Supporting Information for *Molecular Pharmaceutics*

Paclitaxel-Loaded *N*-Octyl-*O*-Sulfate Chitosan Micelles for Superior Cancer Therapeutic Efficacy and Overcoming Drug Resistance

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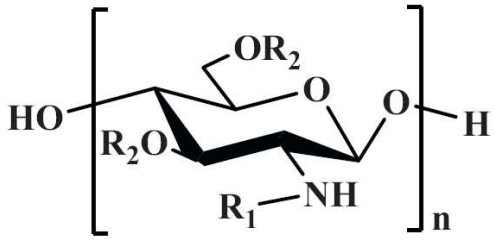
Preparation and characterization of PTX-M. PTX-M (PTX:NOSC, 1:1, w:w) was prepared as follows. Briefly, PTX (16 mg) and NOSC (16 mg) were dissolved in dehydrated ethanol (0.355 mL) and distilled water (4 mL), respectively. The feeding mass ration between PTX and NOSC was 1:1. The PTX solution was then added into the NOSC aqueous solution drop by drop with constant stirring. The mixed solution was subject to dialysis against deionized water overnight, followed by filtration through a 0.45 μm pore-sized membrane. For preparation of PTX-M (PTX:NOSC, 1:4, w:w) with the feeding ratio of PTX:NOSC to 1:4 (w:w), PTX (4 mg) was dissolved in dehydrated ethanol and the other preparation procedure was similar to that described above. The drug-loading efficiencies of PTX-M (PTX:NOSC, 1:1, w:w) and PTX-M (PTX:NOSC, 1:4, w:w) were about 40 % and 11 %, respectively. The PTX concentrations of two different formulations were approximately 2.5 mg/mL and 0.5 mg/mL, respectively. The mean particle diameter and zeta potentials were measured by a Dynamic Light Scattering Analyzer and ZetaPlus Zeta Potential Analyzer (Brookhaven, USA), respectively. There was no significant difference between different PTX-M formulations in the size, polydispersity (PDI) and zeta potential, indicating two micelles have the same physicochemical properties and thus led to cellular uptake approach would be the same.

In vitro **release behavior of PTX-M and PTX/Nr-M.** The i*n vitro* release of PTX-M and PTX/Nr-M was carried out using the modified dialysis. 1 mL of PTX-M or PTX/FITC/Nr-M were added into a dialysis bag (MWCO 10 KDa), which was immersed in 400 mL of release medium at 37 °C with stirring at 100 rpm. The release media were PBS (pH 7.4) with 0.05% Tween 80 (w:v) or FBS free culture medium. At predetermined time intervals, 2 mL of the release medium was withdrawn, followed by replacing with 2 mL of fresh release medium and

filtered through a 0.45 μm pore-sized polycarbonate membrane filter. The amount of PTX released was assayed by HPLC.



R_1= -H, -$COCH_3$, -CH_2-$(CH_2)_6$-CH_3
or -SO_3Na; R_2= -SO_3Na

Figure S1. The structure of NOSC

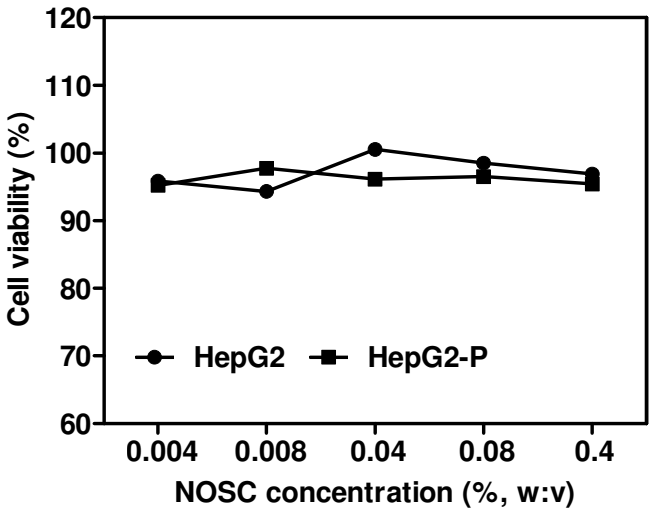


Figure S2. The *in vitro* cytotoxicity of NOSC at different concentrations toward HepG2 and HepG2-P cells.

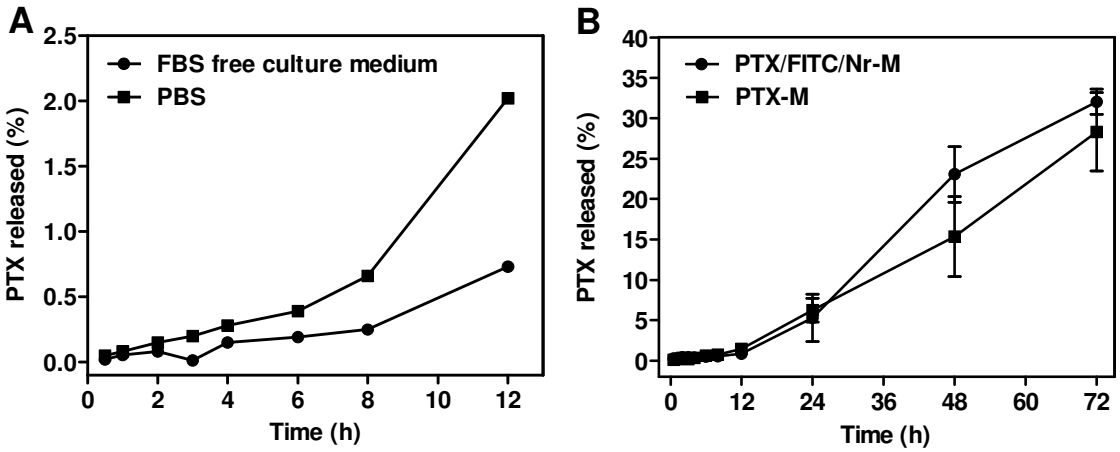


Figure S3. (A) The *in vitro* release of PTX from PTX-M in the PBS buffer and FBS free culture medium for 12 h. (B) The *in vitro* release of PTX from PTX-M and PTX/FITC/Nr-M in the PBS buffer for 72 h.

Table S1. The mean particle diameter, PDI and zeta potentials of PTX-M

	Particle size (nm)	PDI	Zeta potential (mV)
PTX-M (PTX/NOSC, 1:1, w:w)	115.9 ± 1.9	0.22 ± 0.01	-36.7 ± 2.5
PTX-M (PTX/NOSC, 1:4, w:w)	110.9 ± 1.6	0.21 ± 0.01	-33.7 ± 1.5