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Article

Investigation of the effect of dexamethasone-loaded magnetic nanoparticles on MDA-MB-231 cell lines

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Abstract: The MDA-MB-231 cell line is derived from triple-negative breast cancer (TNBC), representing one of the most aggressive forms of breast cancer. Innovative therapeutic strategies, including s targeted therapies using nanocarriers, hold significant promise, particularly for difficult-to-treat cancers such as TNBC. Nanoparticles have transformed the medical field by serving as advanced drug delivery systems for cancer treatment. They play a critical role in overcoming the drug resistance often associated with cancer therapies. When utilized as drug delivery vehicles, nanoparticles can specifically target cancer cells and effectively reduce or eliminate multidrug resistance. Among them, chitosan-coated magnetic nanoparticles (MNPs) have been widely explored for the loading and controlled release of various anticancer agents. In this study, we evaluated the effects of dexamethasone-loaded chitosan-coated MNPs on MDA-MB-231 cell lines. Fourier transform infrared spectroscopy and scanning electron microscopy were employed to verify the successful loading of dexamethasone onto the nanoparticles. To assess cytotoxicity, empty nanoparticles, free drug, and drug-loaded nanoparticles were tested on the cells. The results indicated that empty nanoparticles exhibited no toxic effects. The IC50 value of the free drug was 123 µg/mL, while the IC50 value of the drug-loaded nanoparticles was significantly lower, at 63 µg/mL. These findings confirmed the successful conjugation of dexamethasone to the chitosan-coated MNPs, demonstrating substantial cytotoxic effects on breast cancer cells. Although dexamethasone has been reported to exhibit both tumor-suppressive and pro-metastatic effects, its specific impact on TNBC warrants further investigation in future studies.

Keywords: nanoparticles; dexamethasone; breast cancer; cytotoxicity

1. Introduction

Breast cancer is the most commonly diagnosed cancer among women worldwide and is treatable when detected at an early stage. However, advanced-stage breast cancer is considered incurable by current treatment methods [1,2,3]. Breast cancer is known to be a molecularly heterogeneous disease. The key molecular characteristics include the human epidermal growth factor receptor 2 (HER2), hormone receptors (estrogen and progesterone receptors), and *BRCA* mutations [1,3,4]. These molecular subtypes determine treatment strategies and significantly impact disease management [2].

Treatments of breast cancer encompass local (surgery and radiotherapy) and systemic (endocrine therapy, chemotherapy, anti-HER2 therapy, and immunotherapy)

approaches. Neo-adjuvant therapy is a widely used practice in HER2-positive breast cancer and triple-negative breast cancer (TNBC) [1,3,5]. In metastatic breast cancer, the treatment goals are to prolong survival and maintain quality of life [2,3].

Genetic predisposition, particularly *BRCA1* and *BRCA2* gene mutations, has been reported to play a significant role in the development of breast cancer. Additionally, environmental and lifestyle factors may also influence the risk [4,6,7]. MDA-MB-231 is recognized as a TNBC cell line, and these cells are reported to represent one of the most aggressive forms of breast cancer. They exhibit increased resistance to antitumor compounds, and this resistance has been reported to become more pronounced in 3D spheroid models [8].

Novel treatment methods, such as immunotherapy and targeted therapies (nanocarriers), hold significant promise, particularly for challenging cancers such as TNBC [4,9]. Nanoparticles have revolutionized the field of medicine by being utilized in next-generation drug delivery systems for cancer treatment. They have demonstrated experimental success as drug delivery agents, fundamentally transforming the cancer treatment landscape by enabling more accurate detection methods, diagnosis, and targeted drug delivery to eradicate tumors [10].

Nanocarriers accumulate in tumors through the enhanced permeability and retention effect, along with other complementary mechanisms, such as vascular transcytosis. Because cell membrane transporters cannot remove nanoparticles that accumulate in tumors, lower doses achieve effective results [11]. Nanoparticles play a crucial role in overcoming drug resistance associated with cancer. When used as drug delivery systems, these particles can target and reduce or eliminate multidrug resistance [12,13]. By leveraging the unique pathophysiology of tumors, nanoparticles can actively deliver drugs to cancer cells through increased permeability and retention effects, providing a more effective treatment in cases where traditional therapies are ineffective [12].

Chitosan-coated magnetic nanoparticles (MNPs) have been utilized for the loading and controlled release of various anticancer drugs. Researchers have successfully incorporated drugs such as 5-fluorouracil and gemcitabine into these nanoparticles, demonstrating improved efficacy in target cells [14]. Chitosan-coated MNPs can be directed to the target site using a magnetic field, allowing for the specific delivery of drugs to cancer cells. This approach shows that cancer cells can be targeted while minimizing damage to healthy tissues [15]. Chitosan-coated MNPs exhibit high biocompatibility and a low toxicity profile, suggesting that these nanoparticles can be safely used in cancer treatment [16,17].

Dexamethasone is a synthetic glucocorticoid that presents as an odorless, white crystalline powder with a mildly bitter taste (**Figure 1**). It is a fluorinated steroid, specifically a 9-fluoro-pregna-1,4-diene, characterized by hydroxyl groups at the 11, 17, and 21 positions, a methyl group at the 16 position, and oxo groups at the 3 and 20 positions. Renowned for its anti-inflammatory, immunosuppressive, and pain-relieving properties, dexamethasone is widely used to manage conditions such as postoperative nausea and vomiting, autoimmune disorders, and allergic reactions [19].

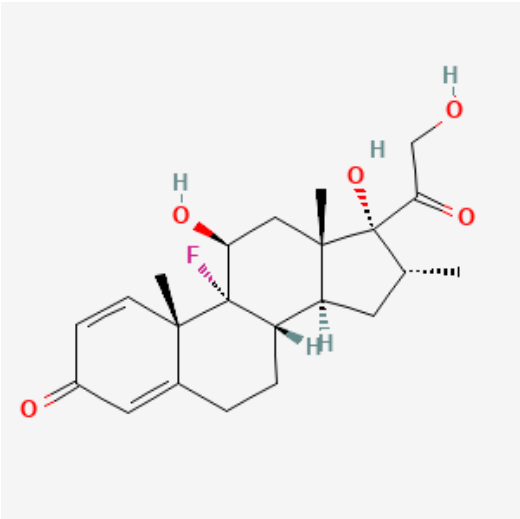


Figure 1. Chemical structure of dexamethasone. Reprinted from National Center for Biotechnology Information [18].

This study investigates the impact of dexamethasone-loaded chitosan-coated MNPs on TNBC (MDA-MB-231) cell lines.

2. Materials and methods

2.1. Synthesis and characterization of magnetic nanoparticles and drug loading analyses

The MNPs (Fe_3O_4) were synthesized using the co-precipitation method. The surface of the synthesized MNPs was designed according to the properties of the drug and polymer to be loaded onto them. To optimize the synthesis of MNPs, parameters such as mixing speed, reagent ratios, and temperature were studied to determine the optimal conditions. The crystal structures of the MNPs were determined using X-ray diffraction (XRD). The shape and size of the MNPs were examined at each stage of synthesis using transmission electron microscopy (TEM). Changes in the functional groups of the MNPs after synthesis were identified using Fourier transform infrared spectroscopy (FTIR). At each stage of synthesis, properties such as size distribution (DLS), zeta potential, vibrating sample magnetometry (VSM), thermogravimetric analysis (TGA), X-ray photoelectron spectroscopy (XPS), and electrical and magnetic characteristics were determined [19].

Specifically, chitosan-coated magnetic iron oxide nanoparticles were prepared by co-precipitating Fe(II) and Fe(III) salts in a 1:2 molar ratio in the presence of chitosan and tripolyphosphate (TPP) using a five-neck glass flask [20]. During the formation of Fe_3O_4 nuclei, chitosan molecules surround these anionic nuclei, and TPP acts as a cross-linker, binding the chitosan molecules around the Fe_3O_4 core. The synthesized chitosan-coated MNPs were characterized using techniques including XRD, XPS, FTIR, TEM, DLS, TGA, VSM, and zeta potential analysis [20]. Dexamethasone was then loaded onto the nanoparticles, followed by stability and release studies [20]. The synthesis and characterization of chitosan-coated MNPs loaded with various anticancer agents are standard procedures in our laboratory, and the results have been and continue to be published in scientific journals. The drugs and

MNPs were mixed in a potassium buffer and rotated at 500 rpm for 24 h at room temperature (**Figure 2**). Drug-loaded MNPs were isolated from unbound drug using neodymium magnets. The drug loading efficiency was determined by measuring absorbance at 240 nm using a UV spectrophotometer (Multiskan GO, Thermo Scientific, United States [US]). FTIR and scanning electron microscopy (SEM), conducted at Kırşehir Ahi Evran University, were employed to confirm the successful loading of dexamethasone onto the MNPs.

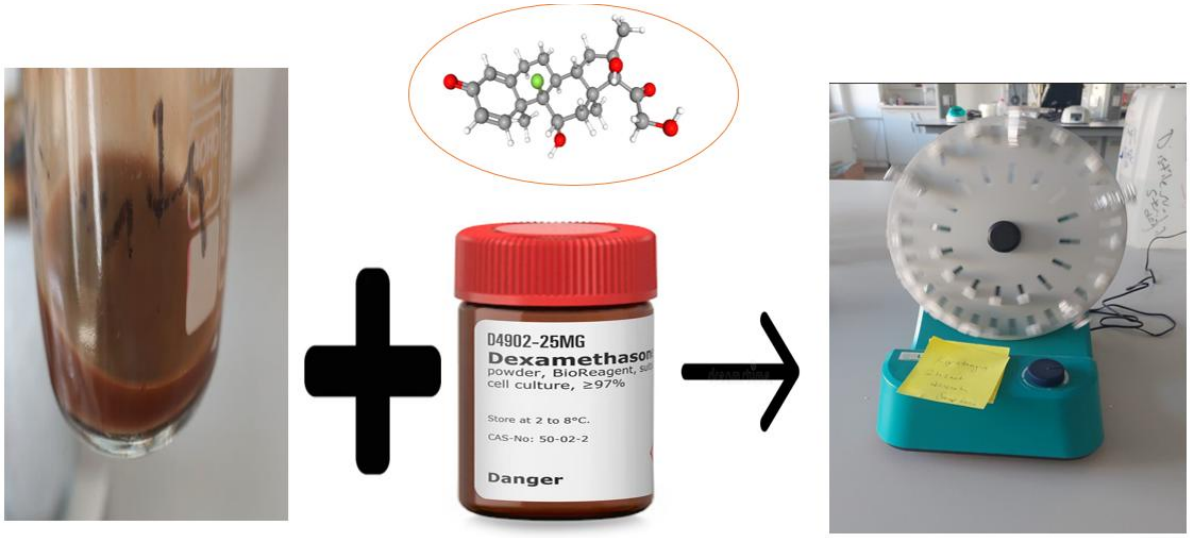


Figure 2. Drug loading analyses. The drug was loaded onto free magnetic nanoparticles by stirring at room temperature for 24 h using a rotator machine.

2.2. Drug release analyses

The *in vitro* drug release study of MNPs, free nanoparticles, and dexamethasone-loaded MNPs was conducted in a sodium phosphate buffer solution (PBS, pH 7.4). At predetermined time intervals, a 10 µL aliquot was withdrawn from the PBS stock solution containing dexamethasone-loaded MNPs. The samples were analyzed at 242 nm using a UV spectrophotometer (Shimadzu UV-1800, Shimadzu Corporation, Japan).

2.3. Cancer cell cultivation

The MDA-MB-231 cancer cell line was cultured in 75-cm^2 flasks using RPMI-1640 medium supplemented with 10% (v/v) fetal bovine serum and 1% (v/v) gentamicin. The cells were maintained in a 5% CO_2 incubator at 37 °C.

2.4. Cytotoxicity analysis in 2D cell cultures

The cytotoxicity of dexamethasone was assessed in 2D cell cultures using an XTT (2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide)-based cytotoxicity assay kit. Viable cells convert the tetrazolium salt XTT into a colored formazan dye through mitochondrial enzymes. The amount of viable cells was determined by colorimetric measurement of this dye. Cells were seeded in 96-well plates at a density of 5,000 cells per well. One column of the plate was reserved as a medium control, and no cells were added to these wells. After seeding, the cells were

treated with serial dilutions of the drug and incubated for 24 to 96 h. Activated XTT solution was then added to each well, and the plates were incubated at 37 °C for 2 to 5 h. The formazan dye in each well was quantified using a microplate reader. Cell growth in wells without drug-loaded MNPs was assumed to be 100%, and the growth in treated wells was calculated relative to this control. The IC_{50} (concentration required to kill 50% of the cells) was determined. Each experiment was performed in triplicate.

2.5. Migration assay

The migration assay was conducted using the method outlined by Liang et al. [21] Cells were seeded at a density of 1.5×10^5 cells per well in six-well plates, with three wells serving as controls and three wells treated with the drug. The plates were incubated for 24 h. Once the well surface was 80% confluent, a straight scratch was made through the cell monolayer using a pipette tip. Microscopic images were taken immediately after creating the scratch (0 h) and at 6-h intervals until wound closure. The images were analyzed using the ImageJ software (National Institutes of Health, US) to evaluate cell migration.

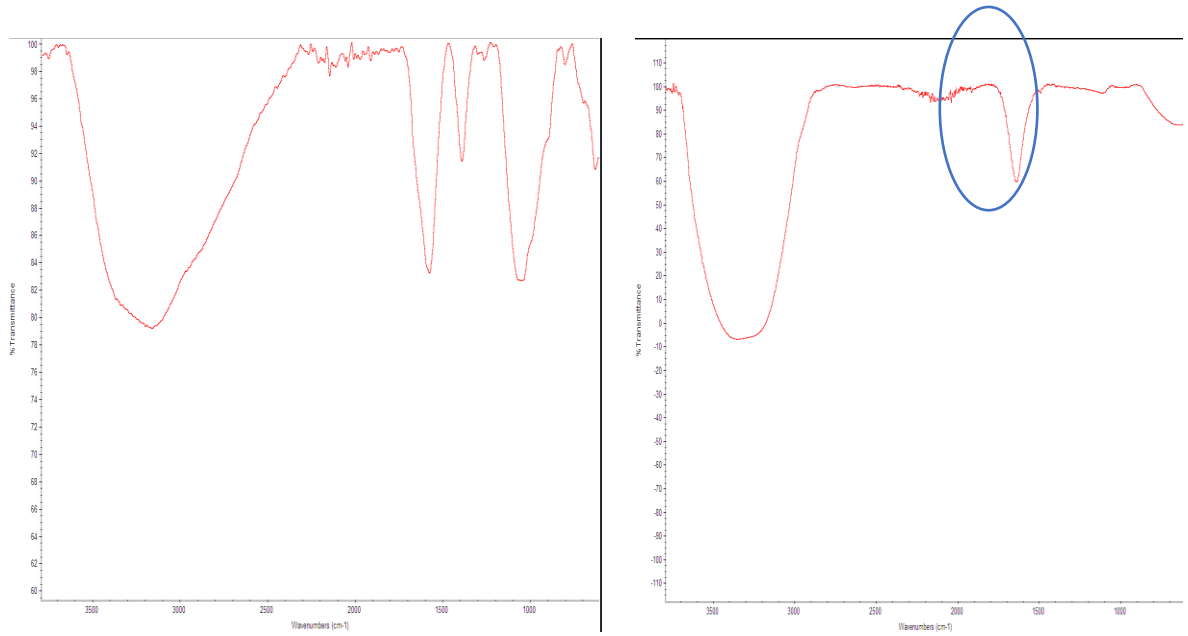
2.6. Cellular internalization of nanoparticles

To determine the cellular uptake of nanoparticles, both neutral and charged nanoparticles were treated with cells. Subsequently, the internalization status of the nanoparticles into the cells was examined under a microscope (BAB-TERS, BAB, Turkey) at 1, 2, 4, 6, 8, and 12-h intervals.

3. Results and discussion

The system consists of Fe_3O_4 MNPs at its core, enveloped by chitosan polymers that serve as drug carriers on the nanoparticle surface. As depicted in **Figure 3**, dexamethasone molecules (marked by blue circles) were bound to the polymer via covalent or electrostatic interactions. This structure was designed to facilitate controlled drug release, enhance biocompatibility, and support targeted therapy. To verify the successful loading of dexamethasone onto the nanoparticles, FTIR and SEM analyses were conducted.

Analysis of the SEM images revealed distinct morphological features. In **Figure 4**, the surface displayed a rough and irregular texture, a characteristic commonly associated with chitosan-coated nanoparticles. This irregularity arises from the uneven coating of the chitosan polymer, which creates a porous and granular structure. Such a structure is likely to enhance drug loading capacity, thereby improving bioavailability. The SEM images confirmed the successful synthesis of chitosan-coated Fe_3O_4 MNPs. In **Figure 5**, the loading of dexamethasone was observed to increase the density of the nanoparticles and form an adhesive structure. The presence of 13.7% carbon content further supported the successful coating of chitosan and the loading of dexamethasone. These findings collectively demonstrate that Fe_3O_4 MNPs were effectively coated with chitosan and subsequently loaded with dexamethasone.



(a) (b)

Figure 3. Fourier transform infrared spectroscopy analysis results. **(a)** Pure dexamethasone. **(b)** Dexamethasone-loaded nanoparticles.

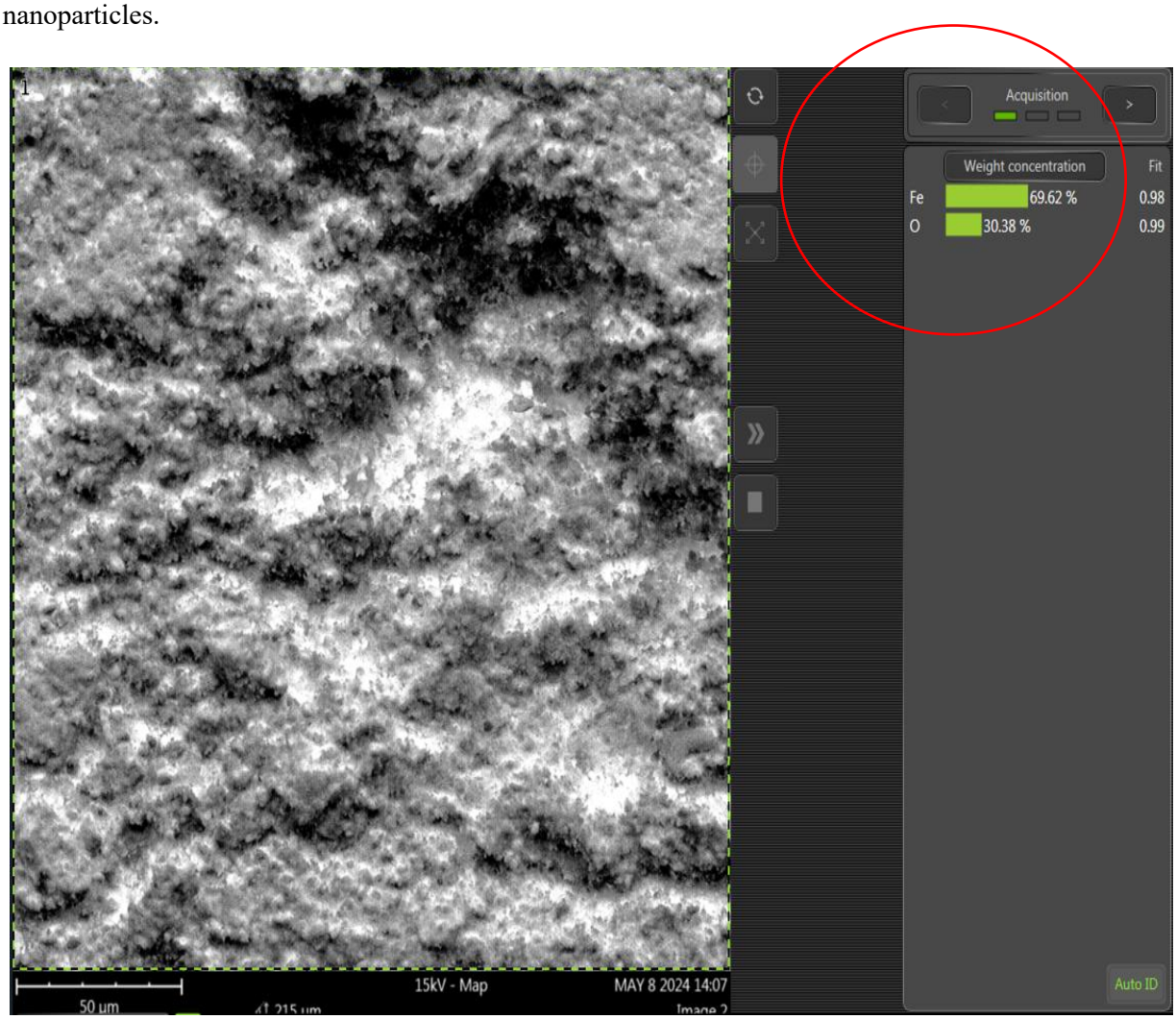


Figure 4. Scanning electron microscopy analysis results of the chitosan-coated magnetic nanoparticles. Scale bar: 50 μm; magnification: **1200**×.

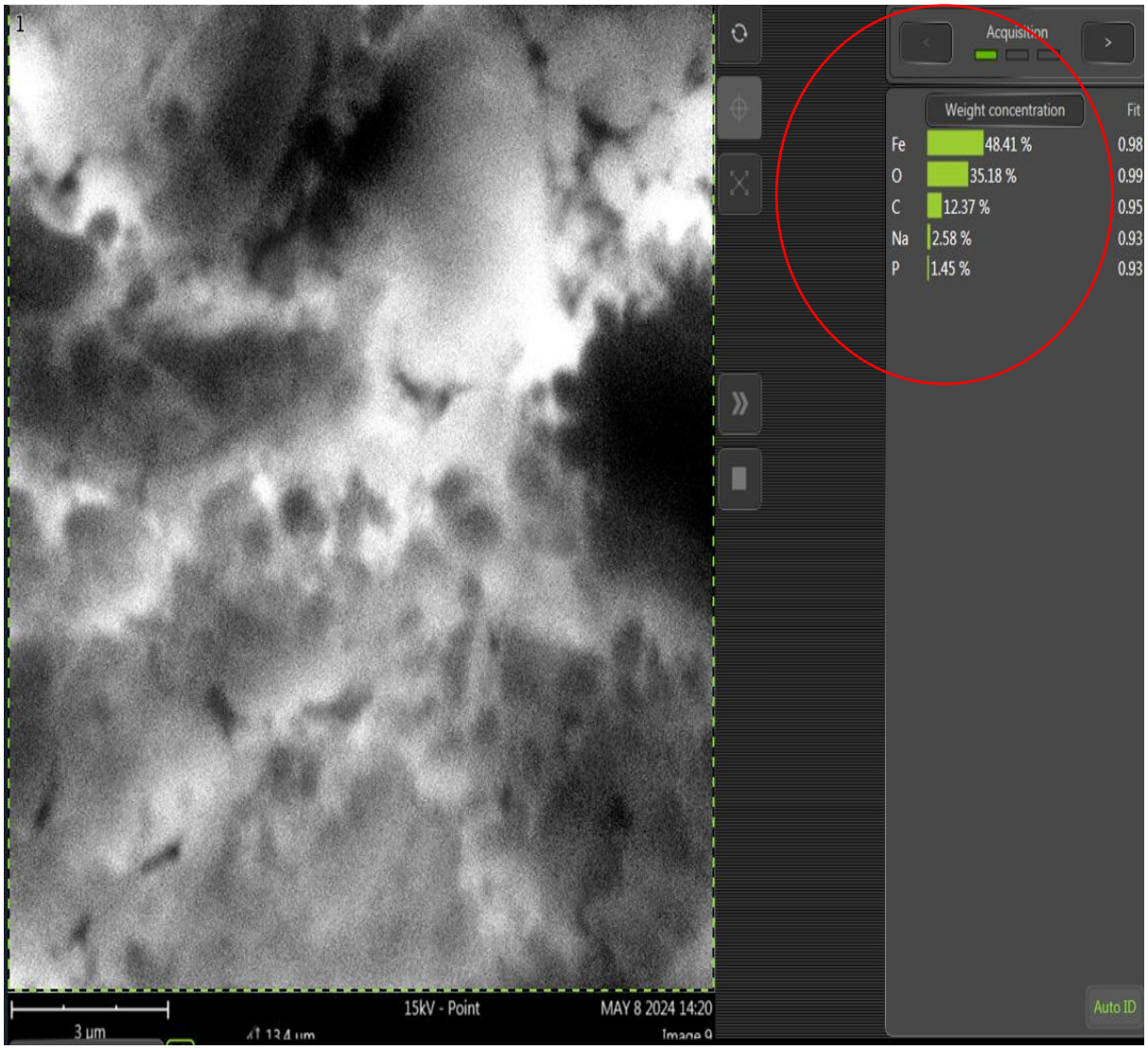


Figure 5. Scanning electron microscopy analysis results of the dexamethasone-loaded chitosan-coated magnetic nanoparticles. Scale bar: 3 μm; magnification: **10**×.

Figure 6 displays the *in vitro* release profiles of dexmethasone from MNPs in PBS solution. The dexamethasone-loaded MNPs exhibited an initial burst release of 56% within the first 72 h. Then, the drug reached a stable state.

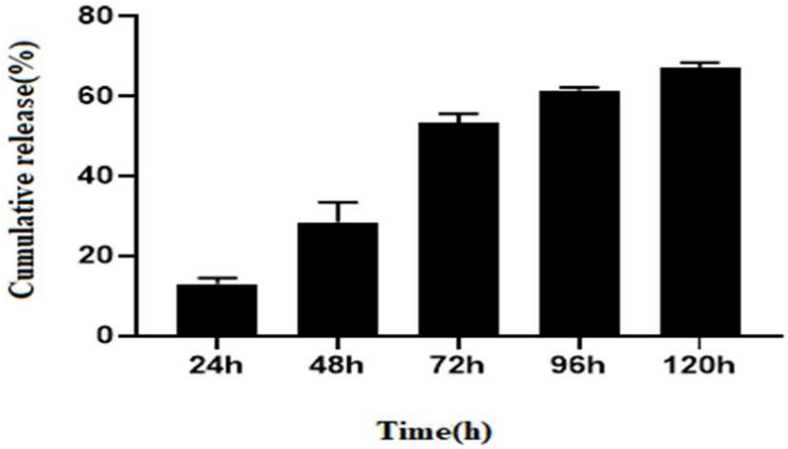


Figure 6. The release of dexamethasone from magnetic nanoparticles across various time points.

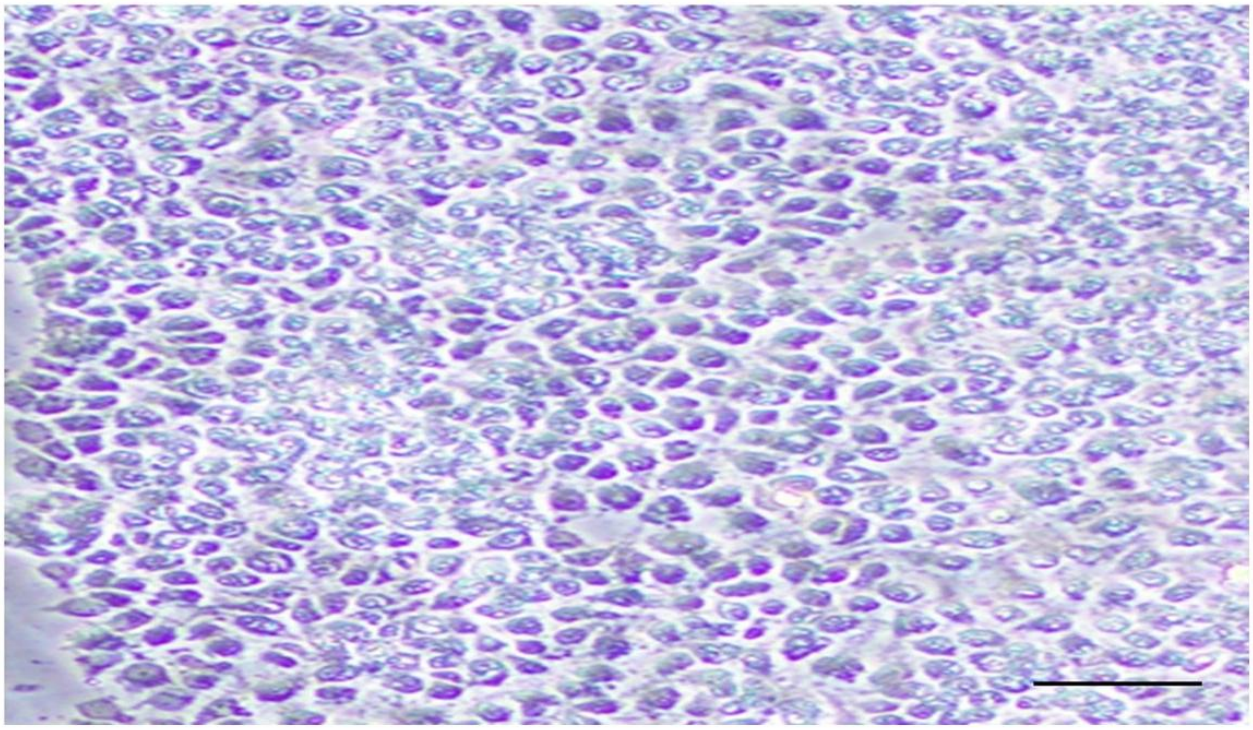


Figure 7. Image of the control MDA-MB-231 cell line. Scale bar: 100 μm; magnification: 10×.

It was observed that chitosan-coated MNPs were internalized by MDA-MB-231 cells. These nanoparticles were expected to be utilized for controlled drug release. The findings revealed a disruption in cellular structural integrity and a decrease in cell density compared to the control group (**Figures 7–9**). Dexamethasone-loaded nanoparticles were shown to enhance the localized effect of dexamethasone while minimizing peripheral toxicity. In the red-marked areas in **Figure 8**, dexamethasone-loaded nanoparticles were observed to be localized either along the cell membrane or dispersed within the cytoplasm.

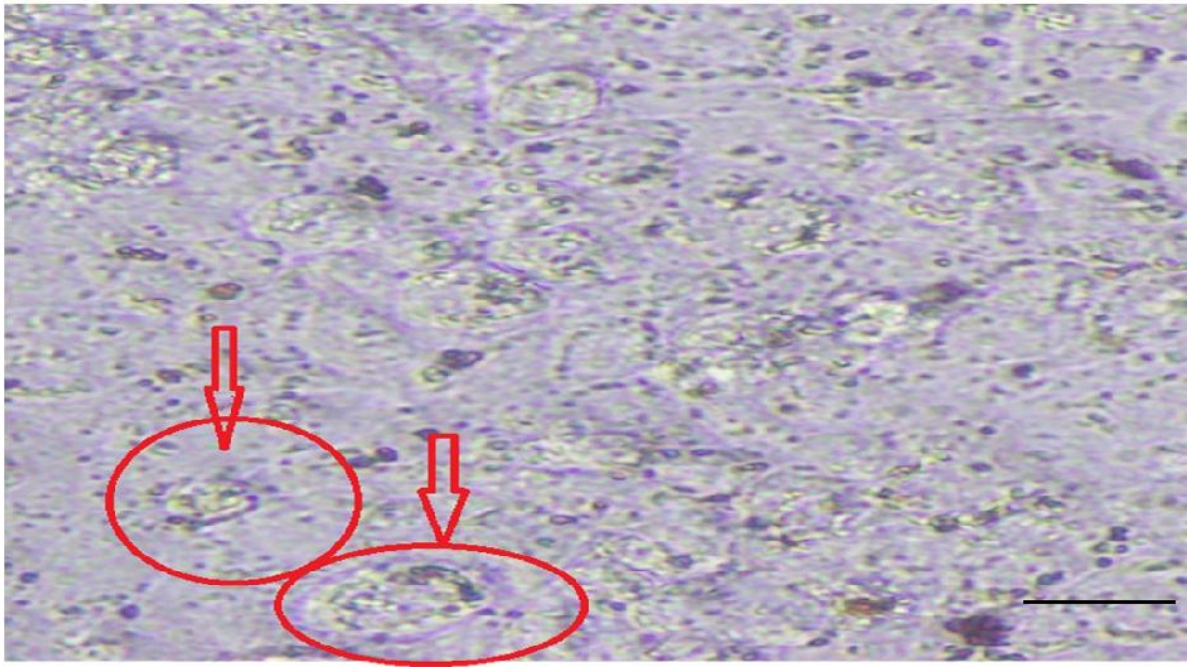


Figure 8. Image of dexamethasone-loaded chitosan-coated magnetic nanoparticles in and around MDA-MB-231 cells post-transfection. Scale bar: 100 µm; magnification: 100×.

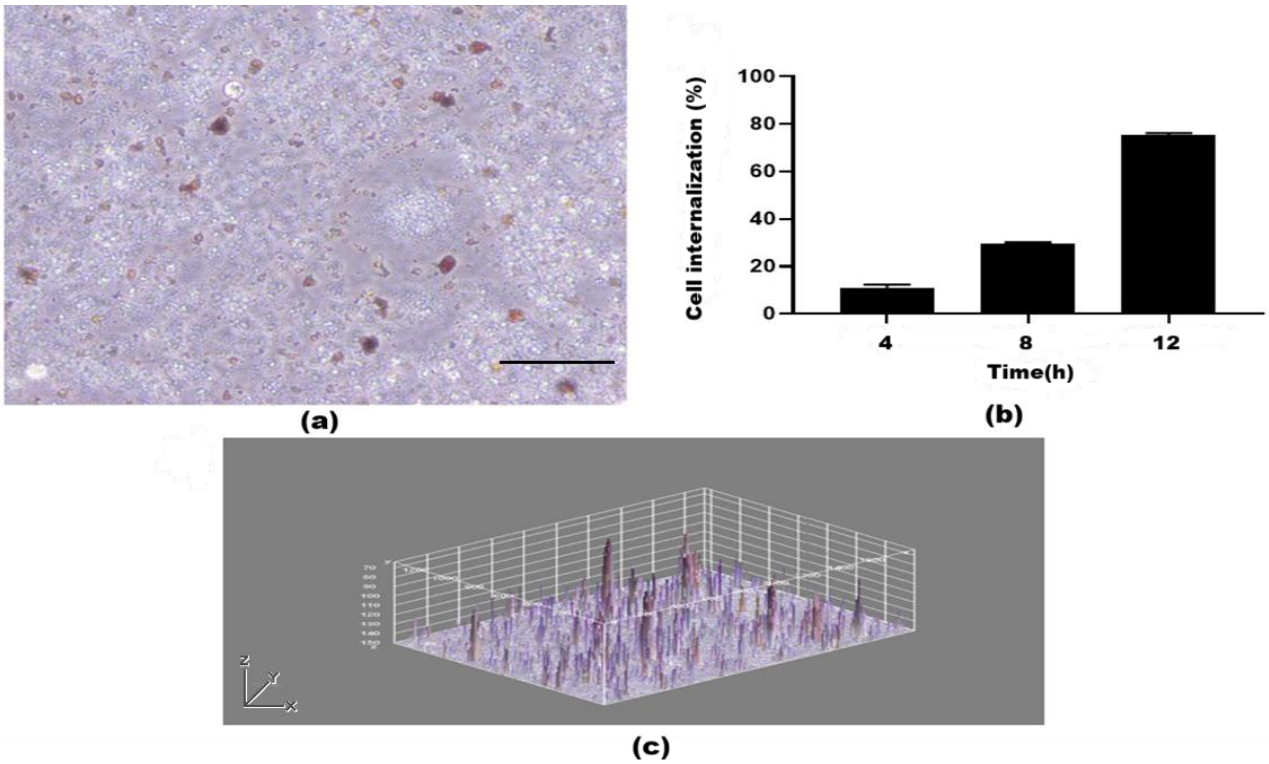


Figure 9. Cell internalization analyses. **(a)** Microscopic image showing cell death following nanoparticle entry. Scale bar: 100 µm; magnification: 10×. **(b)** Time-dependent increase in nanoparticle internalization in cells. **(c)** 3D surface (surface/density) mapping(x: Pixel, y: Pixel, z: Intensity)

Previous studies have demonstrated that chitosan nanoparticles exhibit varying transfection efficiencies depending on their formulation and the cell type. For example, chitosan–DNA nanoparticles have displayed cell type-dependent transfection efficiency, with higher efficiency observed in HEK293 cells compared to other cell types, such as MG63 and mesenchymal stem cells [22,23]. The use of lipochitoplexes—liposome-encapsulated chitosan nanoparticles—has been shown to increase transfection efficiency at least twofold under physiological conditions [24]. In the MDA-MB-231 cell line, as illustrated in **Figure 9**, the transfer of nanoparticles to the cell membrane and interior was confirmed.

Cytotoxicity analysis was conducted using the XTT assay kit. The XTT assay operates on the principle that the yellow tetrazolium salt is cleaved by the metabolic activity of living cells, producing an orange color change. Chitosan-coated MNPs, dexamethasone alone, and dexamethasone-loaded MNPs were administered in diluted form. After 72 h, readings were taken using the ELISA Reader (ELx808, Biotek, US), and the results were analyzed to determine the IC50 doses.

The XTT cytotoxicity analysis revealed that chitosan-coated MNPs exhibited no toxic effects on cell viability. In contrast, dexamethasone alone was found to reduce cell proliferation by approximately 60%. Importantly, when dexamethasone was loaded onto the nanoparticles, its effectiveness increased, potentially due to the controlled release mechanism that more efficiently inhibits cell proliferation. These findings suggest that chitosan-coated MNPs are non-toxic and, when combined with dexamethasone, can act as a more potent therapeutic agent for targeting cancer cells compared to free dexamethasone (**Figure 10**). The free nanoparticles, free drug, and drug-loaded nanoparticles were applied to the cells, and cytotoxicity analysis was performed. According to the obtained results, empty nanoparticles did not show any toxic effect. While the IC50 value of the free drug was 123 μg/mL, the IC50 value of the drug-loaded nanoparticles was 63 μg/mL.

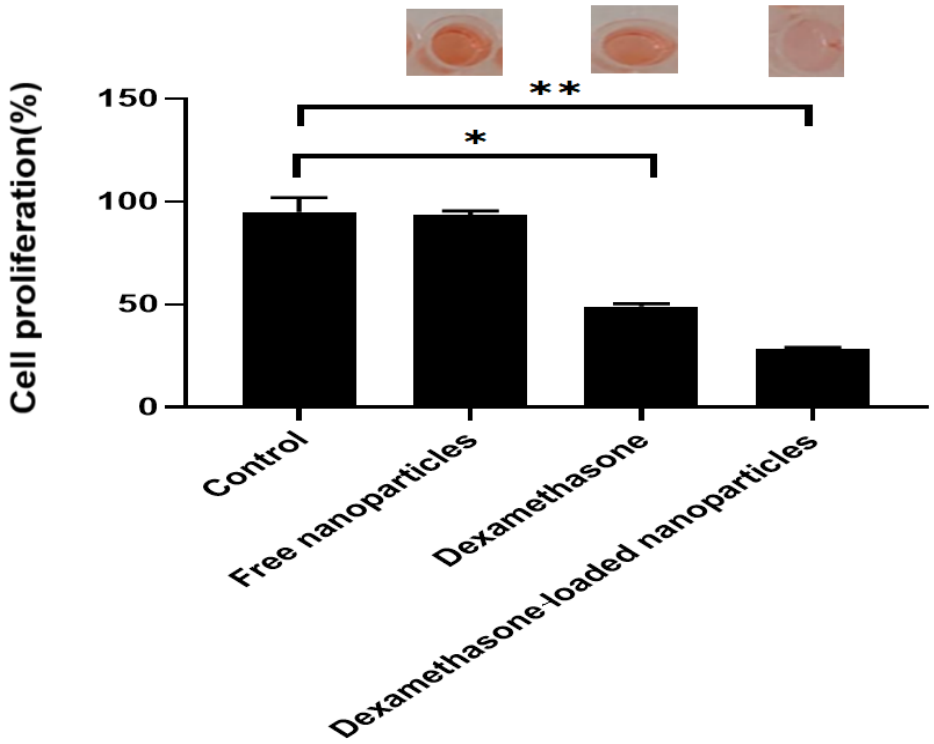


Figure 10. Cytotoxicity analysis of control**,** free nanoparticles, dexamethasone, and dexamethasone-loaded nanoparticles. Note: *p<0.05, **p<0.01**.**

The migration assay showed that dexamethasone-loaded MNP treatment significantly suppressed cell migration (p<0.05; **Figure 11**).

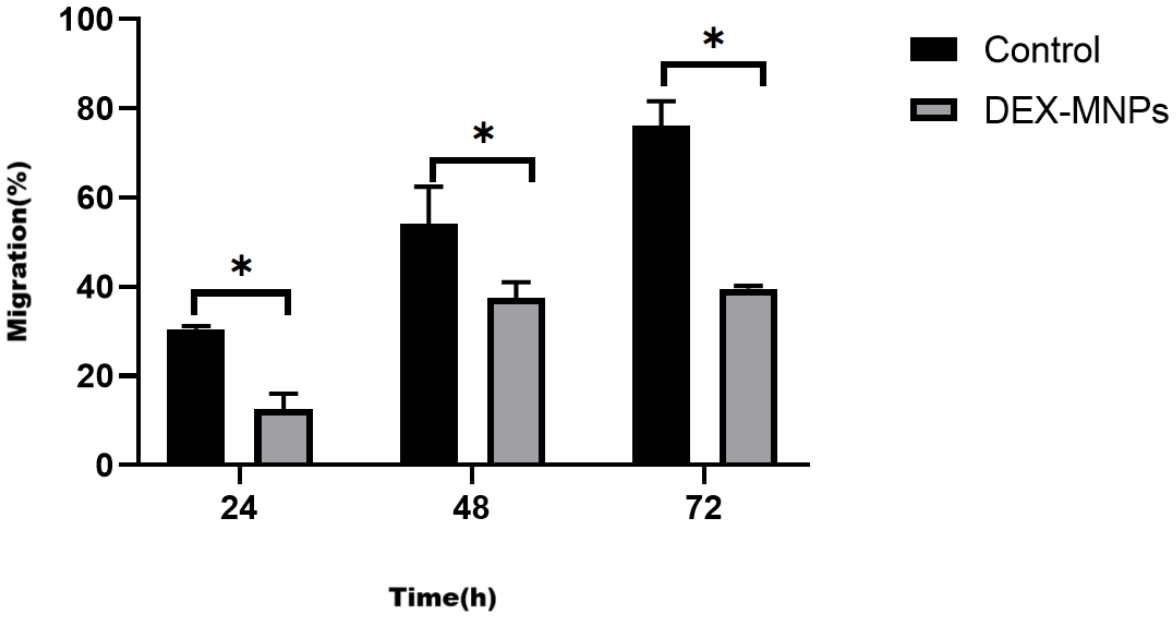


Figure 11. The results of the migration assay. Note: *p<0.05. Abbreviation: DEX-MNPs: Dexamethasone-loaded magnetic nanoparticles.

Dexamethasone is known to influence the tumor microenvironment by regulating blood vessels and the extracellular matrix. These regulations reduce interstitial fluid pressure, tissue stiffness, and solid stress, thereby enhancing the penetration of nanocarriers into tumors. This characteristic indicates that dexamethasone could improve the effectiveness of metastatic breast cancer treatment [25]. However, its use in brain tumors, such as glioblastoma, has been linked to poor outcomes, as high doses may cause more side effects without improving clinical results [26,27]. Furthermore, dexamethasone has been shown to promote metastatic behavior in certain breast cancer cell lines, particularly estrogen receptor-negative cells, by increasing cell count, invasiveness, and migration [28]. It has also been found to promote lung metastasis [29,30].

In this study, dexamethasone was successfully attached to chitosan-coated MNPs, and the MNPs demonstrated significant cytotoxic effects on breast cancer cells (**Figure 9**). These results highlight the effectiveness of MNPs as a delivery system and their potential to amplify the biological impact of dexamethasone on target cells. The findings suggest that further optimization of the surface modification and drug-loading capacity of MNPs is possible. The chitosan coating created a biocompatible environment for controlled drug release, enabling efficient delivery of dexamethasone to target cells (**Figure 7**). Moreover, the magnetic properties of the nanoparticles provide a promising method for targeted drug delivery using external magnetic fields.

However, this study is preliminary, and additional validation of the data is necessary. Key factors such as drug-loading capacity, release kinetics, bioavailability, and targeting efficiency need to be thoroughly examined. *In vivo* studies are also essential to draw more definitive conclusions about the safety and efficacy of this system. Future research should focus on assessing the biological safety and pharmacokinetic properties of the system, as well as testing its effectiveness across various cancer types and larger cell populations. Such data are crucial for evaluating the clinical potential of nanoparticle-based drug delivery systems.

4. Conclusion

In conclusion, the dexamethasone-loaded MNP system developed in this study represents an innovative approach to drug delivery and targeting, with the potential to become a patentable technology in the future.

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Conflict of interest: The authors declare no conflict of interest.

Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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