

Hyaluronic acid coated hollow mesoporous silica nanoparticles for reduction-triggered drug release

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In this work, the reduction-responsive hyaluronic acid (HA) coated hollow mesoporous silica nanoparticles (HMSNs) were developed for the targeted tumour therapy. First, the anticancer drug doxorubicin was retained inside the central hollow cavities of the HMSNs with high loading efficiency. Meanwhile, the adamantane group was anchored on the surface of the HMSNs using the disulphide bond as the reduction-cleavable linkage. Subsequently, the β -cyclodextrin (β -CD) decorated HA was immobilised on the surface of HMSNs by the strong β -CD/adamantane host-guest interactions. Specifically, the β -CD acted as the pore caps to block the loaded drug inside, while HA served as the targeting ligand for the effective cancer therapy. Under the intracellular reductive environment, the nanocomposites displayed reduction-triggered drug release manner. Confocal microscopy observations confirmed the nanocomposites were easily internalised by HeLa cancer cells and released the loaded drug inside. In addition, the cytotoxicity study evidenced that HA decorated nanocomposites exhibited improved biocompatibility and antitumour activity as compared to that without HA modification. Thus, the reduction-responsive nanocomposites could be promising as a drug delivery platform toward the cancer therapy.

1. Introduction: Mesoporous silica nanoparticles (MSNs) have grown and hold great potential in drug delivery applications due to appropriate porous size for the storage of the therapeutic agents [1–3]. In addition, the easy surface modification with silane coupling agent on the surface of silica materials also allows the introduction of various functional groups, which could further control and tailor the properties to meet the specific requirements for delivery applications. To alleviate the side effect concern of nanocarriers themselves, it is highly beneficial to utilise the nanocarriers with higher drug loading capacity for effective therapy [4]. To cope with this challenge, the hollow MSNs (HMSNs) have been further developed [5, 6]. As compared with conventional MSNs, the hollow cavities inside HMSNs allow the storage of more therapeutic cargoes during the drug transportation process.

Over the past decade, major advancements have witnessed in the development of stimuli-responsive MSNs that retained drug inside under physiological conditions (e.g. during the blood circulation) [7–9], while exhibited smart and burst drug release feature in response to biological or external triggers. Since the concentration of reducing agent glutathione (GSH) within cancer cells is generally 10^3 -fold higher than that in the extracellular matrix [10], an enormous amount of research on drug delivery has focused on the construction of reduction-responsive MSNs for the ‘on-demand’ drug release.

Cyclodextrins are compounds made up of cyclic oligosaccharides with the excellent biocompatibility and biodegradability. Furthermore, the axial void cavity inside the cyclodextrins can accommodate various hydrophobic guest molecules with the specific size/shape *via* hydrophobic interaction [11]. By chemically modification on the outer surfaces of MSNs, cyclodextrins could serve as the gatekeeper to block the mesopore channels to retain the loaded drug inside, due to the large size of cyclodextrin ring. To realise the controlled drug release, cyclodextrins were often directly modified on the nanocarriers with the stimulus-labile chemical bond, such as disulphide [12–14], boronate linkage [15], imine [16], and *o*-nitrobenzyl ester [17]. Meanwhile, the cavity of cyclodextrin was able to accommodate the guest molecules for the introduction of other functional groups [12, 15].

However, the grafting density of cyclodextrins is often compromised by using this method, due to the steric hindrance effect of cyclodextrin molecules during the modification process.

Despite the direct chemical grafting method, there is also an alternative tactic, which is to introduce the cyclodextrin *via* the host-guest interaction effect. First, the surface of MSNs was functionalised with guest molecules including adamantane [18, 19], azobenzene [20], benzimidazole [21], coumarin [22] and so on. Then cyclodextrin molecules served as the gatekeeper *via* the noncovalent association with guest units on the MSNs. Among them, adamantane has been most widely used [23–25], since it could form a stable specific inclusion complex with β -CD with a high association constant.

As a water-soluble natural polysaccharide with excellent viscoelasticity, biocompatibility and biodegradability, hyaluronic acid (HA) has been widely used as building units for the construction of biomaterials for tissue engineering and drug delivery application [26, 27]. Moreover, HA selectively interacts with the receptors including CD44 and RHAMM [28, 29], which are over-expressed on the surface of various cancer cells, and facilitate the active targeting to tumour cells for the selective therapy. HA has been reported to modify on the surface MSN for targeted antitumour therapy *via* direct amidation [30, 31] and ionic gelation [32]. Thus, it is of great significance to develop the stimulus-responsive HA fabricated MSNs *via* facial preparation process, such as the supramolecular host-guest interaction.

In an effort to further improve drug release performances and cancer cell targeting ability, the reduction-responsive HA coated HMSNs nanocomposites were prepared in this study. The disulphide bond was utilised as the reduction-cleavable linker between the HMSNs and adamantane group. Taking advantages of the strong β -CD/adamantane host-guest interactions, β -CD was then immobilised on the surface of HMSNs to keep the loaded doxorubicin (DOX) inside. The conjugated HA shell not only increased the aqueous dispersibility and biocompatibility of the nanocarriers but also strongly targeted over-expressed HA-receptor on the surface of tumour cells. In vitro drug release study exhibited the DOX release rate was significantly enhanced in response to the exterior GSH

environment. Confocal observation further exhibited that the DOX was successfully released from the nanocomposites into the cytoplasm in HeLa cells for the treatment. Cytotoxicity study also confirmed the introduction of HA shell increased the biocompatibility and antitumour activity of the nanodrug for the therapy. This kind of reduction-responsive HA coated HMSNs nanocomposites may have great potential for drug delivery application.

2. Experiments

2.1. Materials: All the chemical reagents were analytical graded and used without further purification were used. The surfactant removed sulphydryl group functionalised HMSNs-SH were prepared according to our previous reports [33]. 3-(pyridin-2-ylsulfanyl)propanoic acid and β -CD modified hyaluronic acid (HA-CD) were prepared according to literature procedures [34, 35].

2.2. Characterisation: Transmission electron microscopy (TEM) images were obtained on JEM-1400 (JEOL) at an acceleration voltage of 100 kV. Scanning electron microscope (SEM) images were collected on JSM-7100F (JEOL, Japan) operated at 100 kV. The fluorescence intensities were measured by fluorescence spectrophotometer (RF5301PC, Shimadzu, Japan). Fourier transform infrared (FTIR) spectroscopy was performed on Prestige-21 (Shimadzu, Japan) spectrophotometer. Hydrodynamic diameters and size distributions were determined by Malvern Zetasizer Nano-S dynamic light scattering (DLS) system at 25°C. X-ray photoelectric spectroscopy (XPS) was carried out on Phoibos 100 spectrometer and a monochromatic Mg X-ray radiation source (SPECS, Germany) was used for the wide-range resolution S 2p scans at 12.53 kV. N_2 adsorption-desorption isotherms were recorded on a Micromeritics ASAP 2020M automated sorption analyser. Thermogravimetric analysis was carried out for powder samples using a TGA Q500 recorded from 100 to 900°C in a nitrogen flow at a heating rate of 10°C min⁻¹. Confocal laser scanning microscopy (CLSM) images were acquired by a Leica TCS confocal microscope with a Nikon Eclipse TE2000-S objective.

2.3. Preparation of the nanocomposites: HMSNs-SH (0.5 g) was dispersed in the 30 ml of anhydrous ethanol, to which 1.2 ml of acetic acid and 0.5 g of 3-(pyridin-2-ylsulfanyl)propanoic acid were added, and the suspension was stirred at room temperature for 36 h. The carboxylic acid functionalised nanoparticles with disulphide linkage were collected by centrifugation and washed extensively with methanol, dried under vacuum and denoted as HMSNs-COOH.

For the loading of the drug, HMSNs-COOH (10 mg) and DOX•HCl (5 mg) were dispersed in 1 ml of deionised water assisted by ultrasonication. Then the mixture was stirred for 24 h at room temperature in the darkness. For the attachment of adamantane group, the DOX loaded nanoparticles were collected by centrifugation and re-dispersed in the 3 ml of phosphate buffer (pH 6.0) containing 15 mg of EDC (15 mg) and NHS (12 mg). After stirring for 2 h, 20 mg of 1-adamantanamine hydrochloride was added into the suspension and the mixture was stirred at room temperature for another 12 h. After centrifugation, the product was washed with deionised water for three times and dried under vacuum. The resulted product was denoted as HMSNs-Ad@DOX.

To retain the loaded drug inside, the pore channels of HMSN were finally capped with the HA-CD. Briefly, 10 mg of HMSNs-Ad@DOX were dispersed in 5 ml of deionised water and then 4 mg of HA-CD was added to the suspension. The mixture was stirred at room temperature for 24 h. After centrifugation, the nanocomposites were collected and washed with deionised water for three times. Finally, the nanocomposites were dried under vacuum and denoted as HMSNs-HA@DOX.

2.4. Reduction-triggered DOX release: For the evaluation of DOX loading efficiency, HMSNs-HA@DOX (1.0 mg) were incubated

with DL-dithiothreitol (DTT, 10 μ M) in DMSO (2.0 ml) at room temperature in the dark overnight. The supernatant containing DOX was obtained after the centrifugation. Then the remaining nanoparticles were repeatedly washed with DMSO until the supernatant was nearly colourless. All the supernatants were combined, and the total amount of extracted DOX was determined by the fluorescence emission intensity at 562 nm (excitation at 480 nm).

The reduction-triggered release of loaded DOX from HMSNs-HA@DOX was studied when incubated without or with the GSH stimuli. At first, 4 ml of HMSNs-HA@DOX suspension was transferred into the dialysis bag (MWCO = 3500) and dialysed against the deionised water containing the reducing agent GSH (2 and 10 mM, respectively) at 37°C in the dark. The dialysis medium without GSH stimulus was used as the control. At desired time intervals, 4.0 ml of the dialysis medium was taken out for the analysis, while the same amount of fresh medium was added back. The concentration of the released DOX in the outer medium was measured by the fluorescence spectrometer.

2.5. Cell study: HeLa cells were incubated in DMEM medium containing 10% FBS at 37°C in the 5% CO₂ atmosphere. Briefly, cells were seeded onto glass coverslips in six-well plates with a cell density at 2×10^5 per well in the medium (2.0 ml). When the cell confluence reached around 60–70%, cells were washed with phosphate buffered saline (PBS). Then, the wells were added with free DOX or nanodrug in the medium with the final DOX concentration of 5 μ g ml⁻¹ and the cells were incubated for another 4 h. After that, the cells were washed with PBS twice and fixed with 4% formaldehyde at room temperature for 30 min. Finally, the samples were stained with Hoechst 33342 (blue colour) for 5 min for the confocal observation.

The in vitro antitumour effects of the nanocomposites were quantitatively evaluated by using MTT assay. Briefly, HeLa cells were seeded in 96-well plates with a density of 1×10^4 cells per well in 200 μ l of culture medium. When the cell confluence reached around 60–70%, the medium was removed and the wells were added with various concentrations of free DOX or nanodrug in the medium. After incubation for 24 h, the medium was replaced by a fresh one, followed by the addition of 10 μ l of MTT solution (5 mg l⁻¹). After 4 h of culture, the medium was replaced by DMSO (150 μ l) to dissolve the resulted purple crystals. Cell viability was calculated by comparing the absorbance intensity (490 nm) of the sample group with the control by using a microplate reader.

3. Results and discussion: The β -CD modified HA, HA-CD, was synthesised by the amidation of sodium hyaluronate and aminated β -CD in aqueous solution at first according to the literature [35]. The reduction-responsive HA coated HMSNs were fabricated according to Fig. 1. The HMSNs-COOH containing terminal carboxylic group and disulphide bond linkage were obtained through the disproportionation reaction between sulphydryl groups on the HMSNs-SH and 3-(pyridin-2-ylsulfanyl)propanoic acid. The morphology of HMSNs-COOH was characterised by SEM and TEM (Figs. 2a, c, e), from which the hollow cavity structure was clearly observed. The average diameter of the nanoparticles was determined to be around 150 nm, while the thickness of the mesoporous silica shell was around 20 nm. The hollow space exhibits remarkable advantages compared with conventional MSNs, as it allows the accommodation of more therapeutic agents for drug delivery application.

After accommodation of DOX, the adamantane group was grafted on the surface of nanocarriers via an amidation reaction in water. Since adamantane group tends to be included in the cavity of β -CD via strong host-guest interactions, the HA-CD was easily immobilised on the surface of nanocarriers in water. After the addition of HA-CD to the suspension of HMSNs-Ad@DOX, the β -CD covered the mesopore channels and acted as the gatekeeper to retain the loaded DOX inside. As shown in Fig. 2f, the

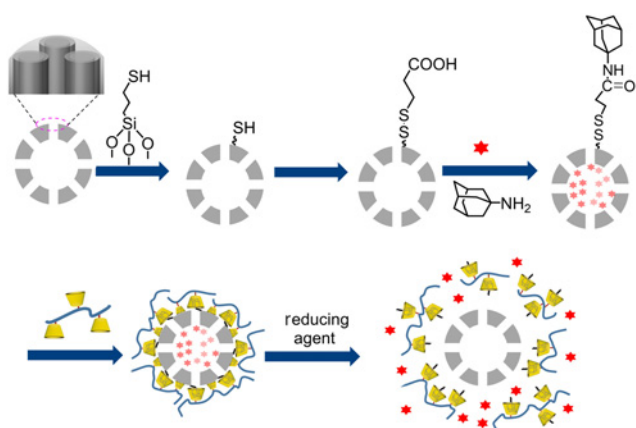


Fig. 1 Synthesis of HMSNs-HA@DOX and the reduction-triggered drug release

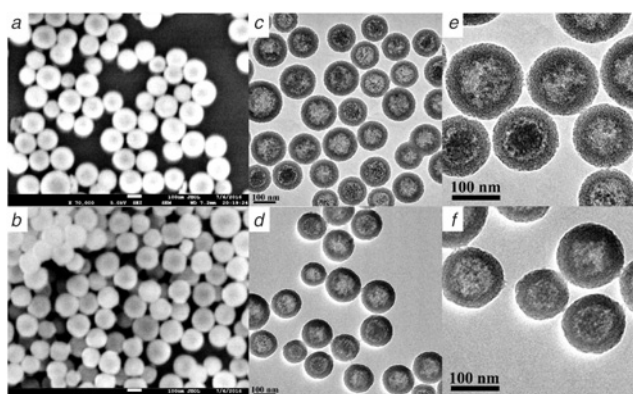


Fig. 2 SEM images of
a HMSNs-COOH
b HMSNs-HA@DOX,
TEM images of
c, e HMSNs-COOH and
d, f HMSNs-HA@DOX

mesoporous structure disappeared and the surface of nanoparticles became blurry, which was ascribed to the HA-CD coating on the HMSNs. Accordingly, the diameter of HMSNs-HA@DOX measured by DLS increased from 156 to 198 nm after the modification with HA-CD, while the size distribution was not changed too much. It could be explained that immobilised hydrophilic HA tent to stretch in water during the analysis, leading to the increment of hydrodynamic diameter of the nanoparticles (see Fig. 3).

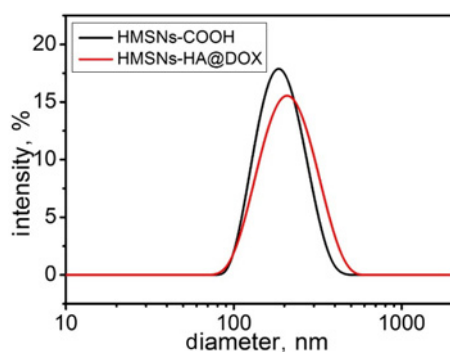


Fig. 3 Size distributions of HMSNs-COOH and HMSNs-HA@DOX in water

XPS was utilised to analysis the elemental composition within the surface of the material. As shown in Fig. 4, the C1s peaks of the nanoparticles gradually increased as the modification proceeded step by step, indicating the C content composition was increased after each modification step. FTIR has also been utilised to track the modification process. Compared with FTIR spectrum of HMSNs-COOH (Fig. 5), new weak peaks around 2855 cm^{-1} was also observed, which was attributed to the stretching vibration of additional C-H bond from the introduced adamantane groups. After the modification with HA-CD, it was observed that the peak intensities at 2855 and 1550 cm^{-1} further increased a bit, ascribing to the C-H stretching vibration of saccharide and N-H bending vibration of amide, respectively. All the XPS and FTIR data confirmed both the adamantane group and HA-CD have been successfully modified on the surface of HMSNs.

The thermogravimetric analysis was performed to roughly determine the organic contents in the resulting nanohybrids. The results shown in Fig. 6 indicated the weight loss of HMSNs-COOH, HMSNs-Ad@DOX and HMSNs-HA@DOX were 11.2, 30.5 and 34.3%, respectively, when the temperature reached 900°C . The difference in weight loss between HMSNs-COOH and HMSNs-Ad@DOX was about 19.3%, which was attributed to the introduction of adamantane group and loading of DOX. In addition, the increased weight loss of HMSNs-HA@DOX compared with HMSNs-Ad@DOX confirmed the successful grafting of HA on the surface of HMSNs.

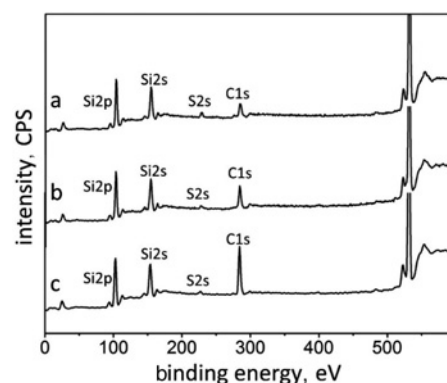


Fig. 4 XPS of
a HMSNs-COOH
b HMSNs-Ad and
c HMSNs-HA

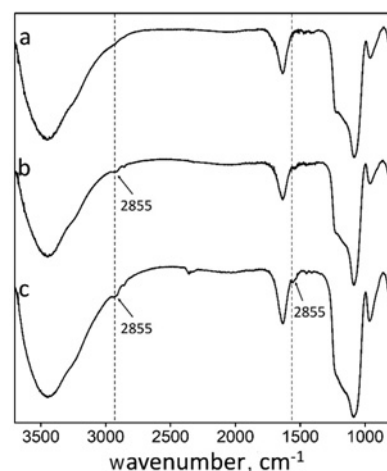


Fig. 5 FTIR spectra of
a HMSNs-COOH
b HMSNs-Ad and
c HMSNs-HA

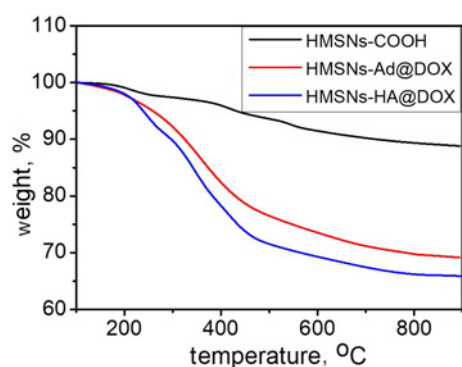


Fig. 6 Thermogravimetric analysis curves for
a HMSNs-COOH
b HMSNs-Ad@DOX and
c HMSNs-HA@DOX

The variation of the pore structure parameters of the nanocarriers after the modification was evaluated by N_2 adsorption–desorption method. As exhibited in Fig. 7, characteristic *IV* type N_2 adsorption/desorption isotherm patterns were obtained, confirming the presence of mesopore channel structure inside the nanoparticles. The structure parameters of the nanocarriers were summarised in Table 1. The specific surface area, pore volume and pore diameter of the HMSNs-COOH were determined to be $1303 \text{ m}^2 \text{ g}^{-1}$, 1.178 mL g^{-1} and 4.02 nm , respectively. After the modification with adamantane group, the specific surface area and pore size distribution of HMSN-Ad only decreased slightly, confirming that the structure of mesopores did not change too much. However, after coating with HA-CD polymer *via* host–guest interactions, the specific surface area and pore volume decreased to 712 and 0.769 mL g^{-1} , respectively. It could be explained that the grafted polymer blocked the pore to some extent in the drying process. The pore size of HMSNs-HA still remained unchanged, which

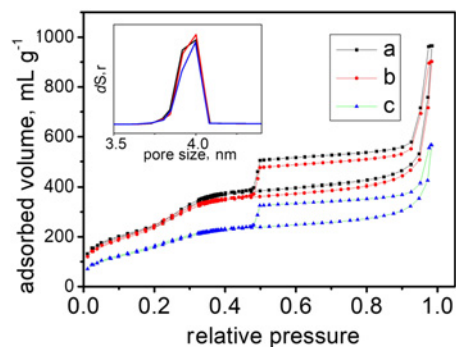


Fig. 7 N_2 adsorption–desorption isotherm and the corresponding pore size distribution inset of
a HMSNs-COOH
b HMSNs-Ad and
c HMSNs-HA

Table 1 Structure parameters of HMSNs-COOH, HMSNs-Ad and HMSNs-HA

Samples	BET surface area, $\text{m}^2 \text{ g}^{-1}$	Pore volume, mL g^{-1}	Peak pore diameter, nm
HMSNs-COOH	1303	1.178	4.02
HMSNs-Ad	1187	0.998	4.01
HMSNs-HA	712	0.769	3.98

indicated that HA was only grafted on the surface of the nanoparticles and did not enter into the mesopore channels. Therefore, the as-prepared HA coated nanocarriers with appropriate mesopore structure and internal space may serve as the ideal vehicles for drug delivery application.

As is well known, the disulphide bond is stable in the physiological environment, while tend to be cleaved in the presence of thiols. After the incubation of HMSNs-HA@DOX with DTT in DMSO for 12 h, the gatekeeper HA-CD was completely detached due to the cleavage of the disulphide bond. Thus, the loaded DOX was dissolved in the DMSO solution and the concentration of dissolved DOX was measured by fluorescence analysis. The loading content of DOX was determined to be about 18.5%, which was much higher than the conventional MSNs. The high drug loading capacity was attributed to the void core space that served as extra reservoirs for the drug storage.

The triggered DOX release behaviour in response to reduction agents was also investigated. As shown in Fig. 8a, very weak fluorescence intensity was observed in solution without the GSH stimulus, indicating that the DOX was successfully retained inside the nanoparticles. After the addition of GSH solution, significant enhancement of fluorescence intensity was observed. Once a part of the disulphide bond was cleaved in response to the GSH, some of the immobilised HA-CD was detached with the mesopore channel open, causing the release of the loaded DOX. The released amount of DOX rates was also studied. As shown in Fig. 8b, only 8% of the loaded DOX leaked out from HMSNs-HA@DOX after continuous incubation in deionised water for 24 h, confirming the excellent blocking efficiency of the gatekeeper without GSH stimulus. In addition, the released amount of DOX drastically increased to 50% after the treatment with 2 mM GSH with the same incubation time. The DOX release rate increased upon increasing concentration of GSH and the released amount further reached

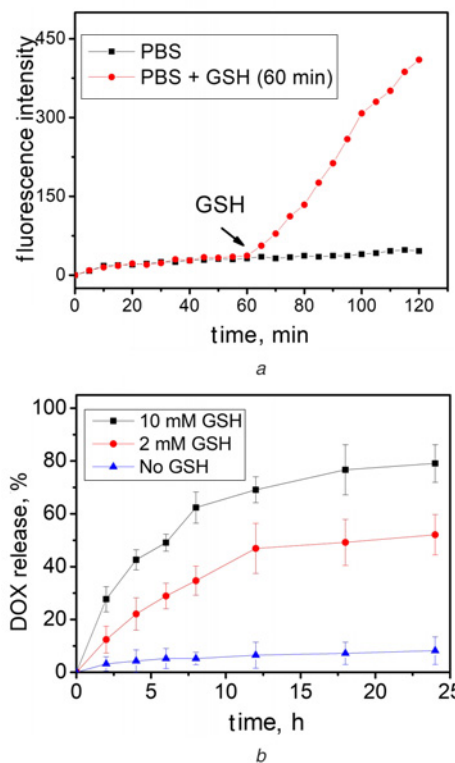


Fig. 8 Triggered release of DOX

a Real-time DOX release from HMSNs-HA@DOX triggered by the addition of GSH (10 mM)
b In vitro release profiles of DOX from HMSNs-HA@DOX in deionised water at 37°C with or without the GSH treatment

78% in response to 10 mM GSH stimulus. In a word, HMSNs-HA@DOX shows a great potential for the triggered release of DOX in the intracellular reduction environment.

Encouraged by the successful *in vitro* drug release, CLSM was employed to visualise the cellular uptake and intracellular DOX release behaviours of HMSNs-HA@DOX. As expected, after incubation with free DOX for 4 h, nearly all the red fluorescence focused in the cell nuclei (Fig. 9), suggesting that the DOX quickly diffused into the cells and interacted with the DNA of cancer cells. However, when HeLa cells were treated with HMSNs-HA@DOX for the same incubation time, only weak DOX fluorescence was observed in the perinuclear region. In this case, the fluorescence of the loaded DOX was self-quenched owing to the aggregation state of DOX retaining inside nanocarriers [36]. On account of high reducing agent level within HeLa cancer cells, DOX was gradually released from the internalised HMSNs-HA@DOX into the cell plasma. After incubations of 12 h, strong DOX fluorescence was finally observed in the cell nucleus region, which was attributed to the efficient reduction-triggered DOX release after the uptake of HMSNs-HA@DOX by HeLa cells for a prolonged incubation time.

The anticancer activity of nanocomposites was evaluated against HeLa cells *in vitro*. The biocompatibility of the nanocarriers themselves without DOX loading was firstly studied. As exhibited in Fig. 10a, the viabilities of HMSNs-HA treated cells were slightly higher than that of HMSNs-Ad treated cells when HeLa cells were incubated with the same concentration of the nanocarriers for 24 h. This observation verified the HMSNs-HA nanocarriers had better biocompatibility than the HMSNs-Ad, indicating the grafted HA polymer could reduce the cytotoxicity of the nanocarriers themselves. Besides, the cytotoxicity of the nanodrug was also studied. As shown in Fig. 10b, the anticancer activity of DOX and DOX-loaded nanoparticles increased along with the increasing the concentration. The free DOX has the best inhibition effect on the growth of HeLa cells, due to its rapid interaction

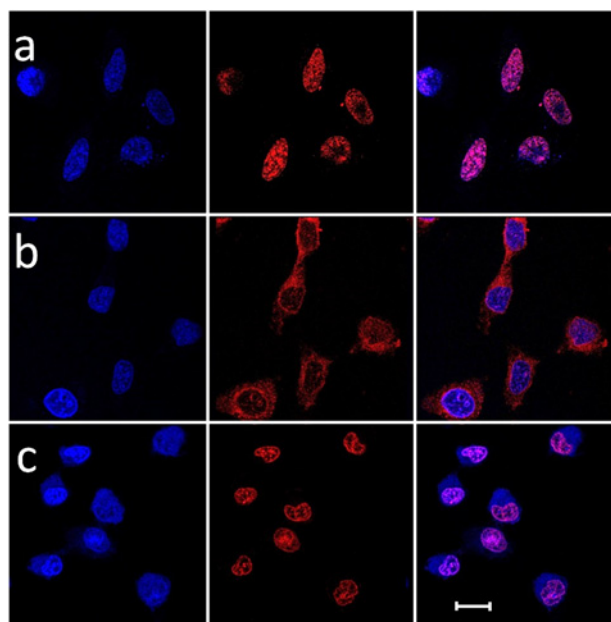


Fig. 9 CLSM images of incubated HeLa cancer cells with free DOX and HMSNs-HA@DOX (equivalent DOX concentration of $5 \mu\text{g mL}^{-1}$)

a Free DOX, 3 h

b HMSNs-HA@DOX, 3 h and

c HMSNs-HA@DOX, 12 h. For each panel, images from left to right show the cell nuclei stained by Hoechst 33342 (blue), DOX fluorescence in cells (red), and overlay of both images. Scale bars correspond to $20 \mu\text{m}$ in all images

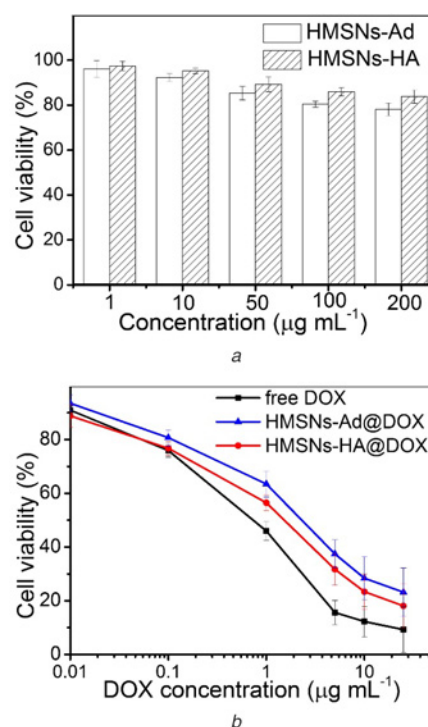


Fig. 10 *In vitro* cytotoxicity study

a Cytotoxicity of HMSNs-Ad and HMSNs-HA nanocarriers against HeLa cells after incubation for 24 h

b Viabilities of HeLa cells after incubation with various dosages of free DOX, HMSNs-Ad@DOX and HMSNs-HA@DOX for 24 h. All the data are presented as the average standard deviation ($n=4$)

with DNA evident by CLMS. The equivalent DOX half maximal inhibitory concentration (IC_{50}) of HMSNs-Ad@DOX was $2.27 \mu\text{g mL}^{-1}$, while the IC_{50} of HA modified nanodrug HMSNs-HA@DOX was $1.52 \mu\text{g mL}^{-1}$. It reveals that HMSNs-HA@DOX afford the improved anticancer activity as compared with HMSNs-Ad@DOX after incubation for 24 h. It should be noted that HeLa cells overexpress CD44 receptors, which strongly interact with HA targeting ligand, leading to the enhanced internalisation amount of HA modified nanodrug and a greater inhibition effect on the growth of HeLa cells.

4. Conclusion: The reduction-responsive HA coated HMSNs were successfully designed and prepared in this study. Disulphide linkage was used to connect the surface of HMSNs and the adamantane group, which strongly bound the β -CD modified HA through host-guest interactions. The β -CD acted as the gatekeeper to retain DOX inside, while the grafted HA served as targeting ligands to interact with the receptors over-expressed on the tumour cells. The disulphide was cleaved under the intracellular reduction environment, resulting in the detachment of HA-CD and release of loaded DOX. CLSM observations indicated that the DOX-loaded nanocomposites could easily be internalised by HeLa cancer cells and release DOX inside. *In vitro* cytotoxicity study also confirmed that the immobilised HA shell conferred increased biocompatibility of the nanocarriers and improved antitumour activity of the nanodrug for the treatment of HeLa cells. Therefore, this kind of nanocomposites shows a great potential in the cancer treatment.

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