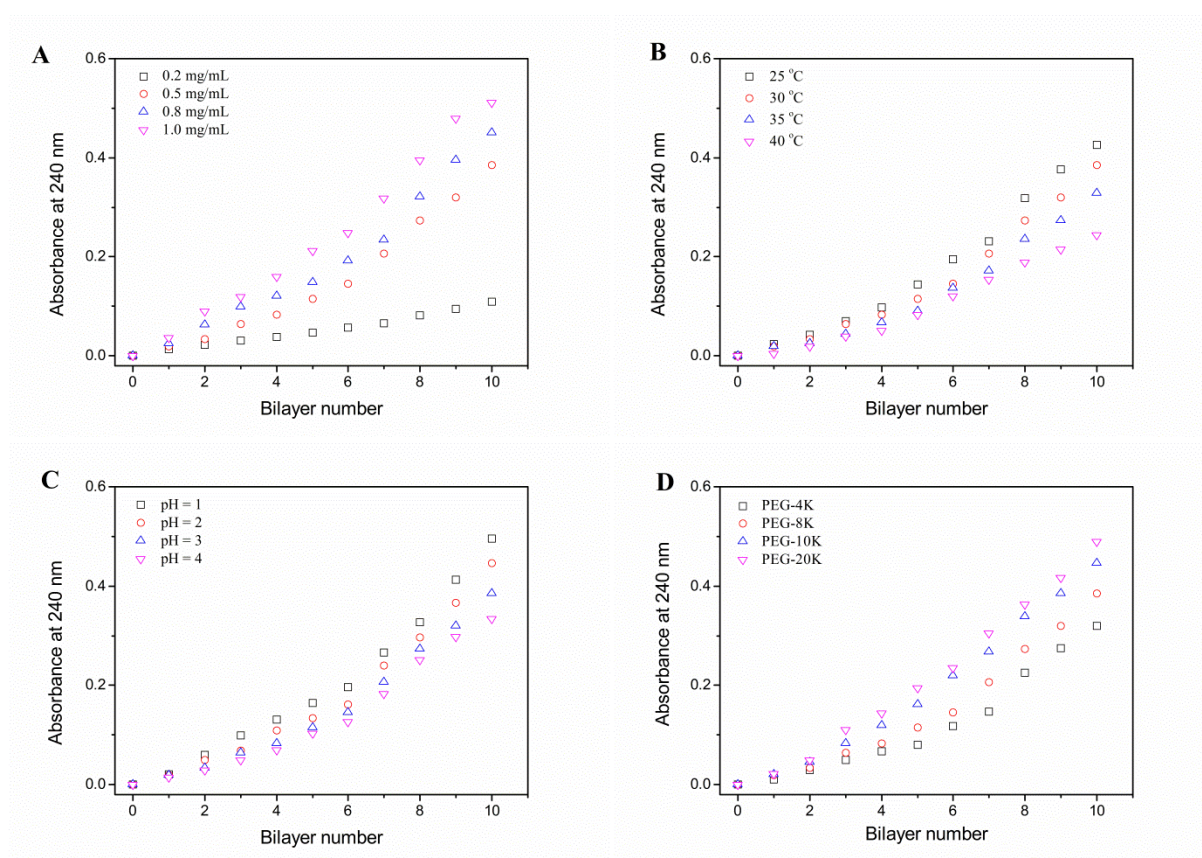
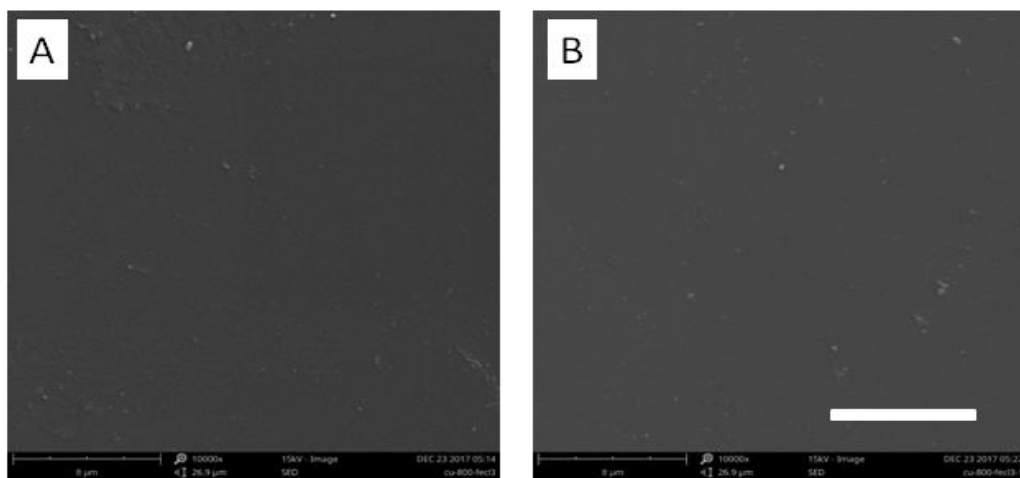


# Zero-order release of gossypol improves its antifertility effect and reduces its side effects simultaneously

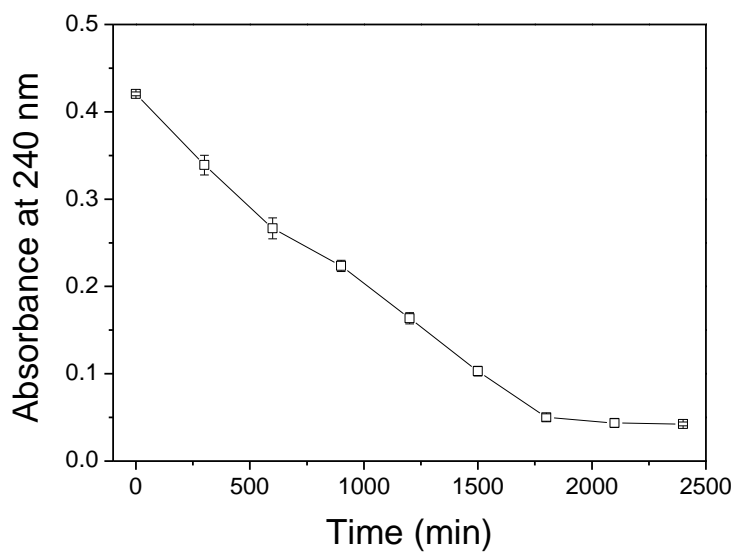
Na Wen,<sup>1,2</sup> Yansheng Dong,<sup>1</sup> Rui Song,<sup>1</sup> Wenpeng Zhang,<sup>1</sup> Chao Sun,<sup>1</sup> Xiaomei Zhuang,<sup>1</sup> Ying Guan,<sup>2</sup> Qingbin Meng,<sup>1</sup> & Yongjun Zhang<sup>2</sup>



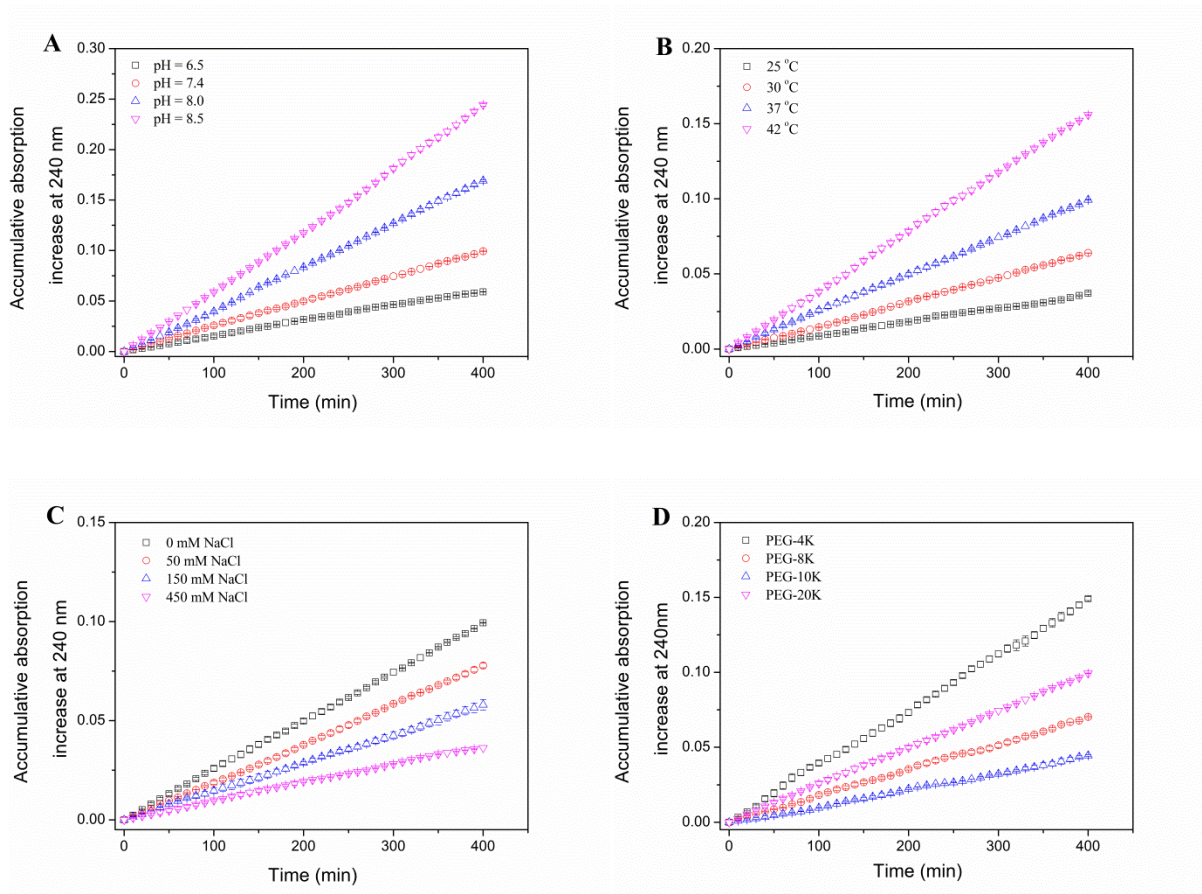
**Figure S1.** Growth of PEG/Gossypol films under various conditions. (A) PEG-8K and gossypol were assembled at different concentrations as indicated.  $T = 30\text{ }^{\circ}\text{C}$ ,  $\text{pH} = 3.0$ . (B) PEG-8K and gossypol were assembled at different temperatures as indicated.  $[\text{PEG}] = [\text{Gossypol}] = 0.5\text{ mg/mL}$ ,  $\text{pH} = 3.0$ . (C) PEG-8K and gossypol were assembled at different pHs as indicated.  $[\text{PEG}] = [\text{Gossypol}] = 0.5\text{ mg/mL}$ ,  $T = 30\text{ }^{\circ}\text{C}$ . (D) PEG with different molecular weights were assembled with gossypol.  $[\text{PEG}] = [\text{Gossypol}] = 0.5\text{ mg/mL}$ ,  $T = 30\text{ }^{\circ}\text{C}$ ,  $\text{pH} = 3.0$ .



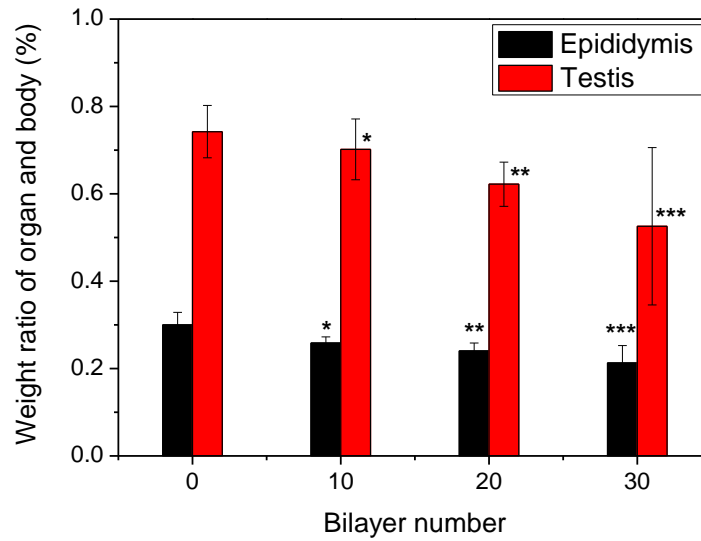
**Figure S2.** SEM images of a 10-bilayer (A) and a 20-bilayer (B) PEG-8K/Gossypol film. Scale bar: 8  $\mu\text{m}$ .



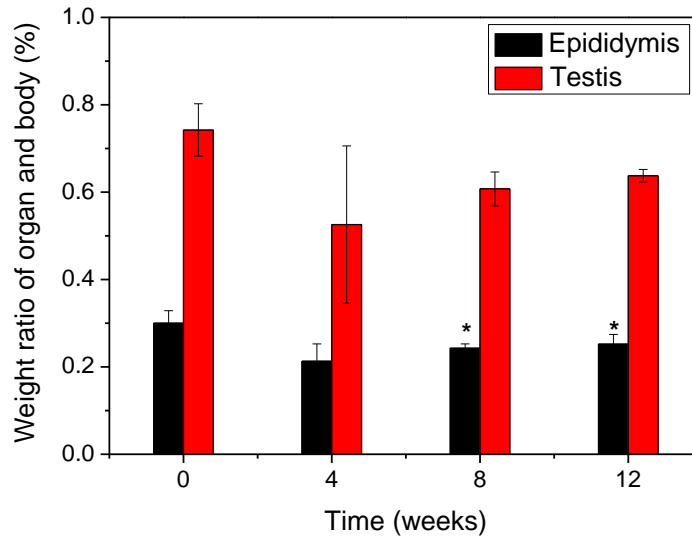
**Figure S3.** Absorbance of a (PEG-8K/gossypol)<sub>10</sub> film in soaked in 50 mM pH 7.4 phosphate buffer at 37°C.



**Figure S4.** Release profiles of gossypol from (PEG/Gossypol)<sub>10</sub> films under various conditions. (A) in 50 mM phosphate buffer of various pH as indicated, T=37°C, (PEG-8K/Gossypol)<sub>10</sub>; (C) in 50 mM pH=7.4 phosphate buffer at various temperatures, (PEG-8K/Gossypol)<sub>10</sub>; (C) in pH=7.4 50 mM PBS with different concentrations of NaCl, T=37°C, (PEG-8K/Gossypol)<sub>10</sub>; (D) in 50 mM pH=7.4 phosphate buffer, T=37°C. The films were fabricated from PEG with different molecular weights as indicated.



**Figure S5.** Weight ratios of testis and epididymis for rats implanted with 0(control), 10, 20, and 30-bilayer PEG-8K/Gossypol films. Data are mean  $\pm$ SD (n=5). \*  $p < 0.05$ ; \*\*  $p < 0.01$ ; \*\*\*  $p < 0.005$  (compared to control group).



**Figure S6.** Weight ratios of testis and epididymis for rats implanted with a 30-bilayer PEG-8K/Gossypol film. Data are mean  $\pm$ SD (n=5). \*  $p < 0.05$ ; \*\*  $p < 0.01$ ; \*\*\*  $p < 0.005$ . (compared to 4 week group).