ORIGINAL ARTICLE

Preparation, the physicochemical assessment, and the cytotoxicity of Cisplatin-loaded mesoporous Silica nanoparticles against head and neck squamous cell carcinoma cell line

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Abstract
The aim of this study was to prepare, the physicochemical assessment and the cytotoxicity testing of cisplatin-loaded mesoporous silica nanoparticles against head and neck squamous cell carcinoma cell line (HNSCC). Cisplatin-loaded mesoporous silica nanoparticles were prepared through the precipitation method. The prepared nanoparticles were evaluated by conventional methods in terms of physicochemical properties. The cytotoxic effect of the nanoparticles and the free cisplatin were assessed on the head and neck squamous carcinoma cell line. The results showed that the prepared nanoparticles with nanometer size and the negative surface charge belonged to the MCM-41 silica family. TEM images established the mesoporous construction and the rod-shaped morphology of the produced nanoparticles. Based on Brunauer-Emmett-Teller (BET) analysis, the specific surface area, pore volume, and pore diameter decreased compared to free mesoporous silica because of drug filling into the mesoporous pores. The nanoparticles showed a two stage release pattern that continued slowly until the 35th day. Mesoporous silica nanoparticles displayed no significant cytotoxic effect on HNSCC. Cisplatin displayed a cytotoxic effect with IC50 of 82.01 μM and 33.67 μM in 24 h and 48 h incubation times, respectively. However, cisplatin-loaded mesoporous silica nanoparticles displayed a cytotoxic effect with IC50 of 26.17 μM and 13.28 μM in 24 and 48 h incubation times, respectively. The results can highlight the capability of cisplatin-loaded mesoporous silica nanoparticles to be applied in the treatment of oral cancerous cells.

Keywords: *Anticancer Effect; Cisplatin, Head & Neck Squamous Cell;   Cytotoxicity; Oral Cancer; Silica Nanoparticles.*

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INTRODUCTION

Oral cancer is one of the most common cancer that impacts the health of people with unbearable death rates [1]. There are some clinical approaches to diagnosis and therapy of this type of cancer including surgery, chemoradiotherapy, magnetic resonance imaging, and tomography. However, these techniques are far from the optimum state yet. So, vital attention is required for the new methods of early diagnosis and therapy of oral cancer. In recent years, different forms of nanomaterials have been produced, signifying a talented way for diagnotherapy of oral cancer [1, 2].

Nanotechnology studies nanometer-sized materials that have been used extensively in various areas in recent years [3]. The increasing use of this technology in the field of medicine and treatment is undeniable. This technology, in fact, by reducing the size of materials to nanometer dimensions, seeks to reduce the toxicity of drugs while increasing their efficiency. Nanoparticles, which are nanometer-sized particles, have completely different properties from similar materials in larger dimensions [4]. This change in properties is due to a reduction in particle size, followed by an increase in the effective surface area of the material [5]. Nanoparticles are used alone or in combination with other conventional anticancer compounds to overcome the multidrug resistance of anticancer agents [6].

Cisplatin or cisplatinum or cis-amino dichloroplatinum (II) (CDDP) is a platinum-based chemotherapy drug used to treat a variety of cancers, including sarcoma, certain carcinomas (such as small cell lung cancer, and has been used for ovarian cancer, head and neck cancer, lymphoma and germ cell tumors. Cisplatin has poor bioavailability and little selectivity for tumor versus normal tissue leading to high-dose requirements and toxicity to normal tissues and also the incidence of multiple drug resistance [7]. These factors limit its clinical usage [8]. Secondary anemia, neutropenia, thrombocytopenia, renal toxicity, elevated blood uric acid or uric acid-induced nephropathy, and auditory toxicity are common complications and side effects of cisplatin [9-11].

Different drug delivery systems have been recommended to overcome the limitation of cisplatin clinical usage to gain the enhanced permeability and retention (EPR) effect and to help the transportation of cisplatin to tumors [7, 8]. Mesoporous silica nanoparticles, which are a type of ceramic nanoparticle, are widely used as drug delivery systems to cancerous cells due to their biocompatibility, large surface area, the presence of multiple pore-like structures, and the possibility of high drug loading as well as easy synthesis [12-14]. Loading of cisplatin into mesoporous silica nanoparticles enhances its bioavailability and selectivity to tumors and then overcomes the mentioned limitations [7].

The aim of this study was to prepare, the physicochemical assessment and the cytotoxicity testing of cisplatin-loaded mesoporous silica nanoparticles against head and neck squamous cell carcinoma cell line.

MATERIALS AND METHODS
Materials

Cetrimonium bromide (CTAB, Purity ≥98%), and sodium hydroxide (NaOH, Purity ≥ 99.0 %) were purchased from Merck (Darmstadt, Hesse, Germany) and tetraethyl orthosilica (Purity ≥ 99.0 %), dimethyl sulfone (Purity ≥98%), cisplatin (Purity ≥98%) and 2,2 triethanol (Purity ≥ 99.0 %) were prepared from Sigma Aldrich (St. Louis, Missouri, USA).

Methods
Preparation of cisplatin-loaded mesoporous silica nanoparticles

The mixture of surfactant (CTAB), distilled water, and sodium hydroxide (NaOH) was stirred on a steerer for up to 80 °C for 30 min. The pH of the solution was then adjusted to 12.2. In the next step, tetraethyl orthosilicate was added to the solution instantly on a magnetic stirrer at 550 rpm. A white precipitate was obtained which was mesoporous silica nanoparticles. The ambient temperature of the solution was maintained at 80 °C for two hours. The resulting precipitate was separated by centrifugation at 15,000 rpm and dried in an oven at 37 °C.

Drug powder (cisplatin) was dissolved in 2,2 triethanol (5 wt%). The prepared nanoparticle powder was added to the drug solution. The resulting mixture was stirred slowly at room temperature for 24 hours in a dark environment.

Physicochemical characterization

To determine the physicochemical properties of the mesoporous silica nanoparticles and the

pattern of drug release from these nanoparticles, common characterization methods were used, which are completely described below.

The particle size and the morphology of nanoparticles

To ensure the nanometer size of the prepared nanoparticles (drug-free silica nanoparticles and drug-containing silica nanoparticles), the dynamic light scattering (DLS) device (DLS, Malvern, Cambridge, Massachusetts, UK) was used. For this purpose, a qualitative suspension of nanoparticles was prepared in distilled water and poured into a special tube of the device. The device reported the particle size chart along with the average particle size. Measurements were performed three times and the average of all three measurements was reported. Transmission electron microscopy (TEM) was also used to reveal structural details and morphology of nanoparticles. For TEM analysis (JEM-2100F; JEOL, Tokyo, Japan), samples were prepared by dropping a solution of nanoparticles in deionized water on a carbon-coated copper TEM grid [15].

Surface charge of nanoparticles

The surface charge of the nanoparticles was measured by a zeta-sizer (DLS, Malvern, Cambridge, Massachusetts, UK). For this purpose, a qualitative suspension of nanoparticles was prepared in distilled water and poured into a special tube of the device. The device reported the zeta potential diagram with its numerical mean. Measurements were performed three times and the average of all three measurements was reported.

Drug loading in nanoparticles

To determine the amount of drug loading percent (DL%) on mesoporous silica nanoparticles, 10 mg of the prepared nanoparticles were dissolved in dimethyl sulfone. Then, ultraviolet absorbtion was taken from the dissolved sample using an ultraviolet spectrophotometer. For this purpose, about one ml of the dissolved nanoparticle solution was poured into a special tube of the device and the absorption number for each of them was read by adjusting Landa Max to 510 nm for cisplatin. Using the following formula, the value of the drug in the total nanoparticles was obtained and expressed as a percentage.

$DL(\%) = ($Actual drug content / Weight of powdered nanoparticles$) \times 100$

The pattern of drug release

To determine the pattern of drug release from nanoparticles, drug dissolution device No.2 (Apparatus 2) was used. Phosphate buffer (300 ml) was poured into each of the 6 wells. Five mg of the prepared nanoparticles were poured into all 6 wells of the device and the pH of the medium was adjusted at 7.4. The temperature of the device was set at 37 C°. The stirrer speed of the device was set to 100 rpm [16, 17]. Samples were taken from the wells every day (one ml) and the absorbance was read using a UV spectrophotometer (Shimadzu-Japan). The sample taken from the wells was replaced with 1 ml of a new buffer medium. The amount of adsorption was converted to concentration. The time-concentration concentration diagram, which is the diagram of the drug release pattern, was plotted.

X-ray diffraction (XRD)

XRD patterns were determined at room temperature for the samples. The samples were exposed to an X-ray diffraction gauge (Siemens D 5000, Germany) and irradiated with a wavelength of 1.5405 Å, a voltage of 40 kV, and a current of 30 mA, and their patterns by the device from an angle (2Theta) of zero to ten registered.

Brunauer-Emmett-Teller (BET) analysis

The BET adsorption and desorption isotherm analysis was used to describe the specific surface area. Dried powder of nanoparticles were located in a BET device (JW-DA model, JWGB company-China). The volume of absorbed nitrogen gas by the material was measured by gradually increasing the gas pressure. Then, with a gradual decrease in gas pressure, the amount of desorbed gas by the material was calculated at a constant temperature [15].

The MTT Assay

The cytotoxic effects of the mesoporous silica nanoparticles, cisplatin and cisplatin-loaded mesoporous silica nanoparticles on HN5 were evaluated via the MTT assay. The HN5 cells were seeded on a 96-well plate (5000 cells/well) in DMEM media supplemented with 10% FBS. Mesoporous silica nanoparticles, cisplatin and cisplatin-loaded mesoporous silica nanoparticles were added to the cells and incubated at 37 °C and 5% CO_2 for 24 and 48 hours. Then, the cells were washed with phosphate-buffered saline (PBS) and

200 μL of the culture medium comprising 0.5 mg/mL MTT was added to the cells, and plates were incubated at 37 °C and 5% CO_2 for four hours. Then, the MTT solution was changed with 200 μL of DMSO and read at 570 nm by means of a spectrophotometric microplate reader (BioTek, EL ×800. USA).

Data analysis

The results were reported as descriptive indicators. Excel 2020 software was used to analyze the data to draw graphs and calculate descriptive indicators.

RESULTS AND DISCUSSION

To ensure the suitability of nanocarriers for different uses, their physicochemical properties must be specified. According to scientific reports, the physicochemical properties of nanoparticles have special effects on their other properties, especially on their interactions *in vitro* and *in vivo* [18]. As the particle size decreases, the surface area increases and then the interaction of the nanoparticles with the environment increases [19, 20]. Zeta potential is one of the key parameters that is commonly used to estimate the stability of a suspension system. As a general rule of the stability reports, a value of zeta potential above 60 mV indicates good stability, while a zeta potential below 5 mV indicates particle aggregation and leads to instability. Values between this range indicate good stability or satisfactory short-
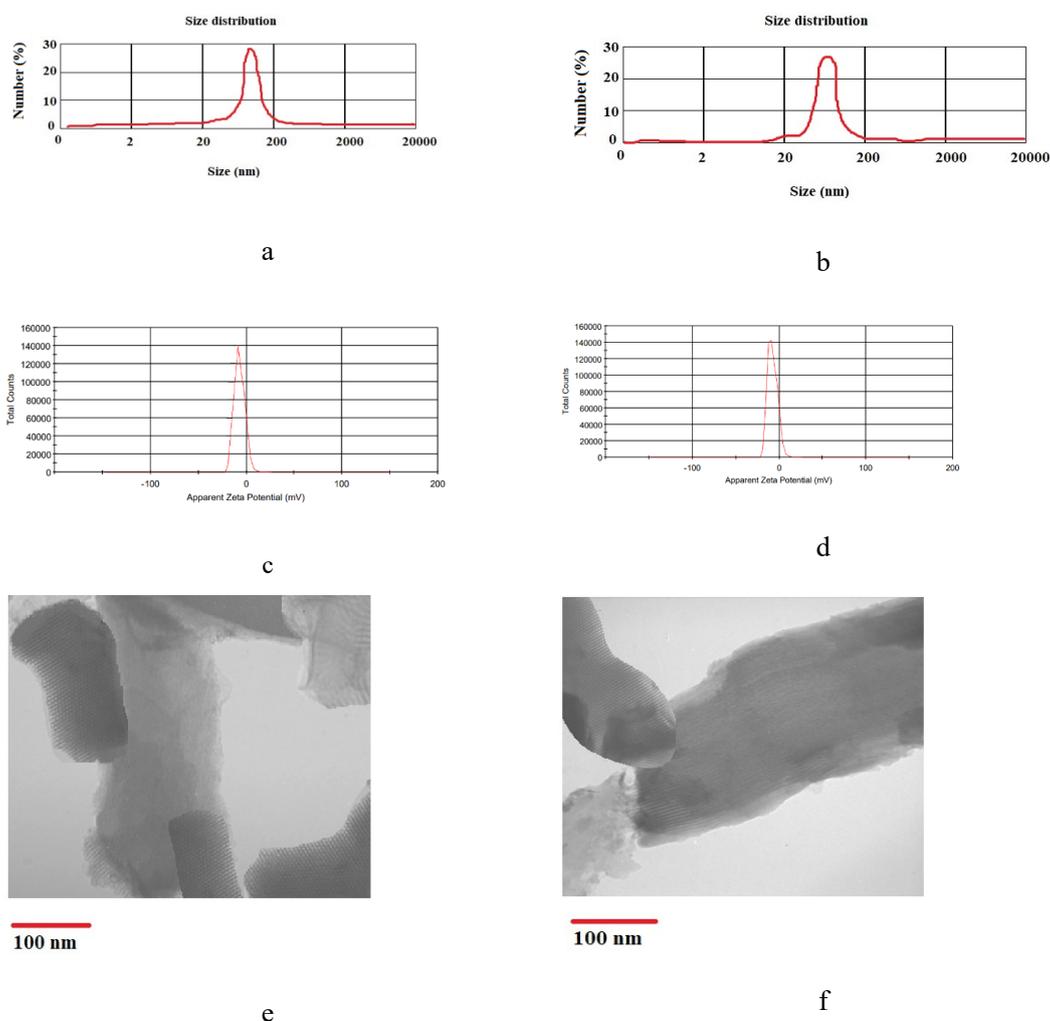

a

b

c

d

e

f

Fig. 1. The average particle size (a and b), the surface charge (c and d) and the TEM images (e and f) for free mesoporous silica nanoparticles and cisplatin-loaded mesoporous silica nanoparticles respectively.

term stability. Studies have also shown that the repulsion charge between nanoparticles is needed to prevent aggregation and adhesion of particles [21, 22]. Fig. 1 (a to d) shows the average particle size and surface charge of the prepared silica nanoparticles (with and without drug) respectively. According to the results, the mean particle size was obtained for free mesoporous silica nanoparticles (70 nm) and for cisplatin-loaded mesoporous silica nanoparticles (130 nm). Numerical values of zeta potential (surface charge) were obtained for free mesoporous silica nanoparticles (-15 mV) and for cisplatin-loaded mesoporous silica nanoparticles (-17 mV). The results showed that the prepared nanoparticles had nanometer size and acceptable zeta potential in terms of stability [23]. TEM images established the mesoporous construction and the rod-shaped morphology for the produced free silica nanoparticles (Fig. 1, e). The loading of drugs into the pores of mesoporous silica can also be observed by TEM image for drug-loaded mesoporous silica nanoparticles (Fig. 1, f). Based on the prior reports, the rod-shaped nanoparticles show a longer circulation time and a minimal uptake by the RES in the body compared with spherical particles [24, 25]. According to *in vivo* biodistribution results reported by Zhao *et al*, rod nanoparticles displayed high ability to overcome fast clearance via RES and had a longer existence in the blood in comparison spherical nanoparticles [26].

Fig. 2 shows the X-ray diffraction pattern of cisplatin-loaded mesoporous silica nanoparticles (Fig. 2, a) and free mesoporous silica nanoparticles (Fig. 2, b). The pattern obtained for both types of material is a crystalline structure representing the mesoporous structure of the MCM-41 family [27]. This structure is preserved by loading the drug. In the X-diffraction pattern, there are four peaks related to the mesoporous structure of the MCN-41 family, including strong peaks (100) and weaker peaks (110), (200), (210) for free nanoparticles [28]. Strong peaks are clearly present in drug-containing nanoparticles, but weaker peaks are present with much lower intensities and are not clearly detectable. These results indicate that the structure of the nanoparticles is preserved after drug loading. In fact, the thickness of the nanoparticles pore's walls has increased following the filling of the pores with drug. Then, the radiation of 2Theta angle has increased compared to the nanoparticles without drug. Karimzadeh *et al.* [29] reported similar results for mesoporous silica nanoparticles loaded with rivastigmine. They reported that the reason for the decrease in peak severity after drug loading was the filling of the pores with the drug, the increase in the thickness of the walls and the increase in the radiation 2theta angle compared to the drug-free nanoparticles.

In vitro dissolution test is a routine test for many dosage forms including tablets, capsules and drug delivery systems like nanomaterials [16, 30]. According to the loading results, the drug loading percentage in nanoparticles was 68% for cisplatin. According to the results, the nanoparticles showed a relatively rapid release pattern in the first 5 days (Fig. 3). The release pattern continued slowly until the 35th day. The pattern of rapid release of nanoparticles in the first days seems to be related to adsorbed drugs
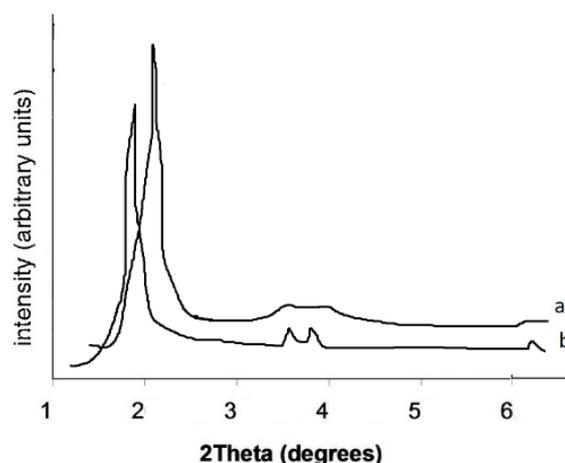

Fig. 2. The X-ray diffraction pattern of cisplatin-loaded mesoporous silica nanoparticles (a) and free mesoporous silica nanoparticles (b).
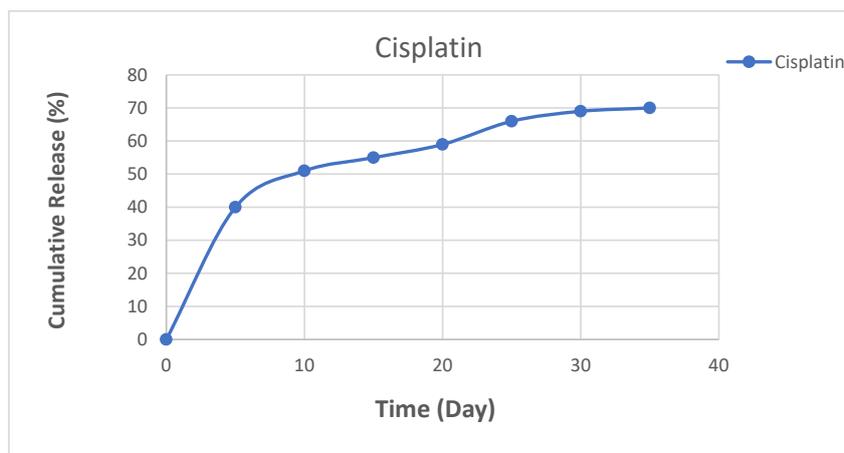
Fig. 3. The release profile of cisplatin-loaded mesoporous silica nanoparticles.
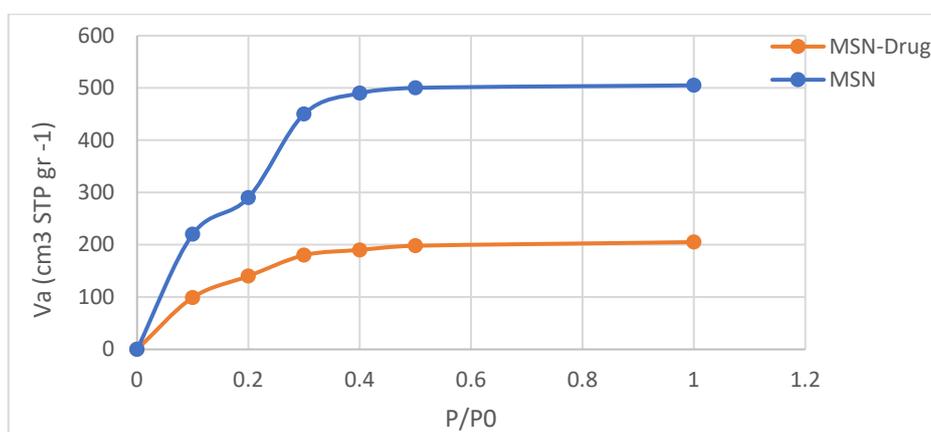

Fig. 4. The isotherm analysis of adsorption and desorption of BET test for free mesoporous silica nanoparticles and drug-loaded mesoporous silica nanoparticles.

with nanoparticles (drugs that are not inside the cavities or have weak interactions with the outer surface of the pores). The continuous and slow release on the sixth to thirty-fifth days is related to the inner drug molecules (inside the pores) that have electrostatic interactions with the cavity wall of the nanoparticles. They provide a pattern of slow-release that is very important in the clinical use of drugs [31, 32]. Memar *et al* [32] reported similar results for the mesoporous silica nanoparticles containing meropenem. According to their results, about 40% of meropenem was released from silica nanoparticles in the first two days and then continued its slow release until the 30th day.

It also should be considered that the sustained-release nanomaterials are preferred for maintenance therapy or as adjuvant therapeutic protocols for the treatment of cancer particularly in patients who metabolize the drug very rapidly and may require dosing 4–6 times/day. We need a burst release formulation or a fast dose administration prior the administration of such a maintenance dose [33, 34]. Chen *et al,* investigated the *in vitro* drug release of 5-FU from silica nanoparticles in phosphate buffer. They used two different release media in pH 7.4 and pH 5.0. Their results showed that 25% of 5-FU released at pH 7.4 compared with 40% of drug release in pH 5.0 in 24 h. No burst release pattern was detected in both the pH conditions [17].

BET analysis

Fig. 4 displays to the outcomes of BET test for free mesoporous silica nanoparticles and drug-loaded mesoporous silica nanoparticles. Based

Table 1. Specific surface area, pore volume and pore diameter for drug-free mesoporous silica nanoparticles and drug-loaded mesoporous silica nanoparticles.

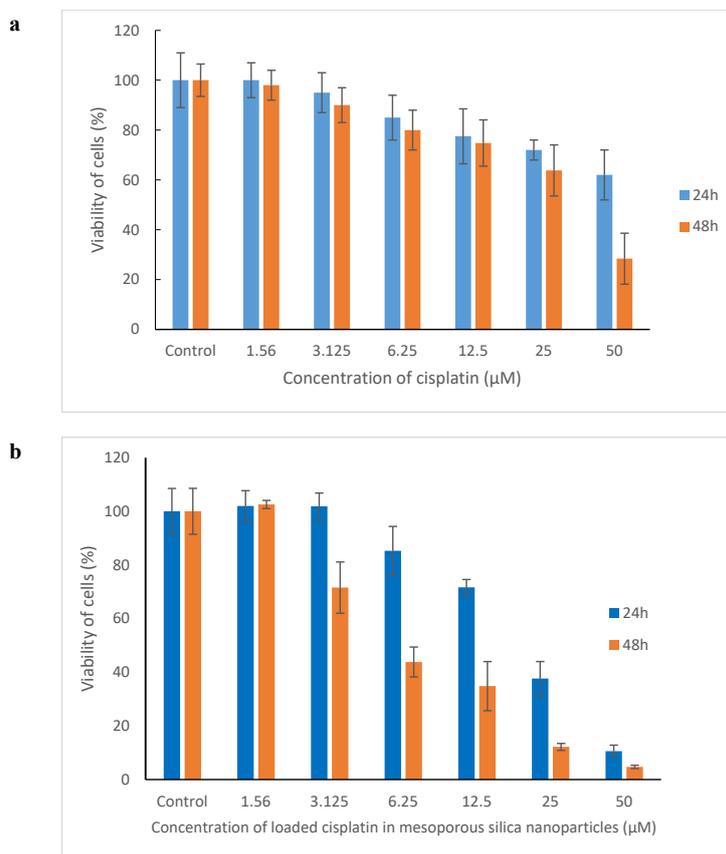| Type of material	Specific surface (m2/g)	pore volume (cm3/g)	pore diameter (nm)
MSN	1080	720	2.43
MSN-drug	798	463	1.23

Fig. 5. Cytotoxicity of several concentration of free cisplatin (a) and cisplatin-loaded mesoporous silica nanoparticles (b) against head and neck squamous cell carcinoma cell line in 24 and 48h.

on the results (Table 1), by loading the cisplatin in mesoporous silica nanoparticles, the specific surface area, pore volume and pore diameter reduced compared to free mesoporous silica. Karimzadeh *et al*. reported similar outcomes for rivastigmine loaded mesoporous nanoparticles [35].

Fig. 5 shows the cytotoxicity of cisplatin-loaded mesoporous silica nanoparticles and cisplatin. Mesoporous silica nanoparticles did not show a significant cytotoxic effect on cells, but cisplatin and cisplatin-loaded mesoporous silica nanoparticles decreased the viability of the cells in a time- and concentration-dependent manner. The IC50 of cisplatin were 82.01 μM and 33.67 μM in 24 and 48 h incubation times, respectively

(Fig. 5, a). However, the IC50 of cisplatin-loaded mesoporous silica nanoparticles were 26.17 μM and 13.28 μM in 24 and 48 h incubation times, respectively (Fig. 5, b).

As mentioned in the literature review, cisplatin is one of the most important drugs used in oral cancer, which has side effects such as secondary anemia, neutropenia, thrombocytopenia, renal toxicity, hyperuricemia or, nephropathy due to uric acid and auditory toxicity has been reported for it [36, 37]. Previous studies have shown that nanoparticles can be used alone or in combination with other conventional anti-cancer compounds to overcome the multidrug resistance of cancer [6, 38, 39].

Ding Wang and colleagues first used porous silica nanoparticles as drug carriers of 5-fluorouracil and curcumin. Their research showed that porous silica nanoparticles as drug carriers enhanced the therapeutic effects of 5-fluorouracil and curcumin [40]. In our study, the IC50 of cisplatin-loaded mesoporous silica nanoparticles were lower than the free form of cisplatin in 24 and 48h. In a study, Mesoporous silica nanoparticles showed cytotoxicity against Hep G2 cells [41]. However, in this study, mesoporous silica nanoparticles had no toxic effect on HN5 cells. Our study displays that mesoporous silica nanoparticles increased the cytotoxic effect of cisplatin against HN5 cells.

In another study, Chen *et al* investigated the effect of mesoporous silica nanoparticles loaded with 5-FU/ß-lap on head and neck squamous cell carcinomas. Their prepared nanoparticles showed more than 60% of cell early and late apoptosis and leading nuclear fragmentation of cancer cells representing the higher anticancer effect of a carrier-based delivery system compared to free drugs. A prominent reduction in tumor volume was detected with the physical mixture of 5-FU+ß-lap as well. However, mesoporous silica nanoparticles loaded with 5-FU/ß-lap meaningfully delayed the tumor growth and sustained the survival of the examined mice model [17].

CONCLUSION

Cisplatin-loaded mesoporous silica nanoparticles can display more potential in destroying the cancer cells compared with free cisplatin. Nevertheless, more research is required for the validation of these results. The present findings can highlight the unharnessed capability of cisplatin-loaded mesoporous silica nanoparticles as an anti-cancer agent to be applied in the *in vivo* studies.

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AUTHORS' CONTRIBUTIONS

All authors contributed to the drafting and scientific revision of the manuscript. SS, EDA, SMD designed the study and had contribution in all steps of study. ZS had contribution in physicochemical experiments, MK and YR had contribution in drafting and final revising of the manuscript.

FUNDING

AVAILABILITY OF DATA

The raw/processed data required to reproduce these findings can be shared at this time.

ETHICS APPROVAL

The ethical code of this investigation is IR.TBZMED.VCR.REC.1399.136, which was accepted by the Ethic Committee of the Tabriz University of Medical Sciences.

COMPETING INTERESTS

No conflict of interest is declared by the authors.

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