TPGS Micelle/Hydrogel Combination for Peritoneal Metastatic and Drug-Resistant Ovarian Cancer

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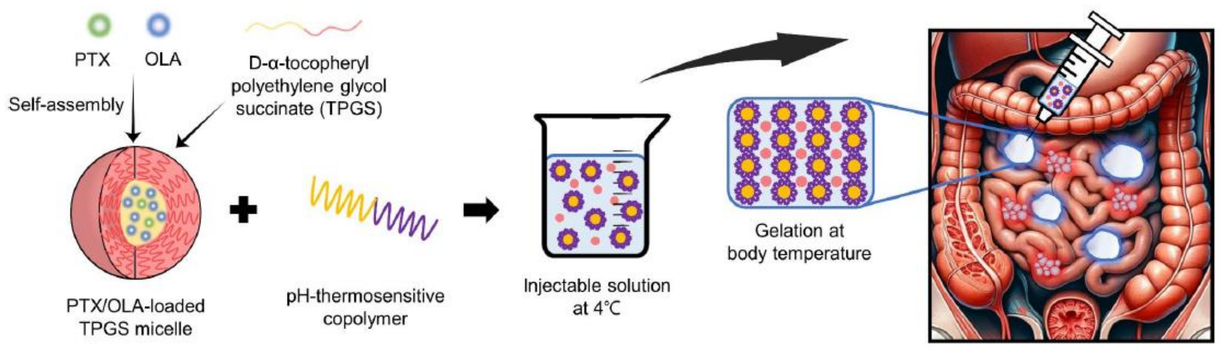
Abstract

Ovarian cancer is often diagnosed at an advanced stage, when peritoneal metastasis has already occurred, and its treatment is further complicated by frequent recurrence and multidrug resistance. Although intraperitoneal chemotherapy can enhance local drug exposure, conventional formulations are limited by rapid clearance and insufficient tumor-selective release. This study aimed to develop an injectable combination formulation of paclitaxel- and olaparib-loaded TPGS micelles incorporated into a pH-thermosensitive hydrogel to improve local retention, overcome drug resistance, and enhance therapeutic efficacy against metastatic ovarian cancer.

Scheme



Results

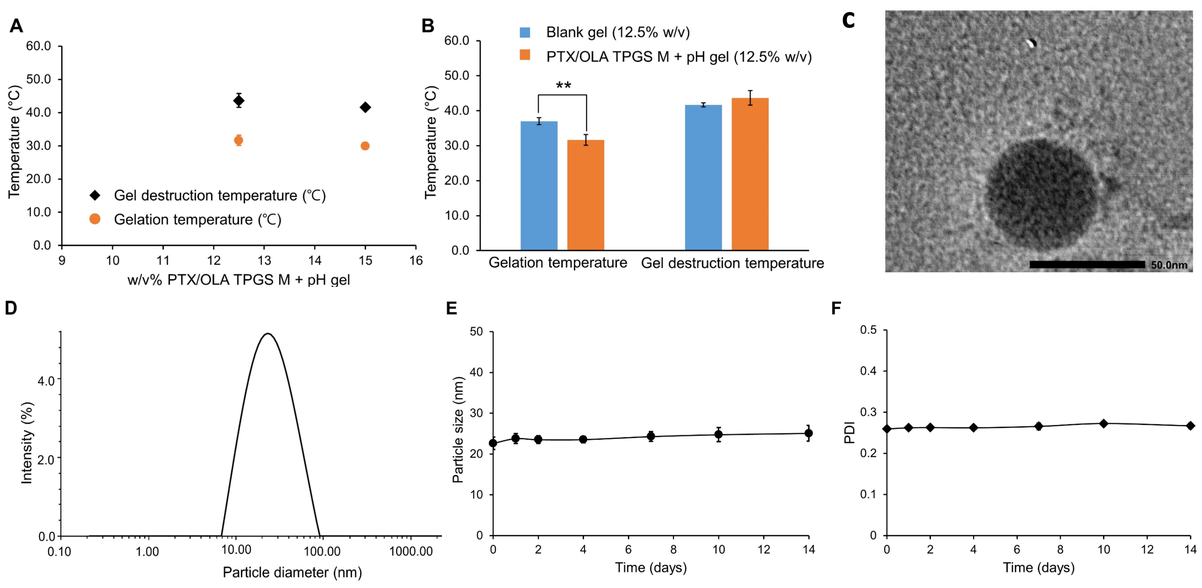
- CI and IC_{50} values of PTX and OLA at different molar ratios

Molar Ratio (PTX: OLA)	HeyA8-MDR IC_{50} (nM)		CI Value
	PTX	OLA	
1:1	1021	1021	0.08
1:2	1755	3509	0.14
2:1	1935	967	0.15
1:4	1540	6161	0.12
4:1	369	92	0.03
1:10	532	5322	0.04
10:1	3606	361	0.27

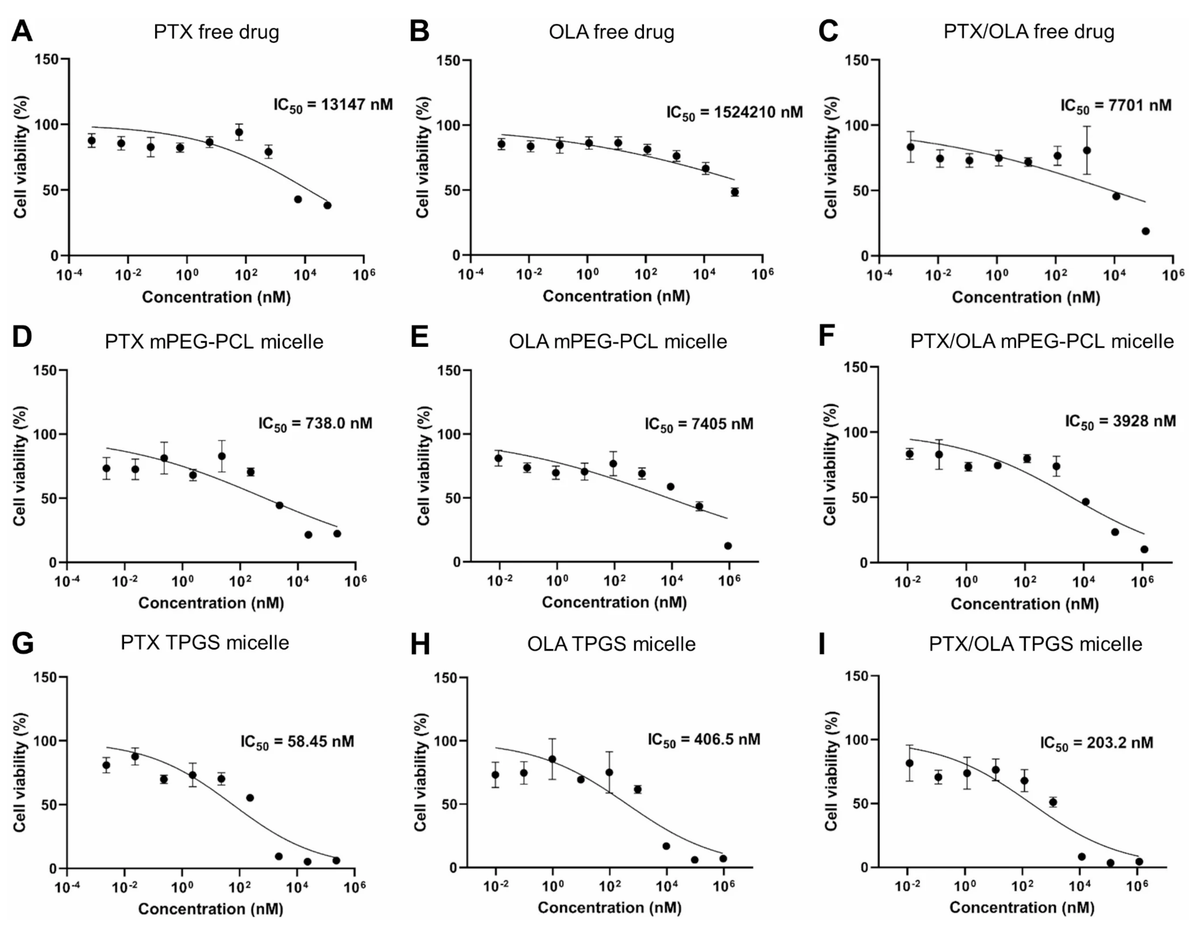
- Physicochemical characteristics of PTX/OLA-loaded TPGS micelles and pH-thermosensitive hydrogel mixtures

Formulation (molar ratio)	TPGS Amount Used (mg)	Gel polymer concentration (w/v %)	PTX Encapsulation Efficiency (EE %)	OLA Encapsulation Efficiency (EE %)	PTX Drug Loading (DL %)	OLA Drug Loading (DL %)	Particle Size (nm)	Poly-Dispersity Index (PDI)	Zeta Potential (mV)
PTX: OLA 1:4	50	12.5	88.4±7.60	83.1±8.48	1.00±0.09	1.90±0.19	22.3±0.62	0.27±0.00	1.30±0.90

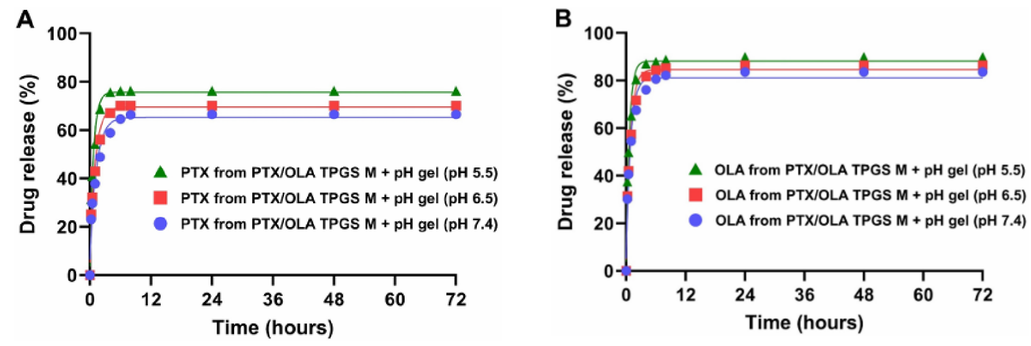
- Characterization of PTX/OLA-loaded TPGS micelles incorporated into a pH-thermosensitive hydrogel. (A) Gelation and gel destruction temperatures at varying polymer concentrations, (B) comparison of gelation and destruction temperatures between drug-loaded hydrogel (12.5% w/v) and blank gel, (c)transmission electron microscopy (TEM) images, (D) particle size distribution, (E) particle size stability over 14 days at 4 °C, and (F) PDI stability over 14 days at 4 °C



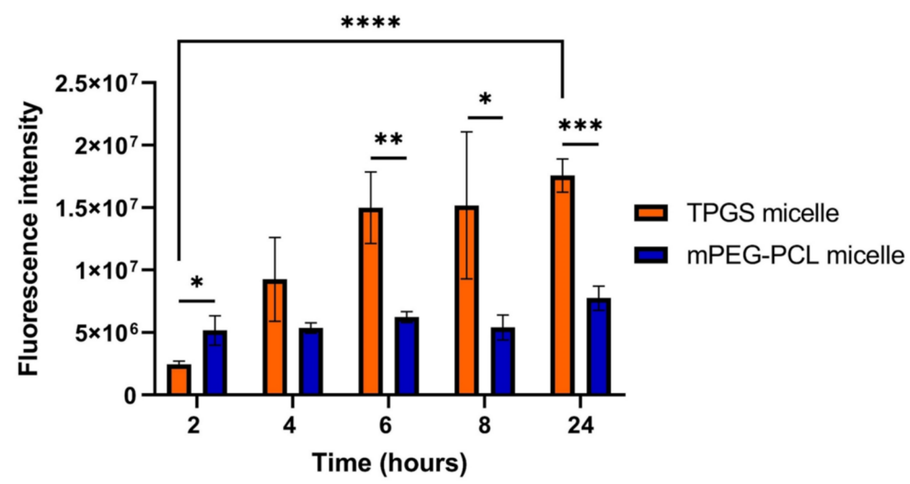
- *In vitro* cytotoxicity analysis of HeyA8-MDR cells after 48 h treatment with (A) PTX free drug, (B) OLA free drug, (C) PTX/OLA free drug, (D) PTX-loaded mPEG-PCL micelles, (E) OLA-loaded mPEG-PCL micelles, (F) PTX/OLA-loaded mPEG-PCL micelles, (G) PTX-loaded TPGS micelles, (H) OLA-loaded TPGS micelles, and (I) PTX/OLA-loaded TPGS micelles



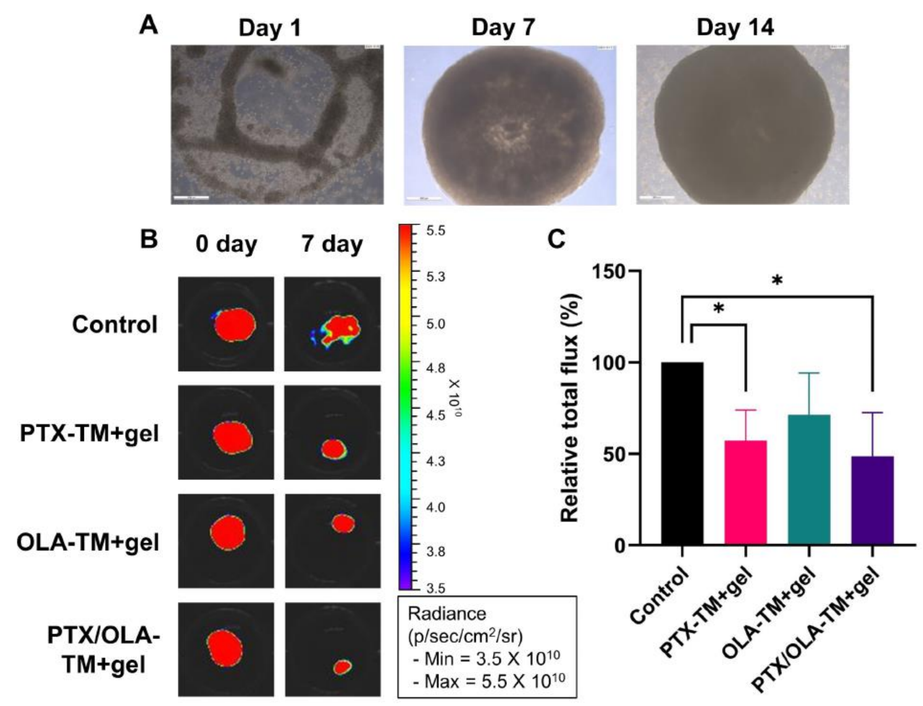
- Drug release profiles of (A) PTX and (B) OLA from PTX/OLA-loaded TPGS micelles incorporated into a pH-thermosensitive hydrogel at different pH conditions



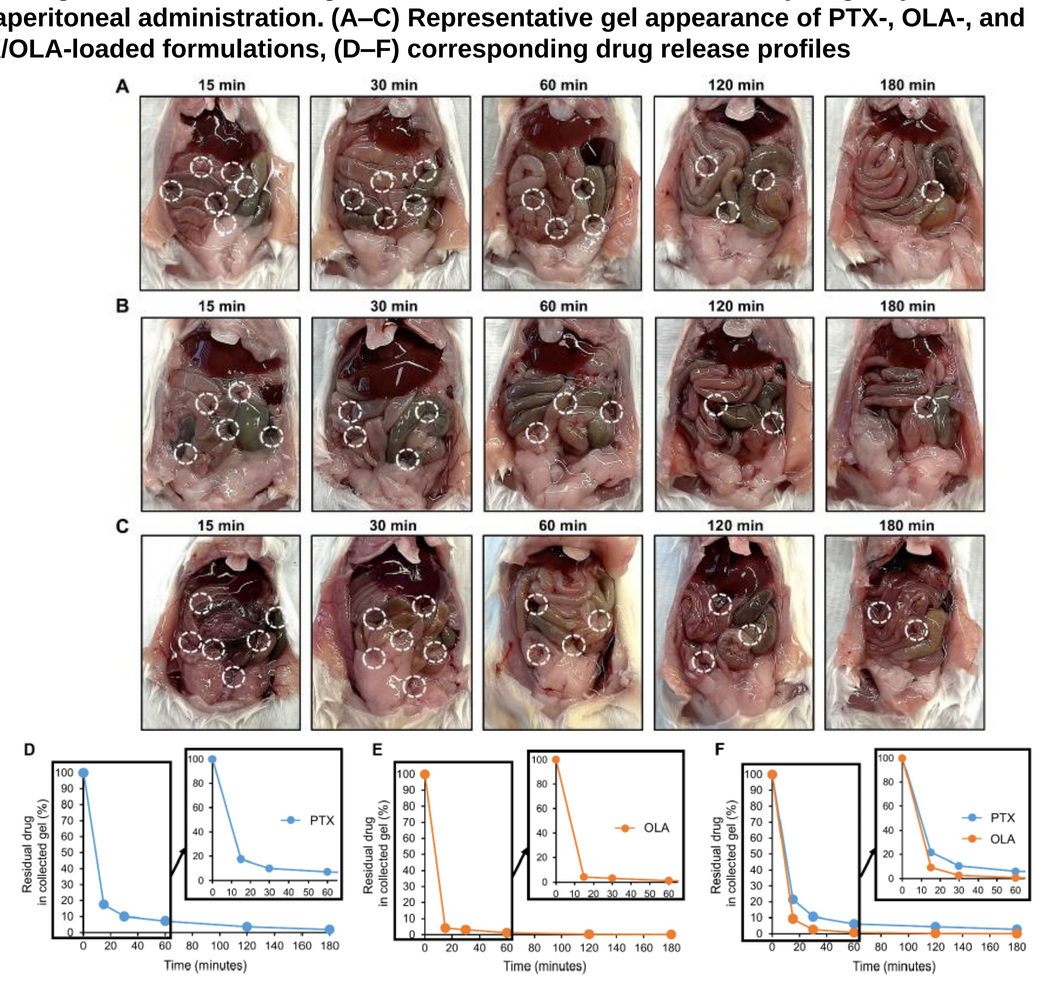
- Cellular uptake efficiency of coumarin 6-loaded TPGS micelles and mPEG-PCL micelles in HeyA8-MDR cells after 2, 4, 6, 8, and 24 h of incubation



- Evaluation of HeyA8-MDR tumor spheroids. (A) Morphological changes on days 1, 7, and 14, (B) representative images of spheroids treated with single and combination formulations, and (C) relative total flux on day 7 compared to the control group



- *In vivo* gel formation and drug release behavior of TPGS micelle–hydrogel systems after intraperitoneal administration. (A–C) Representative gel appearance of PTX-, OLA-, and PTX/OLA-loaded formulations, (D–F) corresponding drug release profiles



Conclusion

The PTX/OLA-loaded TPGS micelle–hydrogel formulation exhibited both temperature- and pH-responsive behavior, remaining in a liquid state at 4 °C and forming a stable gel at 37 °C. The optimized formulation (PTX:OLA = 1:4, 12.5% w/v polymer) demonstrated high drug encapsulation efficiency, small particle size (< 30 nm), and stable physicochemical properties over two weeks at 4 °C. *In vitro* studies showed that TPGS micelles significantly enhanced cellular uptake and cytotoxicity in HeyA8-MDR cells, with strong synergistic effects between PTX and OLA. Drug release studies revealed faster release under acidic conditions (pH 5.5), indicating a pH-dependent and sustained release pattern consistent with *in vivo* observations. In 3D tumor spheroid models, the combination formulation achieved the greatest tumor growth inhibition compared to single-drug systems. However, despite its potent antitumor efficacy, the formulation exhibited *in vivo* toxicity, likely associated with the cationic P(DMAEMA-mPEG) polymer component.