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In vitro and in vivo Anticancer Activity of Nanosize Zinc Oxide Composites of Doxorubicin

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Abstract : Novel nanosize zinc oxide composites of doxorubicin obtained by deposition of 180 nm thick zinc oxide film on the drug surface using DC-magnetron sputtering of a zinc target in the form of gels (PEO+Dox+ZnO and Starch+NaCMC+Dox+ZnO) were studied for drug delivery applications. The cancer specificity was revealed both in in vitro and in vivo models. The cytotoxicity of the test compounds was analyzed against human cancer (HeLa) and normal (MRC5) cell lines using MTT colorimetric cell viability assay. IC50 values were determined and compared to reveal the cancer specificity of the test samples. The mechanistic study of the most active compound was investigated using Flow cytometry analyzing of the DNA content after PI (propidium iodide) staining. Data were analyzed with Tree Star FlowJo software using cell cycle analysis Dean-Jett-Fox module. The in vivo anticancer activity estimation experiments were carried out on mice with inoculated ascitic Ehrlich's carcinoma at intraperitoneal introduction of doxorubicin and its zinc oxide compositions. It was shown that the nanosize zinc oxide film deposition on the drug surface leads to the selective anticancer activity of composites at the cellular level with the range of selectivity index (SI) from 4 (Starch+NaCMC+Dox+ZnO) to 200 (PEO(gel)+Dox+ZnO) which is higher than that of free Dox (SI = 56). The significant increase in vivo antitumor activity (by a factor of 2-2.5) and decrease of general toxicity of zinc oxide compositions of doxorubicin in the form of the above mentioned gels compared to free doxorubicin were shown on the model of inoculated Ehrlich's ascitic carcinoma. Mechanistic studies of anticancer activity revealed the cytostatic effect based on the high level of DNA biosynthesis inhibition at considerable low concentrations of zinc oxide compositions of doxorubicin. The results of studies in vitro and in vivo behavior of PEO+Dox+ZnO and Starch+NaCMC+Dox+ZnO composites confirm the high potential of the nanosize zinc oxide composites as a vector delivery system for future application in cancer chemotherapy.

Keywords : anticancer activity, cancer specificity, doxorubicin, zinc oxide