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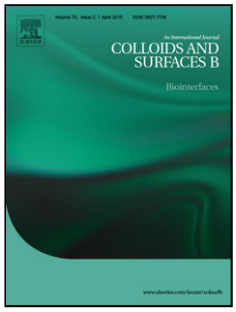

Title: Vitamin E-based redox-sensitive salinomycin prodrug-nanosystem with paclitaxel loaded for cancer targeted and combined chemotherapy

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Vitamin E-based redox-sensitive salinomycin prodrug-nanosystem with paclitaxel loaded for cancer targeted and combined chemotherapy

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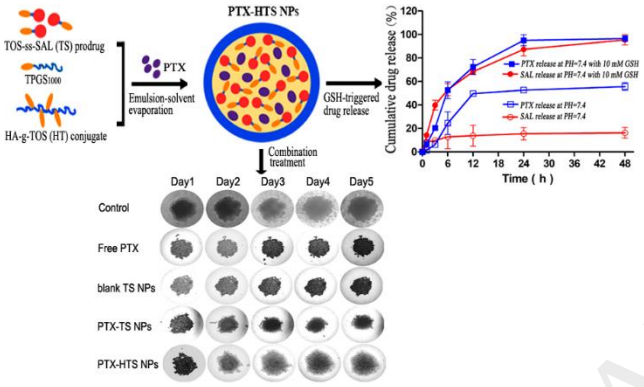
Graphical Abstract



Highlights

- • The TS prodrug conjugates were designed by covalently coupling the lipophilic TOS moiety to SAL via disulfide linkages.
- • The TS prodrug conjugates were readily self-aggregated into stable nanoparticles.
- • The TS prodrug nanoparticles were tumor-targeting and glutathione-sensitive.
- • The TS prodrug nanoparticles were designed for synergistic salinomycin-paclitaxel combination chemotherapy

Abstract: Cancer stem cells (CSCs) can resist conventional chemotherapy to lead to cancer recurrence. For complete eradication of cancers, an effective CSCs therapeutic strategy should be developed to combine with conventional chemotherapy. In this work, a novel vitamin E-based redox-sensitive salinomycin (SAL, an inhibitor for CSCs) prodrug nanoparticles (TS NPs) and hyaluronic acid (HA)-coated TS NPs (HTS NPs) were fabricated to deliver paclitaxel (PTX) for cancer-targeted and combined chemotherapy. Both TS and HTS prodrug NPs had mean diameter of about 200 nm with uniform size distribution, excellent drug loading capacity for PTX, and glutathione-triggered SAL and PTX release profiles. The HTS prodrug NPs had enhanced cellular uptake efficiency over TS NPs due to CD44 receptor-mediated endocytosis, hence exerting stronger potency of SAL upon CSCs-enriched mammospheres formation and G_0/G_1 cell phase arresting. Cytotoxicity and *3D* tumor