Conclusion

Conclusively, the present thesis embodies to design, optimize and characterize polymeric nanoparticles based drug delivery system to target docetaxel, as an antineoplastic agent for improved therapy of breast cancer. This strategy provided not only to enhance chemotherapeutic efficiency but also reduced its associated toxicities observed during conventional treatment. Another important strategy of formulated nanoparticles was the application of PHBV polymer as a base matrix. PHBV exhibits promising properties for sustained release drug delivery. This biodegradable polymer display surface erosion leading to release of encapsulated drug in controlled pattern. In this research passive targeting of docetaxel-loaded nanoparticles was attempted and it exhibited a promising potential in breast chemotherapy. A sensitive, rapid, and precise HPLC analytical method was developed and validated for the estimation of docetaxel in the formulation and rat plasma with a slight modification of earlier reported method. The PHBV nanoparticles were prepared by modified solvent evaporation method and were optimized by adopting quality by design approach. 3-level Box-Behnken Design (BBD) was used to assess the effect of independent variables on responses. The implementation of this multivariate statistical experimental design in formulation process provided stable, optimized nanoparticle after a profound understanding of the inherent relationship between formulation variables and the desired responses. The anticipated range of particle size, zeta potential, and entrapment efficiency were found in desired range. Morphological studies demonstrated smooth and spherical shape of the nanoparticles without any aggregation. Results of solid-state characterization revealed that majority of the drug amount had been converted into

amorphous form due to interaction with the polymer. ^{1}H NMR showed strong evidence of complete pegylation over prepared nanoparticles. Drug release profile exhibited sustained drug release. *In vitro* cytotoxicity conducted using MCF-7 human breast cancer cell line confirmed viable cell reduction and indicated that % inhibition was much higher when treated with nanoparticles in comparison to pure docetaxel. Cell uptake results proved the capacity of the prepared formulations to internalize into cancer cells and to carry chemotherapeutic agents. Hemolysis and platelet aggregation studies demonstrated safe intravenous administration. Pharmacokinetic studies performed following intravenous administration in healthy Charles Foster rats displayed enhanced systemic bioavailability with much higher MRT value. The *in vivo-in silico* assessment showed good prediction accuracy whereas the *in vitro-in vivo* correlation gave non-linear relationship, i.e., limited correlation. Developed nanoparticles were studied for six months at accelerated temperature for stability trial and were found to be stable as no significant change was found concerning their drug content and physical characteristics. Furthermore, *in vivo* anticancer evaluation at the therapeutic dose of the developed formulation demonstrated convincing evidence towards an increase in safety (survival and weight loss check) and efficacy (relative tumor volume data) compared with pure drug and standard formulation (Adriamycin®). Moreover, out of all the four prepared formulations, results suggest that F4 (PHBV-PLH-PE-PEG) inhibited tumor size more significantly. All these characteristic of newly designed system demonstrated as a promising delivery system with targeting potential of docetaxel to the tumor site and thus offering improved therapy to breast cancer.