

Abstract

Multi-drug resistance is a major roadblock in the treatment of lung cancer with current treatment options. It is well established that the MDR-1 OR ABCB-1 gene is responsible for the development of resistance in cancer cells. P-gp is an efflux pump responsible for throwing out chemotherapeutics from the cancer cells and as a result of this critical cytotoxic concentration has been never achieved in resistant cells. Hence, downregulation of the ABCB1 gene will be proved as a masterstroke in the reversal of drug resistance. Current research work was performed to extend the principles of Qbd approach to hybrid nanosystems containing drug powder inhaler for the effective treatment of multidrug resistant lung cancer. Two statistical designs were used to justify feasibility of design and the advantages of Qbd approach for the development of PLHNCs. The particle size and entrapment efficiency are selected as quality Target profile. Plackett-Burman design was used as first design to evaluate 7 high risk variables which has significant effect on the characteristics of the PLHNCs i.e. particle size, entrapment efficiency and physical stability. From the 7 high risk variables only 3 variables i.e. concentration of polymer, Lipid to polymer ratio and drug input has a significant effect on encapsulation efficiency of PLHNCs. Box behnken design has been used as second design to fully elucidate formulation development parameters. Furthermore, optimized PLHNCs formulation has been subjected to step wise development of lyophilization and dry powder development. The developed product shows how efficient developed dry powder of PLHNCs are able to target the respiratory region of the lungs.

The developed PLHNCs formulation with simultaneous loading of Docetaxel and ABCB1 shRNA plasmid has been further evaluated for cytotoxicity, cellular internalization capacity, and therapeutic potential against modified cancer cell lines (in-vitro) and in-vivo studies on Sprague-Dowely rats. Anti-cancer potential and molecular mechanisms of the D-sh-PLHNCs has been evaluated with cell migration assay, apoptosis analysis, P-gp inhibition assay, and cytotoxicity studies on DR-A549 cell line. In-vivo studies revealed that D-sh-PLHNCs have superior efficacy compare to Docetaxel solution. Even inhalation route has been proved significant for the local pulmonary delivery of Docetaxel which is confirmed by higher AUC of Docetaxel in the lungs after intratracheal instillation compares to intravenous delivery. From the results of in-vitro and In-vivo studies, capability of inhalable PLHNCs in lung cancer treatment has been well established using, where further studies may be required to determine the efficacy of PLHNCs over in vivo clinical studies.