Supporting information

1. DLS measurement of drug loaded polymeric micelles

Table S.1 Micelle diameter and PDI (polydispersity index) values of singly-loaded micelles, 2-in-1, or 3-in-1 polymeric micelles (n = 3, Mean ± SD)

Drug(s) in micelles	Micelle diameter (nm)	PDI
Empty*	38.2 ± 1.1	0.175 ± 0.010
PTX	38.8 ± 0.6	0.185 ± 0.009
17-AAG	39.3 ± 2.9	0.187 ± 0.004
RAP	36.9 ± 1.3	0.135 ± 0.006
PTX 17-AAG	38.9 ± 1.1	0.184 ± 0.004
RAP 17-AAG	39.4 ± 1.9	0.182 ± 0.032
RAP PTX	41.0 ± 1.5	0.195 ± 0.007
RAP PTX 17-AAG	43.8 ± 1.3	0.168 ± 0.014

* Empty PEG-*b*-PLA micelles were prepared by the described method in Materials and Methods without drug encapsulation

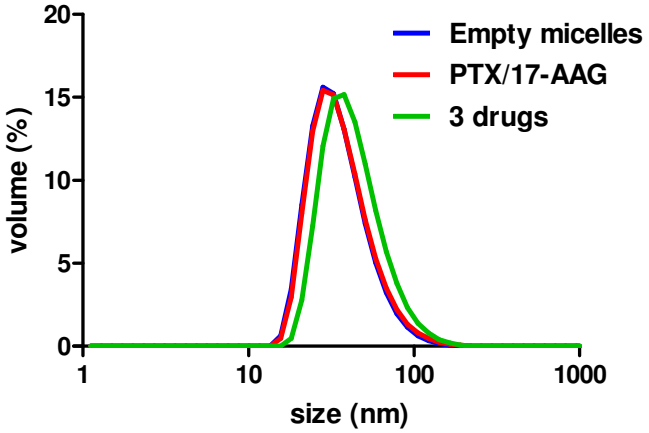

Figure S.1 Particle size distribution of Empty PEG-*b*-PLA micelles, 2-in-1 PEG-*b*-PLA micelles including PTX/17-AAG, and 3-in-1 PEG-*b*-PLA micelles of PTX/17-AAG/RAP (n = 3, Mean)

PEG-*b*-PLA with 4200 g/mol of PEG and 1900 g/mol of PLA (hydrophilic fraction = 0.69) form spherical micelles[1, 2]. As shown in Table S.1 and Figure S.1, no significant change in PDI was observed over multi-drug solubilization, suggesting that the morphological changes do not occur after the drug loading.

2. *In vitro* cytotoxicity experiments for determining drug ratio of PTX/17-AAG and PTX/17-AAG/RAP in MCF-7 breast cancer cell line

In our preliminary studies, we have screened the cytotoxicity by changing the molar ratio of PTX and 17-AAG as free drug (dissolved in DMSO) and found that more than 1:1 molar ratio of PTX and 17-AAG was synergistic in MCF-7 breast cancer cell line (Table S.2). 5:1 molar ratio of PTX and 17-AAG was chosen because 17-AAG could not be minimized due to accuracy of weighing. For RAP/PTX/17-AAG combination, we screened drug synergy by fixing PTX/17-AAG at 5:1 molar ratio and changing RAP concentration. Raising the content of RAP increased synergy (Table S.3); however, considering the encapsulation capacity of PEG-*b*-PLA micelles, we limited the RAP at 1:5:1 ratio to maintain the stability of 3-in-1 micelles

Table S.2. *CI* analysis of 2 drug combination including PTX and 17-AAG in MCF-7 breast cancer cells (free drugs dissolved in DMSO, $n = 3$, Mean $\pm$ SD)

PTX (nM)	17-AAG (nM)	fraction affected*	*CI*	Drug interaction
0.5	0.5	0.258 $\pm$ 0.04	0.94	Synergistic
0.5	5	0.317 $\pm$ 0.03	2.29	Antagonistic
0.5	50	0.517 $\pm$ 0.04	1.58	Antagonistic
5	0.5	0.624 $\pm$ 0.06	0.16	Synergistic
5	5	0.582 $\pm$ 0.02	0.28	Synergistic
5	50	0.534 $\pm$ 0.04	1.29	Antagonistic
50	0.5	0.656 $\pm$ 0.03	1.09	Additive
50	5	0.720 $\pm$ 0.05	0.64	Synergistic
50	50	0.761 $\pm$ 0.02	0.52	Synergistic

* fraction of dead cells upon drug exposure

Table S.3. *CI* analysis of 3 drug combination including PTX, 17-AAG, and RAP in MCF-7 breast cancer cells (free drugs dissolved in DMSO, $n = 3$, Mean $\pm$ SD)

PTX (nM)	17-AAG (nM)	RAP (nM)	fraction affected	*CI*	Drug interaction
50	10	0.5	0.709 $\pm$ 0.02	0.72	Synergistic
50	10	5	0.727 $\pm$ 0.04	0.65	Synergistic
50	10	50	0.733 $\pm$ 0.05	0.69	Synergistic
50	10	500	0.829 $\pm$ 0.02	0.44	Synergistic

3. References

1. Discher, D. E.; Ahmed, F. Polymersomes. *Annu. Rev. Biomed. Eng.* **2006,** 8, 323-41.
2. Richter, A.; Olbrich, C.; Krause, M.; Kissel, T. Solubilization of sagopilone, a poorly water-soluble anticancer drug, using polymeric micelles for parenteral delivery. *Int. J. Pharm.* **2010,** 389, (1-2), 244-53.