Supporting Information

Zwitterionic cross-linked lipoic acid nanocarriers for oral drug delivery

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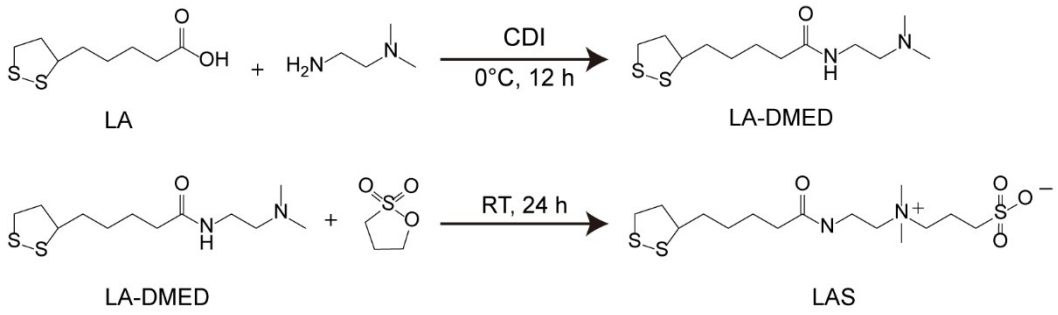
General Methods

Synthesis of LA-DMED. The reaction was carried out under the protection of N_2. LA (20 mmol) and 1,1-carbonyldiimidazole (CDI, 26 mmol) were dissolved in anhydrous chloroform (30 mL), and the reaction was stirred at room temperature for 30 min. Then *N,N'*-Dimethylethane-1,2-diamine (DMED, 100 mmol) was added dropwise in an ice bath, and the reaction was continued for 12 h and then terminated. It was extracted with 10% NaCl aqueous solution (80 mL) three times and then with 10 mM NaOH aqueous solution (80 mL) two times, and the organic phase was separated and dried with anhydrous Na_2SO_4, and the solvent was evaporated by rotary evaporator to give a yellow oil, LA-DMED. 95% yield. ^{1}H NMR (400 MHz,$CDCl_3$): δ 4.18 (t, *J* = 5.7 Hz, 2H), 3.56 (dq, *J* = 8.3, 6.4 Hz, 1H), 3.24 – 3.06 (m, 2H), 2.58 (t, *J* = 5.7 Hz, 2H), 2.46 (dtd, *J* = 13.0, 6.6, 5.4 Hz, 1H), 2.35 (t, *J* = 7.4 Hz, 2H), 2.29 (s, 6H), 1.91 (dq, *J* = 12.7, 6.9 Hz, 1H), 1.77 – 1.58 (m, 4H), 1.55 – 1.36 (m, 2H).

Synthesis of LAS. The obtained LA-DMED (10 mmol) was dissolved in anhydrous chloroform (30 mL), and 1,3-propanesulfonic acid (30 mmol) was added. After stirring for 24 h, a pale yellow solid precipitated and was washed with anhydrous chloroform, resulting in a light yellow solid, LAS, 85% yield. ^{1}H NMR (400 MHz, D_2O): δ 4.59 (d, *J* = 4.9 Hz, 2H), 3.92 – 3.73 (m, 2H), 3.73 – 3.50 (m, 3H), 3.29 – 3.24 (m, 2H), 3.22 (s, 6H), 2.98 (dt, *J* = 8.6, 5.1 Hz, 2H), 2.58 – 2.46 (m, 3H), 2.29 (dq, *J* = 12.0, 7.5 Hz, 2H), 2.02 (dq, *J* = 13.5, 6.9 Hz, 1H), 1.86 – 1.57 (m, 4H), 1.48 (p, *J* = 7.3 Hz, 2H).

Scheme S1. Synthesis of LAS.



Preparation of cLAS. The DMSO solution of LAS (10 mg/mL, 1 mL) was slowly added into 10 mL of water, followed by ultrasonication for 15 min (50 kHz, power 360 W). Subsequently, the solution was irradiated under UV light at 365 nm for about 2 h (7.13 mW/cm²). The resulting solution was then dialyzed against deionized water for 48 h (Spectra/Pore, MWCO 2000) to get cLAS as a pale blue solution.

Preparation of C6- and DiD-loaded cLAS. To load C6 or DiD into cLAS, the C6 or DiD (10 μg/mL) was mixed with cLAS (10 mg/mL) in a volume ratio of 1:10, and the mixture was oscillated at room temperature for 24 h in the dark, followed by centrifugation at 3000×g for 5 min to remove the free C6 or DiD, followed by dialysis for 48 h to remove the free C6 or DiD, eventually obtaining C6@cLAS or DiD@cLAS.

Preparation of C6- and DiD-loaded cLA. The preparation procedure of C6@cLA or DiD@cLA was the same as that of C6@cLAS or DiD@cLAS, except for the substitution of cLAS with cLA.

Statistical Analysis. Results were presented as the mean ± standard deviation (SD) of at least three trials.

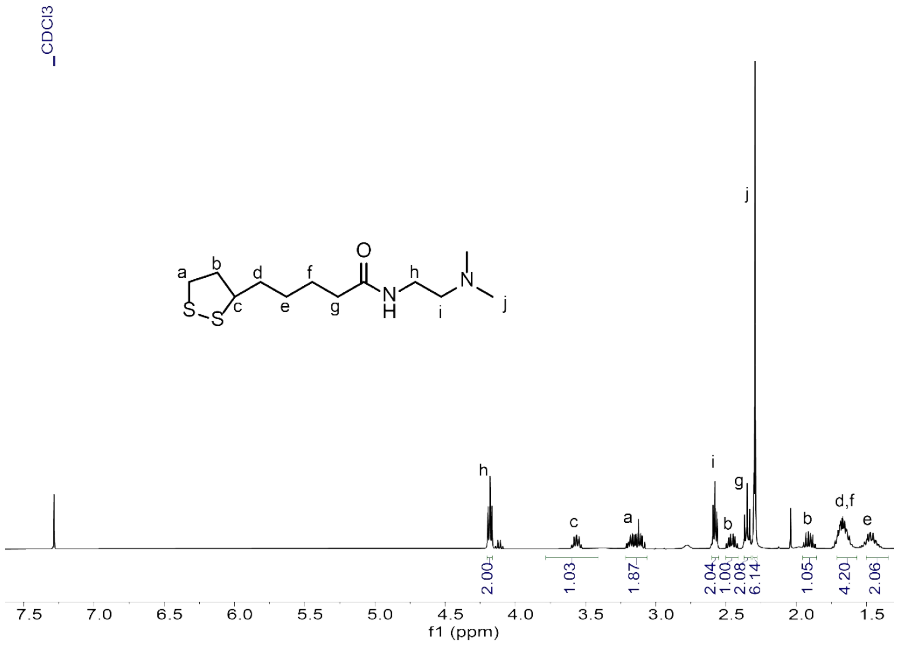


Fig. S1 ^{1}H NMR spectra of LA-DMED recorded in $CDCl_3$.

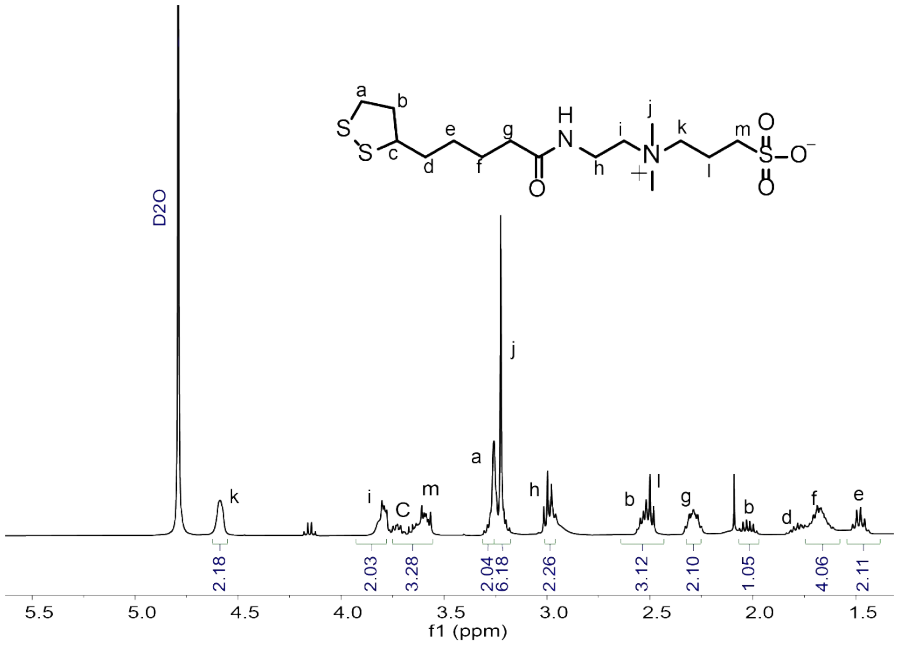


Fig. S2 ^{1}H NMR spectra of LAS recorded in D_2O.

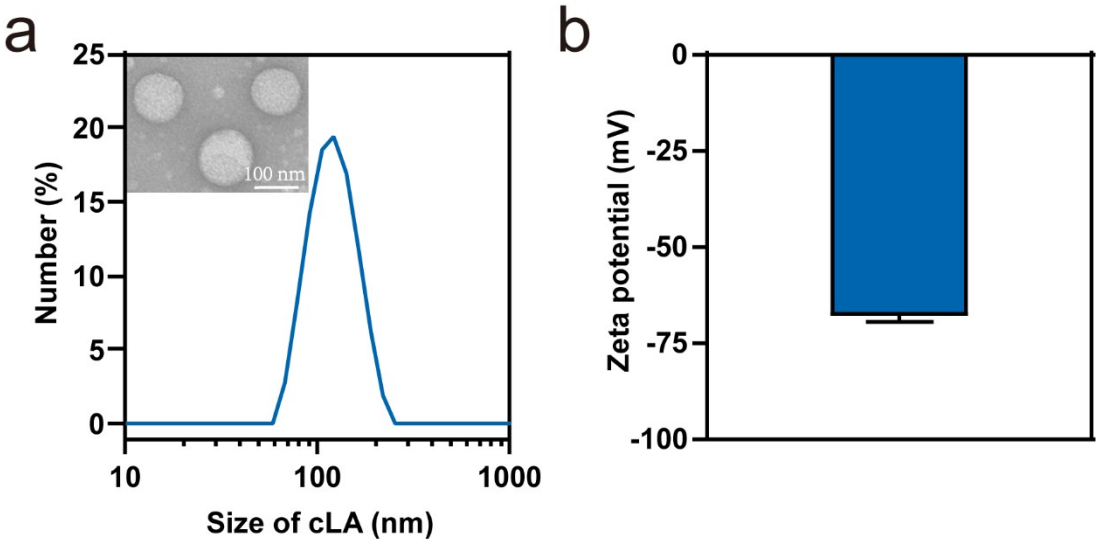


Fig. S3 Characterization of cLA. (a) Hydrodynamic size and TEM image. (b) Zeta potential.

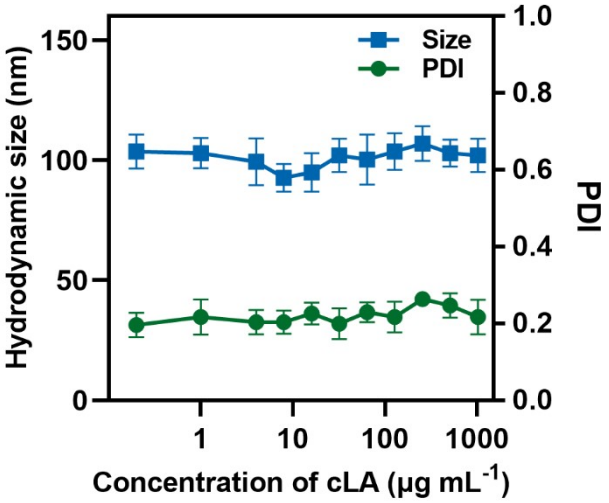


Fig. S4 Dilution stability of cLA.

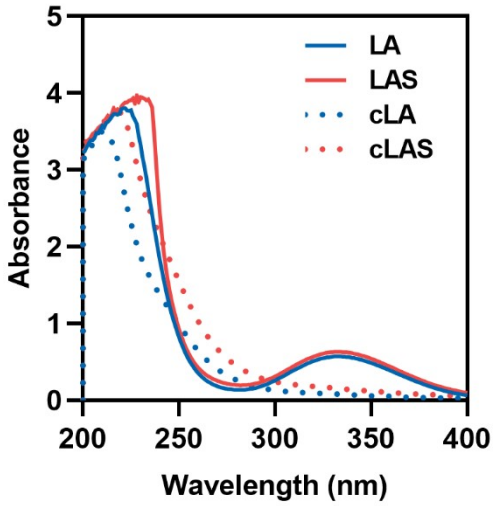


Fig. S5 The UV-visible spectra of LA, LAS, cLA and cLAS in Water.

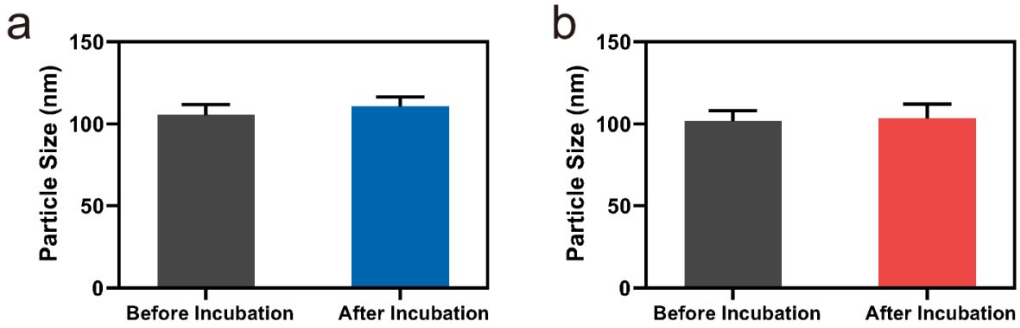


Fig. S6 (a) Particle size changes of cLA before and after sequential incubation in SGF (2 h) and SIF (6 h) measured by DLS. (b) Particle size changes of cLAS before and after sequential incubation in SGF (2 h) and SIF (6 h) measured by DLS.

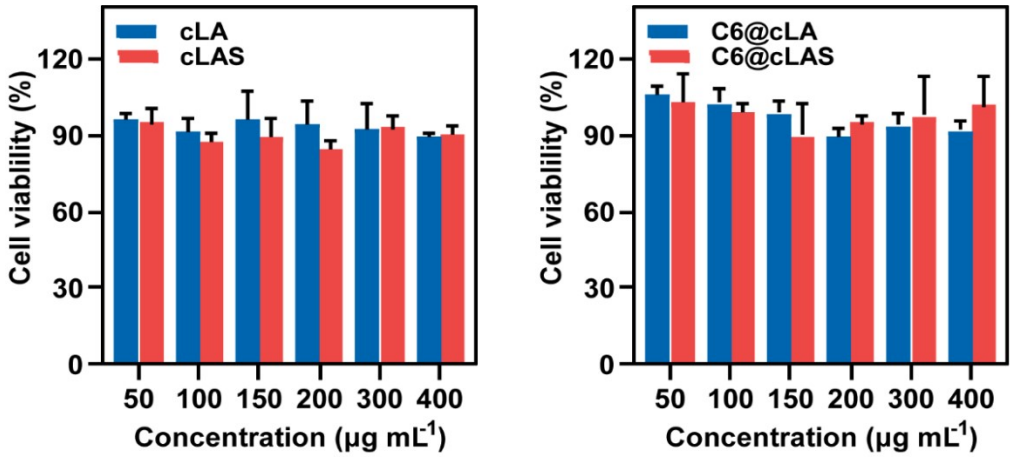


Fig. S7 The viability of Caco-2 cells was determined by MTT after treatment with (a) blank nanoparticles or (b) C6-loaded nanoparticles at the indicated concentrations for 48 h.

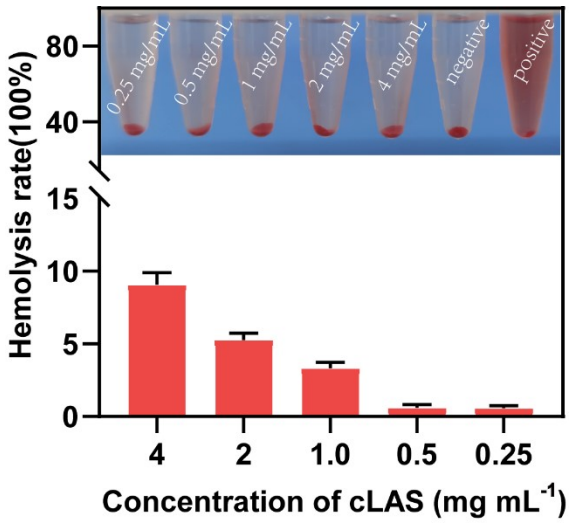


Fig. S8 The hemolysis rate of cLAS.

Table S1. Physicochemical properties of nanoparticles.

Groups	Particle size (nm)	Zeta potential	Entrapment efficiency (%)
C6@LA	118 ± 2.41	- 65 ± 1.35	85.56 ± 0.531
C6@LAS	108 ± 3.02	-10 ± 3.91	87.56 ± 1.545