

Supporting information for:

***In vivo* and *in vitro* evaluation of dihydroartemisinin prodrug nanocomplexes as a nano-drug delivery system: characterization, pharmacokinetics and pharmacodynamics**

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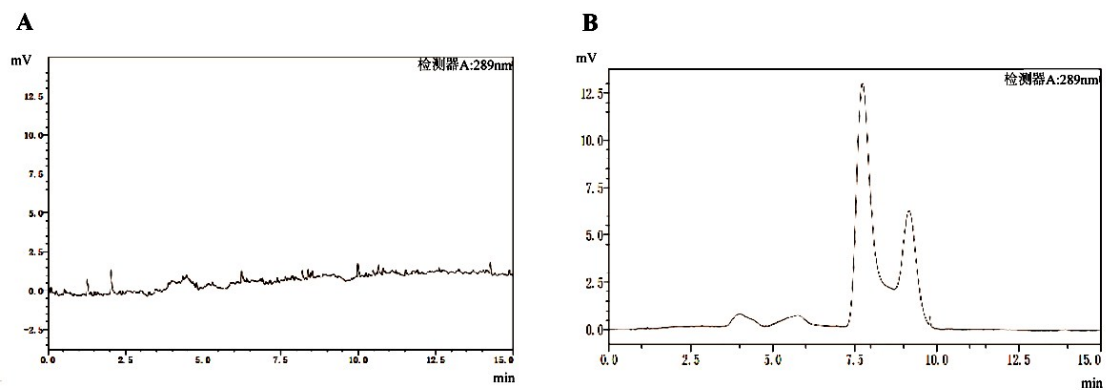


Fig. S1 The HPLC chromatogram of blank (A) and DHA-C₁₂ (B)

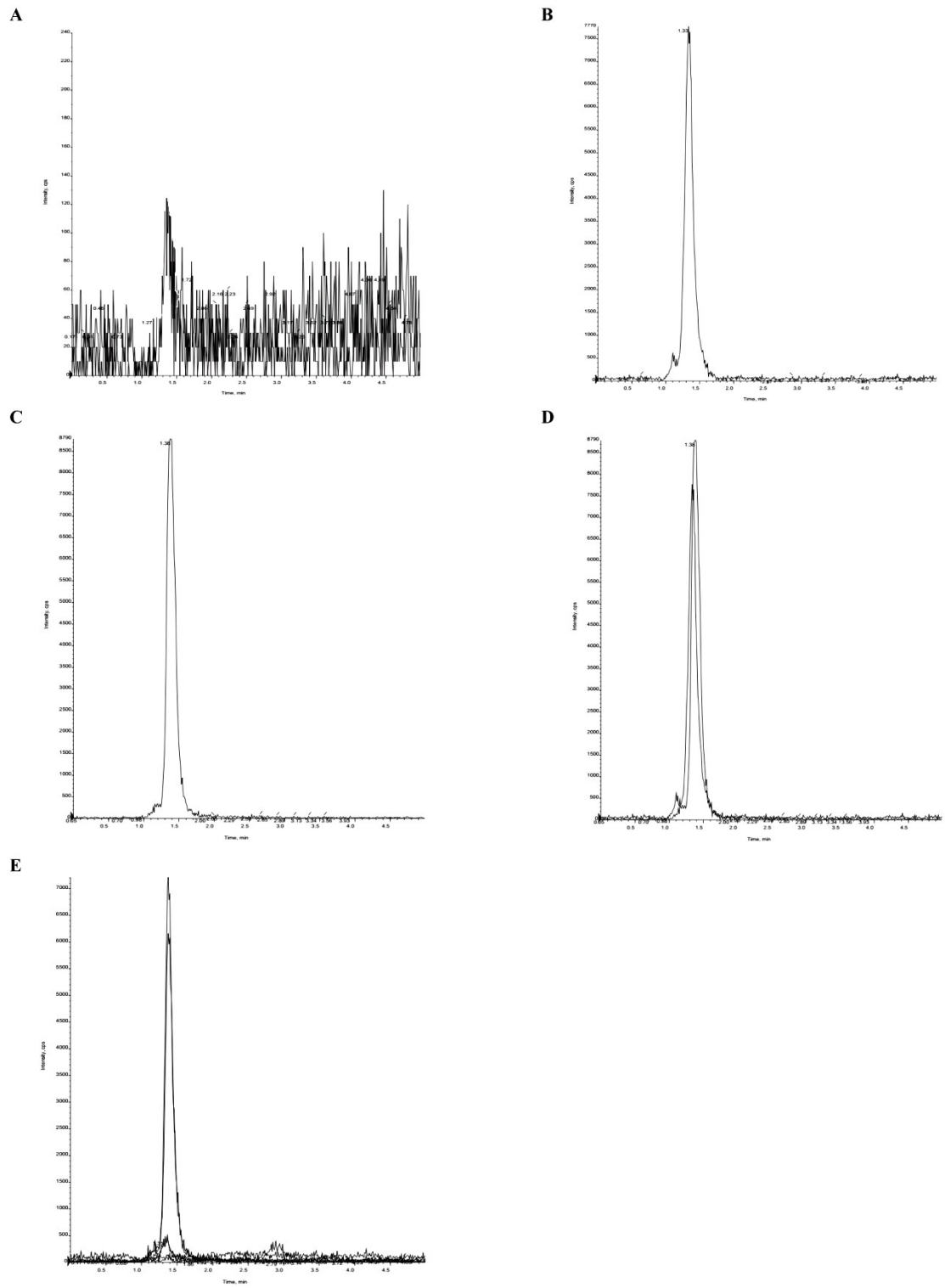


Fig. S2 The HPLC-MS/MS chromatogram of blank rat plasma (A), blank rat plasma with DHA (B), blank rat plasma with ART (C), blank rat plasma with DHA and ART (D), and rat plasma after intravenously administered DHA-Sol for 0.5 h.

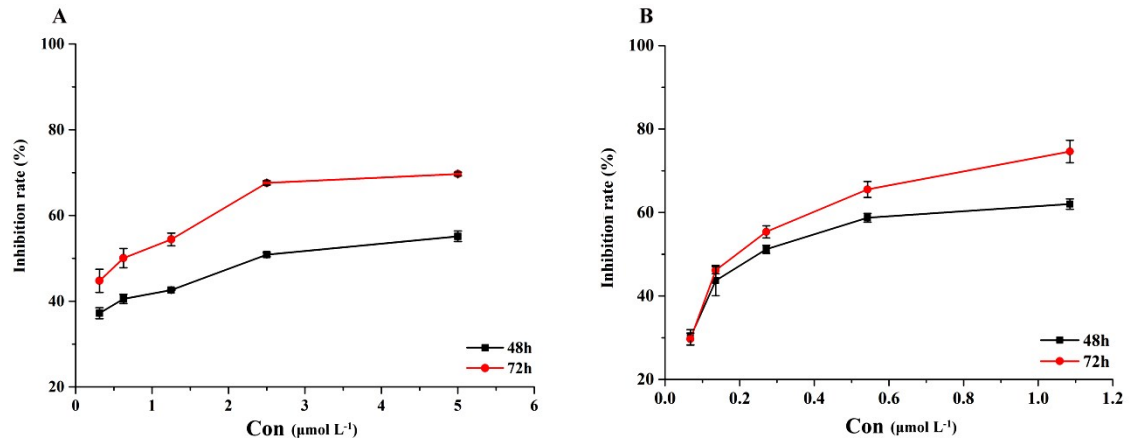


Fig. S3 The inhibition rate of 4T1 cells after treatment with different concentrations of DHA-Sol (A) and DHANPs (B) for 48 h and 72 h

Table S1 The intra- and inter-day precision of HPLC-post-column derivative analysis of DHA

C ($\mu\text{g mL}^{-1}$)	Intra-day precision (%)	Inter-day precision (%)
2.5	0.5	1.4
10	0.3	0.5
48	0.2	0.2

C ($\mu\text{g mL}^{-1}$)	Recovery (%)			Mean (%)	RSD (%)
	1	2	3		
2.5	105.6	108.8	108.1	107.5	1.7
10	95.4	96.4	94.3	95.4	1.1
48	85.9	86.6	86.1	86.2	0.5

Table S2 The recovery of HPLC-post-column derivative analysis of DHA

Table S3 Accuracy and precision for DHA in rat plasma at LLQQ (n = 6)

Analyte	Added Con (ng mL ⁻¹)	Found Con (ng mL ⁻¹)	SD	RSD (%)	RE (%)
DHA	5.0	4.9	0.6	12.2	7.0

Table S4 Accuracy and precision for the determination of DHA in rat plasma (n =6)

Added (ng mL ⁻¹)	Intra-day			Inter-day		
	Found (ng mL ⁻¹)	RSD (%)	RE (%)	Found (ng mL ⁻¹)	RSD (%)	RE (%)
10.0	11.3 ± 1.2	10.6	13.0	11.4 ± 0.6	5.3	14.0
500.0	506.0 ± 30.1	5.9	1.2	510.0 ± 22.3	4.4	2.0
8000.0	7903.0 ± 243.6	3.1	-1.2	8064.4 ± 223.4	2.8	0.8

Table S5 *In vivo* pharmacokinetic parameters of DHA and DHANPs in rats after i.v administration of DHA-Sol at the dose of 0.02 mmol DHA kg⁻¹ (n = 6).

Parameters	AUC _(0-t) ((mmol L ⁻¹)·h)	AUC _(0-∞) ((mmol L ⁻¹)·h)	t _{1/2} (h)	CLz (L h ⁻¹)	Vz (L)
DHA ²⁵	3.86 ± 0.62	4.15 ± 0.73	0.3 ± 0.1	6.1 ± 1.2	2.6 ± 0.3
DHANPs	62.24 ± 21.35	64.19 ± 22.22	3.8 ± 3.6	0.4 ± 0.1	2.0 ± 2.0

Table S6 IC₅₀ of DHA-Sol and DHANPs in 4T1 cells after 48 h and 72 h incubation.

Preparations	48 h ($\mu\text{mol L}^{-1}$)	72 h ($\mu\text{mol L}^{-1}$)
DHA-Sol	2.31 ± 0.10	0.62 ± 0.02
DHANPs	2.47 ± 0.15	1.79 ± 0.13