PREFACE

The development of various nanoparticulate systems in the recent years has gained significant interests for cancer diagnosis and treatment. These carriers are targeted to cancer cells either actively or passively based upon their mode of action. They enhance the accumulation of drug in the tumor site and reduce drug distribution in other organs in order to prevent damage to healthy cells. The idea to work for the present thesis was conceived from drug and dose-related problems of available antineoplastic drugs. Docetaxel is an antineoplastic drug approved as a first-line drug for the treatment of locally or advanced metastatic breast cancer. During chemotherapy, large doses are recommended for treatment, which may induce toxic effects to normal cells and nontargeted organs. The objective of this study is to design and develop a new targeted delivery system comprising of polyhydroxybutyrate-co-hydroxyvalerate (PHBV) polymer loaded with docetaxel with an aim of restricting high dose administration and reduced frequency of dosing. For a drug to be clinically effective, it needs to be suitably protected in the biodegradable and biocompatible polymeric vesicles till its delivery to the targeted site. PHBV polymer is biodegradable, biocompatible and hydrophobic natural polyester. It is produced with low-cost bacterial fermentation technique which makes it more attractive for large-scale pharmaceutical production.

Formulation and optimization of nanoparticles were conducted employing systematic Design of Experiments (DOE), which has attracted attention in the pharmaceutical sector to simultaneously attain multiple objectives with minimal consumption of time and resources. DOE involves stepwise assessment of critical

quality attributes, and factor screening design. Box-Behnken experimental design was employed as response surface methodology to evaluate the effect of independent variables on responses. To obtain a smart delivery system, the optimized nanoparticles were coated with pH sensitive poly (L-histidine). PLH coated formulations were further modified with polyethylene block polyethylene glycol (PE-PEG) to prevent their macrophage uptake. The effect of formulation parameters on selected responses was depicted by 2-D and 3-D response surface methodology (RSM). A graphical and numerical optimization procedure was carried out to obtain predicted value of various factors and response. The final optimized batch of the formulation was evaluated and validated. Also, the computer simulation program (GastroPlus™ 9) was utilized that uses physiochemical measurements and physiological characteristics to simulate the *in vivo* behavior of administered drug and establish *in vitro-in vivo* correlation. Further, the nanoformulations were subjected to detailed evaluations of physicochemical characterization, *in-vitro* drug release, pharmacokinetics, cytotoxicity and anticancer efficacy and the results have been discussed in-depth. These results indicate that the newly developed nanoparticulate system could prove to be a promising drug delivery system for prolonging drug release and achieving the desired drug concentration at the tumor site for longer duration resulting in improved therapeutic efficacy of drug in the treatment of breast cancer.