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Cytoytoxcitiy Assessment of Mesoporous Silica Nanoparticles-Curcumin against Breast and Colon Cancer Cell Lines: In Vitro Study

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CURCUMIN is one of the most promising natural anticancer agents, however, its medical application has been limited by its poor water solubility and bioavailability. Attempts have been made to encapsulate curcumin in different carriers, but the interest in nanocarriers for cancer chemotherapy is growing to develop a biodegradable controlled drug delivery vehicle that improves the bioavailability and solubility of curcumin.

Here we focused on designing a biocompatible delivery system to be used as nanocarrier of the natural anticancer curcumin allowing its application either in vitro or in vivo. Therefore, mesoporous silica was prepared as a nanocarrier for curcumin. Characterization of the prepared nanocarriers was investigated using different techniques. Transmission electron microscopy (TEM) revealed the spherical, smooth surface of the nano-formulation. Dynamic light scattering (DLS) was used for measuring the hydrodynamic size of the prepared nanocarrier. The stability was also studied by zeta potential measurement indicating its high stability. Fourier transform infrared spectroscopy (FTIR) assessment revealed that curcumin was successfully loaded into mesoporous nanoparticles. In vitro studies elucidated that curcumin loaded nanoparticles have a more potent therapeutic effect than free curcumin against both HCT-116 and MCF-7 cancer cells. Curcumin nanocarrier can provide high therapeutic efficacy represented by the inhibition of cancer cells proliferation. Therefore, the development of such novel curcumin nanocarrier with its better curative effect will bring the nutraceutical nanoformulation to be an alternative to the chemotherapeutic drugs.

Keywords: Curcumin; Mesoporous silica nanoparticles; Physicochemical characterization; Drug release profile; in vitro cytotoxicity.

Introduction

Cancer is the most leading cause of deaths worldwide [1]. Despite the significant progress made in its diagnosis and treatment in recent years, cancer is considered as the second most frequent cause of death worldwide. Cancer is a class of diseases capable of growing uncontrollably and invading the nearby normal tissues (metastasis).

Chemotherapy is one of the three pillars of cancer treatment along with surgical treatment and radiation therapy [2]. The conventional chemotherapeutic drugs are non-specifically distributed in all the body tissues affecting both normal and cancerous cells and causing severe side effects as well as low drug concentration in the tumor, thus resulting in dose-related side effects and inadequate drug concentrations

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reaching the tumor. Non-selective drug delivery is a dose-limiting factor that hinder the efficacy of anticancer drugs [3].

Therefore, there is a need to substitute chemotherapeutics with natural products that exhibit the properties to inhibit cancer growth by inducing apoptosis and stop the signaling pathway of cells with no toxicity to the normal cells. Nutraceutical, refers to the combination of natural medicinal compounds and pharmaceutical ones providing health and medical benefits [4]. Curcumin is one of the most promising and most extensively investigated nutraceuticals. It is a popular dietary spice worldwide [5]. Curcumin is a medicinal bioactive compound extracted from rhizome turmeric (Curcuma longa) plant.

Curcumin has a wide array of pharmacological and biological activities against many diseases and can be used as: anti-inflammatory, anti-oxidant, anti-carcinogenic and anti-angiogenesis [6-8]. The anti-carcinogenic action of curcumin might be due to its ability to induce apoptosis by several intracellular signaling pathways [9, 10].

Although curcumin is a promising anticancer agent, it has a restrictive pharmaceutical role. The main limitations for curcumin therapy are poor aqueous solubility, rapid blood clearance, disintegration in physiological pH, low tissue absorption and bioavailability [10, 11].

These limitations can be overcome by developing a new strategy for delivering curcumin specifically to tumor site. Recently, nanotechnology brought the promise to revolutionize many fields in medicine, especially cancer therapy. Interestingly, this technology provides nano-drug delivery system capable of encapsulating chemotherapeutic, controlling its release at tumor site, and prolonging curcumin circulation time [12]. Various types of nanoparticle, have been developed including organic-based nanoparticles (liposomes, polymeric nanoparticles, micelles, nanogels, niosomes, cyclodextrins, dendrimers), inorganic-based nanoparticles (gold, silvers, and silica) and hybrid-based nanoparticles (composite of organic and inorganic) [13, 14]. These types have been studied to increase the potentiality for delivering curcumin to the target site [10, 15, 16].

Silicon is an element found abundantly in earth's crust. Its oxide forms (SiO_2) and (SiO_4) mainly constitute sand and quartz. Silica nanoparticles exhibit unique properties and are considered as a promising candidate for delivering drugs. Silica nanoparticles can be in the solid or porous form. Porous silica nanoparticles are classified according to their pores size into: nanoporous < 2 nm; mesoporous < 100 nm and macroporous > 100 nm [17]. Mesoporous silica nanoparticles (MSNPs) have been extensively studied owing to their unique properties [18, 19].

Recently, MSNPs have become a promising candidate for delivering hydrophobic drugs [20]. Furthermore, they effectively protect drug molecules from denaturation and/or degradation induced by cellular environmental changes such as pH, temperature and enzymes. MSNPs are highly biocompatible and biodegradable [21, 22]. Moreover, mesoporous silica was readily internalized by endocytosis to eukaryotic cells without detectable toxic effects in vitro [23-25].

MSNPs have been highlighted to carry high payload of insoluble drugs [26]. MSNPs as drug nanocarrier enhanced the cytotoxicity of curcumin against breast cancer cells [27]. Camptothecin is an anticancer agent that has low water solubility and side effects. When Camptothecin-loaded MSNPs were administered intravenously in mice bearing MCF-7 breast tumors, they effectively suppressed tumor growth exceeding that of the free drug [28].

In this work, MSNPs have been prepared as promising nanocarriers able to be loaded with curcumin. These nanocarriers enhance curcumin stability and cellular uptake as well as achieving high therapeutic efficacy.

Materials and Methods

Materials

Curcumin (95% total curcuminoid content, 85% Curcumin) from turmeric rhizome, MTT Assay Kit (3-4, 5-Dimethylthiazol-2-yl 2, 5-diphenyltetrazolium bromide), Tetraethyl orthosilicate (TEOS, 99%), cetyltrimethylammonium bromide (CTAB) (99%) and ammonia hydroxide (NH_4OH, 28%) were purchased from Sigma-Aldrich (Germany).

A solution of 2M sodium hydroxide (NaOH), 2-ethoxyethanol ($C_2H_5OCH_2CH_2OH$) and absolute ethanol were purchased from Merck. Deionized (DI) water was used throughout the study.

Preparation of Mesoporous silica nanoparticles (MSNPs)

MSNPs were synthesized by using cationic surfactant CTAB as a template (CTAB as the porogen and 2- ethoxyethanol as the co-solvent) [29]. Typically, 0.5 g of CTAB was dissolved in 70 ml distilled water, and after complete

dissolution, 0.5 ml of ammonium hydroxide (28%) and 30 ml of the co-solvent were added. The mixture was vigorously stirred in a closed vessel at room temperature for 30 min. Then, 2.5 ml of TEOS was dropped into the mixture, which was then vigorously stirred for 24 hours. A white precipitate was collected using centrifugation (Sigma 202, refrigerated centrifuge; Germany) at 5000 rpm for 30 min, washed several times with distilled water and ethanol. Then, the supernatant was further dispersed in ethanol solution (60 ml) containing concentrated HCl (120 µl) and stirred at 30 °C for 3 hours to remove the template (CTAB). This surfactant extraction process was repeated twice to ensure complete removal of CTAB. The particles were then washed thoroughly to remove the surfactant.

Preparation of MSNPs loaded with curcumin (Cur-MSNPs):

For Cur-MSNPs, MSNPs were loaded with curcumin using the following procedure: curcumin (2 mg) was dissolved in 2 ml ethanol and MSNPs (80 mg) were added to 8 ml water and sonicated to completely dissolve, then the two solutions were mixed. This suspension was shaken (100 rpm) at 37°C for 24 hours. Cur-MSNPs were then precipitated by centrifugation at 5000 rpm for 30 min and washed twice to remove any free curcumin. Free curcumin content in the supernatant was measured spectrofluorometer at an excitation λ of 420 nm and emission λ of 550 nm and calculated from the calibration curve in order to determine the loading efficiency of curcumin in MSNPs.

Physicochemical characterization

The morphology of MSNPs was characterized by TEM (FEITecnaiG20, Super twin, Double tilt, LaB6 Gun). Dynamic light scattering (NICOMPTM 380 ZLS, Santa Barbara, California, USA) was used to measure the size distribution of MSNPs. Furthermore, the surface charge of both MSNPs and Cur-MSNPs was examined by Zeta potential/particle sizer (NICOMPTM 380 ZLS, Santa Barbara, California, USA). Also, FTIR measurements of free curcumin, MSNPs and Cur-MSNPs were conducted on a Basic Vector, FT/IR-4100 type A, Germany, spectrometer, and the scanning was done in the range 4000-400 cm^{-1} with a resolution of 4 cm^{-1} and speed 2 mm/sec at room temperature after lyophilization.

Evaluation of curcumin in vitro release profile

In vitro curcumin release profiles from Cur-MSNPs at pH 7.4 and 5.5 were determined using dialysis bag diffusion method for 13 days. The release experiment was performed using a sterilized dialysis bag with 12,000 DA cutoff molecular-weight. Two drug release media with different pH; 7.4 and 5.5 (simulating normal blood and tumor microenvironment, respectively) were prepared using phosphate buffered saline (PBS) solutions. One milliliter of Cur-MSNPs was centrifuged and re-dispersed in the release media (1 mL), and placed into two dialysis bags. The two plugged dialysis bags were placed separately into two 50 ml bottles containing the reales media. At 37 ^{o}C under light-sealed condition, the two bottles were shaken at a speed of 100 rpm. In vitro curcumin release study was done for 13 days at certain time points. In order to quantify the released curcumin concentration, 3 ml was removed from the release media and measured using a spectrofluorometer. The removed media was returned back to the original solution to maintain cumulative drug release.

Released curcumin concentrations were measured at an excitation λ of 420 nm and emission λ of 550 nm, then calculated from the calibration curves.

The cumulative release (CR %) was quantified as follows :

$$CR\ (\%) = \frac{\text{Amount of curcmin released}}{\text{Total amount of curcmin}} \times 100$$

All experiments were performed 3 times and the standard deviation (SD) was calculated using the origin 8.0 software.

In-vitro cytotoxicity evaluation for Cur-MSNPs

The in vitro cytotoxicity of Cur-MSNPs against colon (HCT-116) and breast (MCF-7) human cancer cells was investigated using MTT assay and inverted light microscope images.

The cytotoxic effects of free curcumin and Cur-MSNPs were determined by MTT assay. A series of different concentrations of free curcumin and Cur-MSNPs were added to the well plates. After 24 hours of incubation, the culture medium was discarded and the cells were washed with PBS. About 100 µl of the complete growth culture medium and 50 µl of MTT solution were then added to each well. After 4 hours, 50 µl of the detergent was added for the dissolution of the formed crystals. The absorbance was measured at

570 nm using an ELISA reader (Tecan-Sunrise). Triplicates of each concentration were analyzed. The percentage of the cell viability for treated and untreated cells was expressed as cytotoxicity. The cell viability was expressed by following equation:

$$Cell\ Viability\ (\%) = \left(Abs\ S / Abs\ C\right) \times 100$$

Where Abs S is the absorbance of treated cells (either with free curcumin or Cur-MSNPs), and Abs C is the absorbance of untreated cells (blank control).

Twenty four hours post incubation at 37 ^{o}C in DMEM medium (100 µl) containign 10% FBS, the medium was removed and replenished with another containing various concentrations of free curcumin and Cur-MSNP. Twenty four hours, post treatment, cells were imaged under inverted light microscopy (Leica) with 20x magnification to examine the external morphology of HCT-116 and MCF-7 cells. Prior to digital microscopic imaging of the wells, all the cells were washed well with PBS.

Results and Discussion

Physicochemical Characterization of the Prepared Nanoparticles:

(a) Transmission Electron Microscope (TEM):

TEM images of both MSNPs and Cur-MSNPs are shown in Fig. (1. a and b), respectively. Fig. (1.a) revealed the existence of channel-like pores on their surface. While Fig. (1.b) showed that the prepared nanoparticles kept their spherical shape after loading curcumin.

(b) Dynamic Light Scattering

Upon considering the application of nanomaterial to intracellular drug delivery, the size and shape of nanocarriers should be tuned carefully. It was suggested that nanoparticles in the range of 200–300 nm can be easily taken by endocytosis into the cells [30].

The mean particle size of the prepared MSNPs as determined by dynamic light scattering (DLS) was found to be 122 ± 2.1 nm Fig. (2). The size of the MSNPs enables their selective accumulation in the extracellular medium of tumor tissue due to the enhanced permeability and retention effect (EPR) of cancerous tissue [31].

(c) Zeta Potential Measurements

Zeta potential is an important physicochemical parameter to be determined to achieve a suitable colloidal carrier. The surface charge of the nanoparticles is of interest since it influences the stability of the nanoparticles as well as suspension and interactions of the nanoparticles with the cell membrane.

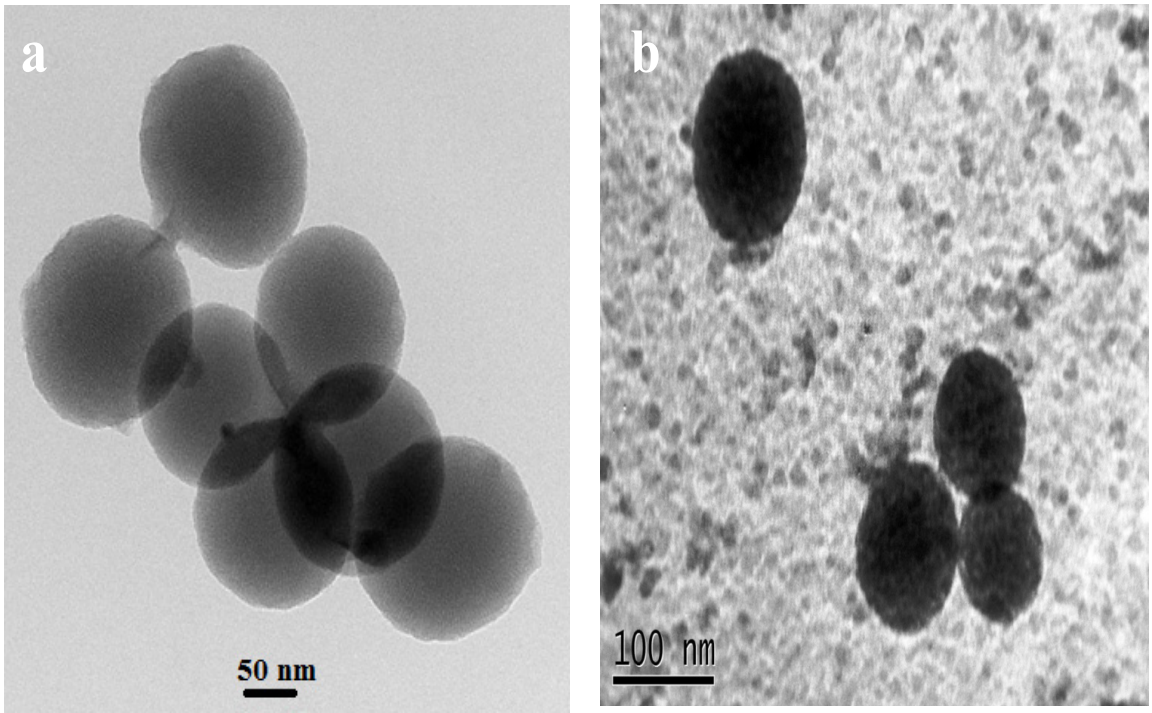

Fig. 1. TEM images of (a) mesoporous silica nanoparticles (MSNPs) and (b) curcumin loaded mesoporous silica nanoparticles (Cur-MSNPs). The scale bars of a & b are 50, 100 nm respectively.

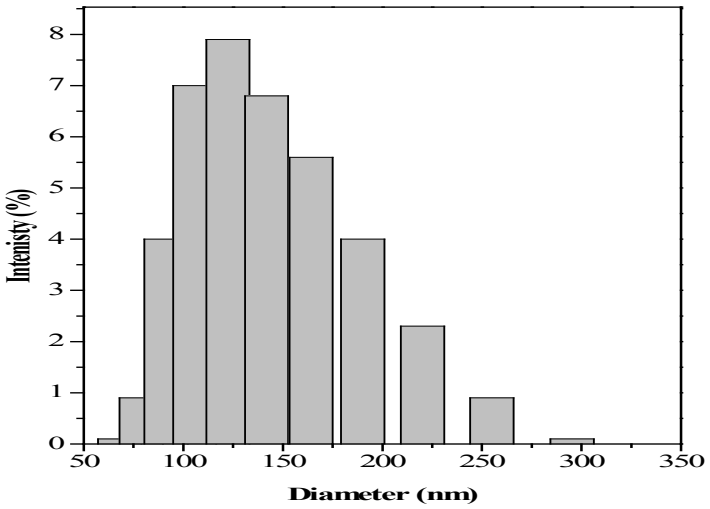

Fig. 2. Particle size distribution of MSNPs.

Zeta potential of both MSNPs and Cur-MSNPs was measured in DI water. The average zeta potential of MSNPs is 47.8 ± 2.7 mV, and that for Cur-MSNPs is 36.2 ± 3 MV. The positivity of the prepared MSNPs formulation is decreased after the loading of curcumin. This is due to the negative charge of curcumin. As the zeta potential increases, the repulsion phenomenon between particles will be greater leading to a more stable colloidal dispersion [32]. From the zeta potential results, both MSNPs and Cur-MSNPs showed high stability.

(d) Fourier Transform Infrared Spectroscopy

FTIR measurements were carried out for free curcumin, MSNPs and Cur-MSNPs over the wave number range 4000 and 400 cm^{-1} to study the porous structure of the prepared nanoparticles and confirm the loading of curcumin Fig. (3). The band at about 1200 cm^{-1} is due to three-dimensional Si–O–Si asymmetric stretching vibrations, indicating a high specific area and fine pore structure. For MSNPs, one can see absorption bands arising from asymmetric vibration of Si–O (1078 cm^{-1}) and symmetric vibration of Si–O (789 cm^{-1}) Fig. (3) [33, 34].

After curcumin loading, the characteristic band of curcumin appeared at 1560 and 1420 cm^{-1} (due to C=O stretching peak of conjugated ketone). In addition, a significant decrease in the intensity of all the characteristic bands of Cur-MSNPs spectrum is noted, suggesting the successful loading of curcumin Fig. (3).

(e) Curcumin Loading Efficiency and In Vitro Release Profile

The loading efficiency of the curcumin loaded MSNPs system was found to be ~ 80 %. In vitro drug (curcumin) release studies were performed at pH 5.5 and 7.4 and the release profile is shown in Fig. (4). It is clear that a very small amount of curcumin is released from Cur-MSNPs in a very slow fashion in PBS simulating normal physiological conditions (pH 7.4). Interestingly, less than 20% of curcumin were released after immersion for as long as 13 days, which is indeed an extraordinarily low drug-released amount in such a long release time period. When the pH value of the release media decreased to 5.5 simulating tumor microenvironment, both curcumin release rate and the curcumin released concentration became remarkably higher. Furthermore, at this lower pH 5.5, about 94% of encapsulated curcumin are released in the medium after 13 days of immersion. Thus, the prepared MSNPs has the advantage of being pH responsive, providing a continuous high release in tumor microenvironment which is considered as an effective way for targeting.

In Vitro Cytotoxicity Evaluation for Cur-MSNPs

(a) MTT Cell Cytotoxicity Assay

In vitro cytotoxicity of free curcumin and Cur-MSNPs against HCT-116 and MCF-7 cancer cells was investigated using MTT assay.

Both HCT-116 and MCF-7 cells were

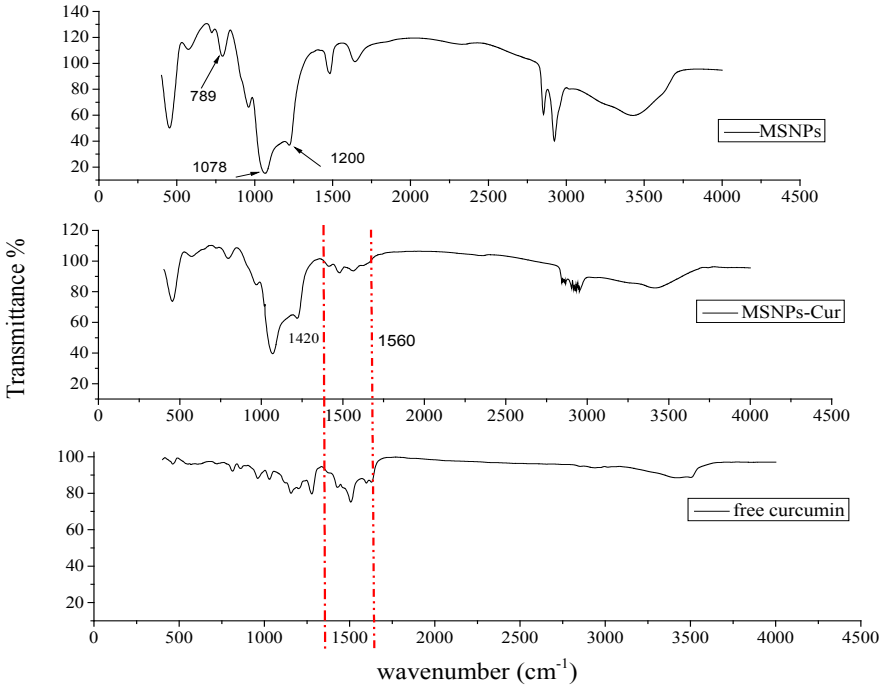

Fig. 3. FTIR spectra for: mesoporous silica nanoparticles (MSNPs), curcumin-loaded mesoporous silica nanoparticles (Cur-MSNPs) and free curcumin.

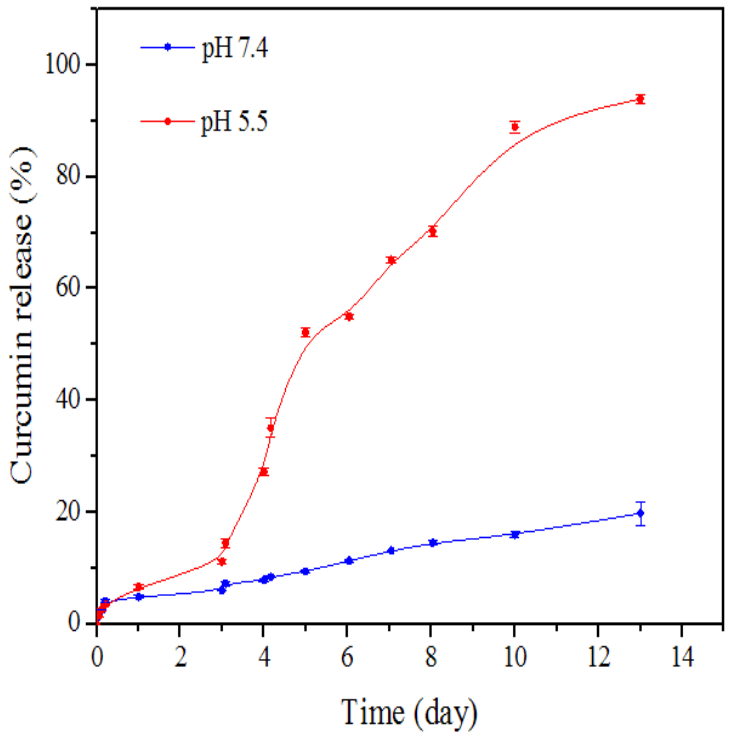

Fig. 4. Drug release profile of Cur- MSNPs at: pH 7.4 simulating normal blood/tissues and pH 5.5 simulating tumor micro-environment.

incubated with different concentrations of free curcumin 18, 14, 10, 6 µg/ ml, for 24 hours. The measured cell viability was 49.23 ± 1.1%, 62.57 ± 1.43%, 66 ± 2.41%, and 73.35 ± 1.85% respectively for HCT-116 cell line, and 44.7 ± 0.9%, 63.35 ± 1.95%, 74.35 ± 0.95%, and 92.4 ± 0.6% respectively for MCF-7 cell line as shown in Fig. (5 a and b). Treatment with free curcumin showed selective toxicity towards various cancer cells that might be due to the fact that curcumin targets many signaling molecules, which cancer cells highly rely on [35].

Similarly, HCT-116 and MCF-7 cells were incubated for 24 hours with Cur-MSNPs in the same curcumin concentrations 18, 14, 10, 6 µg. Fig. (5 a and b) showed that the cell viability was 28.9 ± 1.1%, 36.75 ± 1.25%, 41.25 ± 0.75%, and 46.65 ± 1.85% respectively for HCT-116 cells, while 25.75 ± 0.75%, 30.4 ± 0.8%, 44.55 ± 0.45% and 53.5 ± 1.8% respectively for MCF-7. The cytotoxic effects of Cur-MSNPs were higher than those of the same concentrations of free curcumin in both cell lines. This may be attributed to the ability of Cur-MSNPs to be accumulated into cancer cells, due to the enhanced permeability and retention. It is believed that Cur-MSNPs undergo cellular uptake by endocytosis in various cancer cells. Moreover, the acidic microenvironment of tumor, endosomes and lysosomes, induce the release of entrapped curcumin from the nanocarrier over this prolonged time [36].

In addition, MSNPs enhanced curcumin stability, in cell culture, by protecting it against any degradation induced by pH; in contrast to free curcumin that undergoes rapid degradation in the physiological pH (cell culture) [37, 38].

Thus, Cur-MSNPs can be uptaken well by both HCT-116 and MCF-7 cells, and remarkably improved the intracellular accessibility of the poorly water-soluble curcumin.

(b) Cancer Cells Morphological Examination Using Inverted Microscopy

For better clarification of the cytotoxicity results, optical micrographs of treated and untreated cells have been taken following the above experimental conditions. Fig. (6 a and d) showed untreated (control) HCT-116 and MCF-7 cell lines with their spindle shape, respectively. For HCT-116 and MCF-7 cells treated with free curcumin, most of the cells appeared intact with their normal spindle shape indicating the degradation and rapid clearance of free curcumin from cancerous cells Fig. (6 b and e) respectively. This is in agreement with MTT assay results.

Upon treatment with Cur-MSNPs, the morphology of both HCT-116 and MCF-7 cell lines was dramatically changed, the cells lost their contact and became spherical rather than spindle owing to apoptosis Fig. (6 c and f) respectively. The observed dark aggregates in the Cur-MSNPs treated cells revealed the accumulation of curcumin-loaded nanocarrier inside the cells.

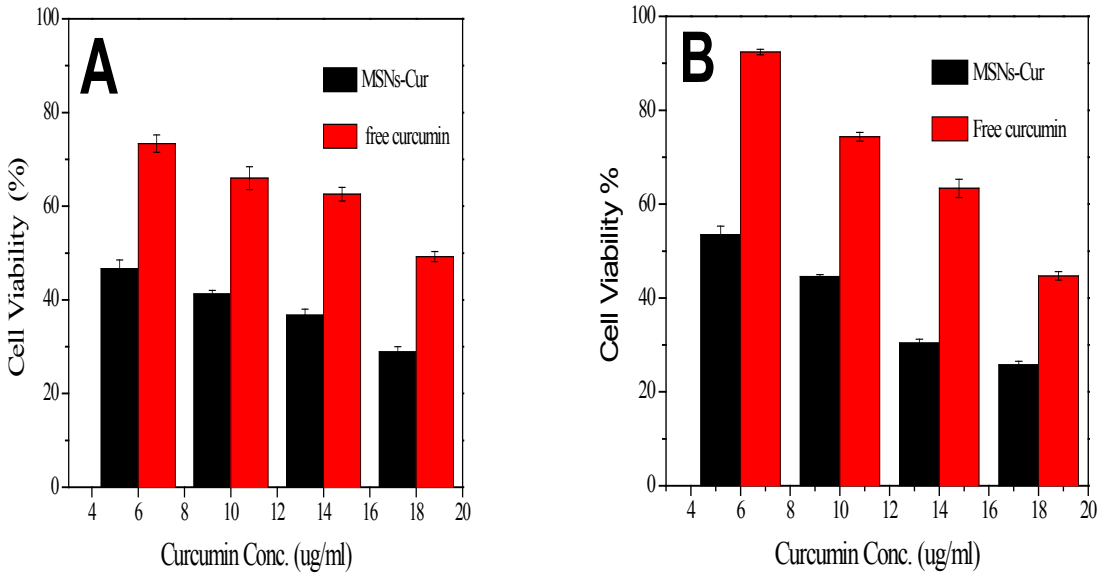

Fig. 5. Viability comparison of (A) HCT-116 cells and (B) MCF-7 cells treated with Cur-MSNPs and free curcumin at different curcumin concentrations of 18 µg/ ml, 14 µg/ ml, 10 µg/ ml, 6 µg/ ml for 24 hr incubation.

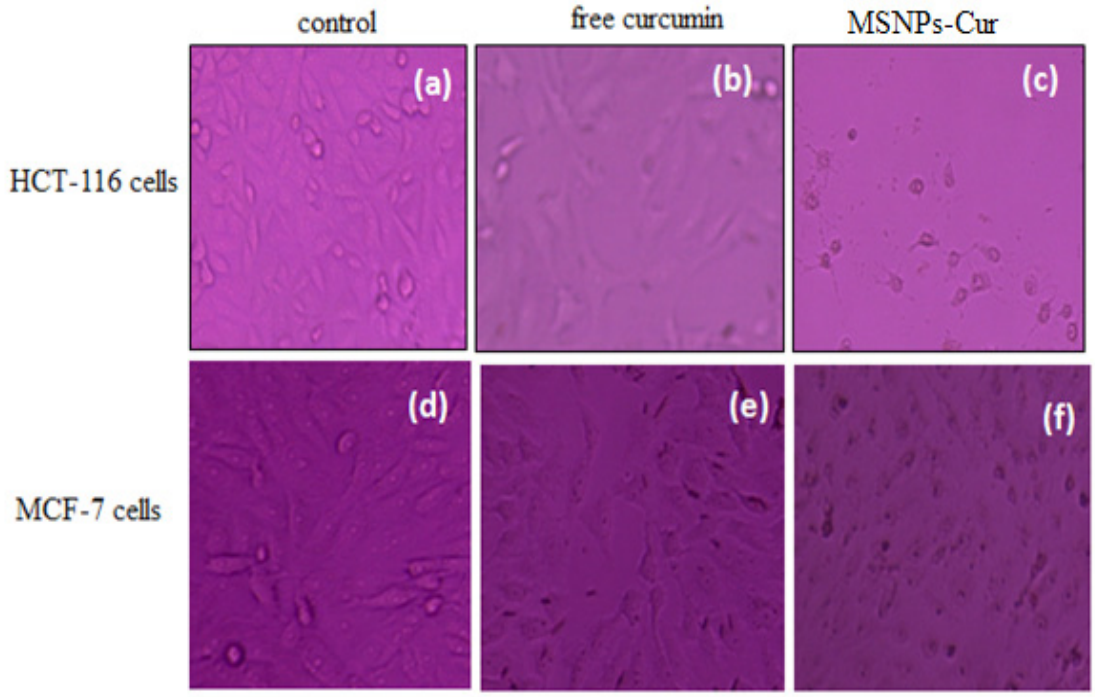

Fig. 6. Inverted microscopy images of: (a) untreated (control) HCT-116 cells, (b) HCT-116 cells incubated with free curcumin, (c) HCT-116 cells incubated with Cur-MSNPs and (d) untreated (control) MCF-7 cells, (e) MCF-7 cells incubated with free curcumin, (f) MCF-7 cells incubated with Cur-MSNPs.

Based on the above results, Cur-MSNPs showed high therapeutic efficacy against colon and breast cancer cells by inhibiting cells proliferation. In contrary, free curcumin showed the less effect owing to its poor bioavailability. The results suggested that the nanostructure silica-based drug vehicles can enhance the bioavailability of the hydrophobic (low solubility) drug curcumin to be utilized as an alternative to chemotherapeutic drugs [39].

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Conflict of Interests

The authors report no conflict of interests. The authors alone are responsible for the content and writing the paper.

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تقييم السمية الخلوية لجزيئات الميزو بورس سيليكا المحملة بالكركم لعلاج أورام القولون والثدى

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يعد الكركمين أحد أكثر العوامل الطبيعية الواعدة المضادة للسرطان ، إلا أن تطبيقه الطبي كان محدودًا بسبب ضعف القابلية للذوبان في الماء والتوافر البيولوجي. بذلت محاولات لتغليف الكركمين في حاملات مختلفة، لكن الاهتمام بنواقل النانو للعلاج الكيميائي للسرطان ينمو لتطوير حهملات لتوصيل الدواء قابلة للتحلل قابلة للتحلل، مما يحسن من التوافر البيولوجي وقابلية ذوبان الكركمين.

ركزنا هنا على تصميم نظام توصيل متوافق حيوياً لاستخدامه كحامل نانوي من الكركمين الطبيعي المضاد للسرطان مما يسمح بتطبيقاته إما خارجيا أو في الجسم الحي. لذلك، تم إعداد السيليكا المثقبة (mesoporous) كحامل نانوى للكركمين. تم توصيف ناقلات النانو المعدة باستخدام تقنيات مختلفة. المجهر الإلكتروني للإرسال (TEM) الذي كشف عن السطح الأملس الكروي للنانو المحضر. تشتت الضوء الديناميكي (DLS) لقياس الحجم الهيدروديناميكي للناقلة النانوية المحضرة. تمت دراسة الثبات أيضًا عن طريق قياس جهد زيتا مما يدل على ثباته العالي. كشف تقييم فوريه للتحليل الطيفي للأشعة تحت الحمراء (FTIR) أن الكركمين تم تحميله بنجاح على الجسيمات المتناهية فى الصغر. في الدراسات المختبرية، أوضحت أن الجسيمات النانوية المحملة بالكركمين لها تأثير علاجي أكثر فعالية من الكركمين الحر ضد كل من خلايا السرطان HCT-116 و MCF-7. يمكن أن يوفر حامل العقار النانوى فعالية علاجية عالية تتمثل في تثبيط تكاثر الخلايا السرطانية. لذلك ، فإن تطوير مثل هذه الناقلات النانوية الجديدة للكركمين يكون لها تأثير علاجي أفضل وسيجعل الكركمين كمادة صيدلانية طبيعية بديلاً عن الأدوية العلاجية الكيميائية.