Supporting Information

Zn-crosslinking of copolymer bearing imidazole pendants to form polymeric nanoparticles for pH-sensitive drug delivery

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S1 EXPERIMENTAL SECTION

S1.1 Materials.

Poly(ethylene glycol) monomethyl ether (CH_3O–PEG2000–OH) and doxorubicin hydrochloride (DOX) were obtained from Beijing Huafeng United Technology Co., Ltd. Copper(I) bromide (Cu(I)Br, 99.5% purity), *N,N,N′,N″,N″*-pentamethyl diethylenetriamine (PMDETA, 99% purity), 2-bromoisobutyryl bromide (BIBB, 98% purity), *Tert*-butyl acrylate (*t*BA), N-(3-Aminopropyl)-imidazole (Imi), sodium hydroxide (NaOH), and $Zn(CH_3COO)_2{\cdot}2H_2O$ were used directly from Aladdin Ind. Co. Tetrahydrofuran (THF), triethylamine (TEA), 1-Ethyl-3-(3-dimethyl aminopropyl) carbodiimide hydrochloride (EDCl), N-Hydroxylsuccinimide (NHS), toluene, and dimethylformamide (DMF) were obtained from J & K Chem. Ltd. Double distilled water was used throughout. Dulbecco's Modified Eagle Medium (DMEM) was purchased from Thermo Fisher Scientific. 10% Fetal Bovine Serum (FBS) was obtained from Biological Industries. MTT reagent was procured from Sigma. DNA fluorescent dye Bisbenzimide H33342 and 100 U/mL penicillin/streptomycin were obtained from Beijing Solarbio Science & Technology. MCF-7 human breast cancer cells were obtained from the Cell Bank of Chinese Academy of Sciences.

S1.2 Synthesis of CH_3O–PEG2000–*b*–PAA_{60}.

CH_3O–PEG2000–Br. After 4.0 g of CH_3O–PEG2000–OH was dissolved in 150 mL of toluene, approximately 40 mL of toluene with traces of water was removed from the mixture at reduced pressure. Then 2.5 mL of TEA was added into the solution at 0 °C. Subsequently, 4.0 mL of BIBB was added dropwise via a constant pressure funnel in 40 min with magnetic stirring, and the reaction was performed with moderate stirring at room temperature. After most toluene was removed at reduced pressure, the product was precipitated in excess cold ether. The precipitate was dried under

vacuum, dissolved in 20 mL of pH 8-9 $NaHCO_3$ aqueous solution, and extracted with CH_2Cl_2. The organic phase was then gathered and dried over $MgSO_4$. Finally, CH_2Cl_2 was removed completely at reduced pressure to obtain the resultant macroinitiator (CH_3O–PEG2000–Br).

CH_3O–PEG2000–*b*–P*t*BA_{60}. CH_3O–PEG_{108}–*b*–P*t*BA_{116} was synthesized via the ATRP of *t*BA with the macroinitiator CH_3O–PEG2000–Br. An amount of 2.000 g of CH_3O–PEG_{108}–Br was dissolved in 6 mL of anhydrous THF. After the mixture was gassed and degassed under N_2, 0.346 g of PMDETA and 5.950 g of *t*BA were charged under degassing by freeze-pump-thaw in N_2 atmosphere, followed by adding 0.286 g of CuBr and then degassing. Subsequently, ATRP was carried out at 45 °C for 8 h. The copper catalyst in the resultant solution was removed with an alumina column, after dilution with THF. The block copolymer CH_3O–PEG2000–*b*–P*t*BA_{60} was precipitated in cold ether and dried in vacuum overnight at room temperature.

CH_3O–PEG2000–*b*–PAA_{60}. The diblock copolymer was dissolved in 5.0 mL of TFA and stirred at room temperature for 24 h. TFA was removed at reduced pressure by a rotary evaporator. The hydrolytic copolymers of CH_3O–PEG2000–*b*–PAA_{60} were obtained by lyophilization for 6 h.

S1.3 DOX-loading capacity (DLC) and DOX-encapsulation efficiency (DEE).

DOX-loading capacity and loading efficiency were calculated by equations as follows：

$$\text{DOX-loading capacity (DLC) (mg/mg)} = \frac{weight\ of\ DOX\ in\ micelles}{weight\ of\ the\ micelles}$$

$$\text{DOX-loading efficiency (DLE) (\%)} = \frac{weight\ of\ DOX\ in\ micelles}{weight\ of\ the\ feeding\ DOX} \times 100\%$$