Preface

The application of nanotechnology to medicine is the basis for the development of nanomedicine. It is a technology in which the drug-loaded nanomedicine of 1-1000 nm exhibit strong interaction between drugs and their targets. Recent advancements in nanotechnology have contributed to the development of nanomedicine systems that enabled specific delivery of several drugs and/or macromolecules including drugs, antibodies, protein, targeting ligands and imaging agents. Anti-cancer drugs usually suffer from low solubility, rapid *in-vivo* degradation, poor pharmacokinetics, undesirable biodistribution and poor permeability across biological barriers. During chemotherapy, large doses are recommended for treatment, which may induce adverse effects on normal cells and the surrounding healthy organs. Thus, the objective of this study was to design and develop targeted delivery systems with the aim of restricting high dose administration and reducing the dose-related adverse side effects and also the frequency of dosing.

Chitosan is a nontoxic, semicrystalline, biodegradable and biocompatible linear polysaccharide of randomly distributed N-acetyl glucosamine and glucosamine units. The amino as well as carboxyl groups of the chitosan molecule usually form a hydrogen bond by lipoprotein interaction with the cell membrane, bringing out an ideal adhesive effect. Docetaxel is a second-generation taxane derived from the needles of the European yew tree. Unlike paclitaxel, docetaxel exhibits linear pharmacokinetics and, due to differences in drug efflux, is retained intracellularly for a longer period. D-α- tocopherol glycol 1000 succinate (TPGS) is a surfactant used for pharmaceutical dosage form preparations. It is a water-soluble derivative of natural Vitamin E, which is formed by esterification of vitamin E succinate with PEG. The TPGS can be used as an absorption enhancer, emulsifier, solubilizer, additive, permeation enhancer and stabilizer. The novelty of this work thus lies in the development of low-dose, bioadhesive and EGFR targeted chitosan nanosystem and redox sensitive nanosystem of docetaxel for the advanced therapy of non-small cell lung cancer. The redox sensitive nanomedicine has high efficacy, specificity and sensitivity and facilitates *in vivo* imaging in lung cancer applications when loaded with an imaging material. The high levels (>20 mM) of glutathione (GSH, a cysteine-containing tri-peptide) in cancer cell microenvironment, compared to that of in blood circulation (2–20 μM),

facilitates for quicker release of the anti-neoplastics from redox-responsive NP that are composed of redox-sensitive disulfide (S–S) bonds. These S–S bonds will be cleaved to trigger the drug delivery from NP in the vicinity of cancer cells.

The design, development, and optimization of nanoformulations were done by employing systematic design of experiments (DoE). DoE involves stepwise assessment of critical quality attributes, screening of factors, experimental design and optimization with minimal consumption of time and resources. PBD (Placket-Burman design) was employed to evaluate the effect of independent factors on the dependent responses and Pareto chart was employed to select the most important factors that highly influence the selected responses. The effect of independent variables on the responses was illustrated by 3D response surface methodology. A graphical and numerical optimization procedure was carried out to obtain the predicted value of various factors and responses. The final optimized batch of the nanoformulation was evaluated and validated.

Further, the prepared nanoformulations were subjected to detailed *in-vitro* evaluations for solid-state characterization, physicochemical characterization, stability studies, *in-vitro* drug release, stability, *in-vitro* cellular uptake, cytotoxicity, wound-healing and apoptosis studies in A549 cell lines. Also, *in-vivo* pharmacokinetic and histopathology studies in Wistar rats, *in-vivo* anticancer efficacy studies in Swiss albino mice were performed and the results are discussed in detail. These results indicate that the newly developed nanoparticulate systems could prove to be promising drug delivery systems for prolonging the drug release and achieving the drug concentration at the tumor site at desired rate and amount for longer duration resulting in improved therapeutic efficacy of the drug in the treatment of lung cancer.