



Pluronic F127 polymeric micelles for co-delivery of Paclitaxel and Lapatinib against metastatic breast cancer: preparation, optimization and *in vitro* evaluation

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Abstract: Varieties of drug delivery systems (DDS) have been designed to overcome PTX solubility problem as well as minimizing PTX side effects on normal cells. In these series of studies the aqueous solubility of PTX is enhanced to some extent but the resistance of cancerous cells is still a challenging issue. The aim of this study was development and characterization of paclitaxel (PTX)-lapatinib (LPT) loaded micelles for simultaneous delivery against metastatic breast cancer. Efflux pump mediated drug resistance influences the efficacy of chemotherapeutic regimens. However, in the newly developed delivery system, LPT was selected to act as chemosensitizer. LPT increases the intracellular level of PTX by inhibition of efflux pumps. Pluronic F127 was selected for preparation of the micelles and its critical micelle concentration (CMC) was determined to be 0.012 mg/ml. D-optimal design was used to analyze the impact of different experimental parameters on PTX encapsulation ratio (PTX EN%) and LPT encapsulation ratio (LPT EN%). PTX EN% was optimized at 68.30% while LPT EN% found to be 70.11%. Micelles morphology was studied by Transmission Electron Microscope (TEM). Laser scattering method Results indicated that size of the optimized micelles is 64.81 nm with acceptable polydispersity index (PDI= 0.309). *In vitro* release studies showed a sustain release pattern (25 hours). PTX-LPT loaded micelles suppressed the proliferation of resistant T-47D cell line ($IC_{50}= 0.6\pm 0.1 \mu\text{g/ml}$) compared to binary mixture of PTX and LPT ($IC_{50}= 6.7\pm 1.2 \mu\text{g/ml}$). Therefore it is concluded that developed formulation might increase the therapeutic efficacy in drug resistant metastatic breast cancer.

Keyword: Drug resistance; D-optimal design; Efflux pump; Chemotherapy; Tyrosine kinase inhibitor; enhanced cytotoxicity