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Diselenide-Linked Redox Stimuli-Responsive Methoxy Poly(Ethylene Glycol)-b-Poly(Lactide-Co-Glycolide) Micelles for the Delivery of Doxorubicin in Cancer Cells

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Abstract : The recent advancements in synthetic chemistry and nanotechnology fostered the development of different nanocarriers for enhanced intracellular delivery of pharmaceutical agents to tumor cells. Polymeric micelles (PMs), characterized by small size, appreciable drug loading capacity (DLC), better accumulation in tumor tissue via enhanced permeability and retention (EPR) effect, and the ability to avoid detection and subsequent clearance by the mononuclear phagocyte (MNP) system, are convenient to improve the poor solubility, slow absorption and non-selective biodistribution of payloads embedded in their hydrophobic cores and hence, enhance the therapeutic efficacy of chemotherapeutic agents. Recently, redox-responsive polymeric micelles have gained significant attention for the delivery and controlled release of anticancer drugs in tumor cells. In this study, we synthesized redox-responsive diselenide bond containing amphiphilic polymer, Bi(mPEG-PLGA)-Se_2 from mPEG-PLGA, and 3,3'-diselanediyldipropanoic acid (DSeDPA) using DCC/DMAP as coupling agents. The successful synthesis of the copolymers was verified by different spectroscopic techniques. Above the critical micelle concentration, the amphiphilic copolymer, Bi(mPEG-PLGA)-Se_2, self-assembled into stable micelles. The DLS data indicated that the hydrodynamic diameter of the micelles (123.9 ± 0.85 nm) was suitable for extravasation into the tumor cells through the EPR effect. The drug loading content (DLC) and encapsulation efficiency (EE) of DOX-loaded micelles were found to be 6.61 wt% and 54.9%, respectively. The DOX-loaded micelles showed initial burst release accompanied by sustained release trend where 73.94% and 69.54% of encapsulated DOX was released upon treatment with 6mM GSH and 0.1% H_2O_2, respectively. The biocompatible nature of Bi(mPEG-PLGA)-Se_2 copolymer was confirmed by the cell viability study. In addition, the DOX-loaded micelles exhibited significant inhibition against HeLa cells (44.46%), at a maximum dose of 7.5 µg/mL. The fluorescent microscope images of HeLa cells treated with 3 µg/mL (equivalent DOX concentration) revealed efficient internalization and accumulation of DOX-loaded Bi(mPEG-PLGA)-Se_2 micelles in the cytosol of cancer cells. In conclusion, the intelligent, biocompatible, and the redox stimuli-responsive behavior of Bi(mPEG-PLGA)-Se_2 copolymer marked the potential applications of diselenide-linked mPEG-PLGA micelles for the delivery and on-demand release of chemotherapeutic agents in cancer cells.

Keywords : anticancer drug delivery, diselenide bond, polymeric micelles, redox-responsive
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