Electronic Supplementary Information (ESI)

for

Reduced graphene oxide gated mesoporous silica nanoparticles as a versatile chemo-photothermal therapy system through pH controllable release

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Schiff’s base reaction mechanism is that nucleophilic addition can be finished by carbonyl of carbonyl compounds and amine compounds. Amine compounds as the nucleophilic reagent and lone pair electrons of nitrogen of amine compounds attack the positive charged carbon atoms of carbonyl compound in this action. Then it can form the intermediate of α-hydroxy amine compounds and the Schiff’s base is formed by dehydration reaction (the action step can be seen in eq. 1 and 2).

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\begin{align*}
\text{C}=\text{O} + \text{RNH}_2 & \rightleftharpoons \text{C}<\text{OH}_{\text{NHR}} \\
\text{C}<\text{OH}_{\text{NHR}} & \rightleftharpoons \text{C}=\text{NR} + \text{H}_2\text{O}
\end{align*}
\] (eq. 1 and 2)

Hydrolysis of Schiff base is dependent on pH. In aqueous solution, the attack of water or hydroxide ion on the Schiff base can form carbinolamine (eq. 3). The Schiff base exists as the conjugate acid (protonated carbinolamine) and the basic amines are expelled from the intermediate (eq. 4). At neutral and alkaline pH values, only a small fraction of the Schiff base exists as the conjugate acid and the attack of hydroxide ion on the protonated Schiff base is the rate-determining step. Under more acidic conditions, in which an appreciable fraction of the Schiff base exists as the conjugate acid, the hydrolysis rates increase with decreasing pH for Schiff bases possessing an electron-withdrawing substituent and decrease with decreasing pH for Schiff bases possessing an electron-donating substituent. Thus, it’s easy to cleave Schiff base-bond in acid condition than it in neutral.

\[
\begin{align*}
\text{C}=\text{NR} + \text{H}_2\text{O} & \rightleftharpoons \text{C}<\text{OH}_{\text{NHR}} \\
\text{C}<\text{OH}_{\text{NHR}} & \rightleftharpoons \text{C}=\text{O} + \text{RNH}_2
\end{align*}
\] (eq. 3 and 4)

Fig. S1. Characterization of the rGO. TEM image (A) and DLS spectra (B) of the rGO.
Fig. S2. TEM image (A) and SEM image of MSN-PEI (B). SEM image of MSN@rGO (C). Reduced graphene oxide nanosheets capped MSN.

Fig. S3. Small-angle XRD patterns of the MSN.

Fig. S4. FTIR spectra of FA, MSN@rGO and MSN@rGO-FA and its local figure.

It shows FTIR spectra of free FA and of MSN@rGO nanoparticles before and after FA conjugation. The well-resolved vibration peak at 1606 cm\(^{-1}\) assigned to the N-H bending vibration of the CONH group was present in the spectrum of MSN@rGO-FA.
nanoparticles. Therefore, the FTIR spectra further confirmed that FA ligands have been successfully grafted onto MSN@rGO nanoparticles.

**Fig. S5.** Zeta potential of MSN-NH$_2$, MSN-PEI, rGO and MSN@rGO.

**Fig. S6.** TGA curves recorded for MSN, rGO, MSN-PEI, DOX@MSN-PEI and MSN@rGO.

**Fig. S7.** Confocal fluorescence images of Hep-2 cells incubated with DOX@MSN@rGO at a DOX concentration of 5 μg/mL for 3 h.
**Fig. S8.** Confocal fluorescence images of A549 cells incubated with DOX@MSN@rGO –FA at a DOX concentration of 5 μg/mL for 3 h.

**Fig. S9.** Cell viabilities of Hep-2 cells incubated for 24h and 48h with different concentrations of the MSNs (A) and MSN@rGO (B) nanocomposites.
**Fig. S10.** Bright field images of Hep-2 cells incubated with PBS (a, b), MSN@rGO-FA nanocomposites (c, d) and DOX@MSN@rGO-FA nanocomposites (e, f) in RPMI-1640 medium for 48 h at 37 °C, without (a, c, e) or with (b, d, f) 980 nm laser irradiation (1.25 W, laser spot, 3mm) for 15 min. Scale bars are 40 μm.

**References**