Facile green synthesis of bismuth sulfide radiosensitizer via biomineralization of albumin natural molecule for chemoradiation therapy aim

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Abstract
High atomic number Z, nanoparticles are able to enhance the photoelectric and Compton effects under X-Ray irradiation resulting in the increase of radiation therapy efficacy. To achieve enhanced radiation therapy, Bi$_2$S$_3$ biocompatible particles coated with bovine serum albumin (BSA) (Bi$_2$S$_3$@BSA HNPs) were prepared through a BSA-mediated biomineralization procedure under green conditions. Then, to achieve improved chemo-radiation combination therapy against HT-29 cancer cells, curcumin (CUR) as natural anti-cancer therapy agent loaded on the Bi$_2$S$_3$@BSA (Bi$_2$S$_3$@BSA@CUR HNPs). Next, this synthesized nanodrug was evaluated for physical and chemical properties and in vitro cytotoxicity studies. Here, in vitro enhanced chemo-radiation combination therapy power was evaluated against HT-29 cell line under 2 Gy and 6 Gy X-Ray irradiation doses. The Bi$_2$S$_3$@BSA HNPs without irradiation rarely affect cell viability which shown the non-toxicity of Bi$_2$S$_3$@BSA HNPs. The result of this study proved that Bi$_2$S$_3$@BSA@CUR HNPs can be used as both proficient vehicles for effective delivery of CUR and radiosensitizer in the treatment of cancer. In addition, the result of this study confirmed that the combination of high Z-element nanoradiosensitizer, Bi$_2$S$_3$@BSA HNPs, with a natural anti-cancer drug, CUR, enhanced therapeutic power against HT-29 cells.

Introduction
Despite many strategies developed for effective treatment of various cancers, global cancer statistics demonstrate that the incidence of cancer met a noticeable increase in through the world. For improving cancer therapy effectively with X-Ray irradiation, high dose irradiation is needed. Unlikely, high dose irradiation can damage normal tissues. High atomic number Z, nanoparticles can desirably enhance the photoelectric, Compton effects and radiation therapy efficacy [1,2]. In addition, by considering nanoparticles power, it is easy to concentrate the high atomic number particles in tumour tissues, and capable to enhance radiation therapy. To date among a lot of studies, colloidal hybrid nanoparticles (HNPs) have been considered as an significant family of multifunctional or enhanced functional nanoparticles [3,4]. HNPs include multiple components in a single nanosized particle. HNPs as novel important properties are attractively considered for biomedical applications. These types of biomaterials have shown abundant application in various biomedical fields, especially, as radiosensitizer [5,6]. Moreover, recent years bismuth compound nanomaterials have attracted huge attention in this field as well. Bismuth is a typical high-Z element with a high X-ray attenuation coefficient (5.74 cm$^2$kg$^{-1}$ at 100 keV) [6]. Obviously, the bismuth compounds have the X-ray computed tomography enhancement efficiency [7]. In addition, the possibility of bismuth nanoparticles for in vivo X-ray computed tomography imaging and photothermal therapy/radiotherapy has been demonstrated very lately [6].

Furthermore, bovine serum albumin (BSA) has received more attention than other biological carrier, especially in cancer treatment because of their unique properties [8]. Rarely toxicity or immunogenicity; biodegradable; stable in circulation; qualifying a long half-life; does not require surfactants or polymeric materials for preparation; easy access to all tumour sites via the blood circulation; high chemical stability; and convenient to administer are likely properties to persuade researcher to use Albumin eagerly. In addition, the amino and carboxylic groups of the BSA structure can be used for surface modification as well.

Curcumin (CUR) is a biologically active component of the Indian spice which derived from the Zingiberaceae family...
known as turmeric (Curcumin longa). Turmeric is used to
treat of various diseases in conventional medicine because of
its anti-oxidative and anti-cancer properties [9,10]. CUR by
down-regulating TNF-inducible NF-κB and AP-1 protein activity
induces apoptosis in various carcinomas. Despite CUR
have chemopreventive, cytotoxic and anti-metastatic properties,
its severe drawback such as its instability reduces bio-
availability and systemic uptake [11]. Nowadays, some
approaches have been successfully used to solve these draw-
backs, such as encapsulating it in cyclodextrins and conjugat-
ing it with silver nanoparticles [12,13].

Herein, we report a BSA biomineralization facile method
for achieving biocompatible BSA coated bismuth sulfide
HNPs (Bi2S3@BSA HNPs). The resulting Bi2S3@BSA HNPs were
characterized by ultra-small size and excellent colloidal stability.
CUR, as a natural anti-cancer drug, was loaded on
Bi2S3@BSA HNPs with physical encapsulation to form of
Bi2S3@BSA@CUR HNPs. Then, anticancer effect of these nano-
particles was investigated, too. Furthermore, the enhanced
efficiency of chemoradiation therapy confirms the radiosensi-
tization and chemotherapeutic effect of
Bi2S3@BSA@CUR HNPs.

Materials and methods

Materials

BSA, Bi (NO3)3, 3–(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl
tetrazolium bromide (MTT) and CUR were achieved from
Sigma Aldrich Chemicals, (St. Louis, MO, USA). All other sol-
vents were purchased from Emerat Chimi Company
(Tehran, Iran).

Preparation of bismuth sulfide hybrid nanoparticles
(Bi2S3@BSA HNPs)

Bi2S3@BSA HNPs was prepared as previously process [2,14].
50 mM Bi (NO3)3 in 1.0 ml of HNO3 solution (2 M) was slowly
added into BSA solution (250 mg BSA in 8.0 ml deionized
water) under vigorous stirring. After 30 min, NaOH (2 M) was
added into BSA solution (250 mg BSA in 8.0 ml deionized
water) under vigorous stirring. After 30 min, NaOH (2 M) was
used to adjust the solutions pH to 12, and the mixture was
allowed to react at room temperature for overnight
under vigorous stirring. The colour of the solution changed from
colourless to dark black, and BSA stabilized Bi2S3 NPs
(Bi2S3@BSA HNPs) were thus formed. The resulting Bi2S3@BSA
HNPs were purified by the dialysis (12 kDa) of the solution
against deionized water for 48 h to remove the excess precursors.

Loading of CUR on Bi2S3@BSA@CUR HNPs
(Bi2S3@BSA@CUR HNPs)

Ten milligrams of Bi2S3@BSA HNPs was dispersed in 2.8 ml of
distilled water under stirring at 400 rpm. CUR (2.5 mg) was
dissolved in 200 μl of acetone and added dropwise to the
above suspension. The mixture was shacked for 24 h under
the dark condition at room temperature. Final formulation

Bi2S3@BSA@CUR HNPs were purified by centrifugation
at 18,000 rpm.

Characterization

The samples were characterized using XRD, FTIR, TEM, UV/Vis
and DLS techniques.

The particle size and morphology of the Bi2S3@BSA@CUR
HNPs were studied using TEM measurements. The sample
was imaged by a transmission electron microscope (TEM;
Cambridge 360–1990 Stereo Scan Instrument-EDS).

The ζ-potential and hydrodynamic size were measured
using a nano/zetasizer (Malvern Instruments, Worcestershire,
UK, model Nano ZS).

A powder X-ray diffractometer system (a Bruker AXS
model D8 Advance diffractometer) was used for measure-
ment of XRD pattern. Samples were exposed to Cu-Kα radi-
ation at 1.542 Å. The measurements were done at 2θ from
10° to 80°.

FTIR spectra were measured using a FTIR spectrophotom-
eter (Bruker, Tensor 27).

The absorption spectrum of the samples was documented
using UV/Vis spectrophotometer (T80) to determine the com-
ponents of BSA and CUR in the final formulation CUR-BSA.

In addition, stability of synthesized nanoparticles was
examined using DLS and UV-vis techniques. The size of nano-
particles was monitored using DLS until 210 days after prep-
paration. Also, the absorbance of synthesized nanoparticles
was read at 261 nm (λ max of Bi2S3) at different times and
compared with each other for determination of precipitation
and further for determination of stability.

In vitro study

Drug release study

To evaluation the drug release behaviour, we incubated
Bi2S3@BSA@CUR HNPs in PBS (pH 7.4 and 4.5) at 37 °C in a
dialysis bag (molecular weight cutoff 12,000 Da) and next
immersed this bag into 45 ml of PBS (2% tween). At selected
time intervals, the exterior solution (2 ml) was withdrawn and
analyzed spectrophotometrically at 428 nm and returned
back to the medium to keep the volume of the drug release
test constant.

Cell culture

The HT-29 cells were proliferated in RPMI1640 medium sup-
plemented with 10% fetal bovine serum (FBS) and 100 mg/ml
penicillin G and 100 mg/ml streptomycin (Gibco, Germany) at
37 °C in 5% CO2 atmosphere.

In vitro anti-tumour activity study

In vitro MTT cytotoxicity assay was performed to compare
anti-tumour effects of Bi2S3@BSA HNPs, Bi2S3@BSA@CUR
HNPs and free CUR against HT-29 cell line. Also, MTT cytotox-
icity assay was further used for determination radiosensitiza-
tion effect of Bi2S3 HNPs under X-Ray irradiation at 2 Gy and
6 Gy doses. The cells were seeded on a 96 well plate at a cell
density of $3 \times 10^4$ cells/well. Every drug was tested in 5 wells. After incubating the cells in a logarithmic phase with medium containing free CUR, Bi$_2$S$_3$@BSA HNPs and Bi$_2$S$_3$@BSA@CUR HNPs at different concentrations for 5 h, the cells were washed multiple times with PBS and further wells filled with fresh medium. Next, the cells were exposed to 2 Gy and 6 Gy doses of X-Ray. After overnight incubation, MTT dye (20 $\mu$l of 2.5 mg/ml) was added to each well. After incubation for an additional 4 h, the percentage of cell viability was determined at 570 nm relative to non-treated and non-irradiated cells. In order to compare irradiated cells with non-irradiated cells, one of the plates does not receive X-Ray.

**Results and discussion**

**Synthesis of Bi$_2$S$_3$@BSA@CUR HNPs**

The many available ways to synthesize Bi$_2$S$_3$ NPs require severe conditions or post-synthetic surface modification. For the biomedical applications, a facile aqueous synthesis under ambient conditions is required [15,16]. Recently, a novel BSA-mediated biomineralization method for achieving biocompatible Bi$_2$S$_3$ NPs was reported [2,14]. The synthesis process is highlighted by two steps: (i) suitable conditions for facilitating the coordination of Bi$^{3+}$ cations with BSA and preventing the former from hydrolysis, (ii) pH-mediated formation of Bi$_2$S$_3$ HNPs upon a quick adjustment of the reaction pH up to 12. In the present synthetic method, BSA has two practical roles. The BSA not only works as a stabilizer but also as a sulfur precursor for forming Bi$_2$S$_3$ HNPs with excellent colloidal stability. The BSA can be denatured to release numerous residues (e.g. 35 cysteine residues) under strong basic conditions [17,18], as an excellent sulfur source for forming metal sulfide NPs [19,20]. Moreover, Biodegradability, stability in blood circulation and a long half-life are some of advantages albumin. Next, the CUR molecules were loaded physically and led to the formation of final formulation (Bi$_2$S$_3$@BSA@CUR HNPs).

**Characterization of Bi$_2$S$_3$@BSA@CUR HNPs**

Optical properties of Bi$_2$S$_3$@BSA@CUR HNPs were examined with UV–Vis absorption spectrophotometry. As shown in Figure 1(a) the loading of CUR to the nanoparticle was examined using UV-Vis absorption. As shown in Figure 1(a), the UV-Vis spectrum peak of the BSA and Bi$_2$S$_3$@BSA HNPs is around 266 nm and 264 nm, respectively. In the UV-Vis absorption spectrum of CUR, it can be seen that a characteristic absorption centred at 424 nm, which has been assigned to the $\pi$-$\pi^*$ transition [21,22]. Figure 1(a) displays the UV-Vis absorption spectrum of the Bi$_2$S$_3$@BSA@CUR HNPs, the peaks in the UV-Vis absorption spectrum around 255 nm and 430 nm corresponds to the BSA and CUR, respectively, successfully loading CUR to the surface of the Bi$_2$S$_3$@BSA HNPs giving rise to the enhanced absorption at 430 nm [23].

Many biomedical claims require nanoparticles to exhibit more colloidal stability. UV–Vis spectrophotometer is one of the techniques used for the evaluation of colloidal stability of nanoparticles [24]. For example, Frankamp et al. measured absorbance of magnetic nanoparticles at 450 nm in order to examine the stability [25]. In this study, the stability of Bi$_2$S$_3$@BSA HNPs and Bi$_2$S$_3$@BSA@CUR HNPs were investigated with UV–Vis absorption spectrophotometer. The absorption value of Bi$_2$S$_3$@BSA HNPs and Bi$_2$S$_3$@BSA@CUR HNPs were recorded at different times at 261 nm as shown in Figure 1(b). As shown in the result, Bi$_2$S$_3$@BSA HNPs and Bi$_2$S$_3$@BSA@CUR HNPs are all very stable even after almost 1 month stored.

As shown in Figure 2(a), we can be seen the unmodified Bi$_2$S$_3$@BSA HNPs exhibited a mean particle size around 60 nm with a PDI of 0.130. Also, the DLS result showed that Bi$_2$S$_3$@BSA@CUR HNPs exhibited a diameter of about 103 nm with a PDI of 0.202. The size of the Bi$_2$S$_3$@BSA@CUR HNPs was slightly larger than that before loading with drug. The stability of the particles is related closely to the surface charge. The same surface charge is favourable for particle stability because it could provide repulsion between the nanoparticles. The Bi$_2$S$_3$@BSA HNPs was negatively charged with a zeta potential of $-32.61$ mV, whereas the zeta potential of Bi$_2$S$_3$@BSA@CUR HNPs was $-26.35$ mV. Thus, it can be
decided that the particles were negatively charged, which provided good physical stability for the as-prepared formulations [26]. One of the other factors used for stability checking is size monitoring at different times. There, we used DLS technique for monitoring the size for 210 days after preparation. As shown in Figure 2(b), the stability checking shows that there is no significant increase in size. These results confirmed the stability of synthesized nanoparticles.

The TEM analysis was conducted to detect the morphology and size of and the results showed that Bi$_2$S$_3$@BSA@CUR HNPs existed in a spherical structure. The Bi$_2$S$_3$@BSA@CUR HNPs has an average diameter of approximately 14.59 ± 3.99 nm measured using TEM as shown in Figure 2(c).

The FTIR technique was used for the successful synthesis of Bi$_2$S$_3$@BSA HNPs and Bi$_2$S$_3$@BSA@CUR HNPs. The comparison of BSA FTIR spectrum with Bi$_2$S$_3$@BSA HNPs FTIR spectrum and match of this result with previously reported results confirmed the successful synthesis of Bi$_2$S$_3$@BSA HNPs. Furthermore, after loading of CUR onto the Bi$_2$S$_3$@BSA HNPs the CUR characteristic bands appeared at Bi$_2$S$_3$@BSA@CUR HNPs FTIR spectrum (Figure 3).

The crystal structure of Bi$_2$S$_3$@BSA HNPs was confirmed using XRD. As shown in Figure 4(a), all reflection peaks of the Bi$_2$S$_3$@BSA HNPs is almost representative of the Bi$_2$S$_3$ structure (JCPDS NO. 43–1471) [27,28]. The BSA coating was confirmed by the appearance of the broad and moderately strong peak at the range of 20–29° which has been assigned to XRD pattern of the BSA [29].

**Drug loading and release study**

The drug loading efficacy was also calculated according to the absorbance of CUR at 428 nm. The drug loading efficacy was 9.84 ± 1.27%.

Also, to reveal the distribution of CUR in cancer cells, the drug release from Bi$_2$S$_3$@BSA@CUR HNPs (Figure 4(b)) were studied. Evidently, we can see that more CUR showed controlled release behaviour. This property is desirable in
anticancer drug delivery, which can facilitate the drug release to suitable site.

**Cytotoxicity assay**

In this work, we used MTT assay to evaluate the anti-tumour effect of Bi$_2$S$_3$@BSA HNPs. Due to excellent properties of designed and prepared Bi$_2$S$_3$@BSA@CUR HNPs, these HNPs showed incomparable synergistic chemoradiation therapy effect. Because of the outstanding biocompatibility of Bi$_2$S$_3$@BSA HNPs, compared to control, the cell viability did not affect significantly in the presence of these HNPs.

As shown in Figure 5, the cell viability decreased with the increase of CUR and Bi$_2$S$_3$@BSA@CUR HNPs concentrations. Particularly, CUR and Bi$_2$S$_3$@BSA@CUR HNPs exhibited dose-dependent cytotoxic effects.

To evaluate radiosensitization power of CUR, Bi$_2$S$_3$@BSA HNPs and Bi$_2$S$_3$@BSA@CUR HNPs, the cells were treated with these particles and then were irradiated with different doses of X-Ray. Also, albeit the cell viability of HT-29 cells decreased under X-Ray irradiation, but this abate in the presence of CUR, Bi$_2$S$_3$@BSA HNPs was increased. Interestingly, we can see more and more decrease in cell viability in the presence of both X-Ray irradiation and Bi$_2$S$_3$@BSA@CUR HNPs.

![Figure 4](image_url) (a) XRD pattern of Bi$_2$S$_3$@BSA HNPs; (b) Release profile of CUR from Bi$_2$S$_3$@BSA@CUR HNPs.

![Figure 5](image_url) Viability of HT-29 cells at different concentration with and without X-Ray irradiation at different doses. **indicates significant difference with \( p < 0.01 \), ***indicates significant difference with \( p < 0.001 \), ****indicates significant difference with \( p < 0.0001 \).
The groups that treated with CUR, Bi$_2$S$_3@$BSA HNPs and Bi$_2$S$_3@$BSA@CUR HNPs with the aid of X-Ray irradiation showed significantly inhabitation effect. The cell viability decreased with increasing radiation dose. These results confirmed the radiosensitization power of CUR, Bi$_2$S$_3@$BSA HNPs, and Bi$_2$S$_3@$BSA@CUR HNPs. The presence of both X-ray irradiation and HNPs showed higher anti-tumour effect which related to the radiosensitization power of high Z-elements [2]. It is well known that the high Z-elements can generate ROS and further can be damage the DNA that leading cells to death [30–32]. In all concentrations, the final formulation, Bi$_2$S$_3@$BSA@CUR HNPs, showed tip top anticancer effect. These results are well matched with previously reported results that high Z-elements and CUR can be enhanced the therapeutic efficacy [10,14]. In addition, result of this study confirmed that the combination of high Z-element nanoradiosensitizer with natural anti-cancer drug, CUR, enhanced therapeutic power against HT-29 cells.

**Conclusion**

In conclusion, a biodegradable and stealthy nanostructure has been successfully developed through BSA-mediated biomineralization method for drug delivery in living cell. In the present synthetic method, BSA has two practical roles. The BSA not only worked as a stabilizer but also as a sulfur precursor for forming Bi$_2$S$_3$ HNPs with excellent colloidal stability. Also, Bi$_2$S$_3@$BSA@CUR HNPs exhibited attractive controlled release ability for CUR. This Bi$_2$S$_3@$BSA@CUR HNPs represents an essential approach for efficiently cancer therapy. In vitro cytotoxicity assay was performed to compare anti-tumour effects of Bi$_2$S$_3@$BSA@CUR HNPs and free CUR with and without of irradiation. The result of this study proved that Bi$_2$S$_3@$BSA@CUR with the aid of X-Ray irradiation increased therapeutic efficacy and can be used as a proficient vehicle for effective delivery of CUR in treatment of cancer. Compared to control group the presence of both X-ray irradiation and Bi$_2$S$_3@$BSA@CUR HNPs showed 40%, 47% and 57% increased of cytotoxicity towards HT-29 cells at 25 μg/ml, 50 μg/ml and 100 μg/ml concentration, respectively.

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**Disclosure statement**

No potential conflict of interest was reported by the authors.

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