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Design and fabrication of dual-targeted delivery system based on gemcitabine conjugated human serum albumin nanoparticles

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For cancer chemotherapy, dual -targeted drug delivery systems have a significant role as potent vehicle. Gemcitabine (Gem; 2′-deoxy-2′,2′-difluorocytidine), a nucleoside pyrimidine analogue, is the main anticancer used for treating various solid tumors such as breast cancer. Cancer chemotherapy with Gem faces two major limitations including the development of tumor resistance against drug over time and rapid deamination of Gem into inactive metabolite, 2′,2′- difluorodeoxyuridine (dFdU). To date, many attempts have been employed to overcome the short plasma circulation time of Gem. In this study, to enhance the low stability of Gem and improving its intracellular delivery, it was conjugated to human serum albumin (HSA) via dithiodipropionic anhydride (DTDPA) as a disulfide linker, to fabricate Gem-HSA nanoparticles. In the firs step, 3,3′-dithiodipropionic acid functionalized Gem was synthesized and was directly conjugated to HSA to produce the Gem-HSA conjugate and fabricate HAS nanoparticles, simultaneously. In order to evaluate the structural properties of synthesized products, 1H NMR and FT-IR were performed. Moreover, for confirming the conjugation between HSA and Gem, HPLC was implemented. Nanoparticles were characterized in terms of size, zeta potential, shape, and conjugation ratios. Drug release behavior, *in vitro* cytotoxicity, cellular uptake and apoptosis induction capability of nanoparticles were also assessed in order to evaluate the efficiency of designed nanoparticles. Nanoparticles have shown spherical shape with diameter around 200 nm and negative charge. The release rate of Gem was dependent to the concentration of glutathione and pH. Folate-targeted HSA nanoparticles have shown higher cytotoxicity, cellular uptake and apoptosis induction on folate receptor overexpressing MDA-MB-231 cells in comparison to non-targeted nanoparticles. Finally, it is considered that the developed dual-targeted nanoparticles would be potent in improving the stability of Gem and its selective delivery to cancer cells.

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