Supplementary Material

A novel controlled release formulation of the Pin1 inhibitor ATRA to improve liver cancer therapy by simultaneously blocking multiple cancer pathways

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Table S1

Pharmacokinetic parameters of ATRA in BALB/c nu/nu mice after implantation of ATRA pellet or injection of ATRA-PLLA particles (mean ± SD, n = 4).

Parameter	ATRA pellet	ATRA-PLLA
C_{max} (μg/L)	622.17 ± 216.56	2704.21 ± 495.42**
$AUC_{(0-t)}$ (μg/L×h)	2633.29 ± 664.01	10498.52 ± 3061.31*
$t_{1/2}$ (h)	7.32 ± 0.64	5.80 ± 4.78

* $p < 0.05$ between the ATRA-PLLA and ATRA pellet.

** $p < 0.01$ between the ATRA-PLLA and ATRA pellet.

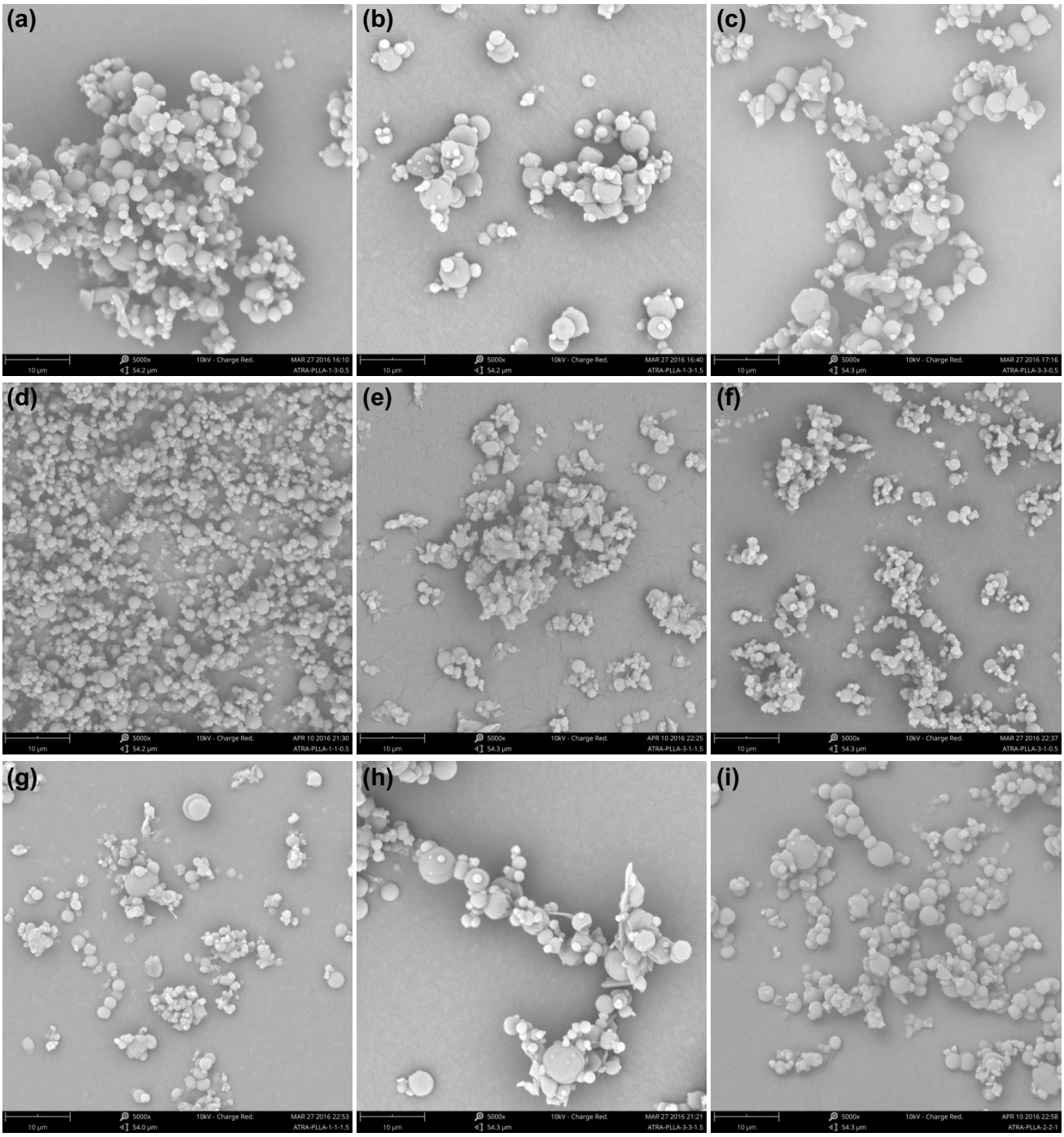

Fig. S1. SEM images of ATRA-PLLA particles prepared by the SAS process under different conditions (a) 1%, 3% and 0.5 mL/min; (b) 1%, 3% and 1.5 mL/min; (c) 3%, 3% and 0.5 mL/min; (d) 1%, 1% and 0.5 mL/min; (e) 3%, 1% and 1.5 mL/min; (f) 3%, 1% and 0.5 mL/min; (g) 1%, 1% and 1.5 mL/min; (h) 3%, 3% and 1.5 mL/min; (i) 2%, 2% and 1 mL/min (the parameters are ratio of ATRA and PLLA, PLLA concentration, and flow rate of solution, respectively).

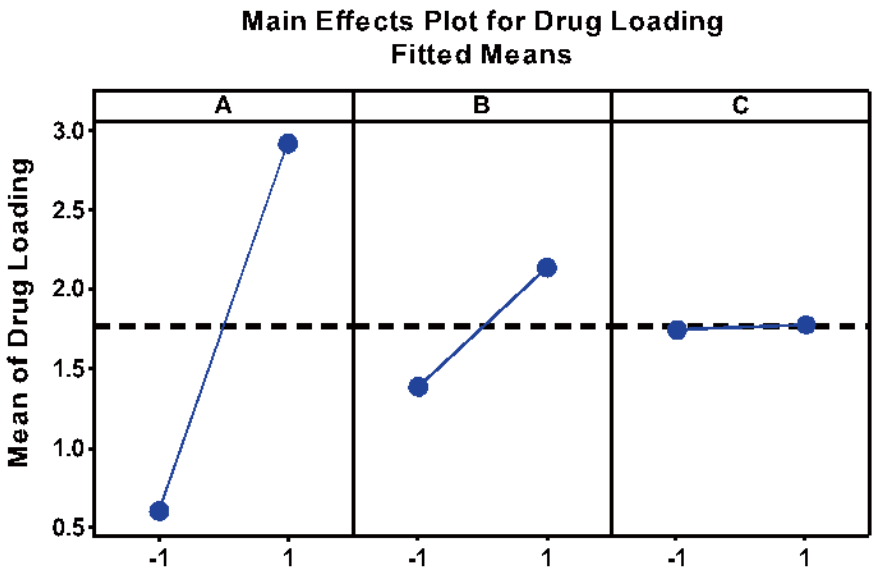

Fig. S2. Main effects plot for drug loading. Factors A, B and C represent the ratio of ATRA and PLLA (%), PLLA concentration (%), and flow rate of solution (mL/min) in the SAS process, respectively. The -1 and 1 value of the X axis respectively represent the low and high factor settings in the experimental design.

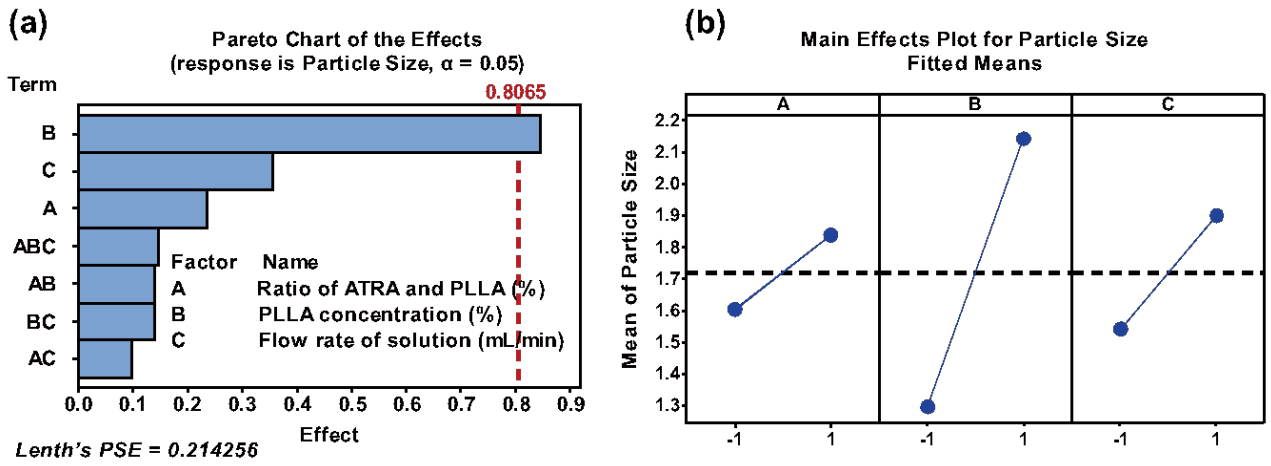

Fig. S3. (a) Effect of the factors on particle size. Factors A, B and C represent the ratio of ATRA and PLLA (%), PLLA concentration (%), and flow rate of solution (mL/min) in the SAS process, respectively. (b) Main effects plot for particle size. The -1 and 1 value of the X axis respectively represent the low and high factor settings in the experimental design.

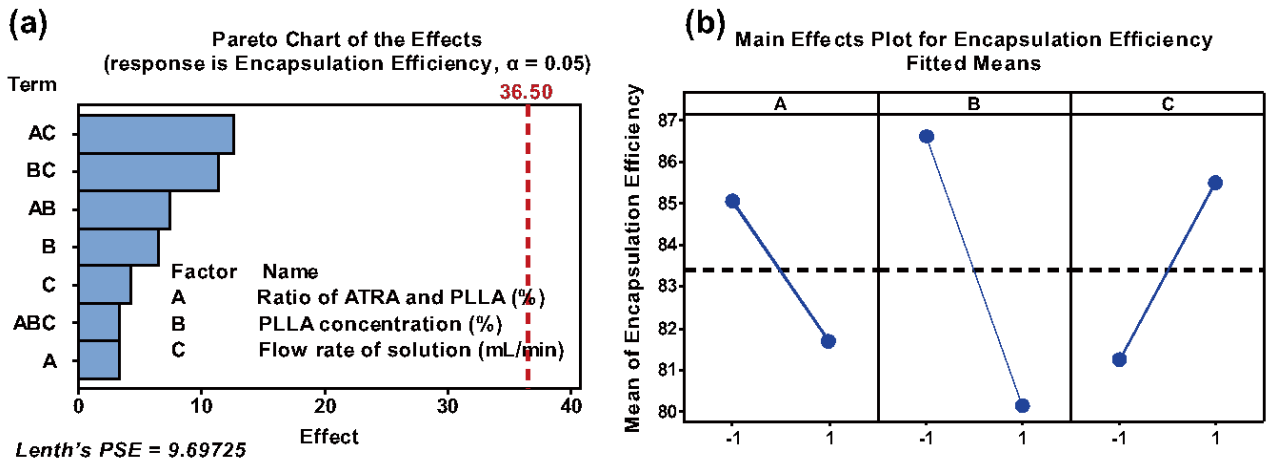

Fig. S4. (a) Effect of the factors on encapsulation efficiency. Factors A, B and C represent the ratio of ATRA and PLLA (%), PLLA concentration (%), and flow rate of solution (mL/min) in the SAS process, respectively. (b) Main effects plot for encapsulation efficiency. The -1 and 1 value of the X axis respectively represent the low and high factor settings in the experimental design.

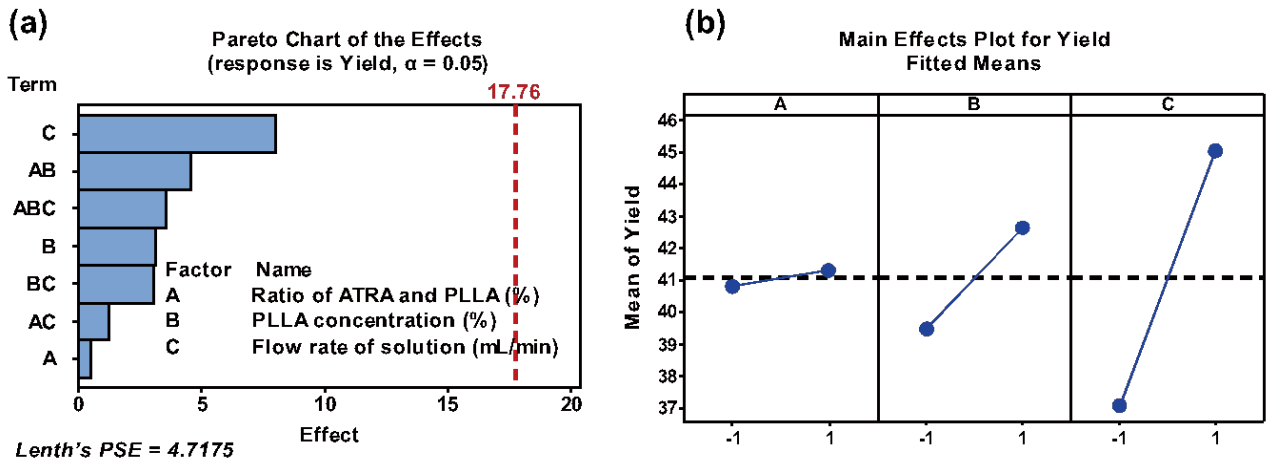

Fig. S5. (a) Effect of the factors on yield. Factors A, B and C represent the ratio of ATRA and PLLA (%), PLLA concentration (%), and flow rate of solution (mL/min) in the SAS process, respectively. (b) Main effects plot for yield. The -1 and 1 value of the X axis respectively represent the low and high factor settings in the experimental design.

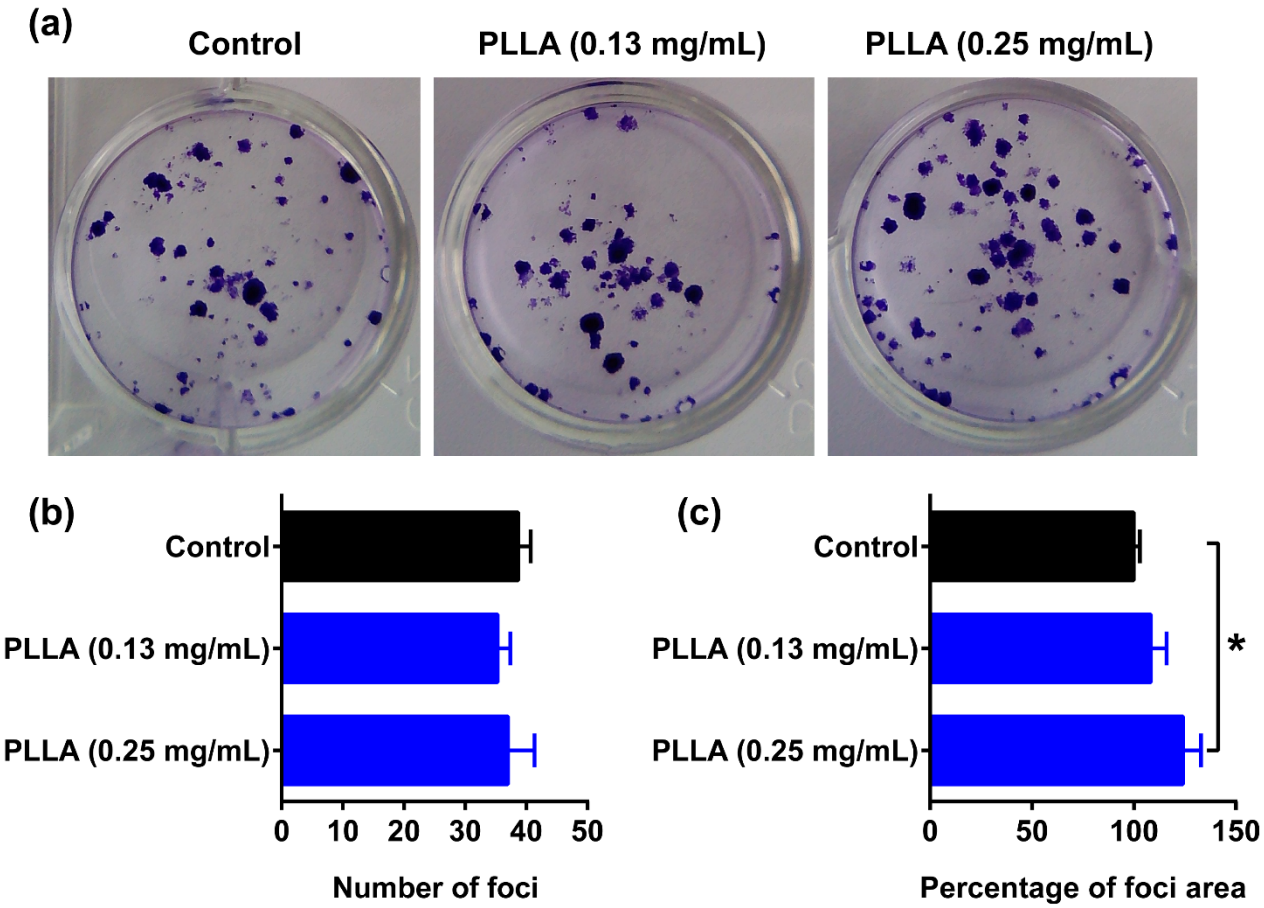

Fig. S6. (a) Image, (b) number, and (c) area of foci formed by HuH7 cells treated with the indicated concentration of blank PLLA particles for 72 h. Untreated cells were used as control. Each value is the mean ± standard deviation of triplicate determinations; *$p < 0.05$.

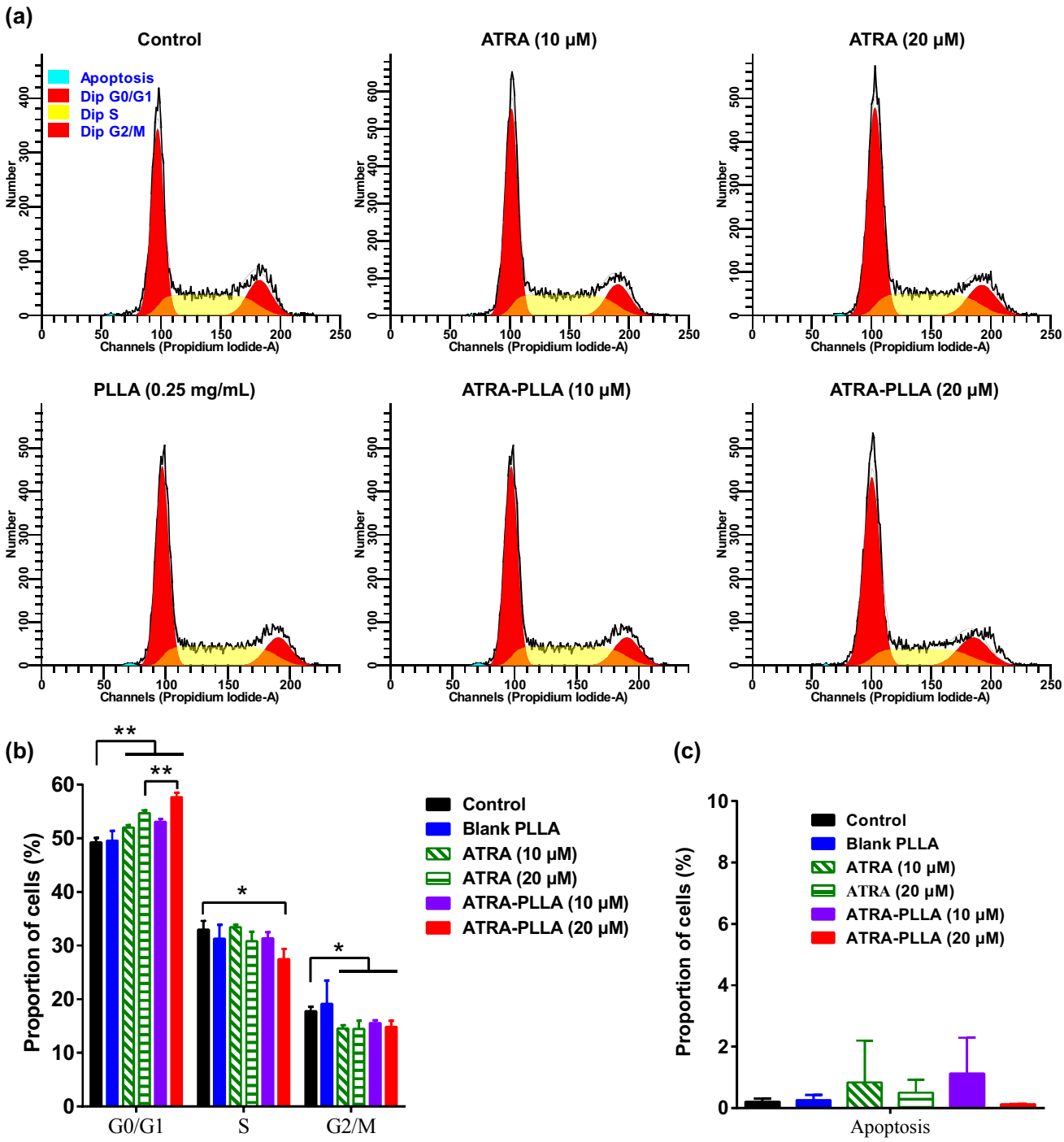

Fig. S7. Effects of blank PLLA particles, free ATRA, and ATRA-PLLA particles on cell cycle and apoptosis of HuH7 cells after treating for 72 h. (a) Representative histograms of cell cycle distribution and apoptosis (the apoptotic sub-G1 cell population) in all groups. (b) Quantitative information on the cell cycle distributions. (c) Quantitative information on the apoptosis. Each value is the mean ± standard deviation of triplicate determinations; *$p < 0.05$, **$p < 0.01$.

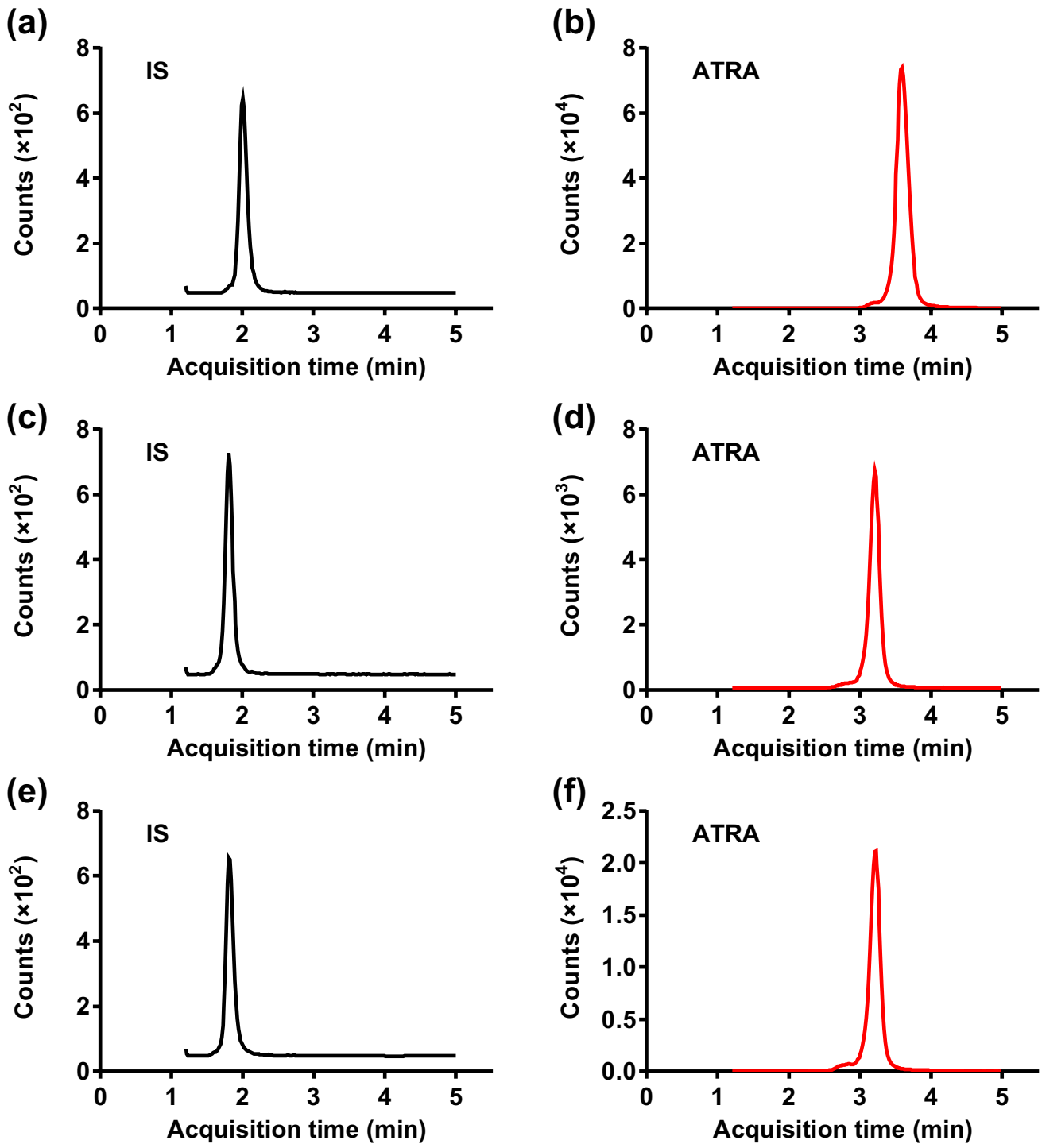

Fig. S8. Representative MRM chromatograms. (a and b) Blank plasma samples spiked with IS and ATRA; (c and d) plasma samples collected after implantation of ATRA pellet and further spiked with IS; (e and f) plasma samples collected after injection of ATRA-PLLA particles and further spiked with IS. IS: MRM precursor-to-product ion transition of *m*/*z* 325.2−266.2. ATRA: MRM precursor-to-product ion transition of *m*/*z* 299.2−255.2.