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RESEARCH ARTICLE

Curcumin-loaded albumin nanoparticles synthesis, characterization and *in-vitro* evaluation of cytotoxic effects against U-87 MG cells

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ABSTRACT

Objective(s): Curcumin (Cur) as a natural bioactive compound has shown potential capability to fight a variety of malignancies. In this study, bovine serum albumin nanoparticles (BSA NPs) were applied to improve bioavailability and increase the effectiveness of the hydrophobic curcumin against human glioblastoma brain cancer cells.

Methods: BSA NPs were synthesized and Cur was loaded in nanoparticles, based on desolvation method. Characterization studies were performed using dynamic light scattering, UV-Visible spectroscopy, field emission scanning electron microscopy, transmission electron microscopy (TEM) and differential thermal analysis (DTA). Curcumin release from albumin nanoparticles was investigated *in vitro* and finally the cytotoxicity evaluation against U-87 MG cell line was studied by MTT method.

Results: The curcumin loaded nanoparticles (BSA-Cur NPs) showed a homogeneous spherical shape with mean particle size and polydispersity index (PDI) of 182.1 ± 2.02 nm and 0.105 ± 0.02, also drug loading content (DL%) and encapsulation efficiency (EE%) were obtained 11.73% and 83.26%, respectively. Cur showed a sustained release from BSA NPs with maximum release percentage of 30% after 48 hours. The results of MTT assay revealed that after 48 h treatment BSA-Cur NPs have more cytotoxicity on U-87 MG cells compared to free Cur, owning IC50 values of 33.08 ± 0.1.27 and 17.43 ± 1.37, respectively.

Conclusions: According to the results of this study, albumin nanoparticles can be considered as a promising carrier for improving the effectiveness of curcumin in drug delivery against glioblastoma.

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INTRODUCTION

Glioblastoma multiforme is the most common type gliomas and the most fatal tumor among brain maligments (1). Even for the patients being treated, the average survival rate is about 14 months (2). The current clinical treatment for this disease is surgery followed by chemotherapy and radiotherapy. However, in addition to the difficulty of surgically removing all tumor cells, the resistance of

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glioblastoma multiforme cells to radiation therapy and the severe side effects of chemotherapeutic drugs lead to failure in the treatment process (3). Recently, the potential of phytochemicals in combating various types of malignancies including brain cancers has received much attention. These bioactive compounds, having a natural origin and less toxicity to normal cells, can be a good alternative to chemotherapy drugs. Curcuminoids are promising phytochemicals in this field which are extracted from the rhizome of *Curcuma longa* plant (4). The most important constituent of the curcuminoids, curcumin (1,7-bis-[4-hydroxy-3-methoxyphenyl]-1,6-heptadiene-3,5-dione), has been demonstrated in various studies as an effective agent against glioblastoma tumor cells (5-9). Curcumin is able to inhibit the growth, proliferation, migration and differentiation of glioblastoma initiator cells and induce apoptosis. This effectiveness of curcumin achieves through affecting or regulating different pathways and molecular targets including caspase activity, NF-KB transcription factor, PI3K/AKT signaling, matrix metalloproteinase, p53 tumor suppressor and cell cycle arrest (10). Despite the beneficial effects of curcumin, its bioavailability is low due to poor solubility in aqueous medium, poor absorption, rapid metabolism and rapid systemic removal (11). Along with strategies such as the development of modified curcumin analogues and derivatives to improve the bioavailability, the use of nanocarriers has had promising results in recent years. To date, various nanocarriers such as liposomes, magnetic nanoparticles, natural and synthetic polymer nanoparticles, mesoporous silica nanoparticles, solid lipid nanoparticles, polymer micells, nanocrystal suspentions, nanogels, etc. have been introduced as curcumin delivery systems (12, 13). In this regard, albumin is one of the compounds with unique properties which has been widely studied as a nanocarrier for delivery of various hydrophilic and hydrophobic anticancer drugs Including curcumin to the tumor targets. Albumin is the most abundant plasma protein which is produced in about 10-15 gram per day by hepatocytes in the human body and is responsible for plasma osmotic pressure, blood pH regulation, and the transport of a variety of molecules, fatty acids, and minerals (14, 15). Albumin nanoparticles are biocompatible, biodegradable and non-immunogenic, and posesses high solubility in aqueous medium and the binding site of hydrophobic drugs, so can be a good candidate to delivery of curcumin and improve its bioavailability in physicochemical conditions. On the other hand, albumin has been used as a nanocarrier of curcumin in studies against various cell lines such as MCF-7, MDA-MB-231, SK-BR-3, and Caco-2 (16-18). However, the anti-cytotoxic effect of curcumin-loaded albumin nanoparticles against U-87 MG cancer cells has not been investigated. Therefore, in the present study, albumin nanoparticles were synthesized and loaded with curcumin and in addition to charachtrization of the prepared nano-formulation, its anti-cancer effect was investigated against gliobalstoma cancerous cells *in-vitro*.

MATERIALS AND METHODS

Materials and cells

Curcumin (Cur), bovine serum albumin (BSA), glutaraldehyde (25% aqueous solution), phosphate buffer saline (PBS), 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) and RPMI-1640 medium were purchased from Sigma Aldrich, US. Fetal bovine serum (FBS), trypsin-EDTA solution and penicillin/streptomycin antibiotics were prepared from Gibco, US. Other solutions were used with HPLC grade. The U-87 MG human glioblastoma cell line was purchased from the Pasteur Institute Cell Bank, Iran.

Preparation of Cur loaded BSA NPs

The nanoparticles were prepared based on desolvation method. Briefly, 100 mg BSA was dissolved in distilled water through strring for 30 min at 400 rpm. Then 8 ml of ethanol solution containing dissolved Cur (1 mg per 1 ml ethanol) was added dropwise at the rate of 1.5 ml/min to BSA solution. After turbidity of the solution which indicated the formation of nanoparticles, 60 µL glutaraldehyde (8% solution in water) was added as a crosslinker to stabilize the nanoparticles. The resulting reaction mixture was stirred at 400 rpm for 24 h and finally the process of nanoparticles purification was performed by centrifuging at 11000 rpm and washing by distilled water in three cycles.

Charactrization of Cur loaded BSA NPs

Prepared Cur loaded BSA NPs (BSA-Cur NPs) was analyzed using dynamic light scattering (DLS) technique by Horiba SZ-100 nanoparticle analyzer for particles size and polydispersity index (PDI) determination. Also FESEM and TEM

microscopic imaging with TESCAN MIRA 3 and ZEISS LEO 906 E instruments, respectively, were used for morphological studies of nanoparticles. For FESEM analysis, after drying a drop of the nanoparticles suspension on a glass slide, gold coating was applied for conductivity. TEM sample was prepared by drying the nanoparticles suspension on a copper grade at room temperature. PL-STA 1640 instrument was used for differential thermal analysis (DTA) via heating the samples up to 600 °C in air atmosphere with a heating rate of 10 °C/min. For UV-Vis spectra achieving as well plotting the standard calibration curve of Cur, UNICO 2150-UV spectrophotometer was used and through this, the drug loading content (DL%) and encapsulation efficiency (EE%) were determined using the following equation by obtaining the amount of drug in the supernatant of the centrifugation step and analyzing it at the characteristic peak of the Cur and inserting the absorbance value in the formula obtained from the calibration curve.

DL (%) = (amount of Cur in nanoparticles) / (amounts of nanoparticles) × 100

EE (%) = (amount of Cur in nanoparticles) / (amount of initial loaded Cur) × 100

In-vitro release study

The release behavior of Cur from BSA NPs was investigated *in-vitro* in neutral pH. For this purpose, 1 ml of BSA-Cur NPs suspention was enclosed in dialysis bag with mulecular cut-off of 12 kDa and immersed in PBS release medium containing 2% tween 80 at 37 °C. In time intervals between 15 min to 48 h, 3 ml of medium was withdrawn an analyzed by UV-Vis spectrophotometer and an equal amount of fresh medium was added to it. Each experiment was repeated triplicate and finally the cumulative release percentage graph was plotted against time.

Cell culture and cytotoxicity assay

U-87 MG cells were cultured in RPMI 1640 medium containing 1% penicillin/streptomycin antibiotics mixtures and 10% FBS solution and incubated at 37 °C in atmosphere containing 5% carbon dioxide. Subsequently, for cytotoxicity investigating, MTT colorimetric assay was used. The U-87 MG cells with a density of 5×10^3 cells per well were seeded in a 96-well plate and incubated for 24 h. Then, the medium was removed and a fresh medium containing free Cur or BSA-Cur NPs with the concentrations of 5, 15, 20, 30, 45 µg/mL was added to the wells. After 48 h incubation, media removed and fresh media containing MTT solution (0.25 mg/mL in RPMI medium) was added to each well and incubated for more 3 h at 37 °C. Next, after withdrawing the media, the formed formazan crystals were dissolved by adding 200 µl of DMSO to each well in 20 min. The optical density (OD) of the formazan solution was measured using Bio Tek ELx808 microplate reader at 570 nm. Untreated cells were tested as control group. The cell viability (%) was determined using the following equation:

% cell viability = (OD of sample - OD of control) / OD of control × 100

All experiments were performed with three replications and one-way ANOVA method was used for statistical analysis and P value < 0.05 was considered the significance criterion.

RESULTS AN DISSCUTION

Physicochemical properties

To confirm the formation of nanoparticles, microscopic images and hydrodynamic size of BSA-Cur NPs were obtained. According FESEM and TEM images (Fig. 1a and 1c), the BSA-Cur NPs were successfully synthesized and have a spherical morphology with smooth surfaces as well, a suitable size distribution. In addition, the result of DLS analysis showed that the average size of BSA-Cur NPs was 182.1 ± 2.02 nm. Also, BSA-Cur NPs with a PDI of 0.105 ± 0.02 have a narrow size distribution which is consistent with the results of microscopic images. In a similar synthesis method performed by Hassanpour et al. in 2020, the size of curcumin-loaded albumin nanoparticles was 197 ± 2 nm, which was close to the results of present research (17). Various studies have shown that nanoparticles with this dimension range are efficient in drug delivery to tumors. For example, a study by Xuan Xie et al. in 2016 showed that the cellular uptake of MDR cells for the doxorubicin nanoparticle drug delivery system with particle size of 143.0 nm was higher than that of the free doxorubicin (19). Indeed, as cancer progresses, tumor growth is associated with angiogenesis. The new blood vessels lack continuous epithelium organization and membrane of normal blood vessels and as a result, they possess wide fenestrations. Therefore, nanoparticles with dimensions less than 200 nm can easily penetrate the tumor tissue and be trapped in the tumor environment due to an incomplete lymphatic system (enhanced permeability and retention or EPR effect) (20). In addition, the

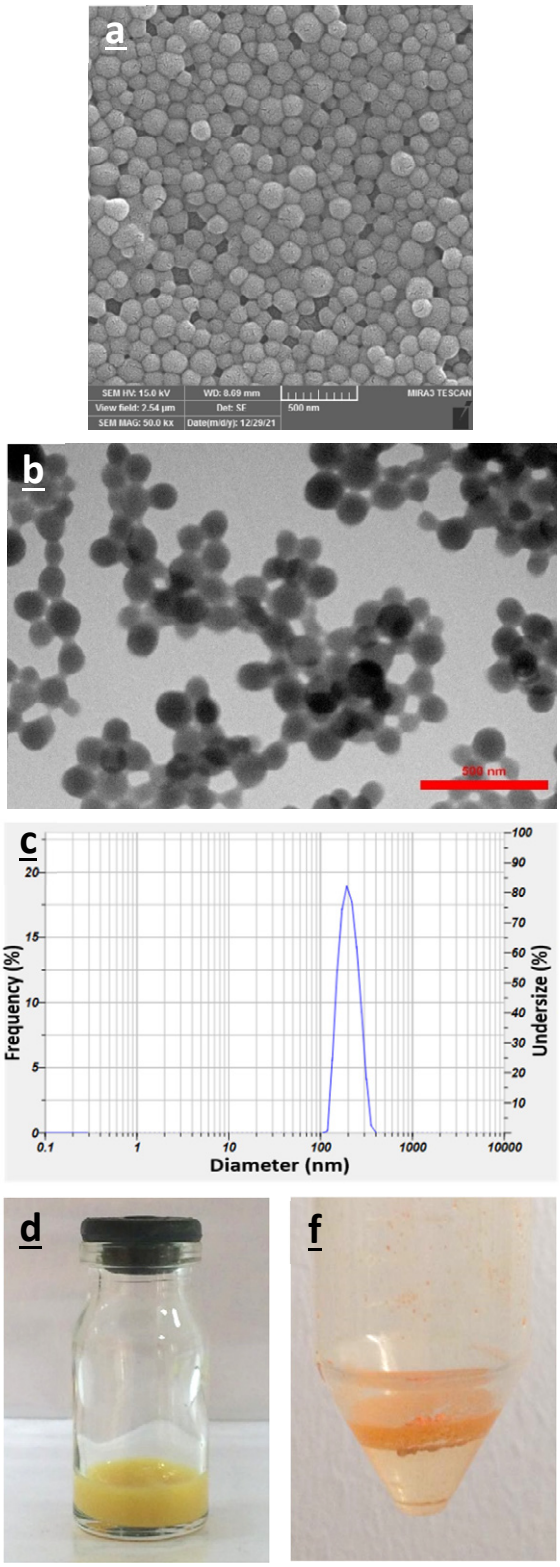

Fig. 1. (a), (b) and (c) FESEM and TEM images and DLS particle size histogram of BSA-Cur NPs, respectively. (d) BSA-Cur NPs suspension in water, (f) Free Cur suspension in water.

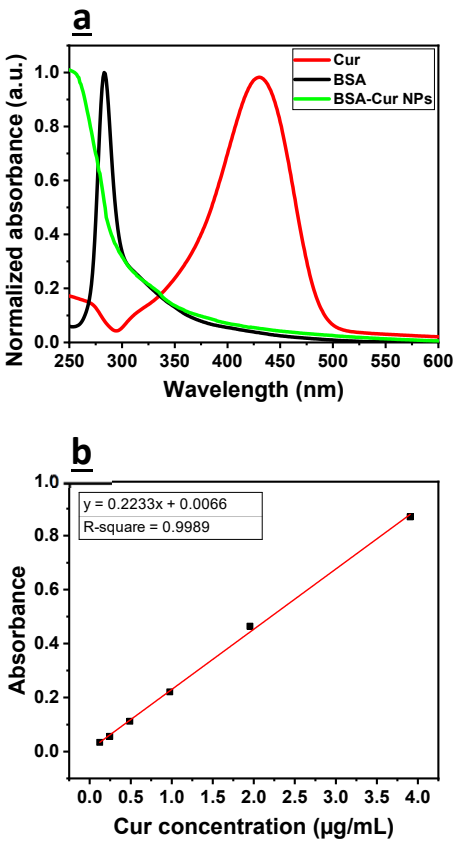

Fig. 2. (a) UV-Vis spectra of Cur, BSA and BSA-Cur NPs, (b) calibration curve of Cur

therapeutic agent must be protected from removal by the mononuclear phagocytic system (MPS) and the reticuloendothelial system (RES) in order to have a sufficient half-life in the bloodstream and reach the target tumor site. In this regard, as well, NPs with dimensions below 400 nanometers can be very useful (21). So, the nanodrug can be safe from the two defense mechanisms mentioned (MPS and RES). Therefore, the BSA NPs prepared here, while having appropriate dimensions in terms of tumor targeting, by loading Cur, improved its solubility in aqueous medium (according to Fig. 1d and 1f), which in turn can help the transport and bioavailability of hydrophobic Cur in the physiological environment of the body.

The UV-Vis spectra for Cur, BSA, and BSA-Cur NPs were obtained in wavelength range of 250 to 600 nm (Fig. 2a). BSA absorption characteristic peak was observed at 283 nm attributed to phenyl rings of the aromatic amino acids (Trp, Tyr, and Phe) (22). Cur also showed absorption peak at 430 nm, however, characteristic peaks of BSA and Cur were not observed in the nanoparticles spectrum, which was indicated the changes in albumin structure while formation of NPs and entrapping of Cur in the nanoparticles matrix (23). In addition, the standard calibration curve of Cur was plotted by measuring the absorbance of different concentrations at 430 nm (Fig 2b). As well, the drug loading content (DL%) and encapsulation efficiency (EE%) were obtained equal to 11.73% and 83.26%, respectively, using the equations mentioned above. These values are higher than DL% and EE% values obtained in a study by Saleh et al. via a similar preparation method on curcumin-loaded albumin nanoparticles, which were 3.4% and 71.3%, respectively (24). This difference may be due to the larger particle size obtained in the above study (246.1 ± 15.4 nm) than in research. The smaller size of the nanoparticles increases the surface energy and could be effective in loading more amounts of drug into the nanoparticles.

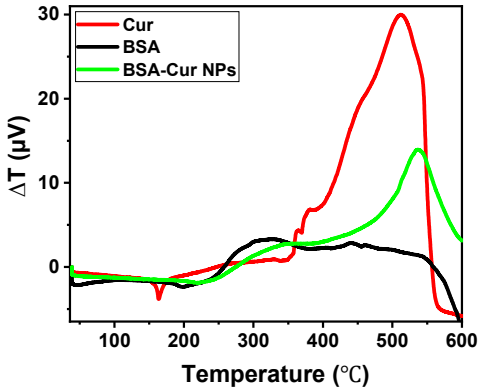

Fig. 3. DTA curves of Cur, BSA and BSA-Cur NPs

Differential thermal analysis

DTA curves of Cur, BSA and BSA-Cur NPs are illustrated in Fig 3. A small endothermic peak at 163 °C in Cur curve could be attributed to the melting of the compound. Also, exothermic peaks at 364 °C and 381 °C as well as the strong exothermic peak at 511 °C may be related to decomposition stages of Cur (25). Furthermore, wide peak in the BSA curve with maximum intensity at 311 °C could be due to its decomposition. In the BSA-Cur NPs DTA curve, the endothermic peak related to Cur was disappeared and the exothermic peak was shortened and shifted to a higher temperature of 536 °C, which indicated that the nanoparticles have a more stability and much amorphous structure than free Cur which is advantageous in drug delivery applications. In studies conducted by Bhushan et al. and Tirkey et al., it has also been reported that by loading of nicosamide and 5-Fluorocytosine drugs, respectively, in albumin nanoparticles, the drugs peaks get disappeared in DTA thermogram, indicating amorphous structure of the nanoformulation (26, 27). Indeed, greater amorphous phase in pharmaceutical systems, due to higher free energy and lower density, leads to increasing of the solubility of the pharmaceutical agents (28).

In-vitro release study

Fig 4 shows the cumulative release percentage curve of Cur over time from BSA-Cur NPs. Having a biphasic release behavior, about 20% of Cur molecules were released from BSA NPs in the first 6 h. This release was related to molecules present at or near the surface of the nanoparticles matrix. Subsequently, about 10% of the trapped drug molecules in the BSA NPs matrix were released within the next 42 h in a sustained and controlled manner may be due to diffusion of Cur molecules throughout the BSA NPs matrix. Overall, after 48 h, 30% of the Cur was released from the nanoparticles. This low release of Cur in the PBS medium indicates the stability of the nanoparticles and it can be expected that the BSA NPs in the physiological conditions transport the drug with less leakage into the bloodstream and reduce side effects for normal cells, and finally release the drug cargo by enzymatic degradation of albumin after accumulation in the tumor environment due to EPR (16).

Cytotoxicity study

The anti-cancer activity of free Cur and Cur loaded BSA NPs was studied against U-87 MG human glioblastoma cells via determining the cytoxicity using MTT assay. Fig. 5 shows the percentage of cell viability after 48 h treatment with free Cur and Cur-BSA NPs at different concentrations of Cur. As it is shown, the cytotoxicity of free Cur increased significantly (P value < 0.05) with increasing concentration up to 30 µg/mL. However, no significant difference was observed in the cytotoxicity of free Cur with increasing concentration from 30 µg/mL to 40 µg/mL (P value > 0.05), which can be due to the hydrophobic nature of curcumin and its agglomeration in aqueous medium that inhibits more cellular uptake. Also, the cytotoxicity of BSA-Cur NPs increased with concentration in the studied values (P value < 0.05). On the other hand, at all studied concentrations, the cytotoxicity of BSA-Cur NPs was significantly higher than that

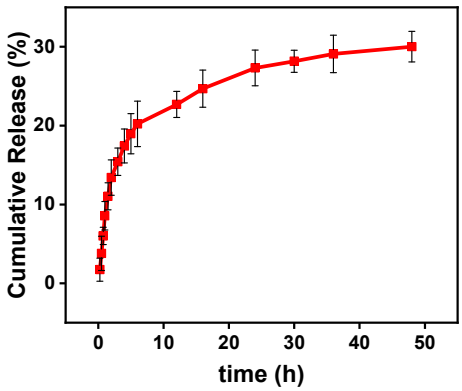

Fig. 4. Cumulative release curve of Cur over time from BSA NPs

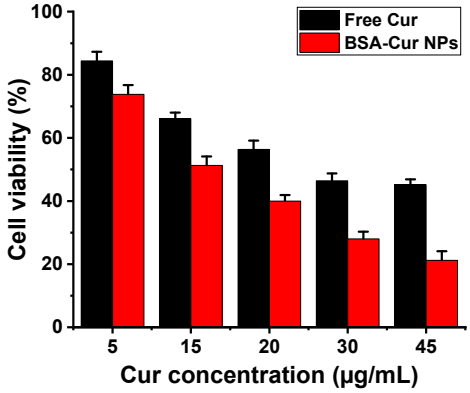

Fig. 5. Cytotoxicity of free Cur and BSA-Cur NPs on U-87 MG cells after 48 h treatment

of free Cur (P value < 0.05). In addition, the half maximal inhibitory concentration (IC_{50}) values for free Cur and BSA-Cur NPs were obtained 33.08 ± 0.1.27 and 17.43 ± 1.37 µg/mL, respectively. In this regard, in a study, Arzani et al. used PLGA nanoparticles for loading of curcumin against human glioblastoma U-87 MG cancer cells. The results of their study showed that the value of IC_{50} after 72 h was 32.90 µg/mL (29). Also, the studies performed by Erfani-Moghadam et al. on the mPEG-OA nanocarriers loaded with curcumin against U-87 MG cells illlustrated that after 48 h treatment, the value of IC_{50} reached to about 25 µg/mL (30). The results of present study showed that albumin nanoparticles were more effective in improving the anti-cancer properties of curcumin against U-87 MG cells than the nanocarriers used in the above studies. Furthurmore, micrographs of the cells in Fig. 6 show that after 48 h, the untreated cells had a normal morphology and intact nuclei. However, the cell viability had been significantly reduced in cells treated with free Cur and BSA-Cur NPs. Morphological changes were also observed so that the cells shrank and nuclei had undergone condensation into sharply delineated masses probably due to apoptosis. On the other hand, according to the images, viability of the cells treated with BSA-Cur NPs was lower than the free Cur, which conforms with the results of MTT test. Altogether, these results showed that BSA-Cur NPs were able to more effectively inhibit the growth and proliferation of U-87 MG cancerous cells compared to free Cur. This result could be due to the increased solubility of Cur through loading it into the hydrophilic BSA NPs and subsequently improved bioavailability of Cur.

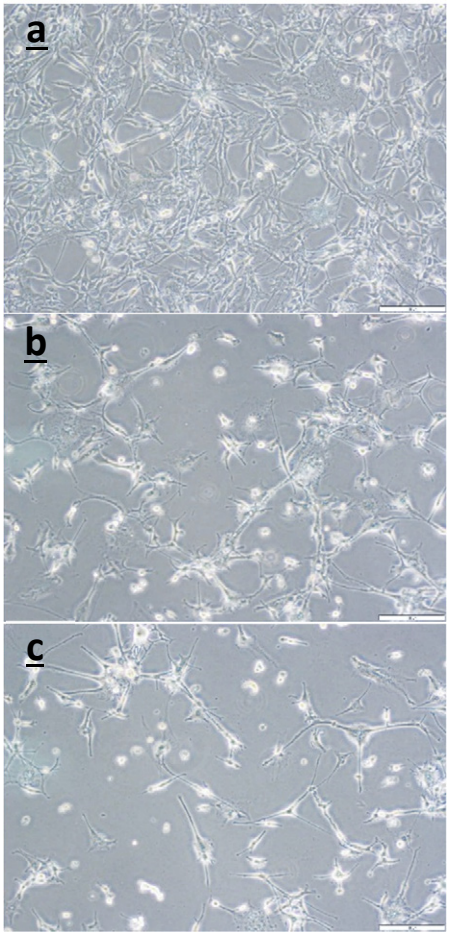

Fig. 6. Optical microscopic images of U-87 MG cells after 48 h, (a) Untreated cells, (b) The cells treated with Cur, (c) The cells treated with BSA-Cur NPs at concentration of 30 µg/mL

CONCLUSION

In the present study, curcumin-loaded albumin nanoparticles were prepared successfully. According to the results, the prepared nano-formulation had suitable physicochemical properties for cancer drug delivery applications. Curcumin release from nanoparticles followed sustained and controlled manner *in-vitro*. The results of cytotoxicity evaluation showed that the loading of curcumin on albumin nanoparticles by improving the bioavailability of curcumin in aqueous medium increased its effectiveness against U-87 MG cancer cells and therefore this nano-formulation can be considered as a promising candidate in anti-glioblastoma studies.

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CONFLICTS OF INTEREST

None.

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