fnd an alternative vesicular carrier. Niosomes meet this requirement [22].

Niosomes, or non-ionic surfactant vesicles, are unilateral or multilamellar spheroidal structures. Niosomes are preferred as an efective alternative to the conventional liposomes, as they ofer several advantages, including greater stability, lower cost, biodegradability, biocompatibility, non-immunogenic, and low toxicity, and they can be stored more easily for industrial production in pharmaceutical applications [23].

To improve stability and circulation half-life, niosomes maybe coated with appropriate polymer coatings, such as polyethylene glycol (PEG), creating PEGylated niosomes. PEG coating also helps reduce systemic phagocytosis, which results in prolonged systemic circulation and reduced toxicity profles [24].

Therefore, this study aimed to encapsulate an appropriate amount of the herbal medicine curcumin (the main ingredient in turmeric rhizome) inside PEGylated Cationic Nano-Niosomes containing a nonionic surfactant for drug delivery to cancer cells (MCF-7 Breast Cancer Cell Lines) and slow release of the encapsulated drug to reduce its side effects on healthy cells and increase drug effectiveness on cancer cells.

Materials and methods

Materials

The materials and compounds used in this study are listed in Table 1.

TABLE 1 Main materials required for the project

Row	Material/fragment	Specifications
1	Tween 60	Tween 60 (Polyethylene glycol sorbitan monostearate) (Sigma-Aldrich Co., P1629)
2	Cholesterol	CHOL (Cholesterol) (Sigma-Aldrich Co., C8667)
3	Polyethylene glycol 2000-conjugated phospholipids	(DSPE-mPEG2000) (Nanocs Inc., USA) (1,2- distearoyl-sn-glycero-3 phosphoethanolamine-N-[(polyethylene glycol)2000)
4	DIL fluorescent dye	1-′1, Dioctadecyl 3,3,3′,3′ tetramethylindocarbocyanine perchlorate (Abcam Co., ab189809)
5	DOTAP cationic phospholipids	1,2-dioleoyl-3-trimethylammonium-propane (Avanti Polar Lipids, Inc., 890890P)
6	Curcumin	Curcumin (Sigma-Aldrich Co., C1386)
7	Chloroform	Chloroform (Sigma-Aldrich Co., C2432)
8	PBS	Phosphate buffered saline (Sigma-Aldrich Co, P4417)
9	Dialysis bags	Spectra/Pore®Dialysis membrane (12,000–14,000 molecular weight cut off)
10	Isopropanol	Isopropyl alcohol (Sigma-Aldrich Co., W292907)
11	DAPI fluorescence dye	DAPI 2-(4-Amidinophenyl)-6-indolecarbamidine dihydrochloride (Sigma-Aldrich Co., D9542)
12	Filters (0.22 and 0.45 µm)	
13	MCF-7 breast cancer cell lines	MCF-7 (The Iranian Biological Resource Center, Tehran, Iran)
14	MCF-10A healthy breast cell lines	MCF-10A (The Iranian Biological Resource Center, Tehran, Iran)

Methods

The curcumin-containing nano-niosomes were prepared by lipid film deposition method in which a lipid thin film was formed by evaporating an organic solvent. The contact of thin film with water and sample dissolution resulted in a vesicular phase by the following steps.

Lipid phase mixing

PEGylated cationic niosomes containing Tween 60: Cholesterol: Phospholipid DSPE-MPEG2000: DOTAP cationic phospholipid with a molar ratio of 59.5: 25.5: 5: 10 were synthesized in combination with curcumin at 0.5 mg/mL. To do this, the total lipid was dissolved in 3 mL of chloroform together with curcumin medicine and dried by a rotary evaporator (at 50 °C) to form a thin film, which was kept at 4 °C overnight to dry more.

Addition of phosphate buffer to the lipid thin film

Phosphate buffer (3 cc) was added to a round-bottom balloon containing the thin lipid film and connected to a rotary evaporator at 150 rpm at 60 °C for 60 min to create multilamellar vesicles (MLVs) containing two or more concentric layers.

Production of nano-niosomes by the sonication process

The sonication method was used to reduce the size of MLV niosomes and to form small unilamellar vesicles (SUVs) containing only one layer of fat. To reduce the size of MLV niosomes, the probe of a sonicator was placed in a colloidal solution of niosomes in an ice container. The sonication process was then performed with a 60% amplitude for 30 min (15 and 10 seconds on/off, respectively) to produce single-walled niosomes.

Filtration process

Particles with larger sizes were separated from smaller particles using a 0.45 µm filter to homogenize the solution obtained in the pre-filtration stage. To filter sterilizer, the solution was finally passed through a filter with a pore diameter of 0.22 µm.

Determining the loading rate of curcumin in niosomes

To evaluate the loading rate of curcumin in niosomes, the prepared niosomes were mixed with isopropyl alcohol solution in a 1:20 ratio, and their absorbance rate was determined by ultraviolet-visible (UV-Vis) spectrophotometry at 429 nm. Finally, the concentration of curcumin was obtained according to the equation of a curcumin calibration curve in isopropanol.

Ex vivo examination of curcumin release from nano-niosomes

The release of curcumin encapsulated in niosomes was investigated under sink conditions in PBS at 37 °C (the body temperature) and pH 7.4 with stirring and adding 1 mL of the sample into a dialysis bag (12,000–14,000 molecular weight cut off). The amount of curcumin released from the vesicle was determined by spectrophotometry at regular intervals by removing 1 mL of the medium and replacing it with the same amount of fresh PBS.

Microscopic analysis of curcumin-containing nano-niosomes

The morphology of curcumin-containing nano-niosomes was examined by transmission electron microscopy (TEM) and scanning electron microscopy (SEM). For SEM analysis, 5 µl of the suspension was poured onto a glass plate to form a thin layer, and the excess water was allowed to evaporate. The sample was coated with gold and the image was taken with a SEM system (model EM3200, KYKY, China). For TEM digital images, some samples were coated on 200 copper mesh, and the images were obtained by a cryoTEM (FEI Tecnai 20, type Sphera, Oregon, USA).

Molecular interaction and Stability of curcumin-containing niosomes

A drop of the niosome sample was dried on the glass, and then placed between two KBr tablets. The FTIR spectrum was obtained by an FTIR spectrophotometer (Model 8300, Shimadzu Corporation, Tokyo, Japan). The stability of curcumin-containing niosomes at 4 °C was examined in terms of size, zeta potential, polydispersity index, and drug loading rate for 60 days.

Cellular Uptake of Nanoniosome–Containing Curcumin

To determine and compare the cellular uptake behavior of Cur-Nio and free curcumin, MCF7 cells were seeded on to 6-well plates at a density of 1.5 × 105 cells/well. Then, the cells were incubated with free curcumin, Cur-Nio (20 $\mu g.mL^{-1}$), and blank nanoniosomes. After 3 h, cells were washed twice with fresh cold PBS (pH 7.4) and fixed with the 96% ethanol solution. The nuclei were counterstained with DAPI (0.15 $\mu g.mL^{-1}$, Thermo Fisher Scientific, The United States) and visualized under a fluorescence microscope (BX61, Olympus, Japan).

The cytotoxicity of curcumin-containing niosomes on MCF-7 breast cancer cell lines and compared with healthy MCF-10A

Breast cancer cell lines using the MTT assay 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT): This colorimetric assay is based on the reduction and breakdown of yellow tetrazolium crystals with chemical formula of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT). MTT is reduced by the succinate dehydrogenase system, an enzyme of mitochondrial respiratory chain. The reduction and breakdown of this chain produce blue Formazan crystals that are easily visible under a microscope.

The amount of produced color is directly related to the number of metabolically active cells. Formazan crystals are insoluble in water

and must be dissolved in water by DMSO before colorimetry.

Finally, the optical density (OD) of the resulting solution can be read at a wavelength of 570 nm. Unlike other methods, the stages of washing and collecting cells, which often result in the loss of some cells, are excluded in this method, and all the test stages from the beginning of cell culture to read the results with a photometer are performed in a microplate, leading to high repeatability, accuracy, and sensitivity of the test. For this test, each well was initially filled with 200 µl of DMEM culture medium containing 10,000 MCF-7 cells.

To evaluate the effect of cytotoxicity, cells were treated with different concentrations of curcumin-containing niosomes for 48 h. Then, the MTT solution was added with 0.1 volume of the well medium and cells were incubated at 37 °C for 3 h. Finally, 150 µl of the DMSO solution was added to each well to dissolve the insoluble crystals of Formazan, and the OD of the obtained solution was read at 570 nm using an ELISA reader.

The cell viability (%) was calculated using the following formula:

Cell viability (%) = (mean OD in control group/mean OD in the test group) × 100

All the aforementioned steps were done to evaluate the effect of curcumin-containing niosomes on healthy MCF-10A breast cell lines compared with with cancer cells.

Finally, the IC_{50} (a concentration of the drug that inhibits the growth of 50% of cells) was obtained using Graphpad Prism Software.

Ex vivo transfer examinations

MCF-7 and MCF-10A cells (15×10^4) were grown as monolayers in 6-well plates for 24 h. The cells were then washed with DMEM culture medium and incubated with the optimal formula of curcumin-containing PEGylated cationic niosomes at 37 °C for 3 h. The cells were washed three times with PBS and fixed with a 4% paraformaldehyde solution (Thermo Scientific, USA). Nuclear staining was performed using DAPI (0.125/g/mL) for 15 min. The cellular uptake of curcumin was assessed by a fluorescent microscope (Olympus, Japan).

Results

The size and polydispersity index (85.4 and 0.177 nm, respectively) of the produced curcumin-containing nano-niosomes, which were resized by sonication (with a power of 60% amplitude), were determined using a nanosizer. The Zeta potential (+ 14.83) of the surface of manufactured curcumin-containing nano-niosomes resized by sonication (with a power of 60% amplitude), was determined using a Zetasizer. The curcumin loading rate inside the niosomes was determined using a UV spectrophotometer and a standard curcumin curve (Figure 1). The results indicated an amount of 98.24% ± 0.11 for loaded curcumin.

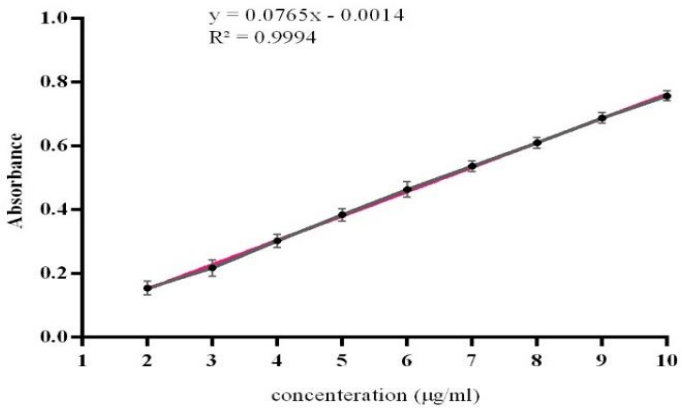

FIGURE 1 The standard curcumin curve in isopropanol

The results of three repetitions of the calculated curcumin release rate from the optimized niosomes are depicted in Figure 2. The amounts of curcumin released from the formulation of curcumin-containing nano-niosomes in PBS were calculated over intervals of 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, 36, 48, and 72 h using a standard curcumin curve in PBS. The drug release pattern (Figure 2) shows a maximum amount of 29.39% for curcumin released from nano-niosomes in 72 h.

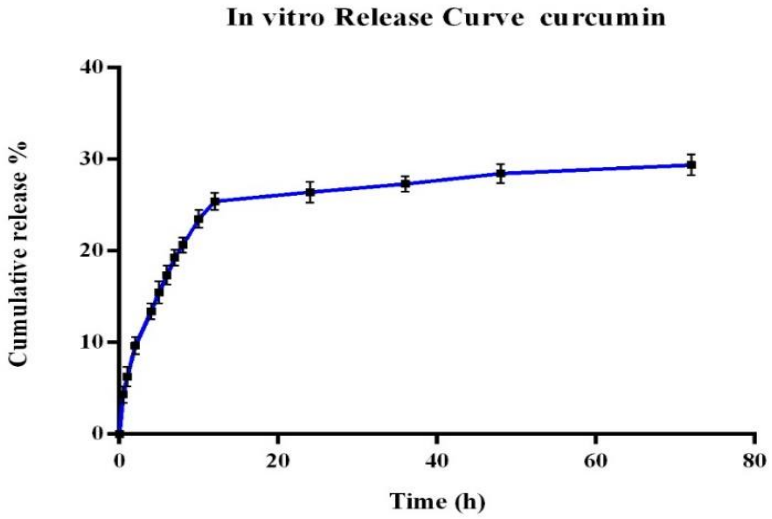

FIGURE 2 Curcumin release curve in PBS

The SEM images revealed the spherical shape and a uniform structure of the drug-containing nano-niosomes. In SEM images, the average diameter of five nano-niosomes was determined at about 85 nm (Figure 3), which corresponded to the results of DLS method.

The multilamellar membrane and spherical structure of drug-carrying nano-niosomes are observed in TEM images (Figure 4).

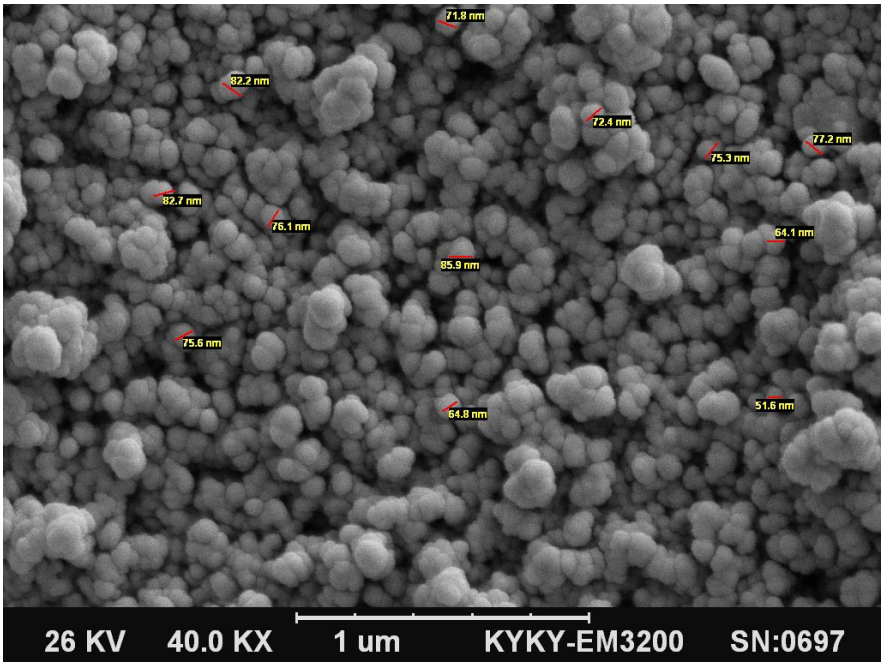

FIGURE 3 SEM image of curcumin-containing nano-niosomes (40,000x)

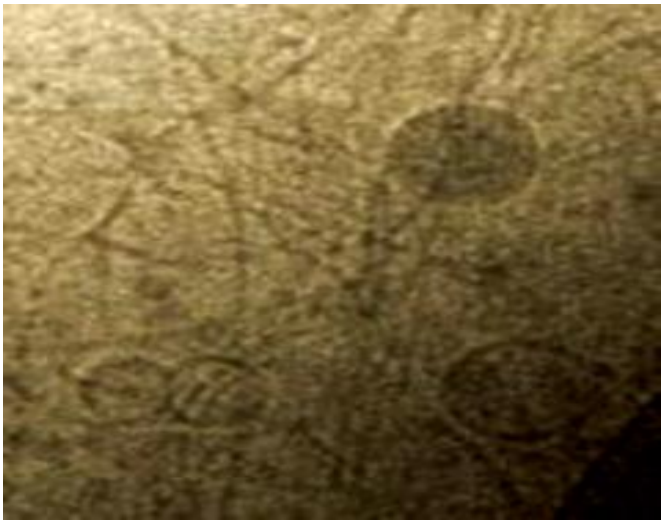

FIGURE 4 TEM image of curcumin-containing nano-niosomes

Figure 5 illustrates the FTIR spectrum of the produced curcumin-containing PEGylated cationic nano-niosomes. The stability of curcumin-containing niosomes at 4 °C was examined in terms of size, zeta potential, polydispersity index, and drug loading rate for 60 days and no significant changes were found in these parameters in niosomal curcumin formulations from freshly prepared samples (p-value < 0.05).

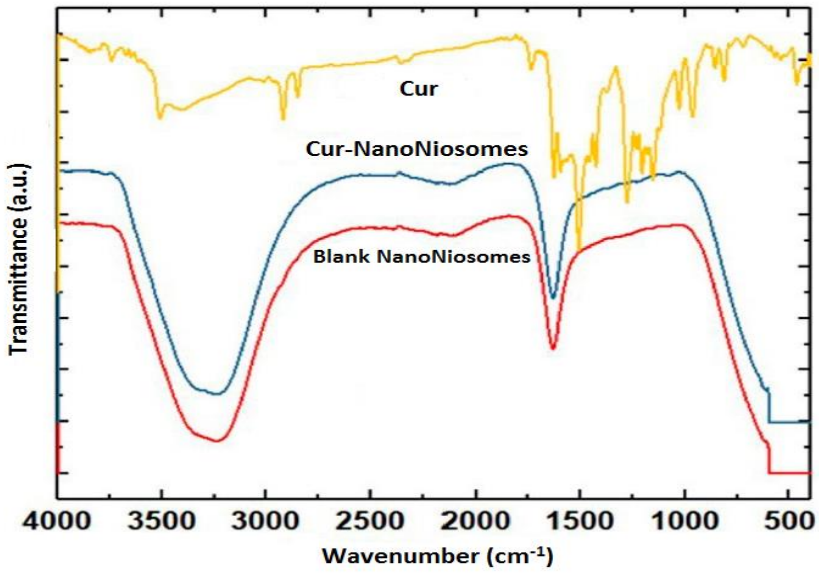

FIGURE 5 FTIR spectrum of the produced curcumin-containing PEGylated cationic nano-niosomes

Figures 6 (a and b) demonstrate cell viability in the presence of niosomal curcumin by the MTT assay during 48 h. MTT assays showed that the proliferation of MCF-7 and MCF-10A cell lines wasnhibited by niosomal curcumin. The IC_{50} values of niosomal curcumin for MCF-7 and MCF-10A cells were 14.90 ± 0.19 and 64.22 ± 0.36, respectively. This indicates that the concentration of healthy MCF-10A cells is 4.3 times more than niosomal curcumin to reach the IC_{50} value of MCF-7 cells, suggesting that the effect of curcumin-containing niosomes is very lower on healthy cells.

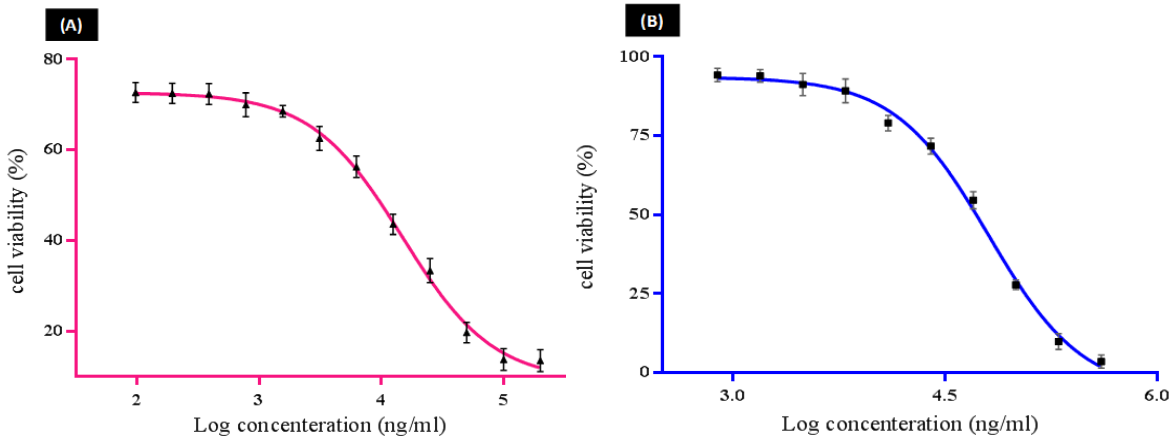

FIGURE 6 Cell viability in the presence of niosomal curcumin: (**A**) MCF-7 breast cancer cell lines, (**B**) healthy MCF-10A breast cell lines

Figure 7 depicts fluorescence microscopy images of the niosomal curcumin transfer to MCF-7 and MCF-10A cells. Qualitatively, a brighter green/green-blue color is observed in MCF-7 cancer cells compared with healthy MCF-10A cells treated with niosomal curcumin. This indicates more entry of niosomal curcumin into cancer cells than healthy cells.

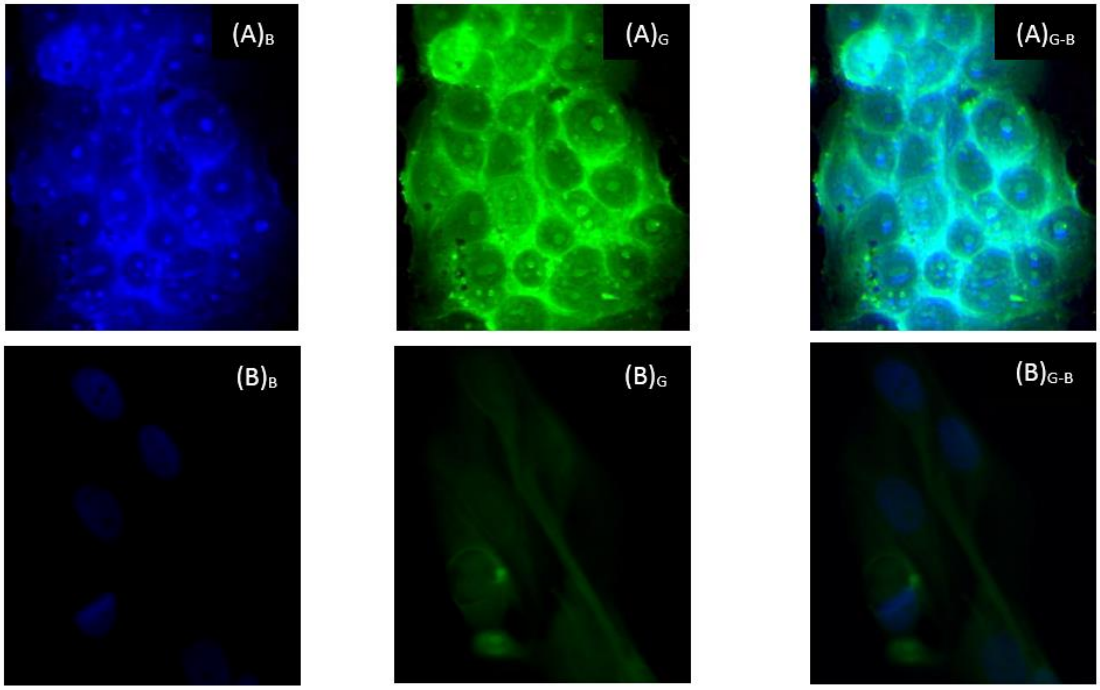

FIGURE 7 Fluorescence microscopy images of MCF-7 and MCF-10A cells incubated with niosomal curcumin. The cells were treated with DAPI staining to stain the cell nuclei, and niosomes were stained using Dil dye.

Comparison of niosomal curcumin cell uptake for MCF-7 (**A**) and MCF-10A and (**B**) cell lines

Blue: nucleus fluorescence, **Green:** niosome fluorescence, and **Green-Blue:** overlapped fluorescence of the nucleus and niosomes

Discussion

Scientific and technical spotlights, innovations, and advantages of this article include acquiring technical knowledge of fabricating nano-niosomes containing a herbal bioactive ingredient as a nanosystem containing the herbal medicine curcumin, proper loading of curcumin (with anti-cancer effect) approximately 100% inside nano-niosomes with a size of < 100 nm to intensify the effectiveness of this medicine in cancer treatment, preparation of nano-niosomes containing a body-compatible herbal bioactive substance with a slow release curve, and good stability in terms of size, zeta potential, drug loading rate, and polydispersity index after 2 months, and a cost-effective production relative to liposomes.

Given the valuable properties mentioned above, the produced curcumin-bearing niosomal nanocarrier has a slow-release curve and is biocompatible with the body, which can be used in the preparation of drug delivery systems containing similar hydrophobic drugs as an effective approach in the treatment of various cancers. Niosomes are nonionic surfactants composed of amphipathic molecules that are ideal models of cellular biomembranes that function by minimizing detrimental effects on the health of cells and tissues. Due to their bioavailability and biodegradability along with nano-size, nano-niosomes have been used in many applications in a wide range of fields such as nanotherapy, cancer diagnosis and treatment, gene delivery, cosmetics, food industry, and agriculture, as well as in various pharmaceutical, medical, health, and environmental industries [25,26].

According to various studies, curcumin is the active ingredient in rhizome of the medicinal herbal turmeric with antioxidant, anticancer, and anti-inflammatory properties.

Owing to the short biological half-life, low solubility, and low absorption of free curcumin in the body, the use of nano-niosomes as curcumin-transferring carriers to cancer cells plays an important role in the stability of this drug in the body. In this study, curcumin was loaded into nano-niosomes to increase the drug stability in the body for delivery to cancer cells. In the produced nano-niosomes, the main components are biodegradable nonionic surfactants that are generally nontoxic. Our innovation includes acquisition of the technical knowledge of fabricating nano-niosomes containing a herbal bioactive ingredient as a nanosystem with the herbal medicine curcumin, proper loading of curcumin (with anti-cancer effect) at > 95% inside nano-niosomes with a size of < 100 nm to intensify the effectiveness of this medicine in cancer treatment, and preparation of PEGylated cationic nano-niosomes containing a body-compatible herbal bioactive substance with a slow release curve and good stability in terms of size and surface loading after 2 months of production.

The main purpose of our study was to examine the effects of pre-treatment of curcumin-loaded PEGylated nanoniosome as a sensitizing agent for MCF-7 cell line in comparison to free curcumin. First, the curcumin-loaded PEGylated nanoniosome was characterized using various techniques. The mean diameter of nanoparticles was almost 100 nm at the nanoscale size, which facilitates their entry to the blood barrier and increases their concentrations in cancer cells (27). The zeta potential value was reported to be negative, and there was an electrostatic repulsion between vesicles resulting in the stability and homogeneity of nanoniosomes (28). The higher transition temperature (Tc) of Tween 60 (55°C) and a lower HLB value (14.9) led to the highest entrapment efficiency of curcumin as a lipophilic drug (29).

Tween 60 has a high transfer temperature and an impermeable bilayer that reduces the release rate of curcumin and leads to a continuous release. Moreover, PEGylation of nanoniosomes improves their stability, enhances drug loading, reduces nanoparticle size, and decreases the drug-release rate in niosomal formulations (27). The endocytosis mechanism of Cur-Nio plays a crucial role in penetrating and increasing the accumulation of curcumin into cells, causing a higher intensity in green and turquoise blue fluorescence. In other words, the nanoniosomal curcumin delivery system was more efficient in the delivery and localization of curcumin compared with the free one that crosses through cell membrane by a diffusion process. These findings are in agreement with a number of studies conducted in this regard (30).

According to the mentioned valuable properties, the produced curcumin-carrying liposomal nanocarrier has a slow-release curve and is biocompatible with the body, which can be used in the preparation of drug delivery systems containing similar hydrophobic drugs as an effective strategy in treatment of various cancers.

Conclusion

The main purpose of this study was to examine the effects of pre-treatment of curcumin-loaded PEGylated nanoniosome as a sensitizing agent for MCF-7 cell line compared with free curcumin. In this study, the herbal medicine curcumin, as the main ingredient of turmeric rhizome, was used in a niosome nanosystem to intensify and increase the medicine effectiveness in the treatment of cancer cells. Curcumin-containing niosomes were produced using the lipid phase by thin film fabrication method and reduced to a nanometer size by sonication. The average diameter (85.4 nm) of drug-carrying nano-niosomes was determined using a nano-sizer. The size of nano-niosomes (< 100 nm) was further determined by SEM and TEM images, which almost corresponded to that measured with the nano-sizer amd the surface load of the

drug-carrying nano-niosomes was +14.83. In general, a new curcumin-containing PEGylated nanoniosome was developed to enhance the sensitivity of breast cancer cells instead of using free curcumin. The results demonstrated that PEGylated nanoniosomes have nanoscale size, spherical shape, high entrapment efficiency, and a controlled release pattern.

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Conflict of interest

The authors declare no conflict of interest in publishing this article.

Research involving human and animals rights

This article does not contain any studies with human participants or animals performed by any of the authors.

Availability of data and material

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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