Supporting Information

pH and reduction-activated polymeric prodrug nanoparticles based on 6-thioguanine-dialdehyde sodium alginate conjugate for enhanced intracellular drug release in leukemia

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1.1 Determination of the feed molar ratio of ASA and 6-TG

Dialdehyde alginate consists of oxidized units and non-oxidized uronic acid units. After the degree of oxidation （DO）is determined, the following two equations can be established:

$$W = n_o M_o + n_{no} M_{no} \qquad (1)$$

$$\frac{n_o}{n_{no}} = \frac{DO}{1\text{-}DO} \qquad (2)$$

Where W is the weight of the dialdehyde alginate sample; n_o and n_{no} are the molar content of the oxidized units and non-oxidized uronic acid units, respectively. M_o and M_{no} represent the molecular weights of the oxidized units and non- oxidized uronic acid units, respectively. M_o=196 for the oxidized units; M_{no} = 198 for non-oxidized uronic acid units

The solution of the two equations can give the molar content of oxidized units in the sample:

$$n_o = \frac{W}{\left[M_o + \frac{1\text{-}DO}{DO} \times M_{no}\right]}$$

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According to the value of n_o, the feed amount of 6-TG can be determined, and the feed molar ratio of ASA and 6-TG is calculated。

1.2. Calculation of the substitution degrees of 6-TG in 6-TG-DSA

$$DS=\frac{n_{6\text{-}TG}}{n_o+n_{no}}=\frac{W_{6\text{-}TG}}{M_{6\text{-}TG}}\times\frac{DO\times Mo+(1-DO)\times M_{no}}{100-(W_{6\text{-}TG}/M_{6\text{-}TG})\times(167.2-2+16)}$$

Where $n_{6\text{-}TG}$ is the molar content of 6-TG in 6-TG-DSA; $W_{6\text{-}TG}$ is the content of 6-TG in 6-TG-DSA (mg/100 mg polymer); $M_{6\text{-}TG}$ represents the molecular weight of 6-TG; others are the same as above

1.3. Fluorescence characterization of the Schiff base bonds in 6-TG-DSA

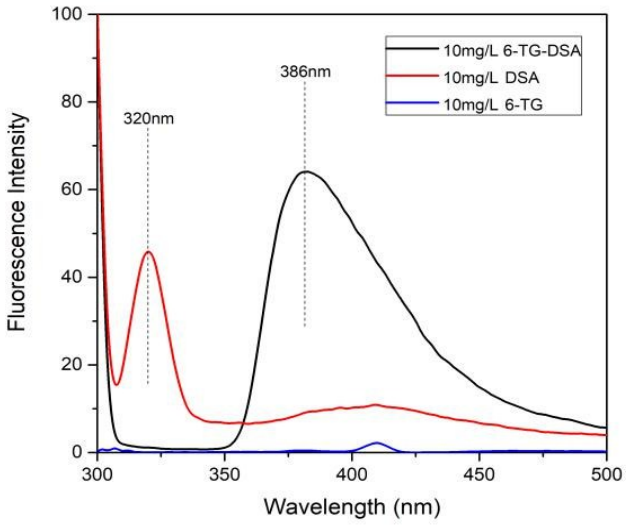

Fig. S1. Fluorescence emission spectra of 6-TG-DSA, DSA and 6-TG excited at 288 nm by laser.

1.4. The stability of nanoparticles in the cell culture medium

Table S1. The mean diameters and distribution of PPN-3 incubated with cell culture media at different time

Time (h)	D_h (nm)	PDI	ζ (mV)
0	119.6 ± 0.14	0.075 ± 0.011	-29.2
24	125.8 ± 0.18	0.084 ± 0.014	-28.8
48	130.2 ± 0.22	0.095 ± 0.019	-25.2

1.5. TEM images of PPN

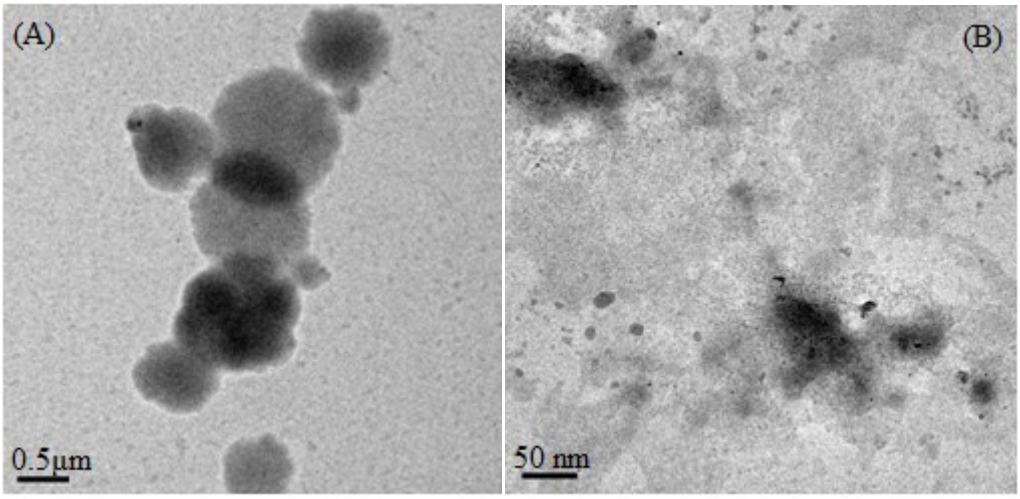

Fig. S2. TEM images of PPN at pH 7.4 with 10 mM GSH (A) and at pH 5.0 with 20 mM GSH (B).

1.6. Fluorescence characterization of the acid hydrolysis of Schiff base bonds in 6-TG-DSA

To confirm the acid hydrolysis of Schiff base bonds, 6-TG-DSA was dissolved in acetic acid solution at pH 5.0 to a concentration of 10 mg/L, and then used for determination of the change of the fluorescence emission intensity over time. As shown in Fig. S3, the fluorescence emission intensity of 6-TG-DSA at 386 nm decreased with time, almost completely disappeared at 5 h, indicating the complete hydrolysis of Schiff base bonds (HC=N) in 6-TG-DSA.

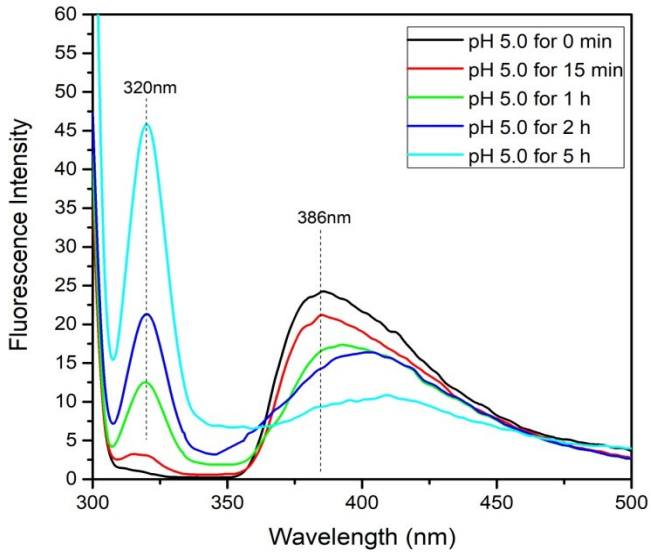

Fig. S3. Florescence emission spectra (λex = 386 nm) of 6-TG-DSA (10 mg/L) in acetic acid solution at pH 5.0 for 5h.