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Smart Drug Conjugated Silica Nanoparticles for Controlled and Sustained Release

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Abstract

Drug delivery system (DDS) is crucial for modern cancer treatment. Traditional drug delivery process is to load drugs into various carriers via physical interactions, which always gives rise to the burst release and leakage of the loaded drugs. This thesis aims to develop a novel delivery platform with controlled and sustained drug release ability, where doxorubicin (DOX, a model anticancer drug) is conjugated to the surfaces of model carriers, silica nanoparticles (SNs), via different “smart” linkers. pH and glutathione (GSH) are utilized as the stimuli of these “smart” linkers to construct pH and intracellular microenvironment redox responsive drug-carrier conjugated delivery systems to selectively deliver drugs.

The pH regulated drug delivery system was developed to conjugate DOX to the surfaces of silica nanoparticles by acid responsive hydrazone bonds. The drug delivery system showed good stability under physiological pH of 7.4 to avoid premature drug leakage in blood circulation, and sustained release under acidic extracellular environment of cancer cells to effectively inhibit tumor growth. *In vitro* cytotoxicity study against Hela cells and HEK 293 cells indicated the drug delivery system revealed such a system could release more drugs in tumor cells than normal cells.

The intracellular microenvironment redox responsive drug delivery system was established by introducing dithiodibutyric acid (DTDB), which contained redox responsive disulfide bonds, to silica nanoparticle surfaces. In the absence of reducing

reagents of GSH or dithiothreitol (DTT), such a drug delivery system presented good stability to prevent drug leakage, but in the presence of GSH or DTT, the disulfide bonds could be effectively cleaved to release the preloaded drugs. The *in vitro* cytotoxicity study indicated this drug delivery system could be stable in blood circulation and effectively released the preloaded drugs inside cells after conjugation. Due to the different GSH levels in cancer cells and normal cells, intracellular microenvironment redox responsive system could be more toxic to cancer cells.

In summary, DOX-silica nanoparticles conjugates with pH regulated hydrazone bonds or intracellular microenvironment redox responsive disulfide bonds had the capability in controlled and sustained drug release, which could effectively eliminate drug leakage during the delivery course and release sufficient amount of drugs in tumors to inhibit their growth.

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