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Amifostine-Conjugated pH-Sensitive Calcium Phosphate-Covered Magnetic-Amphiphilic Gelatin Nanoparticles for Controlled Intracellular Dual Drug Release for Dual-Targeting in HER-2-Overexpressing Breast Cancer

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Abstract

We developed a surfactant-free method utilizing amifostine to stably link a targeting ligand (Herceptin) to amphiphilic gelatin (AG)-iron oxide@calcium phosphate (CaP) nanoparticles with hydrophobic curcumin (CUR) and hydrophilic doxorubicin (DOX) encapsulated in the AG core and CaP shell (AGIO@CaP-CD), respectively. This multi-functional nanoparticle system has a pH-sensitive CaP shell and degradable amphiphilic gelatin (AG) core, which enables controllable sequential release of the two drugs. The dual-targeting system of AGIO@CaP-CD (HER-AGIO@CaP-CD) with a bioligand and magnetic targeting resulted in significantly elevated cellular uptake in HER2-overexpressing SKBr3 cells and more efficacious therapy than delivery of targeting ligand alone due to the synergistic cell multi-drug resistance/apoptosis-inducing effect of the CUR and DOX combination. This nanoparticle combined with Herceptin and iron oxide nanoparticles not only provided a dual-targeting functionality, but also encapsulated CUR and DOX as a dual-drug delivery system for the combination therapy. This study further demonstrated that the therapeutic efficacy of this dual-targeting co-delivery system can be improved by modifying the application duration of magnetic targeting, which makes this combination therapy system a powerful new tool for *in vitro*/*in vivo* cancer therapy, especially for HER2-positive cancers.