Nanoprodrugs encapsulated with mesoporous silica nanoparticles for combined with photothermal therapy for the treatment and care of gastric cancer

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Abstract

In this study, mesoporous silica nanoparticles (MSNs) were surface-modified with polymer poly(HEMA-co-PEGMA via surface-initiated atom transfer radical polymerization and a multifunctional nanoplatform MSNP@poly(HEMA-co-PEGMA-g-doxorubicin (DOX)/Rhodamine 6G (R6G) was developed to combine photothermal (PTT) and chemotherapy therapy effectively. PTT induced by near-infrared (NIR) radiations might further destroy gastric cancer cell lines while the small-dye molecule was co-loaded into the MSNP pores. A 65 % higher cumulative drug release over 50-h occurs when the cis-aconitic anhydride link breaks under low-pH stimulation (typical physiological environment). High temperatures accelerated reversible covalent bond breakage. The accumulative release of the drug increased by 24.3 %, illustrating that higher temperatures can decrease the time needed to complete blood drug concentrations by 24.3 %. More than 90% of gastric tumour cells were destroyed after 48 h following exposure to NIR light irradiation with the prodrug delivery system, compared to DOX alone in vitro cytotoxicity tests. Because of this, rapidly reversible chemical bond breaking and photothermal activity in MSNP@poly(HEMA-co-PEGMA-g-DOX/R6G) increased the synergic impact of the chemotherapy, which offers tremendous promise in combination with the treatment and care of gastric cancer therapy.

1. Introduction

Conventional chemotherapy includes taking oral or intravenous anticancer drugs, which flow through the systemic circulation to the tumour and destroy cancer cells, among other things [1]. Most cancer patients choose chemotherapy, even when it isn’t the best option. Nanotechnology has advanced rapidly in the last decade and holds significant promise for tumor-targeted drug delivery systems [2–4]. Noncovalent interaction/bifunctional covalent bond-drug combined as a small prodrug can be used to encapsulate the drug and release it at a predetermined rate [5–7]. Drug solubility and circulation time can be improved, and drug distribution to tumor locations via enhanced permeability and retention effects, allowing specific targeting and controlled drug release when paired with the stimuli response. There are several limits to preclinical chemotherapy alone; for intense, the model drug doxorubicin (DOX), which is widely used for the construction of tumor-targeted drug carriers, is an antitumor anthracycline drug with potent cardiotoxicity and an absence of relevant cancer cell lines, leading to severe toxic effects [8]. Due to cancer cells with low DOX absorption efficiency, frequent drug administration is required, leading to a build up of drug resistance in the body. Consequently, combining chemotherapeutic and other treatments is one of the most successful strategies to boost the impact of tumor treatment [9]. Anticancer drug doxorubicin (DOX) and a photoinitiator dihydro porphyrin (Ce6) were then adsorbable onto M-MSNPs developed by Liu and his colleagues after designing and synthesizing magnetic mesoporous silica nanoparticles (M-MSNP) [10–12]. Combining chemotherapy and photodynamic treatment
with alginate/chitosan polyelectrolytes on M-MSNPs generated higher singlet oxygen in tumor cells following laser irradiations to increase anticancer effects [13–15].

Tumor cells are killed by photothermal treatment (PTT), which uses NIR light irradiations to raise organs’ temperature to a hyperthermic level (over 40 °C). Adjuvant tumor therapy PTT has attracted significant interest recently [16–18]. When PTT and chemotherapy are used together, a photothermal effect is produced using the chemotherapeutic and photothermal drugs, which have a synergic impact as the rise’s temperature, killing tumor cells effectively [19]. Multimodality treatment outperforms single chemotherapy in anticancer efficacy and its ability to reverse tumour cells’ multidrug resistance. Consequently, improving multi-functionalized carrier composites that may integrate PTT and chemotherapy into one is of tremendous importance for increasing the beneficial impact of the tumor [20]. The FDA recognizes a small organic molecule, Rhodamine 6G (R6G), for therapeutic application and is commonly utilized as a PTT agent in cancer treatment [21]. Poly(N-isopropyl acrylamide-acylamide) nanogels encapsulating the doxorubicin NIR R6G dye and (DOX) were designed and prepared by Chen et al can successfully encapsulate DOX and R6G and generate a transition phase that triggers DOX release [22]. On the other hand, NIR radiation triggers the DOX release from the drugs-loaded nanoparticles only when the temperature increases, resulting in a reduced synergistic impact of PTT and chemotherapy if the temperature increase is insufficient [23]. It is vital to fabricate multifunctional nanocarriers to address the issues. When DOX and R6G are used in tandem, they can generate a mildly acidic environment inside cells, releasing DOX. This enhances the synergistic action of DOX and R6G [24].

Generally, a drug delivery system should be stable over a lengthy period and prevent the release of loaded pharmaceuticals in the bloodstream or normal tissues [25–27]. The system should release the drugs quickly in response to the local environment once they have reached and accumulated in tumor tissues via passive and active targeting and cell uptake by cancer cells. Mesoporous silica nanoparticles have gained considerable attention due to their potential use as on-demand drug carriers [28]. MSNP investigation has thus far concentrated on the fabrication of cargo release in response to external stimuli such as redox, pH changes, enzyme activities, and photoirradiation. Because various tissues and cellular compartments have varied pH values, pH-Responsive drug delivery is commonly utilized [29–32]. Compared to normal tissues and blood, tumor tissues have an extracellular environment that is more acidic (pH 6.5). In contrast, cancer cells’ endosomes and lyses have pH values that are much lower (5.0–5.5). Various pH-responsive delivery methods have been developed to release drugs into tumour tissues at the right time. Even though pH variations stimulate drug release, it is frequently not enough to enhance drug delivery effectiveness and reduce adverse effects for anticancer treatments [33].

Multifunctional nanoprodrug MSNPs-based platforms for chemotherapy and PTT were devised and developed in this work, enabling the administration of DOX and R6G and a regulated release of DOX from the nanoprodrug platforms (figure 1). In a nutshell, the MSNP complex nanoparticles MSNP@poly(HEMA-co-PEGMA-g-DOX/R6G) co-loaded with the DOX/R6G were fabricated by precise reconfiguring the poly (HEMA-co-PEGMA) on the exterior of MSNPs, replanting DOX on the polymeric covalent reversible-bonding, and afterward incorporating R6G into the MSNP pores. In the presence of NIR laser irradiation and MSNP@poly(HEMA-co-PEGMA-g-DOX/R6G), the high photothermal conversion efficiency and strong NIR absorption rate of R6G can persuade the weak acidic environment within tumor cells. The photothermal ability of cancerous cell lines prompted the DOX release, which synergic performed with photodynamic therapy to successfully constrain the growth of tumour cells, illustrating the excellence of photothermal.

2. Experimental section

2.1. Fabrication of MSNP@Poly(HEMA-co-PEGMA-g-DOX/R6G)

2.1.1. Fabrication of MSNP-NH2

Using previously described methods [34–36], we could fabricate MSNPs with large pore sizes. Finally, the mixture of deionized water, cetyltrimethylammonium bromide (CTAB), FC2, and triethanolamine was agitated for one hour at 80 °C (500 cycles per minute). For the next two hours, 8 ml of tetraethyl orthosilicate was added. The samples were gathered, and the template agents were removed to acquire MSNP formation. The MSNP (1.0 g) was then heated at 90 °C in anhydrous toluene before being distributed. 3-Aminopropyl Triethoxysilane (silane coupling agent, 1.0 ml) was added to the RB-flask by drop and kept at 120 °C for one day. Using centrifugation and vacuum drying, MSNP-NH2 was obtained.

2.1.2. Fabrication of the MSNP-Br initiator

Triethylamine (2.5 ml), MSNP-NH2 (0.6 g), and 1.2 ml of 2-bromo-2-methylpropionyl bromide (1.2 ml) were mixed to anhydrous ice-cold THF, and the mixture was stirred for 5 min (50 ml). Following the dropwise
additions, the reactions were stirred for 3 h at 0 °C and then for 48 h at room temperature. Obtaining initiator MSNP-Br included filtering, washing with water, and drying.

2.1.3. Fabrication of MSNP@Poly(HEMA-co-PEGMA)

1,1,4,7,10,10-hexamethyl-triethylenetetramine (30.5 μl), CuBr₂ (3.8 mg) and MSNP-Br (0.2 g) in a water/methanol solution (2 ml) were all poured into a dry reaction flask and displaced three times through N₂. Once the monomers HEMA and OEGMA had been introduced to the reaction flask, a water/methanol solution (4 ml) was poured into the vessel. Finally, a solution of ascorbic acid was added to the process, evaporating in water/methanol (3 ml). It was necessary to heat the reaction mixture to 50 °C, let it drop to room temperature for 20 h, and then wash it multiple times with methanol and THF to achieve a greenish precipitate after stirring for 5 min at 500 revolutions per minute. The crude product was disseminated in acetylacetone/ethanol (5/1) solution, it was sonicated for 5 min and stirred (1000 rpm) at 30 °C for 24 h. After collecting and drying the residue for 24 h, the white MSNP@poly(HEMA-co-PEGMA) product was achieved.

2.1.4. Fabrication of pH-responsive DOX prodrugs

In 10 ml of dimethylformamide, we dissolved 80 mg of DOX.HCl and 80 mg of CA. A total of 13.0 μl of triethylamine was combined and allowed to react at 30 °C in the dark condition for one day. Before washing the combination with NaCl solution of pH 7.4 and 3.0, ethyl acetate was used to dilute it. After adding anhydrous MgSO₄, the organic phase was stored and dried, and the purified organic phase delivered the red powder CA-DOX.

2.1.5. Fabrication of MSNP@Poly(HEMA-co-PEGMA-g-DOX)

In a round-bottom flask, MSNP@poly(HEMA-co-PEGMA), anhydrous dichloromethane (DCM), 4-dimethylamino pyridine (7.0 mg), and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (7.0 mg) were mixed with a stirrer and exposed to argon bubbles for 25 min. Anhydrous DCM (3 ml) was used to dissolve 20 mg of CA-DOX, and the solution was progressively poured into the reactor above. The unreacted CA-DOX was removed by centrifuging the precipitates (5500 rpm, 15 min) and washing them with 70 ml of water after 24 h of reaction in the dark. MSNP@poly was obtained by lyophilizing the precipitates (HEMA-co-PEGMA-g-DOX).

MSNP@poly (HEMA-co-PEGMA-g-DOX) (25 mg) was mixed with 100 ml of 1 M hydrochloric acid and put at 30 °C for one day to test the grafting effectiveness of the mesoporous silica prodrug. After collecting the
The following procedures loaded a mesoporous silica prodrug with the photothermal small molecule dye R6G.

2.1.6. Fabrication of MSNP\textregistered poly(HEMA-co-PEGMA-g-DOX/R6G)

The following procedures loaded a mesoporous silica prodrug with the photothermal small molecule dye R6G. Methanol (5 ml) and R6G (30 mg) were swirled at 30 °C at 12 h with MSNP\textregistered poly(HEMA-co-PEGMA-g-DOX) (30 mg) and R6G (200 rpm). Centrifugation (5600 rpm, 10 min) was used to extract the unloaded R6G, then washed with a 10 % methanol/water solution and dried to produce MSNP\textregistered poly(HEMA-co-PEGMA-g-DOX)/R6G. MSNP\textregistered poly(HEMA-co-PEGMA)/R6G was used to control the sample without DOX. This experiment was done three times to get an accurate reading of R6G, which was determined by dissolving 10 mg of R6G in 10 ml of methanolic solution and measuring the absorbance peak at 795 nm. The reading was then compared to the R6G concentration-absorbance curve (figure 1).

2.2. Characterization of nanoparticles

FT-IR spectra of nanoparticles were recorded on a VERTEX 70 spectrometer (Bruker, Germany). The specific surface area and pore size were analyzed by nitrogen adsorption-desorption isotherms which was determined by ASAP 2010 Micromeritics analyzer (USA). Before the test, the nanoparticles were thoroughly dried and then degassed for 6 h at 150 °C and 1.3 kPa vacuum, after which the samples were tested at −195.5 °C. The structure and morphologies of particles were provided by a JEM-2100F (Japan) transmission electron microscopy (TEM) with an accelerating voltage of 80 kV and a JEOL JSM-6490LA (Japan) scanning electron microscopy (SEM). Thermogravimetric-S-2 analysis (TG) was performed using a STA449 (NETZSCH, Germany). The hydrodynamic diameter (Dh) of the nanoparticles was determined by dynamic light scattering measurements with a SZ-100Z nanoparticle analyzer (HORIBA, Japan). A Shimadzu HPLC system integrated with LC 10 ATVP pump and a Rheodyne injector (model 7125, 20 μl loop) was used for chromatographic method development and validation. Chromatographic resolution was accomplished on a RP LiChrospher® C18 column (100, 250 mm × 4.6 mm, 5 μm; Merck), at 35 °C of column temperature. Both the moieties eluted using an isocratic mobile phase comprised of aqueous buffer (0.025% w/v OSA; pH adjusted to 3.0 with OPA) and ACN mixed in a ratio of 37 : 63 parts, respectively. The total flow rate of mobile phase was 1 ml min\textsuperscript{−1}, with a total runtime of 10 min. The eluent was monitored at 231 nm for both the drugs using a Shimadzu SPD-M10 UV-PDA detector. Confocal laser scanning microscopy (CLSM) images were obtained using a Leica TCS SP5 II microscope (Germany).

2.3. In vitro controlled release

The acid-triggered release performance of the bonded DOX was evaluated by exposing the prodrug to pH 5.0, 6.0, and 7.4 buffer media at 37 °C, 42 °C, and 50 °C. Briefly, nanoparticles were dispersed in 4 ml of 1 × PBS buffer at pH 7.4 and placed in dialysis bags (molecular weight cutoff (MWCO) = 3.5 kDa), placed in 40 ml of different pH buffers (pH 7.4, 6.5, and 5.0) and shook continuously at 150 rpm at 37 °C, 42 °C, and 50 °C. Drug release was calculated by measuring the absorbance of supernatant withdrawn from the samples. The results of each experiment were averaged from three separate tests. The formula was used to determine the total cumulative emission of DOX [37].

5 mg prodrug systems were dissolved in 1.5 ml of acidic pH 5.0 buffer and then put into 15 ml of the same buffer solution and exposed to the drug release analysis using drug dissolving equipment. This was repeated two times. Laser irradiation was performed on one group for 5 min every 1 h, whereas the other group received no treatment. The DOX concentration was determined by measuring the medium’s absorbance at 480 nm and taking a sample per hour.

2.4. Analysis of NIR-induced photothermal effects

To irradiate 100 μl of the MSNP\textregistered poly(HEMA-co-PEGMA-g-DOX/R6G) dispersion with the NIR laser, three different polymer concentrations were generated (100, 200, and 500 μg ml\textsuperscript{−1}). A −1 digital thermometer immediately measured the solution’s temperature following irradiation. PBS solution and MSNP\textregistered poly(HEMA-co-PEGMA-g-DOX) were used as negative control samples in the same way as the positive samples. Temperatures of 25 °C were used for all photothermal experiments [38].

2.5. Hemolysis assays

Rat whole blood (n = 4) was obtained from the department of general medicine, the first people’s hospital of Wenling. To investigate the hemolysis properties of the nanomaterials [39], MSNP\textregistered poly(HEMA-co-PEGMA) was diluted to different concentrations in 0.01 M of PBS at pH 7.4 to ascertain the hemolytic activity. For this experiment, 150 μl of the diluant was immersed in a suspension of rat whole blood containing 4.0 %, which was
incubated before centrifuging. At 540 nm, 100 μl of the supernatant was taken, and the absorbance was measured. The negative and positive controls were PBS and deionized water, and each trial was performed thrice.

2.6. Cellular uptake of nanomaterials

A 24-well plate was inoculated with SNU-668 cells, and they were allowed to grow for 24 h. 0.5 or 1 h, without NIR laser (1.5 W cm⁻²) irradiation, new culture media with MSNP@poly(HEMA-co-PEGMA-g-DOX/R6G) or DOX alone with similar DOX concentrations (45 mg L⁻¹) was combined and incubated. After 5 min, cells were left in the dark after being washed thrice with PBS. Fluorescence microscopy examined cells fixed with Hoechst 33342 (2 μg ml⁻¹ in PBS). SNU-668 cells were then rinsed thrice and covered. All the experiments were conducted thrice.

2.7. In vitro cytotoxicity

SNU-668 cells were purchased from the Cell Bank of the Chinese Academy of Sciences (Shanghai, China). MSNP and MSNP@poly(HEMA-co-PEGMA-g-DOX/R6G) were assessed in SNU-2668 cells using an MTT assay. 4 × 10⁵ cells/well in 96-well plates were incubated for 24 h, and SNU-668 cells grown in DMEM were added and cultured for 24 h. Afterward, new culture media with varying quantities of MSNP, MSNP@poly (HEMA-co-PEGMA-g-DOX/R6G), and DOX alone were established in the experiment. All the 96-well plates were then incubated for 20- or 44 h following therapy, depending on whether one group had been exposed to NIR laser radiation for 6 min or not after the first incubation period of 4 h. After co-incubation for 24 h, the culture media were removed and replaced by 100 μl of fresh media, including MTT solution (10% v/v). After another 1 h of incubation, the absorbances at 450 nm were measured using a microplate reader (Model 680, BIO-RAD). The cytotoxicity of samples was determined by comparing the percentages of live cells in the treated and control groups [40–45].

3. Results and discussion

3.1. Fabrication and characterization of MSNP@poly (HEMA-co-PEGMA-g-DOX)/R6G

An improved approach resulted in an MSNP with a larger pore size. As per the previous investigations, the particle size of roughly 100 nm makes MSNP an excellent dispersion medium bonding and loading of DOX small molecules. Figure 3 suggests that some polymeric chains were embedded onto the MSNP internal surface. Figure 3 showed the average MSNP pore size was reduced, suggesting that some polymeric chains were embedded onto the MSNP internal surface. Figure 3 shows the thermogravimetric analysis (TGA) bends of various MSNP. MSNP-Br, MSNP@poly(HEMA-co-PEGMA), and MSNP@poly(HEMA-co-PEGMA-g-DOX) lost weight when heated to 900 °C in an N2 environment, losing 10.1%, 18.2%, and 28.2% respectively, suggesting that the polymer made up around 7.9% of the nanocarrier’s weight. It was also found that the drug was well-bonded. The FT-IR spectra (figure 2(F)) for the CTAB show peaks at 2921 and 2853 cm⁻¹ due to C-H stretching vibrations, which vanish after eliminating the templating agents. When using surface-initiated ATRP, the ATRP initiator should be fixed to the MSNP surface before loading the polymer. It was found that the FT-IR spectra of MSNP-Br had a new peak at around 1536 cm⁻¹, which was shown to represent the bending vibration of the N-H group secondary amine that had been attached to the MSNP surface by MSNP-Br amidation to formation. The CO bond from the COOH was ascribed to the absorption band at 1732 cm⁻¹. The FT-IR spectra of MSNP-Br had a new peak at around 1536 cm⁻¹, which was shown to represent the bending vibration of the N-H group secondary amine that had been attached to the MSNP surface by MSNP-Br amidation to formation. The FT-IR spectra of MSNP-Br had a new peak at around 1536 cm⁻¹, which was shown to represent the bending vibration of the N-H group secondary amine that had been attached to the MSNP surface by MSNP-Br amidation to formation. 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Figure 2. Characterizations of MSNP-polymer. (A) Transmission electron microscopy (TEM) image of MSNP-polymer. (B) Scanning electron microscopy image of MSNP-polymer. (C) Size distributions measured by DLS analysis. (D) Zeta-potential and (F) FT-IR spectra of MSNP-OH, MSNP-NH₂, MSNP-Br, and MSNP@poly(HEMA-co-PEGMA-g-DOX/R6G), respectively.

Figure 3. (A) N₂ adsorption-desorption isotherm spectra of MSNP-NH₂, MSNP@poly(HEMA-co-PEGMA), and MSNP@poly(HEMA-co-PEGMA-g-DOX/R6G). (B) Barrett-Joyner-Halenda pore size distribution plots of MSNP-NH₂, MSNP@poly(HEMA-co-PEGMA), and MSNP@poly(HEMA-co-PEGMA-g-DOX/R6G). (C) TGA curves MSNP-NH₂, MSNP-Br, MSNP@poly(HEMA-co-PEGMA), and MSNP@poly(HEMA-co-PEGMA-g-DOX/R6G). (D) UV–vis absorption spectral analysis of free DOX, free R6G, MSNP-NH₂, MSNP-Br, MSNP@poly(HEMA-co-PEGMA-g-DOX), and MSNP@poly(HEMA-co-PEGMA-g-DOX/R6G).
The hydrophobic dye R6G was incorporated into the MSNP. This nanoparticle appearance shift showed that the dye had been successfully encapsulated. According to the UV-vis spectra (figure 3(D)), MSNP@poly(HEMA-co-PEGMA-g-DOX) showed an increase in absorbance at 484 nm when DOX was conjugated. Absorption peaks at 797 nm were visible in the MSNP@poly(HEMA-co-PEGMA-g-DOX/R6G) solution after adding R6G. Polymer-modified MSNP nanoparticles were also shown to disperse nicely in the water, ascribed to the MSNP’s surface. Figure 3(D) shows the distribution of particle sizes before and after adjustment. The particle size and polydispersity remained below 0.3 after surface modification of the polymer. Only a slight increase in particle size and polydispersity was displayed after three days of standing. A lack of polymer modification resulted in larger particle sizes and an increased polydispersity index from 0.74 to 0.845. It showed that the polymer’s surface modification aids in the efficient dispersion of MSNP. The enhanced loading amount was attributable to the broad MSNP pore, which required dye space for storage, and the loading of R6G was 9.98 wt %. Maintaining the overall system’s photothermal stability is easier because R6G is kept in the MSNP pores and is less likely to be abruptly released during blood circulation.

3.2. DOX release profile and photothermal property

Poly(HEMA-co-PEGMA-g-DOX/R6G) release patterns in vitro under an acidic extracellular pH in malignant tumors (pH = 6.5–6.9) compared to normal tissue under physiologic conditions (7.2–7.4) are depicted in figures 4(A)–(F). After 50 h, less than 21% of DOX was discharged from the nanocarrier at pH 7.4, at which it was present. Thus, anhydride cis-aconitic, an active chemical bond that may be broken in an acidic environment, will slow down the DOX release because it is more stable and less susceptible to breaking in a non-acidic environment. A drop in pH resulted in DOX release rates of 65.2 % (pH = 6.9) and 85.1 % (pH = 6.0) at identical incubation durations (about 50 h), demonstrating a clear pH–response controlled drug release behaviour. Drugs with this release characteristic are less harmful to normal physiological tissues since they don’t leak throughout the circulation, improving drug consumption. This lower pH breaks reversible covalent links among the nanoparticles and drug molecules, allowing the drugs to collect in tumor tissue and increase their ability to destroy cancer cell lines.

Under NIR light, R6G has a high photothermal conversion efficiency, which raises system temperature. As the temperature rises, the drug’s release rate will be affected, and the ability of tumor cells to apoptosis. To better understand the release of drugs at varying pH levels, we conducted experiments at 37 °C, 42 °C, and 50 °C (figure 4(B)). pH 7.4 data indicated no significant influence on DOX release, with a relatively quick first 4 h followed by a gradual leveling off. The last release remained steady at around 25% of its initial value. There were

![Figure 4](image_url)

Figure 4. (A) In vitro DOX release profiles of MSNP@poly(HEMA-co-PEGMA-g-DOX/R6G) at pH 5.0, 6.5, and 7.4. (B)–(D) In vitro DOX release curves of MSNP@poly(HEMA-co-PEGMA-g-DOX/R6G) at the same pH (5.0, 6.5, and 7.4) and various temperatures (37 °C, 42 °C, and 50 °C). (E) DOX cumulative release from MSNP@poly(HEMA-co-PEGMA-g-DOX/R6G) with and without three cycles of NIR (2 W cm⁻²) irradiation. (F) Temperature curves of PBS, MSNP@poly(HEMA-co-PEGMA-g-DOX), and MSNP@poly (HEMA-co-PEGMA-g-DOX/R6G) at various concentrations under NIR irradiation. Data are presented as mean ± standard deviation (SD).
no significant changes in drug release rate or cumulative release when the temperature increased because of the more stable and less prone cis-acetyl group at pH 7.4. Within 0–4 h, the temperature rises substantially impacted the drug release, making the reach drug around 61% of the fast release in a pH 6.5–5.0 environment. After 4–50 h, the release rate became extremely sluggish, and the ultimate cumulative release showed no association with temperature. A rise in the temperature caused molecules to move more quickly. It thus facilitated DOX release from the polymer attached to the MSNP surface while simultaneously increasing the solubility of DOX and thus enhancing the therapeutic efficiency and pH sensitivity of the drug delivery method.

pH and NIR photothermal effects are synergistic; therefore, the release behavior of low pH was studied while NIR was alternately turned on and off. Dox release in a simulated lysosomal environment is shown in figure 4(E), which illustrates the influence on DOX release under 808 nm NIR laser (1.5 W cm\(^{-2}\), 5 min) (pH 5.0). A significant rise in DOX release occurred after the initial laser irradiation (1 h), and the drug release rose by up to 9% 2 and 3 h after the first treatment. A minor difference in the DOX release behavior was observed after irradiating NIR for 4 h, with a cumulative drug release of more than 67%, surpassing the non-laser irradiation form (44.2%) by around 24%. Our findings confirm our findings, which show that the rise in temperature generated by laser irradiation significantly influences DOX release. NIR laser-induced technique for rapid drug release allows for higher drug concentrations in the bloodstream and improved anticancer effects.

The R6G-loaded system’s photothermal conversion efficacy is a crucial metric to consider. Figure 4(F) demonstrates that after 6 min of continuous irradiation with 808 nm NIR laser (1.5 W cm\(^{-2}\)), temperature deviations in both PBS and MSNP@poly(HEMA-co-PEGMA-g-DOX) without R6G loading were not noticeable and that laser radiation without photothermal molecule R6G did not lead to normal cell death. After six minutes of continuous irradiation, as shown in figure 4(F), the temperatures of the prepared samples increased in proportion to the concentration increase. It was found that the temperature of the combination increased by about 12.7 °C and 17.5 °C when MSNP@poly(HEMA-co-PEGMA-g-DOX/R6G) at the concentration of 0.2 mg ml\(^{-1}\) and 0.5 mg ml\(^{-1}\), which indicates improved photothermal effectiveness that can attain the desired of producing higher thermal to destroy tumor cells and quicken the failure of acid-responsive bonding, which is necessary to kill tumor cells.

3.3. Biocompatibility assessment of MSNP@Poly(HEMA-co-PEGMA)
An evaluation of the carrier material’s cytotoxicity and biocompatibility is crucial. Nanoparticles must greatly inhibit tumor cell development following drug loading [46–48]. A hemolysis assay and an MTT assay were used to determine the biocompatibility of MSNP@poly(HEMA-co-PEGMA) as an anticancer drug carrier in tumor treatment. A well-known fact is that MSNP is a soft substance ideal for delivering pharmaceutical applications (figure 5). ATRP initiation covered the mesoporous silica surface with polymer grafting to give the system pH-responsive characteristics. Hemolysis rates of less than 5% were reported when MSNP@poly(HEMA-co-PEGMA) was co-cultured with red blood cells (figure 5). Various cell lines, including SNU-668, were used to test the cytotoxicity of MSNP@poly(HEMA-co-PEGMA) for 12 and 24 h. To figures 6(A)–(B), increasing the concentration of MSNP@poly(HEMA-co-PEGMA) did not significantly decrease cell growth or proliferation.
Because of its high biocompatibility, the anticancer drugs may be delivered by MSNP@poly(HEMA-co-PEGMA).

3.4. Cytotoxicity and fluorescence findings

The proliferation of MSNP@poly(HEMA-co-PEGMA-g-DOX/R6G) and DOX to SNU-668 cells was evaluated by the MTT analysis [49–51]. The cytotoxicity curves showed that both MSNP@poly(HEMA-co-PEGMA-g-DOX/R6G) and DOX alone had substantial negative impacts on the proliferation and growth of SNU-668 cells (figure 7). This correlation between cell viability and concentration was evident in the 24 and 48 h incubation studies, with a steady decline in cell survival as DOX concentrations rise (figures 7(A)–(B)). The antitumor activity of MSNP@poly(HEMA-co-PEGMA-g-DOX/R6G) at the exact dosage of DOX without 808 NIR laser was marginally smaller than the DOX alone, mainly for DOX alone is a slight drug that is easily absorbed by cancer cells and is uptake in a nonspecific manner by passive diffusion. It is slower to enter cells by phagocytosis than DOX alone, so we use MSNPs to attach to DOX, which have particle sizes of roughly 100 nm compared to DOX alone. DOX could be entirely released into the intracellular milieu because of the system’s dynamical covalent bonding-controlled drug release behavior, which necessitates lowering the pH of the MSNP.

When the concentrations of MSNP@poly(HEMA-co-PEGMA-g-DOX/R6G) were low, NIR laser irradiations of MSNP@poly(HEMA-co-PEGMA-g-DOX/R6G) were marginally fewer cytotoxic than DOX alone, probably for the R6G concentrations were too less to produce sufficient warmth to stimulates the faster DOX release or attain PTT to deactivate the cancer cells. Its cytotoxicity was the same and even marginally greater than DOX alone at a 5 μg ml⁻¹ concentration of MSNP@poly(HEMA-co-PEGMA-g-DOX)/R6G. An example of a chemical–photothermal synergy occurs when a high concentration of R6G photosensitizer causes irreversible cell destruction while breaking reversible covalent bonds rapidly, resulting in drug release. DOX
alone was fatal to the cells at the drug concentration \((10 \text{ mg ml}^{-1})\) in NIR laser radiations, efficiently decreasing the efficient dosage of MSNP@poly(HEMA-co-PEGMA-g-DOX/R6G) to 20 mg/ml. For these reasons, combining chemotherapy and PTT with MSNP@poly(HEMA-co-PEGMA-g-DOX/R6G) can enhance the inhibitory impact on tumor cells when exposed to NIR laser irradiation.

SNU-668 gastric cells have their nanoparticles internalized by CLSM images (figure 8). Red fluorescence is emitted by DOX alone. Fluorescence in the nucleus of cells is produced when Hoechst33353 is activated by UV light. Individual blue fluorescence was observed in cells cultivated without drug-loaded nanoparticles; no red fluorescence was found (figure 8). Figure 8 shows a slight red glow in cancer cells and initially in the cytoplasm after 30 min of MSNP@poly(HEMA-co-PEGMA-g-DOX/R6G) co-culturing with that the drug-coloaded nanoparticles were progressively endocytosis currently in the cancer cells. Fluorescence from MSNP’s nucleus rapidly increased over time, suggesting that DOX from drug-loaded nanoparticles had progressively dropped from the MSNP surface and concentrated in the nucleus. MSNP@poly(HEMA-co-PEGMA-g-DOX/R6G) is well endocytosed by the cancer cells and can be used to treat gastric cancer cells \([52–54]\). The cells were treated with NIR light to see whether it may speed up cell absorption and release of drugs. After revealing to the NIR light, the DOX red fluorescence became more concentrated in the nuclei of the cells. In addition to increasing the cell membrane’s permeability and sensitivity, the higher temperature also speeds up the breakdown of acid-sensitive links, resulting in a faster release of DOX. MSNP@poly(HEMA-co-PEGMA-g-DOX/R6G) may be successfully endocytosis by cancer cells in the fast release anticancer drugs and photothermal action, which has future use for gastric cancer therapy.

4. Conclusions

Splicing a biocompatible polymer onto the mesoporous silica surface, using covalent reversible bonding to incorporate the anticancer DOX drug, and co-loaded the photosensitizer organic R6G small molecule into MSNP, a new pH-response drug delivery framework was established for combination chemotherapy and PTT of gastric cancer therapy. Additionally, photothermal conversion speeds up the rate at which reversible covalent bonds are broken, increasing the release of DOX and decreasing drug concentrations needed for the same cell lethality. This results in improved biosafety and a reduction in the treatment preparation cost. With its photothermal activity and reversible chemical bond breakdown, MSNP@poly(HEMA-co-PEGMA-g-DOX/R6G) has significant promise in combination with the treatment and care of gastric cancer therapy by boosting the synergistic impact of chemotherapy.

Figure 8. CLSM images of SNU-668 cells incubated for 1 h, incubated with MSNP@poly(HEMA-co-PEGMA-g-DOX/R6G) with or without NIR laser (2 W cm\(^{-2}\)) for 30 min and 1 h. Scale bars of the picture 20 \(\mu\)m.
Data availability statement

No new data were created or analysed in this study.

Notes

The authors declare no competing financial interest.

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References

[1] Schultz E, Collares T, Lucas C G and Seixas F K 2018 Synergistic and additive effects of ATRA in combination with different anti-tumor compounds Chem. Biol. Interact. 285 69–75
[2] Li Y, Atkinson K and Zhang T 2017 Combination of chemotherapy and cancer stem cell targeting agents: preclinical and clinical studies Cancer Letters. 396 103–9
[3] Liang X, Gao C, Cui L, Wang S, Wang J and Dai Z 2017 Self-assembly of an amphiphilic janus camptothecin–fluorouracil conjugate into liposome-like nanocapsules for more efficacious combination chemotherapy in cancer Adv. Mater. 29 1703135
[4] Gotwals P et al 2017 Prospects for combining targeted and conventional cancer therapy with immunotherapy Nat. Rev. Cancer 17 286–301
[5] Redondo-Blanco S, Fernández-J, Gutiérrez-del-Rio I, Villar C J and Lombó F 2017 New insights toward colorectal cancer chemotherapy using natural bioactive compounds Frontiers in Pharmacology 8 109
[6] Qin S-Y, Cheng Y-I, Lei Q, Zhang A-Q and Zhang X-Z 2018 Combinational strategy for high-performance cancer chemotherapy Biomaterials 171 178–97
[7] Yan Y, Kumar A B, Finnes H, Markovic S N, Park S, Dronca R S and Dong H 2018 Combining immune checkpoint inhibitors with conventional cancer therapy Frontiers in Immunology 9 1739
[8] Zhang Y, Huang F, Ren C, Yang L, Liu J, Cheng Z, Chui L and Liu J 2017 Targeted chemo-photodynamic combination platform based on the DOX prodrug nanoparticles for enhanced cancer therapy ACS Appl. Mater. Interfaces 9 13016–28
[9] Liu C, Chen G-B, Chen H-H, Zhang J-B, Li H-Z, Sheng M-X, Weng W-B and Guo S-M 2019 Cancer cell membrane-cloaked mesoporous silica nanoparticles with a pH-sensitive gatekeeper for cancer treatment Colloids Surf. B, 175 477–86
[10] Wang L et al 2019 Nitric oxide stimulated programmable drug release of nanosystem for multidrug resistance cancer therapy Nano Lett. 19 6800–11
[11] Iannazzo D, Pistone A, Salamò M, Galvagno S, Romeo R, Gisfré S V, Branca C, Visalli G and Di Pietro A 2017 Graphene quantum dots for cancer targeted drug delivery Int. J. Pharm. 518 185–92
[12] Ganiuja A, Khan S, Hafeez B B, Behrman S W, Yallapu M M, Chauhan S C and Jaggi M 2017 Mirna nanotherapeutics for cancer Drug Discovery Today 22 424–32
[13] Habibi Jouybari M, Hosseini S, Mahboobnia K, Boloussarz L A, Moradi M and Irani M 2019 Simultaneous controlled release of 5-FU, DOX and PTX from chitosan/PLA/5-FU/g-C3N4-DOX/g-C3N4-PTX triaxial nanofibers for breast cancer treatment in vitro Colloids Surf., B 179 495–504
[14] Álvès C G, de Melo-Diogo D, Lima-Sousa R, Costa E C and Correia I J 2019 Hyaluronic acid functionalized nanoparticles loaded with IR780 and DOX for cancer chemo-photothermal therapy Eur. J. Pharm. Biopharm. 137 86–94
[15] Ashrafizadeh Set al 2021 Long non-coding RNAs in the doxorubicin resistance of cancer cells Cancer Letters 508 104–14
[16] Riley R S and Day E S 2017 Gold nanoparticle-mediated photothermal therapy: applications and opportunities for multimodal cancer treatment WIREs Nanomedicine and Nanobiotechnology 9 e1449
[17] Li X, Lovell J F, Yoon J and Chen X 2020 Clinical development and potential of photothermal and photodynamic therapies for cancer Nat. Rev. Clin. Oncol. 17 657–74
[18] Hai L, Iua X, He D, Zhang A, Wang T, Cheng H, He X and Wang K 2018 DNA-functionalized hollow mesoporous silica nanoparticles with dual cargo loading for near-infrared-responsive synergistic chemo-photothermal treatment of cancer cells ACS Appl. Nano Mater. 1 3486–97
[19] He S, Jiang Y, Li J and Pu K 2020 Semiconductor polycomplex nanoparticles for photothermal ferrotherapy of cancer Angew. Chem. Int. Ed. 59 10635–8
[20] Jin J et al 2018 Graphidyne nanosheet-based drug delivery platform for photothermal/chemotherapy combination treatment of cancer ACS Appl. Mater. Interfaces 10 8436–42
[21] Shao J, Ruan C, Xie H, Li Z, Wang H, Chu P K and Yu X-F 2018 Black-phosphorus–incorporated hydrogel as a sprayable and biodegradable photothermal platform for posturgical treatment of cancer Adv. Sci. 5 1700848
[22] Chen J, Ning C, Zhou Z, Yu P, Zhi Y, Tan G and Mao C 2019 Nanomaterials as photothermal therapeutic agents Prog. Mater. Sci. 99 1–26
[23] Vines J B, Yoon J-H, Ryu N-E, Lim D-J and Park H K 2019 Gold nanoparticles for photothermal cancer therapy Frontiers in Chemistry 7 167
[24] Doughty A C V, Hoover A R, Layton E, Murray C K, Howard E W and Chen W R 2019 Nanomaterial Applications in Photothermal Therapy for Cancer Materials 12 779
[25] Zhou Q, Zhang L, Yang T and Wu H 2018 Stimuli-responsive polymeric micelles for drug delivery and cancer therapy Int. J. Nanomed. 13 2921–42
[26] Yao Y, Zhou Y, Liu L, Xu Y, Chen Q, Wang Y, Wu S, Deng Y, Zhang J and Shao A 2020 Nanoparticle-based drug delivery in cancer therapy and its role in overcoming drug resistance Frontiers in Molecular Biosciences 7 193
[27] Biffi S, Volan R, Bortot B, Zauli G and Secchiero P 2019 Actively targeted nanocarriers for drug delivery to cancer cells Expert Opinion on Drug Delivery 16 481–96
[28] Palmerton Mendes L, Pan J and Torchilin V P 2017 Dendrimers as nanocarriers for nucleic acid and drug delivery in cancer therapy Molecules 22 1401
[29] Qiao Y, Wan J, Zhou L, Ma W, Yang Y, Luo W, Yu Z and Wang H 2019 Stimuli-responsive nanotherapeutics for precision drug delivery and cancer therapy WIREs Nanomedicine and Nanobiotechnology 11 e1527
[30] Saraf S, Jain A, Tiwari A, Verma A, Panda P K and Jain S K 2020 Advances in liposomal drug delivery to cancer: An overview J. Drug Delivery Sci. Technol. 36 101549
[31] Shanmuganathan R, Edison T N J I, Lewis-Oscar F, Kumar P, Shanmugam S and Pugazhendhi A 2019 Chitosan nanopolymers: An overview of drug delivery against cancer Int. J. Biol. Macromol. 130 727–36
[32] Bahrami B, Hojjat-Farsangi M, Mohammadhi H, Anvari E, GhalamfarSa G, Yousefi M and Jafidi-Niaagh F 2017 Nanoparticles and targeted drug delivery in cancer therapy Immunology Letters 190 64–83
[33] Mullick Chowdhury S, Lee T and Willmann J K 2017 Ultrasound-guided drug delivery in cancer Ultrasonography (Seoul, Korea). 36 171–84
[34] Deng B, Ma P and Xie Y 2017 Reduction-sensitive polymeric nanocarriers in cancer therapy: a comprehensive review Nanoscale 9 12723–95
[35] da J, Schoffer N, Matte C R, Charqueiro D S, de Menezes E W, Costa T M H, Benvenutti E V, Rodrigues R C and Hertz P F 2017 Directed immobilization of CGTase: The effect of the enzyme orientation on the enzyme activity and its use in packed-bed reactor for continuous production of cyclodextrins Process Biochem. 58 120–7
[36] Li X, Xing L, Hu Y, Xiong Z, Wang R, Xu X, Du L, Shen M and Shi X 2017 An RGD-modified hollow silica@Au core/shell nanoplatorm for tumor combination therapy Acta Biomater. 62 273–83
[37] Gulzar A, Gai S, Yang P, Li C, Ansari M B and Lin J 2015 Stimuli responsive drug delivery application of polymer and silica in biomedicine J. Mater. Chem. B 3 6599–622
[38] Hu J-I, Liu M-D, Chen Y, Gao F, Feng S-Y, Xie B-R, Li C-X, Zeng X and Zhang X-Z 2019 Immobilized liquid metal nanoparticles with improved stability and photothermal performance for combinational therapy of tumor Biomaterials 207 76–88
[39] Subarkhan M K M and Ramesh R 2016 Ruthenium(II) arene complexes containing benzhydrazide ligands: Synthesis, structure and antiproliferative activity Inorganic Chemistry Frontiers 3 1245–55
[40] Subarkhan M K M and Ramesh R 2016 Ruthenium(ii) arene complexes containing benzhydrazide ligands: synthesis, structure and antiproliferative activity Inorganic Chemistry Frontiers 3 1245–55
[41] Giriraj K, Mohamed Kasim M S, Balasubramaniam K, Thangavel S K, Suresh S, Shanmugam P and Karri C 2022 Various coordination modes of new coumarin Schiff bases toward Cobalt (III) ion: synthesis, spectral characterization, in vitro cytotoxic activity, and investigation of apoptosis Appl. Organomet. Chem. 36 e00536
[42] Pillaiadugula R, Haribabu J, Mohamed Subarkhan M K, Echeverria C, Karvembu R and Gopakrishnan N 2021 Effect of morphology and (Sn, Cr) doping on in vitro antiproliferation properties of hydrothermally synthesized 1D GaOOH nanotubes Journal of Science: Advanced Materials and Devices 6 351–63
[43] Swaminathan S, Haribabu J, Mohamed Subarkhan M K, Gayathri D, Balakrishnan N, Bhuvanesh N, Echeverria C and Karvembu R 2021 Impact of aliphatic acyl and aromatic thiourea substituents on the anticancer activity of Ru(ii)-p-cymene complexes with acylhioamide ligands—in vitro and in vivo studies Dalton Trans. 50 16311–25
[44] Kalaiarasi G, Mohamed Subarkhan M, Fathima Safwana C K, Sruhti S, Sathiyar Kamatchi T, Keerthana B and Kumar S L A 2022 New organoruthenium(II) complexes containing N, X-donor (X = O, S) heterocyclic chelators: Synthesis, spectral characterization, in vitro cytotoxicity and apoptosis investigation Inorg. Chem. Acta 535 120663
[45] Mohamed Subarkhan M K, Ramesh R and Liu Y 2016 Synthesis and molecular structure of arene ruthenium(II) benzhydrazide complexes: Impact of substitution at the chelating ligand and aren moiety on antiproliferative activity New J. Chem. 40 9813
[46] Xu L, Wang H, Tian H, Zhang M, He J and Ni P 2021 Facile construction of noncovalent graft copolymers with triple stimuli-responsiveness for triggered drug delivery Polym. Chem. 12 2152–64
[47] Mohammadinejad R et al 2020 In vivo gene delivery mediated by non-viral vectors for cancer therapy J. Controlled Release 325 249–75
[48] Natarajan S K and Selvaraj S 2014 Mesoporous silica nanoparticles: Importance of surface modifications and its role in drug delivery RSC Adv. 4 14328–34
[49] Swaminathan S, Haribabu J, Mohamed Subarkhan M K, Manonmani G, Senthilkumar K, Balakrishnan N, Bhuvanesh N, Echeverria C and Karvembu R 2022 Coordination behavior of acylthiourea ligands in their Ru(ii)-p-cymene complexes—structures and anticancer activity Organometallics 41 1621–30
[50] Wang Y, Jin J, Shu L, Li T, Lu S, Subarkhan M K M, Chen C and Wang H 2020 New organometallic ruthenium(ii) compounds synergistically cytotoxic, antitumatastic and antiangiogenic activities for the treatment of metastatic cancer Chemistry – A European Journal 26 15170–82
[51] Mohamed Subarkhan M, Prabhu R N, Raj Kumar R and Ramesh R 2016 Antiangioproliferative activity of cationic and neutral thiosemicarbazone copper(ii) complexes RSC Adv. 6 25082–93
[52] Karki N, Tiwari H, Tewari C, Rana A, Pandey N, Basak S and Sahoo N G 2020 Functionalized graphene oxide as a vehicle for targeted drug delivery and bioimaging applications J. Mater. Chem. B 8 8116–48
[53] He C et al 2021 A solid lipid coated calcium peroxide nanocarrier enables combined cancer chemo/chemodynamic therapy with O2/H2O2 self-sufficiency Acta Biomater. 122 354–64
[54] Kundu M, Chatterjee S, Ghosh N, Mannia P, Das J and Sill P C 2020 Tumor targeted delivery of umbelliferone via a smart mesoporous silica nanoparticles controlled-release drug delivery system for increased anticancer efficiency Mater. Sci. Eng. C 116 111239