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PII: S0378-5173(18)30572-6
DOI: https://doi.org/10.1016/j.ijpharm.2018.08.010
Reference: IJP 17695

To appear in: *International Journal of Pharmaceutics*

Received Date: 10 May 2018
Revised Date: 20 July 2018
Accepted Date: 8 August 2018

Please cite this article as: Y. Du, L. Ling, M. Ismail, W. He, Q. Xia, W. Zhou, C. Yao, X. Li, Redox Sensitive Lipid-camptothecin Conjugate Encapsulated Solid Lipid Nanoparticles for Oral Delivery, *International Journal of Pharmaceutics* (2018), doi: https://doi.org/10.1016/j.ijpharm.2018.08.010

Redox Sensitive Lipid-camptothecin Conjugate Encapsulated Solid Lipid Nanoparticles for Oral Delivery

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Abstract: Camptothecin (CPT) is an important topoisomerase I enzyme (*Topo* I) targeting anti-cancer drug, but its oral administration is limited by poor bioavailability and severe side effects. In this study, a redox sensitive CPT prodrug loaded solid lipid nanoparticles (SLN) system for oral delivery was developed. First of all, CPT-palmitic acid conjugate *via* a cleavable disulfide bond linker (CPT-SS-PA) was synthesized and encapsulated into SLN. The drug release of SLN was evaluated in neutral environment, simulated gastrointestinal fluid and reductive DTT solution. The results indicated that CPT-SS-PA SLN maintained chemical structural stability in simulated physiological environment but exhibited quick reduction-response release of CPT in the presence of DTT. Furthermore, *in vitro* cytotoxicity of CPT-SS-PA SLN was tested against cancer cell lines, and the cellular uptake behavior for oral delivery was checked by confocal laser scanning microscopy (CLSM) using Caco-2 cells model. From the data, CPT-SS-PA SLN revealed high anti-cancer activity and enhanced Caco-2 cell absorption. Finally, the oral bioavailability and intestinal safety of CPT-SS-PA SLN was preliminary evaluated by *in vivo* pharmacokinetic and histopathological study, respectively. This study demonstrated that CPT-SS-PA SLN could be developed as an effective CPT oral delivery system due to its enhanced oral bioavailability and reduced intestinal side effect.

Keywords: solid lipid nanoparticles, oral administration, reduction-response, lipid-drug conjugate,