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Supporting Information

Sub-50 nm Core–Shell Nanoparticles with pH-Responsive Squeezing Release Effect for Targeting Therapy of Hepatocellular Carcinoma

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Synthesis of PMADGal via RAFT polymerization

The synthesis of PMADGal is described below, in step 1-3 (Figure S1).

Step 1： Synthesis of 6-O-methacryloyl-diacetone-D-galactose (MADAGal)

In a three-neck flask, 20 g diacetone-D-galactose (75.4 mmol) was dissolved in 100 mL anhydrous pyridine, and then 18 mL methacrylic anhydride (113.1 mmol) was added dropwise using a constant pressure funnel. The reaction was performed at 65°C for 5 h and quenched by 70 ml of deionized water for another 1 h. After that, the mixture was cooled overnight and then extracted 3 times with 100 ml of petroleum ether. The combined extracts were first washed with 200 mL of 5% aqueous sodium hydroxide solution, deionized water and saturated copper sulfate solution in turn, then were washed with deionized water for three times and dried over anhydrous sodium sulfate. After the solvent was evacuated off, the crude product was purified by a silica column to get colorless oil, and the yield of monomer was 62%.

Step 2: Synthesis of PMADAGal by RAFT polymerization

Typically, MADAGal (1.23 g, 3.75 mmol), CPADB (41.9 mg, 0.15 mmol) and AIBN (2.5 mg, 0.015 mmol) were dissolved in dioxane (3 ml) to give a ratio of [monomer]:[RAFT]:[initiator]=25:1:0.1. The mixture was deoxygenated under high-purity nitrogen for 30 min, and then reacted in an oil bath at 75 °C for 15 h. After that, the product was precipitated in excess n-hexane and dried under vacuum to obtain the pink product PMADAGal. The monomer conversion obtained from ^{1}H NMR was 75%,

and the theoretical molar mass of PMADAGal was 6500 g/mol.

Step 3: Deprotection of isopropylidenes on the galactose moiety

The PMADAGal (1g) was dissolved in 10 ml of TFA/H_2O (9/1, v/v) and stirred for 12 h at room temperature. The mixture was dialyzed against Milli-Q water (MWCO 3500), and lyophilized to obtain a light pink PMADGal with a theoretical molar mass of 5000 g/mol.

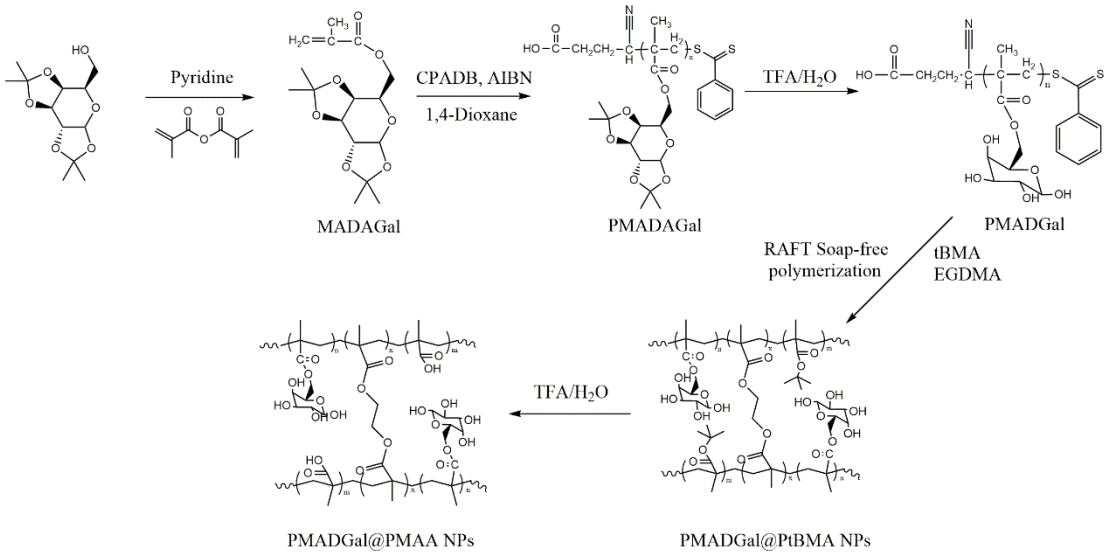

Figure S1 Synthetic pathways for PMADGal@PMAA NPs

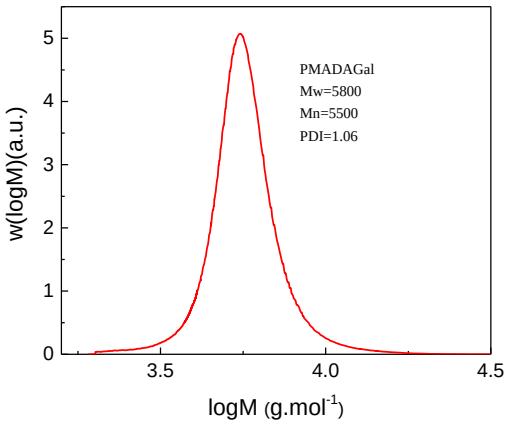

Figure S2 GPC traces of PMADAGal

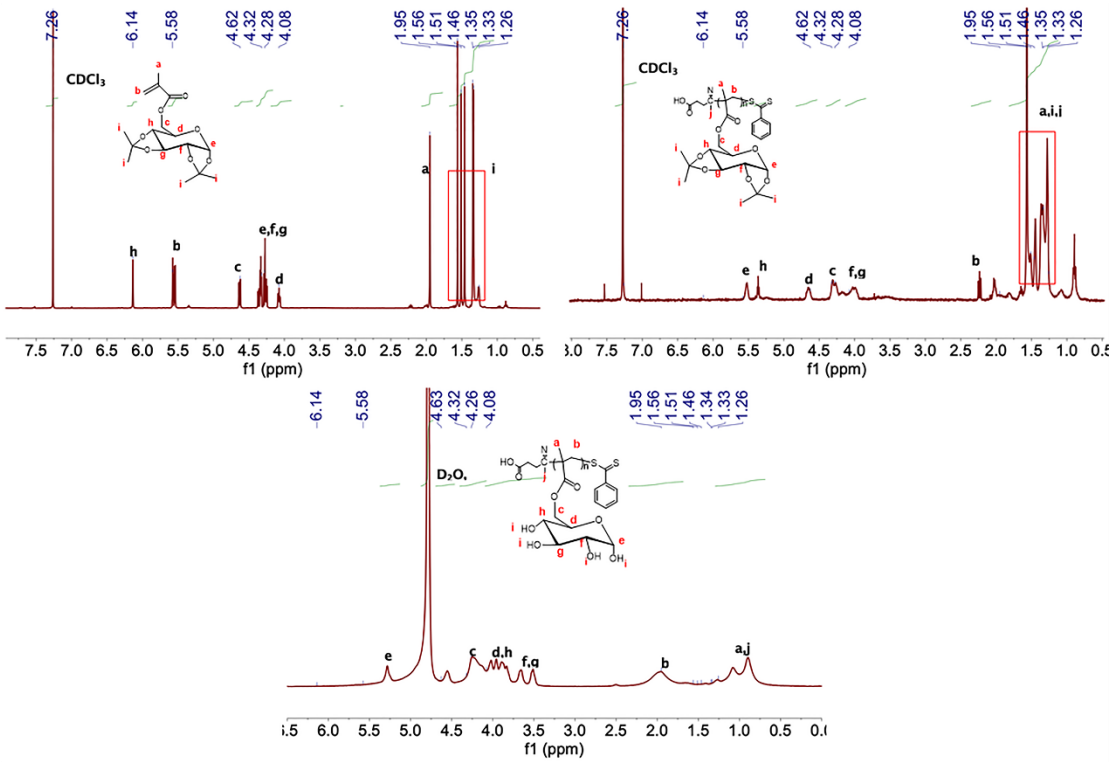

Figure S3 ^{1}H-NMR spectra of MADAGal (a), PMADAGal (b) and PMADGal(c).

Figure S4a shows the FTIR spectra of products in the three-step reactions. After esterification, the stretching vibration peak of hydroxyl group at 3400 cm^{-1} disappeared in the spectrum of MADAGal. The new appearance of peaks at 1660 cm^{-1} and 1750 cm^{-1} can be ascribed to C=C and C=O stretching vibration, respectively. The disappearance of C=C stretching vibration peak at 1660 cm^{-1} after RAFT polymerization confirms the successful synthesis of PMADAGal. In the spectrum of PMADGal, there is a strong adsorption peak at 3435cm^{-1} after deprotection of isopropylidene on the galactose moiety. In the same time, the isopropylidene adsorption peaks at around 1373 cm^{-1} disappeared. These changes indicate that macroRAFT agent PMADGal was successfully synthesized.

Figure S4b shows the FTIR spectra of PMADGal@PtBMA and PMADGal@PMAA NPs. It can be found characteristic peaks of the tert-butyl at 1392 cm^{-1} and 1367 cm^{-1}in the FTIR spectra of PMADGal@PtBMA-10%, PMADGal@PtBMA-20% and PMADGal@PtBMA-30% NPs. In order to obtain pH-responsive NPs, the tert-butyl roups on the PtBMA NPs were removed with trifluoroacetic acid. After hydrolysis, the

intensities of hydroxyl groups at around 3400 cm^{-1} in the spectra of PMADGal@PMAA NPs are obviously enhanced. In the same time, the peaks at 1392 and 1367 cm^{-1} also disappeared, indicating the deprotection of tert-butyl groups from PMADGal@PtBMA NPs.

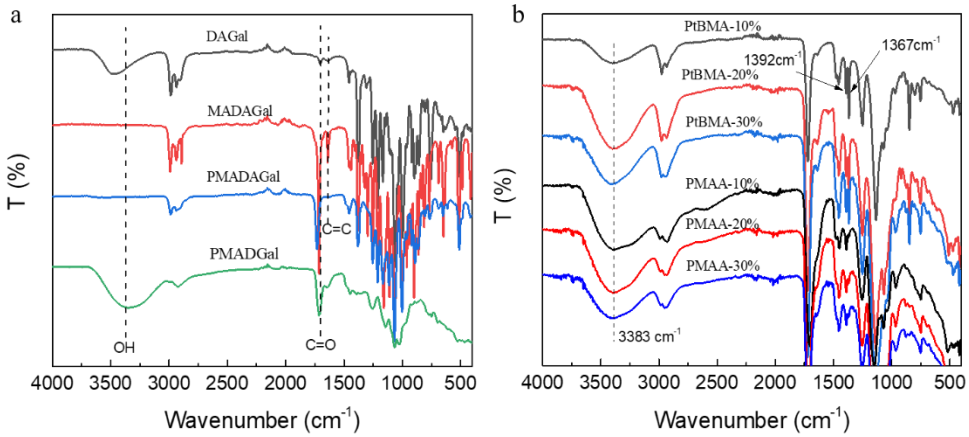

Figure S4 FTIR spectra of DAGal, MADAGal, PMADAGal, PMADGal (a) and PMADGal@PtBMA and PMADGal@PMAA NPs with three different crosslinking degrees (b).

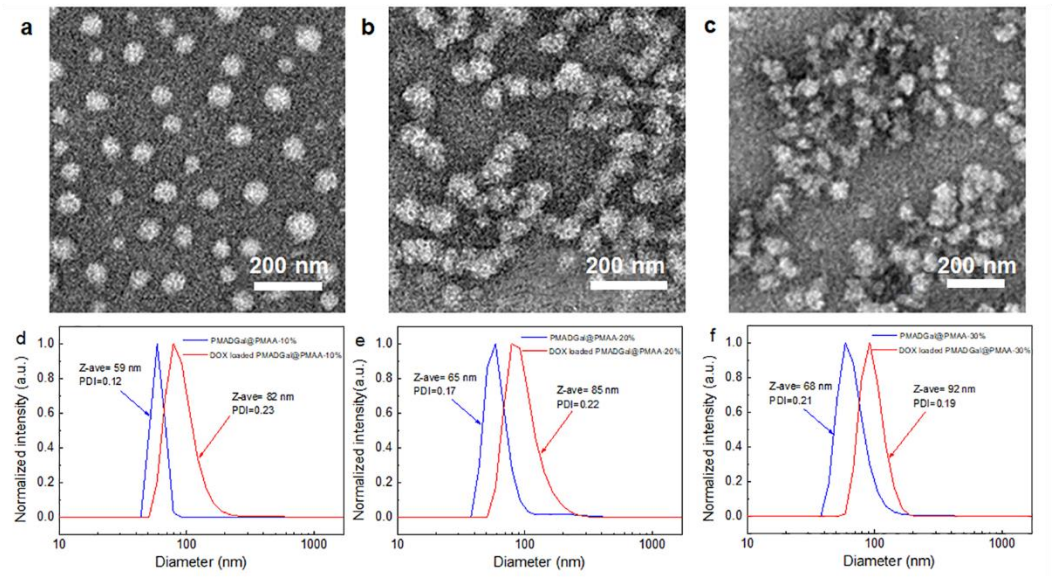

Figure S5 TEM images of DOX loaded PMADGal@PtBMA-10%, PMADGal@PtBMA-20% and PMADGal@PtBMA-30% NPs; size distributions of DOX loaded PMADGal@PtBMA-10%, PMADGal@PtBMA-20% and PMADGal@PtBMA-30% NPs measured by DLS.

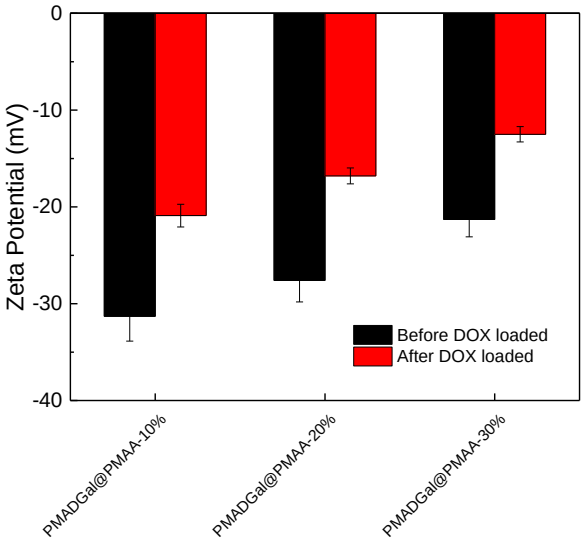

Figure S6 Zeta potentials of PMADGal@PMAA-10%, 20% and 30% NPs before and after DOX loading

Table S1 IC50 of free DOX and DOX loaded PMADGal@PMAA-20% NPs toward HepG2 and HeLa cells, and the corresponding polymer concentration

code	Cell	DOX loading content (μg/mg)	IC50 (μg/ml)	Polymer concentration at IC50 (μg/ml)
Free DOX	HepG2	/	5.1	/
	HeLa		6.2	/
PMADGal@ PMAA 20% NPs	HepG2	326	6.3	19.3
	HeLa		16.9	51.8