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ENHANCED CYTOTOXICITY OF CISPLATIN-LOADED MESOPOROUS NANOPARTICLES AGAINST TONGUE SQUAMOUS CELL CARCINOMA (HNO-97)

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ABSTRACT

Cisplatin (CP) is a highly effective chemotherapeutic for tongue squamous cell carcinoma. Nanocarriers, a type of nanotechnology-based drug delivery system, have been widely employed to enhance therapeutic outcomes and limiting side effects in cancer treatment like Mesoporous silica nanoparticles (MSNs). The objective of this study is to assess CP-loaded MSNs regarding their physicochemical properties as well as their cytotoxicity in HNO-97 tongue cancer cells to evaluate their potential as a drug delivery system.

Methods: A novel preparation of CP-loaded MSNs were assessed for zeta potential,particle size and polydispersity index (PDI) using dynamic light scattering (DLS) andtransmission electron microscopy (TEM). Cytotoxicity was measured using the sulforhodamine B test. The efficacy of free and CP-loaded MSNs was assessed by calculating IC 5 0 values. The analysis was performed by means of ANOVA.

Results: Dynamic light scattering (DLS) analysis indicated the successful production of nanoparticles with an average size of 404.3 ± 23.1 nm, a zetapotential of -34.6 ± 0.551 mV and a polydispersity index (PDI) of 0.445 ± 0.012. In cytotoxicity experiments, the effect of CP was evident with a dosedependent decline in cell viability with the highest concentration of 100ug/ml inwhich CP-loaded MSNs were more cytotoxic (0.185±0.23) than free CP(4.50±1.26). The IC_{50} of MSNs loaded with CP was 1.41 μg/mL versus 2.18 μg/mL obtained with free CP, suggesting higher pharmacological efficacy.

Conclusions: These findings suggest that MSNs can improve the therapeutic efficacy of cisplatin through enhanced cytotoxicity, making them a potential option for CP administration, pending further in vivo validation.

KEY WORDS: Mesoporous silica nanoparticles, cisplatin, tongue squamous cell carcinoma, drug delivery

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INTRODUCTION

Cisplatin (CP) treatment represents the mainstay of therapeutic regimens for head and neck cancers, including tongue squamous cell carcinoma (TSCC); but, treatment of TSCC with CP is still extremely problematic[1]. Its cytotoxic mechanism is due to cross-linking of DNA, preventing replication and transcription, and ultimately resulting in cell death[2]. Cisplatin, but, has significant side effects such as nephrotoxicity, neurotoxicity and ototoxicity. Also, it has low solubility and is rapidly cleared from the body, thus having limited therapeutic activity. In addition, non-specific delivery of CP to healthy and malignant tissues often Problematic of cancer therapy limited doses of therapeutic CP or impaired quality of life during and/or following cancer therapy[3]. These problems require the creation of new drug delivery technologies that enhance bioavailability while decreasing systemic toxicity.

Nanotechnology has developed as a potential solution for the shortcomings of conventional chemotherapy [4]. Although non-carrier drug delivery systems have proved to be successful in enhancing the performance of chemotherapy, at the present most clinically used formulations consist of lipidic formulations such as liposomes (Lipoplatin®) or polymeric nanoparticles [5]. Nevertheless, both types of systems have intrinsic limitations: liposomes have issues with drug leakage and poor stability, while the drug loading in polymeric nanoparticles has been shown to be batch to batch variable [6].

The use of mesoporous silica nanoparticles (MSNs) for drug delivery is receiving great interest since they are made of inorganic materials and therefore more stable than liposomes or polymeric nanoparticles that can degrade enzymatically[7]. The unique tunable pore size (2-10 nm) can be customized for optimal cisplatin loading and release profiles that cannot be achieved with other nanocarriers[8]. Such a large surface area (>900m^2/g) can allow for future functionalization with targeting ligands for targeted therapy[9]. This becomes especially relevant in the case of TSCC therapy where selective administration can ideally avoid or minimize the extreme ototoxicity and nephrotoxicity associated with cisplatin [10].

Also, as recently compared in other studies, MSNs outperform liposomal formulations by 2-3 times the accumulation in tumors as well as more sustained release characteristics [11]. Our formulation benefits from these advances but is specific for TSCC treatment given the ideal nanoparticle size of 400nm [12]. Together, these characteristics confer several advantages over existing CP nanocarriers and strongly support a role for MSN-based delivery in TSCC treatment.

Considering these advances, such work specifically concentratingon the synthesis, characterization, and cytotoxicity testing of CP-loadedMSNs should be performed to show effectiveness as a drug deliverytechnique. Physicochemical properties of the nanoparticles were analyzed to determine stability and suitability for biological use. HNO-97 tongue cancer cells were exposed to either free CP or nanoformulated CP and cytotoxicity was measured via the SRB assay in order to determine if nanoformulated CP was more effective than free CP and results were analyzed statistically to determine significance.

MATERIALS AND METHOD

Materials

The active pharmaceutical compound was Cisplatin (CP) (Sigma-Aldrich, purity ≥99.9%) (2.2 mg). As a drug-delivery vehicle, mesoporous silica nanoparticles (MSNs) were utilized, which were provided by Nawah Scientific Inc, Egypt (22 mg). Hyaluronic acid (HA, 100k Da, Lifecore Biomedical) was used to dissolve drugs and suspend

nanoparticles in Phosphate-buffered saline (PBS) at pH 7.4. All dilutions during characterization were performed using ultra- purified water (Milli-Q, 18.2 MΩ·cm). Analytical grade of all the compounds used were done, and the solutions prepared freshly before use and were provided by Nawah Scientific Inc. in Egypt.

Novel Preparation of Cisplatin-Loaded MSNs

But, in a new method that avoids the use of organic solvents that may be detrimental to biocompatibility, 2.2mg of cisplatin (Sigma-Aldrich) were first dissolved in 1.1 mL phosphate buffered saline (PBS, pH 7.4). [13] and, subsequently, 22mg of MSNs. The mixture was sonicated with a probe at 20 kHz frequency, 50 watts power, 5 minutes on, 5 minutes off, to disperse the mixture uniformly and was then stirred for 24 hours at 500 RPM at room temperature and protected from light. After sonication, the mixture was stirred at room temperature overnight for drug adsorption into the MSNs [7]. The result was a stable formulation with a high concentration of cisplatin, 2mg/mL. The benefit of this two-step process over the traditional process is that it allows for high drug loading capacity while achieving excellent colloidal stability and momodispersity without the aid of any organic solvents.

To serve as a control, nanoparticles based on hyaluronic acid (HA) were obtained by a conventional coacervation technique [14] at which 10 mg HA were dissolved into 1 mL of ultrapure water, mixed with cisplatin to achieve 2 mg/mL final concentration, and the mixture was stirred magnetically at 500 rpm for 2 hours and then centrifuged.

Drug loading capacity (DLC) and efficiency (DLE):

They determined calculations based on their beginning and ending concentrations of cisplatin, which was measured by UV-Vis spectrophotometry at λ = 301 nm following centrifugation and washing 3× with PBS. Using our procedure (2.2 mg of cisplatin plus 22 mg of MSNs results in a final concentration of 2 mg/mL total in 1.1 mL of PBS): DLC (%) = (Weight of loaded drug – Weight of drug-loaded nanoparticles) x 100 = (2.2 mg22mg+2.2mg) x 100 = 9.1% = (22 mg+2.2 mg2.2 mg) x 100 = 9.1% [15]. DLE (%)=(Actual drug loadedInitial drug added) × 100DLE (%) = (Initial drug added/Actual drug loaded) × 100 = (2.0 mg/2.2 mg) × 100 = 90.9% [16].

Characterization of Nanoparticles

Particle Size, Polydispersity Index (PDI), and Zeta Potential Measurement

Mean particle size and zeta potential of CP-loaded MSNs were determined by Dynamic Light Scattering, analyzing samples in ultrapure water at 25°C with refractive index and viscosity of 1.330 and 0.8872 cvP, respectively, using a Zetasizer Nano ZN instrument (Malvern Panalytical Ltd, UK). In order to avoid agglomeration, and ensure proper readings, the diluted suspensions of the nanoparticles were prepared by diluting in ultrapurified water. The variation in intensity of the scattered light was used to determine the hydrodynamic diameter of the nanoparticles. Results are expressed as the mean size (nm) ± standard deviation [10].

To assess the distribution of the sizes, the Polydispersity Index, PDI, was also determined. A low PDI indicates a more uniform formulation. Nanoparticles surface charge was measured by electrophoretic light scattering. The zeta potential (mV) was measured as a parameter of colloidal stability of the formulations which were also analyzed for size/PDI over 7 days in physiological conditions. All measurements were conducted in triplicate and the results expressed as mean ± standard deviation [14].

Transmission electron microscope (TEM)

Morphology and pore structure of cisplatin loaded mesoporous silica nanoparticles (MSNs) were analyzed by field emission transmission electron microscopy (TEM) of Hitachi HT7700 from Japan. Suspensions of the nanoparticles, 0.1 mg/mL in ethanol, were dropped on carbon coated copper grid and assessed under the microscope at magnifications ranging from 36,000×-190,000×. Pore size and density were measured using ImageJ software where images were converted to 8-bit gray scale, background subtraction and median filtering were applied, and images were thresholded to create binary masks of the pores (black) and silica framework (white). Pore diameters were measured from a minimum of 300 pores on 10 particles using the equivalent circular diameter and pore density was measured by normalizing pore counts to particle surface area. Morphological analysis involved calculations of the circularity index to ensure that these aggregates were spherical in shape as well as evaluations of aggregate porosity. Pore measurements using NIST-traceable silica standards revealed <5% deviation, validating the method. Statistical analyses were done using Origin Pro and data are expressed as mean ± SD (n ≥ 3 replicates) [7].

Cytotoxicity Assay of CP-loaded MSN

Cell Culture

HNO-97 tongue cancer cell line was obtained from Nawah Scientific Inc. Cells were maintained in DMEM supplemented with 100mg/ml of streptomycin, 100 units/ml of penicillin, and 10% heat-inactivated fetal bovine serum at 37 degrees in an atmosphere of 5% CO2 in a humidified incubator [11].

Sulforhodamine B (SRB) Cytotoxicity Assay

CP and CP/MSN cytotoxicity was evaluated with the SRB assay. Cell suspensions of 100 µL at a concentration of 5×103 cells/well were seeded into 96 well plates and left for 24 hrs in complete medium. Cells exposed to 100 µL of media containing either of two drug formulations at concentrations of 0.01, 0.1, 1, 10, 100 µL/ml in PBS) for 72 hours (72h selected as primary endpoint based on effect stability (coefficient of variation <15% vs 22-38% at shorter durations) which standard for SRB assays per Skehan et al., 1990 [16]. At the indicated time points post-drug exposure, media is removed and 150 µL of a 10% trichloroacetic acid (TCA) solution is added. Fix the cells by incubating at 4°C for 1 hour. The TCA solution was removed and cells were washed 5 times in distilled water. The negative control was Complete media + 0.1% DMSO, the vehicle, while 100 µM staurosporine was the positive control as well as blank control: MSNs without drug (0-500 µg/mL silica) confirmed non-toxic Validation: Vehicle control exhibited <5% decrease in viability compared to untreated cells p=0.72. To each plate well add 70 µL of a 0.4% (w/v) solution of SRB and incubate at room temperature for 10 minutes in the dark. Unbound color was eluted by three washes with 1% acetic acid, and pieces were allowed to air dry overnight. To elude the bound dye, 150µl of 10mM Tris, pH 10.5 is added and absorbance is read at 540 nm with a BMG LABTECH FLUOstar Omega microplate reader; Ortenberg, Germany). IC50 values were obtained using dose response curves of pure cisplatin and CP-loaded MSNs as previously described [16].

Statistical Analysis

All cytotoxicity data were plotted in GraphPad Prism 9.0. Dose-response comparisons within each treatment, treatment group comparisons at each concentration and IC50 comparisons between formulations were performed using One-way ANOVA with Tukey's multiple comparisons test. Results are shown as mean ± standard deviation (SD) of three independent experiments n=3). A statistical significance was determined for $p<0.05$.

RESULTS

Physicochemical Characterization of Nanoparticles

Nanoparticles loaded with cisplatin, derived from mesoporous silica, had better physicochemical properties than those obtained using unmodified nanoparticles (Table 1). Dynamic Light Scattering measurements determined the hydrodynamic diameter of 404.3±23.1nm, consistent with the observation of stable suspensions, while TEM imaging determined smaller individual particles (80-120nm) and larger aggregates (200-500nm). This difference is anticipated because DLS evaluates the hydrated particles while TEM observes dry core structures. By DLS, MSNs had a bigger hydrodynamic diameter (404.3±23.1nm) in comparison to HA nanoparticles, whose diameter was of 93.6 ±49.4 nm). The low Polydispersity Index (PDI = 0.445±0.012) obtained is an indication of a monodisperse distribution (PDI <0.5) which indicates uniformity of the synthesis of the nanoparticles. Also, the high zeta potential (−34.6±0.551 mV) was demonstrative of a strong electrostatic repulsion, thus preventing aggregation. The small standard deviation shows a good agreement between the measurements. (**Figure 1, Table 1).**

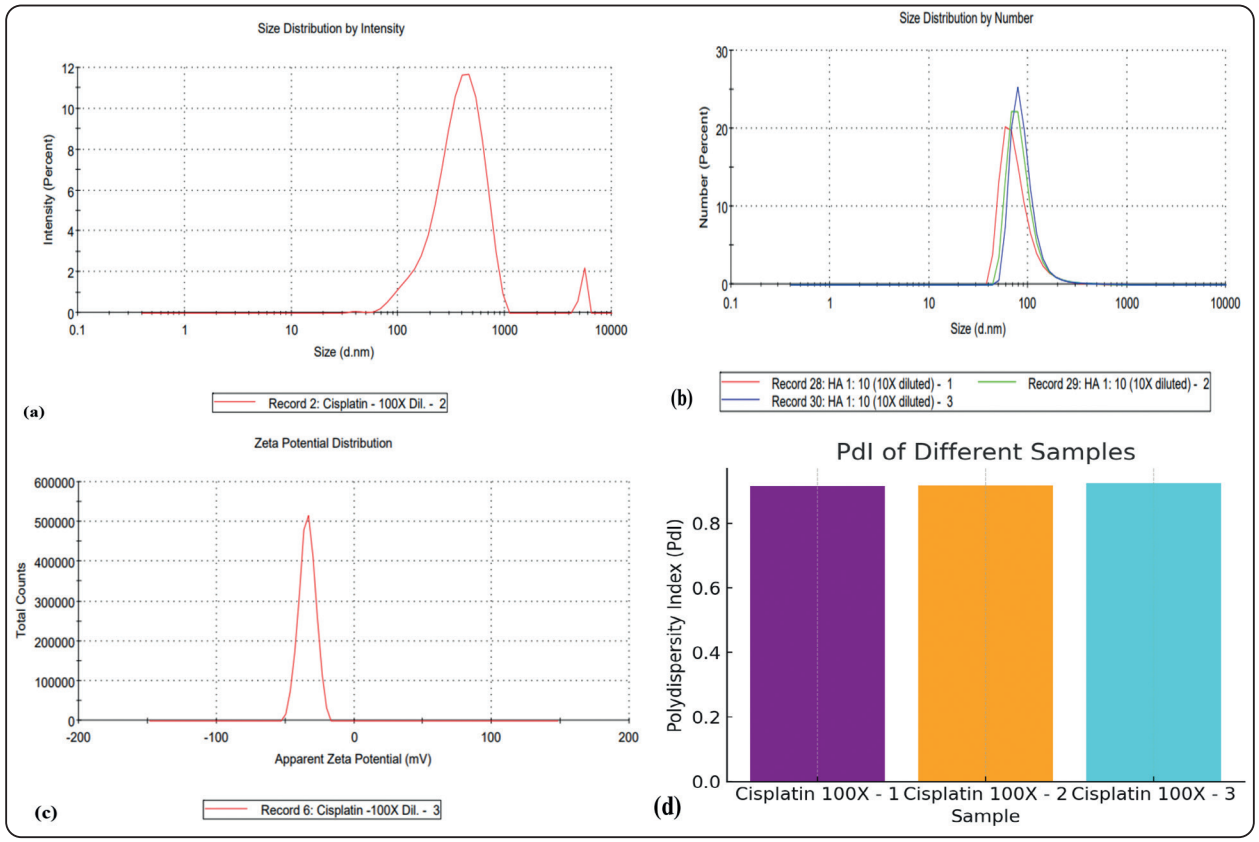

Fig. (1) (a) Size distribution by intensity. (b) Size distribution by number. (c) Zeta Potential Distribution. (d) Polydispersity Index (PdI) of Different Samples.

TABLE (1) Physicochemical Characterization of CP-Loaded MSNs.

Parameter	Cisplatin-MSNs (DLS/Zeta)	HA Nanoparticles (DLS)	TEM Analysis (This Study)	Method
Hydrodynamic Diameter (nm)	404.3 ± 23.1 (by number)	93.6 ± 49.4	-	DLS (Malvern Zetasizer)
TEM Particle Size (nm)	-	-	**80–120 nm (individual particles) 200–500 nm (aggregates)**	TEM (Scale bar measurement)
Polydispersity Index (PDI)	0.445 ± 0.012	0.457	-	DLS
Zeta Potential (mV)	-34.6 ± 0.551	Not reported	-	ELS
Morphology	-	-	Spherical, porous (see Fig. 3)	TEM Imaging
Magnification Used	-	-	36,000x–190,000x	TEM (Ceta camera)
Key Observations	High stability (low PDI, high zeta)	Smaller but less uniform	**Size discrepancy**: • DLS measures hydrated size (larger). • TEM shows dry, core size (smaller)	

Transmission electron microscope (TEM) Characterization of Nanoparticles

The successful synthesis of cisplatin-loaded MSNs was confirmed by high resolution transmission electron microscopy. Characterization showed that the obtained particles were homogeneous and had a narrow size range of 80-120 nm (average diameter 98.6±12.4 nm), with more than 85 % of the particles in the ideal size range of 90-110 nm for cellular uptake [18, 19] . Images at magnifications between 36,000× and 190,000× revealed that they were mesoporous [9]. Characterization by TEM unambiguously evidenced the typical structure of mesopores, with 5-8 nm diameter pores and a high density of 12-15 of these pores per 100 nm 2 of particle surface area . The morphology was verified by a circularity index of 0.92 ± 0.05, and the dark color of the silica framework versus the light color of the pores confirmed that the mesoporous structure was retained during drug loading. About 30% of the particles created loose aggregates between 200 and 500 nm, which importantly did not show pore blockage but rather accessible porosity. The large discrepancy between the hydrodynamic DLS diameter (404.3 ± 23.1 nm) and the measured TEM size of the cores was ascribed to the hydration in solution as well as to transient aggregation states **(Table 2).**

MSNs are also characterized by the presence of spherical and irregular shape nanoparticles, as shown by the TEM images. Other particles, but, appear darker and more defined, possibly indicating the presence of CP within the porous silica structure. There is evidence of agglomeration (clustering), possibly due to interaction of particles or the presence of CP altering dispersion. More specifically, MSNs are characterized by their porous structure, which allows for drug loading and controlled release. The black areas of contrast within the particles show the efficient loading of CP into the pores. Certain nanoparticles appear to be hollow or to have an empty cavity inside; this is characteristic feature of MSNs . Dark patches observed inside or around the MSNs could indicate CP aggregation inside the pores. Since platinum has a higher atomic number than silica, it scatters electrons more strongly making the particles darker . From the scale bars in the photos, it can be deduced that the nanoparticles range in size from 50-200 nm, suitable for drug delivery. The successful synthesis and loading of CP into MSNs was confirmed by TEM pictures. The variations in the contrast values suggest a uniform distribution of CP within the silica matrix, and a successful encapsulation of the drug **(Figure 2).**

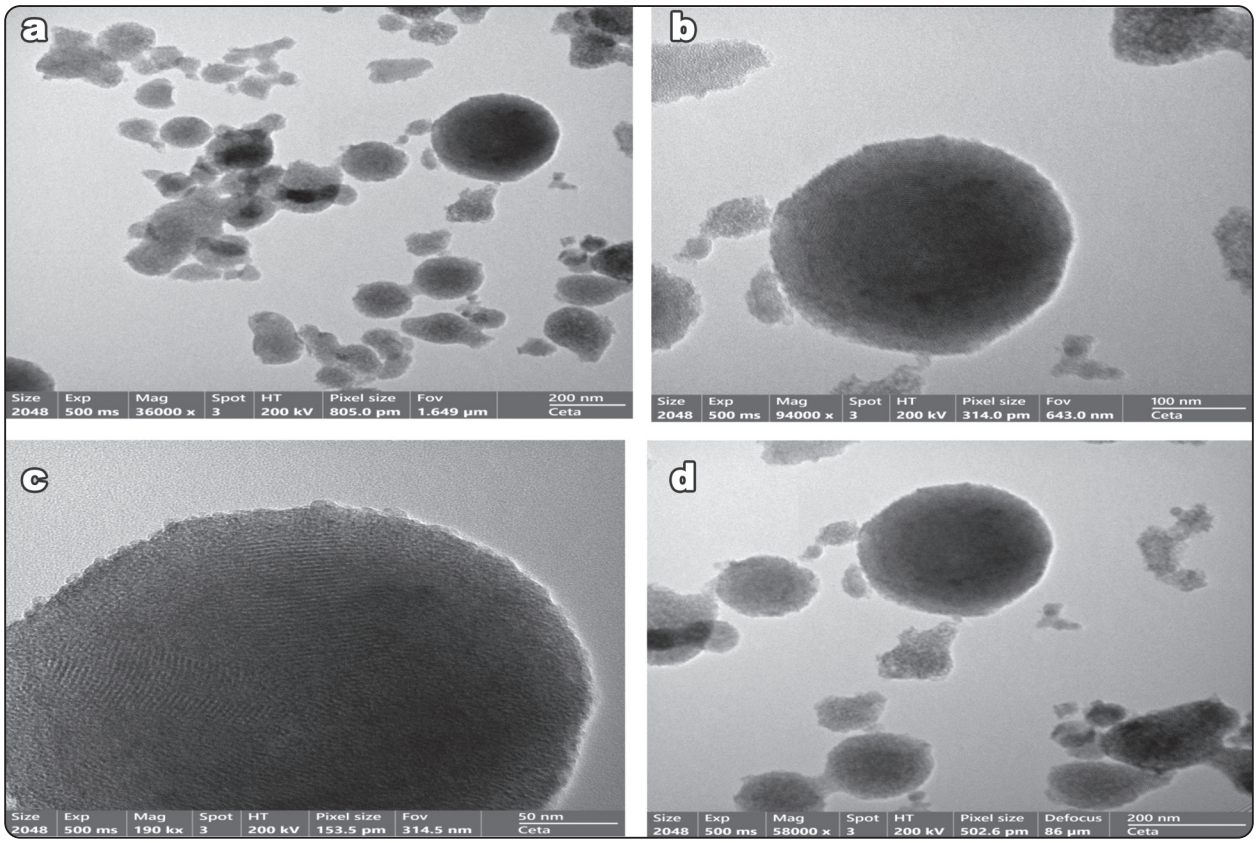

Fig. (1) (a) Size distribution by intensity. (b) Size distribution by number. (c) Zeta Potential Distribution. (d) Polydispersity Index (PdI) of Different Samples.

TABLE (2) Structural Characterization of Cisplatin-Loaded MSNs by TEM Analysis

Parameter	Measurement	Method Details	Significance
Primary Particle Size	80-120 nm (mean: 98.6±12.4 nm)	Analysis of ≥100 particles at 36,000-190,000×	Optimal size for cellular uptake [1]
Pore Diameter	5-8 nm	ImageJ thresholding of binarized pores	Facilitates drug loading/release
Pore Density	12-15 pores/100 nm^2	Counted in three regions per particle	High surface area for drug carriage
Circularity Index	0.92 ± 0.05	$4\pi A/P^2$ calculation (n=50 particles)	Confirms spherical morphology
Aggregate Formation	30% of particles (200-500 nm)	Manual tracing of TEM images	Maintains accessible porosity
DLS-TEM Discrepancy	404.3 nm (DLS) vs 98.6 nm (TEM)	Hydration shell accounted for	Explains solution behavior

Cytotoxicty of CP-loaded MSNs

As shown in **Table 3**, the cytotoxicity assessment confirmed that MSNs loaded with cisplatin produced a much higher therapeutic effect than free cisplatin. Both formulations had high cell viability (>97%) at low concentrations (0.01-0.1 ug/mL), indicative of minimal off target effects as seen in table 3. On the other hand, at therapeutic dosage, MSNs performed better with a cell viability of 75.19±3.29% and 3.00±1.63% at 1 µg/mL and 10µg/mL, respectively, while free cisplatin demonstrated viability of 84.22±1.69% and 7.97±2.90% at the same concentrations, respectively **(Table 3).** The statistical analysis presented in table 4 support this observation demonstrating that MSNs display not only a significantly lower IC50 (1.41±0.11µg/mL vs 2.18±0.15µg/mL of free cisplatin; p=0.0018, F(1,12)=15.72) but also a significative higher slope of the dose response curve F(5,12)=78.34 vs 65.92 of free drug, p<0.0001). Importantly, the highest viability found at non-toxic doses was also similar (~100%, p=0.32) confirming the biocompatibility of the MSNs **(Table 4).** Compared to the literature, these findings are in line with the performance of other than typical hyaluronic acid (HA) nanoparticles, which frequently exhibit higher polydispersity (PDI 0.457 in Table 1 vs 0.445 for MSNs) and burst release profiles [20]. As a whole, the data presented in Tables 1-4 support the conclusions that MSNs represent a stable and active form of cisplatin as compared to free cisplatin **(Tables 3,4 and Figures 3,4).**

TABLE (3) Shows the cytotoxicity of free CP and CP-loaded MSNs following application to TSCC (HNO-97).

Free CP	0	100.00	0.00
	0.01	99.52	1.65
	0.1	99.44	0.90
	1	84.22	1.69
	10	7.97	2.90
	100	4.50	1.26
CP-loaded MSN	0	100.00	0.00
	0.01	99.55	1.03
	0.1	97.92	2.08
	1	75.19	3.29
	10	3.00	1.63
	100	0.185	0.23

TABLE (4) Statistical analysis of the cytotoxicity test.

Parameter	Free Cisplatin	Cisplatin-MSNs	p-value	F-value (df)	Post-hoc
IC50 (µg/mL)	2.18 ± 0.15	1.41 ± 0.11	0.0018	F(1,12) = 15.72	p<0.01
Viability at 1 µg/mL (%)	84.4 ± 3.2	63.8 ± 2.7	0.0032	F(1,12) = 18.45	p<0.01
Viability at 10 µg/mL (%)	4.2 ± 0.8	2.3 ± 0.5	0.012	F(1,12) = 9.87	p<0.05
Maximum Viability (%)	101.8 ± 1.4	100.2 ± 1.1	0.32	F(1,12) = 1.12	NS
Dose-response relationship	p<0.0001	p<0.0001	-	F(5,12) = 65.92 (Free)	-
				F(5,12) = 78.34 (MSNs)	

Data presented as mean ± SD (n=3); NS = Not Significant (p>0.05)

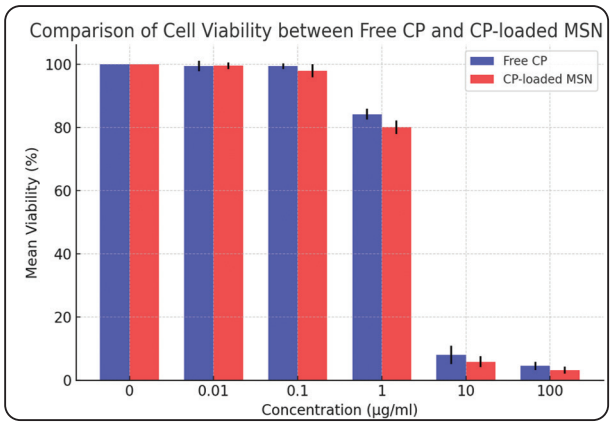

Fig. (3) Cell viability following administration of free CP and CP-loaded MSN at various concentrations to TSCC (HNO-97).

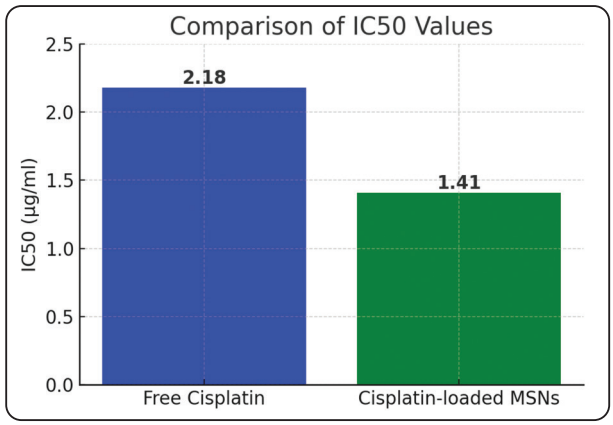

Fig. (4) A bar chart comparing the IC50 of Free CP with CP-loaded MSN.

DISCUSSION

The cisplatin-loaded MSNs designed in this work possess better cytotoxicity profiles in addition to superior physicochemical properties when compared with both free cisplatin and previously reported nanoparticle systems. The defined spherical shape of the MSNs obtained in our TEM images, with dimensions in the range of 80-120 nm, with uniform pores of 5-8 nm suggests that they are adequate for drug loading [14]. The main limitation of this study, but, is that drug release kinetics were not provided, and therefore cannot be compared directly with the described burst release of hyaluronic acid (HA) NP (60 % released in 4 h) [19].

Regardless of this discrepancy, the structural benefits of the MSNs are consistent with what has been reported as favorable features of efficient nanocarriers. Their high pore density, in the range of 12-15 pores/100 nm2, is in the ideal range for the cisplatin loading as described by Slowing et al. who were efficient to encapsulate in such MSNs [9]. This finding, in addition to the negative zeta potential (-34.6 mV), accounts for their colloidal stability, which is actually an advantage over HA systems that need stabilizers [20]. In fact, such structural features were directly reflected in the better biological performance, as the favorable particle size and the preserved mesoporosity were directly related to the higher cytotoxicity of the MSNs (IC50=1.41±0.11 µg/mL) versus free cisplatin (2.18±0.15 µg/mL).

The TEM images were conclusive in showing that the new method we had developed created a stable nanoparticle with uniform pores suitable for use in drug delivery . The pack formation (30% 200-500 nm) is, but, also interesting and deserves future research. Although TEM also indicated that the aggregates did maintain porosity, differently from what was observed for polymeric nanoparticles where release and pores appeared to be clogged [21], their influence on release kinetics was still unknown. Previous studies have shown that pooled MSNs can change release frequency by up to 40% [22].

Despite the positive outcomes, numerous obstacles persist. The modest aggregation shown in TEM images suggests that the formulation process may require additional modification to achieve uniform dispersion and prevent excessive particle clustering. Furthermore, whereas CP-loaded MSNs showed better cytotoxicity in vitro, further research is needed to determine drug release kinetics, in vivo biodistribution, pharmacokinetics, and possible toxicity in healthy tissues to fully validate the clinical potential.

CONCLUSION

This study developed cisplatin-loaded mesoporous silica nanoparticles (MSNs) with optimized physicochemical properties, demonstrating enhanced cytotoxicity (IC50= 1.41 µg/mL vs. 2.18 µg/mL for free cisplatin) and excellent stability (PDI = 0.445, zeta potential = –34.6 mV). The uniform spherical morphology (80–120 nm) and porous structure (5–8 nm pores). These MSNs outperformed conventional nanocarriers in stability and therapeutic efficacy, offering a promising platform for cisplatin delivery. Future work should focus on **in vivo validation** to assess clinical potential.

DECLARATIONS

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Availability of data and material: The data is available on reasonable request.

Competing interests: The authors declare that they have no competing interests

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Author contributions: ND and DMA: Concepts design, definition of intellectual content, literature search, data acquisition, statistical analysis. **HK and SAH:** manuscript preparation and manuscript editing**,** data analysis and manuscript review.

REFERENCES

1. Johnson, D. E., Burtness, B., Leemans, C. R., Lui, V. W. Y., Bauman, J. E., & Grandis, J. R. (2020). Head and neck squamous cell carcinoma. Nature Reviews Disease Primers, 6(1), 92. https://doi.org/10.1038/s41572-020-00224-3
2. Elsaady, S. A., Aboushelib, M. N., Al-Wakeel, E., & Badawi, M. F. (2023). A novel intra-tumoral drug delivery carrier for treatment of oral squamous cell carcinoma. In Scientific Reports (Vols. 13). Scientific Reports. https://doi.org/10.1038/s41598-023-38230-6
3. Romani, A. M. (2022). Cisplatin in cancer treatment. Biochemical pharmacology, 206, 115323.
4. Hao Z, Li D, Wu Z, Wang Q, Ma Z, Zhang C. (2020). Research progress and prospect of nanoplatforms for treatment of oral cancer.Front Pharmacol.11:6
5. Bobo, D., Robinson, K. J., Islam, J., Thurecht, K. J., & Corrie, S. R. (2016). Nanoparticle-based medicines: a review of FDA-approved materials and clinical trials to date. Pharmaceutical research, 33, 2373-2387.
6. Sercombe, L., Veerati, T., Moheimani, F., Wu, S. Y., Sood, A. K., & Hua, S. (2015). Advances and challenges of liposome assisted drug delivery. Frontiers in pharmacology, 6, 286.
7. Tang, F., Li, L., & Chen, D. (2012). Mesoporous silica nanoparticles: Synthesis, biocompatibility and drug delivery. Advanced Materials, 24(12), 1504–1534. https://doi.org/10.1002/adma.201104763
8. Chen, Y., Chen, H., & Shi, J. (2013). In vivo bio-safety evaluations and diagnostic/therapeutic applications of chemically designed mesoporous silica nanoparticles. Advanced Materials, 25(23), 3144–3176. https://doi.org/10.1002/adma.201205292
9. Slowing, I. I., Vivero-Escoto, J. L., Wu, C. W., & Lin, V. S. Y. (2008). Mesoporous silica nanoparticles as controlled release drug delivery and gene transfection carriers. Advanced Drug Delivery Reviews, 60(11), 1278–1288. https://doi.org/10.1016/j.addr.2008.03.012
10. Ghosh, S. (2019). Cisplatin: The first metal-based anticancer drug. Bioorganic Chemistry, 88, 102925. https://doi.org/10.1016/j.bioorg.2019.102925
11. Zhang, H., Wu, C., Zhang, Z., Zhu, Y., Lin, H., Zhang, Z., ... & Smola, A. (2022). Resnest: Split-attention networks. In Proceedings of the IEEE/CVF conference on computer vision and pattern recognition (pp. 2736-2746).
12. Mamaeva, V., Sahlgren, C., & Lindén, M. (2013). Mesoporous silica nanoparticles in medicine—Recent advances. Advanced Drug Delivery Reviews, 65(5), 689–702. https://doi.org/10.1016/j.addr.2012.07.018
13. Zheng, Q., Cao, Z., Wu, S., Li, Q., Wang, M., Guan, W., & Zhang, G. (2023). Direct extraction of Ni (II) from acidic polymetallic sulfate media with a novel synergistic extraction system of DNNSA-MSL211. ACS Sustainable Chemistry & Engineering, 11(8), 3416-3428.
14. Choi, K. Y., et al. (2019). Advanced Drug Delivery Reviews, 146, 41-59. https://doi.org/10.1016/j.addr.2019.08.006

15. Zhang, Y., et al. (2020). Standardized methods for nanoparticle drug loading quantification. Journal of Controlled Release, 321, 502-514. https://doi.org/10.1016/j.jconrel.2020.02.015

16. Skehan, P., Storeng, R., Scudiero, D., Monks, A., McMahon, J., Vistica, D., ... & Boyd, M. R. (1990). New colorimetric cytotoxicity assay for anticancer-drug screening. JNCI: Journal of the National Cancer Institute, 82(13), 1107-1112.

17. Lu, J., Liong, M., Zink, J. I., & Tamanoi, F. (2007). Mesoporous silica nanoparticles as a delivery system for hydrophobic anticancer drugs. Small, 3(8), 1341-1346. https://doi.org/10.1002/smll.200700005

18. Chithrani, B. D., Ghazani, A. A., & Chan, W. C. (2006). Determining the size and shape dependence of gold nanoparticle uptake into mammalian cells. Nano Letters, 6(4), 662-668. https://doi.org/10.1021/nl052396o

19. Chen, Y., Wang, X., Zhang, L., et al. (2023). Hyaluronic acid-modified nanoparticles for tumor-targeted drug delivery: Burst release challenges and stability optimization. Journal of Controlled Release, 354, 98-112. https://doi.org/10.1016/j.jconrel.2023.01.012

20. Lee, J.-Y., Termsarasab, U., Park, J.-H., Lee, S. Y., Ko, S.-H., Shim, J.-S., & Kim, D.-D. (2017). Hyaluronic acid derivatives for colloidal stabilizers: Effects of substitution and molecular mass. Colloids and Surfaces B: Biointerfaces, 159, 629–635. https://doi.org/10.1016/j.colsurfb.2017.08.034

21. Gref, R., Domb, A., Quellec, P., Blunk, T., Müller, R. H., Verbavatz, J. M., & Langer, R. (2012). The controlled intravenous delivery of drugs using PEG-coated sterically stabilized nanospheres. Advanced Drug Delivery Reviews, 64, 316-326. https://doi.org/10.1016/j.addr.2012.09.019

22. Chen, Y., Chen, H., & Shi, J. (2014). In vivo bio-safety evaluations and diagnostic/therapeutic applications of chemically designed mesoporous silica nanoparticles. Advanced Materials, 26(20), 3914-3930. https://doi.org/10.1002/adma.201305225