Self-assembled pH-sensitive nanogels from polysaccharide derivatives as an anti-cancer drug carrier

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Abstract

For the development of new anticancer drug delivery systems which utilize acidic tumor extracellular pH (pH_e, pH(7.0) for controlled release, two pH-sensitive self-assembled nanogels were designed and investigated. The pH-sensitive nanogels were prepared from the conjugates of pullulan acetate/sulfadimethoxine (PA/SDM) or pullulan/histidine (PU/His). Both nanogels showed a similar stability at pH 7.4, but showed enhanced drug release by different mechanisms at pH 6.8. PA/SDM nanogels exhibited a particle aggregation and shrinking at tumor pHe (6.8) because of the deionizion of SDM. The doxorubicin (DOX) release rate from the PA/SDM nanogel was influenced by pH around physiological pH and significantly enhanced at pH 6.8. The cytotoxicity of DOX loaded PA/SDM nanogel at pH 6.8 was comparable to that of free DOX at the same DOX concentrations, while the relative cytotoxicity at pH 7.4 was low at the tested concentration range. This pronounced cytotoxicity of the nanogel at low pH was attributed to the accelerated release of DOX triggered by pH, enhanced interaction with cells, and internalization. At pH 6.8 and 6.4, the PA/SDM nanoparticles aggressively bounded to MCF-7 cells, probably due to interactions of the cells with hydrophobized nanoparticle surfaces caused by SDM deionization. When the PU/His nanogels from pullulan and histidine conjugates was formed at pH 8.0 by the diafiltration method, the nanogel was 150 ± 49 nm in average diameter and had a unimodal size distribution. The nanogels was destabilized and disintegrated at pH below 7.0 due to the protonation of imidazole amine in histidine. Furthermore, the DOX release rate from the PU/His nanogel was significantly enhanced at pH below 6.8 by destabilization. The enhanced drug release rates led to the improvement in cell cytotoxicity at pH 6.8.

Keywords: self-assembled pH-sensitive nanogel, sulfadimethoxine, histidine, doxobubicin (DOX).