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PEG-peptide based Doxorubicin delivery systems

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Statement of the Problem: pH responsive Drug Delivery Systems (DDS) have been developed to increase therapeutic activity of the drugs and to overcome multidrug resistance problem of cancer cells. One of the drawbacks of the DDS with pH sensitive moieties where drug molecules are hold via intermolecular interactions is considerable release of the cargo at physiological pH. Although chemically attaching the drug to the carrier molecule can minimize the drug release at neutral pH, these configurations suffer from slow release at acidic conditions as well. In this study, a pH responsive DDS containing both pH responsive functional groups and acid cleavable chemical bond between drug and carrier molecule was proposed.

Methodology & Theoretical Orientation: mPEG-peptide based doxorubicin delivery system (mPEG-AT1-DOX) containing pH responsive histidines and hydrazone bond was developed and its performance was compared with peptide-free DDS, mPEG-DOX having hydrazone bond.

Findings: Hydrodynamic diameters of mPEG-DOX were determined as 9±0.5 and 7±0.5 nm at pH 7.4 and pH 5.0, respectively. The mPEG-AT1-DOX, on the other hand, exhibited a size distribution between 20 and 100 nm centered at about 40 nm at acidic pH much larger than its mean size at neutral pH measured as 12±2 nm. Enhanced pH responsiveness of mPEG-AT1-DOX was also confirmed by the comparison of the percentage of DOX release values of both DDS evaluated at pH 7.4 and pH 5.0. Cytotoxicity of the DDS was assessed using A549 cell line. DOX equivalent absolute IC50 values were obtained as 1.8±0.9, 40.3±10.9 and 10.2±1.4 μM for free DOX, mPEG-DOX and mPEG-AT1-DOX, respectively.

Conclusion & Significance: Superior pH sensitivity and cytotoxicity of mPEG-AT1-DOX indicated utilization of both pH responsive functional groups and acid cleavable chemical bond can be a promising approach in the design of DDS for cancer therapy.

Biography

Beste Balci has graduated from the Department of Chemical Engineering at Izmir Institute of Technology. She had completed her MSc degree at the Biofunctional Materials Laboratory at the same institution under the supervision of Assistant Professor Ayben Top. During her MSc studies she had focused on the development of PEG-peptide based pH responsive drug delivery systems for cancer therapy. Currently, she is pursuing her PhD at Kyoto University, Japan.

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