Abstract

The thesis reports evaluation of poly (styrene-alt-maleic anhydride) (PSMA) based nanosystems for combinatorial delivery of drug and nucleic acid in cancer therapy. Effect of different types of cationic structures in modulating the intracellular gene delivery properties of poly (styrene-alt-maleic anhydride) was systematically evaluated. Based on this evaluation, suitable combinations of cationic moieties were selected and employed to design graft copolymers of poly (styrene-alt-maleic anhydride) which would be used for combinatorial delivery of drug and nucleic acid. The first polymeric nanosystem was developed by grafting isonicotinic acid and arginine-acetyllysine conjugate to the PSMA backbone through short glycol chains. Isonicotinic acid was employed to impart endosomolytic property to the polymeric carrier and arginine-acetyllysine conjugate could facilitate the nucleic acid binding. Click reaction was used to improve the grafting efficiency of amino acid residues. Second nanosystem was developed by imparting stimuli sensitive nature to the graft co-polymer. Arginine-histidine conjugates were grafted to PSMA backbone through disulfide linkages. Multiple disulfide linkages in the polymer can facilitate release of the loaded active agents in response to the glutathione rich environment of cancer cells. pH sensitive behavior of histidine molecules renders dual stimuli responsive nature to the polymeric graft. The designed nanocarriers were biologically safe and efficient in co-delivering the loaded active agents to cancer cells, in vitro and in vivo. Our study demonstrated improved antitumor efficacy of developed polymeric nanosystems carrying doxorubicin and PLK-1 siRNA as compared to conventional doxorubicin therapy.