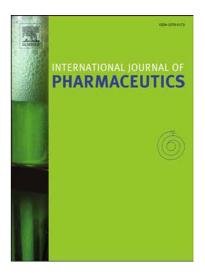
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Redox Sensitive Lipid-camptothecin Conjugate Encapsulated Solid Lipid Nanoparticles for Oral Delivery

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Abstract: Camptothecin (CPT) is an important topoisomerase I enzyme (Topo I) targeting anticancer 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 anticancer 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,

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