Preface

Lung cancer is the second most common cancer worldwide. It arises from abnormal epithelial cells in the airways of the lungs, and it is the major cause of cancer-related deaths worldwide. Smoking and tobacco consumption are the major risk factors for lung cancer. Anticancer 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, this study aimed to design and develop targeted delivery systems to restrict high-dose administration and reduce the dose-related adverse drug effects. The application of nanotechnology to medicine is the basis for developing nanomedicine. It is a technology in which the drug-loaded nanomedicine of 1-1000 nm exhibits strong interaction between drugs and their targets. Recent advancements in nanotechnology have contributed to developing nanomedicine systems that enable specific delivery of several drugs or macromolecules, including drugs, antibodies, protein, targeting ligands and imaging agents.

Chitosan (CS) is the positively charged deacetylated derivative of chitin extracted from crustaceans shells. It is a natural polymer widely used in pharmaceutical and biomedical applications. In contrast, alginate is a natural anionic polysaccharide from brown algae species, including *Laminaria* and *Ascophyllum*. It is commonly used in pharmaceutical and biological applications due to its biocompatibility, non-toxicity, and rheological properties. TPGS is an FDA-approved pharmaceutical excipient with numerous advantages, such as excellent biocompatibility and enhanced drug solubilization. It is also an inhibitor of ATP-dependent P-glycoprotein and hence overcoming the multi-drug resistance during cancer therapy. The researchers extensively explored lung cancer-specific receptors in developing single-receptor targeted nanomedicines. However, due to the large heterogeneity in lung cancer, the biological

response of single-receptor targeted nanomedicine is comparably limited. The higher expression of folate and EGF receptors are frequently found in patients with NSCLC (88% and 80%, respectively); therefore, their therapeutic ligands can be used in the combination. The clinical applications of folic acid (FR) and cetuximab (EGFR) are also approved by USFDA. To enhance penetration and accumulation, dual-receptor targeted drug delivery is proposed here, which may provide better chemotherapeutic outcomes and improved patient care in lung carcinoma. The novelty of this work thus lies in the development and characterization of polymeric nanomedicine for advanced lung cancer therapy. The Docetaxel (DXL) loaded CS-NPs, and cabazitaxel (CZT) loaded CSA-NPs were successfully prepared and characterized. The physicochemical parameters of prepared nanoparticles, such as particle size, surface charge, and polydispersity, were in the acceptable range. The XRD analysis revealed the physical state of chitosan and chitosan-alginate based nanoparticles. The surface chemistry was performed by XPS analysis that supported the conjugation of cetuximab (CTXmab) and folic acid on the surface of the nanoparticles. *In-vitro* drug release studies indicated a pH-dependent drug release with a faster release rate at pH 5.5. The C6 dye loaded dual receptor-targeted nanoparticles showed enhanced cellular uptake in A549 cells. Moreover, the MTT assay against A549 cells revealed that the cytotoxicity of dual-receptor targeted nanoparticles of DXL and CZT was much superior to that of non-targeted nanoparticles and their clinical formulations.

Further, *in-vivo* histopathological and pharmacokinetic evaluations of DXL and CZT loaded nanoparticle formulations exhibited better safety and improved pharmacokinetics in Wistar rats compared to their marketed formulations. Moreover, the *in-vivo* anticancer activity was performed on B(a) P-induced lung cancer mice model. The results demonstrated that the animal groups treated with dual receptor targeted nanoparticles of both the drugs exhibited significantly higher ($P<0.001$) anticancer activity than the marketed formulations.