Chapter 7

Summary and Conclusions

7 Summary and conclusions

Present work involved development and evaluation of Cabazitaxel encapsulated nanoparticle-based drug delivery systems for targeted cancer therapy. The HA-stabilized CS nanoparticles, prepared by ionic gelation, exhibited promising characteristics such as a size range of 120-130 nm, homogeneity, and a stable zeta potential. The nanoparticles were evaluated for solid-state characterization that confirmed successful drug encapsulation with high encapsulation efficiency and drug loading capacity for cabazitaxel (CBT). The presence of TPGS and Cmab on the nanoparticle surface was confirmed by XPS, indicating effective functionalization. Drug release studies revealed a pH-dependent controlled drug release following swelling and diffusion-controlled mechanisms. *In vitro* studies on the MDA-MB-231 cell line demonstrated enhanced cytotoxicity, cellular uptake, and cellular responses, including mitochondrial depolarization and nuclear condensation, due to receptor-mediated endocytosis. The nanoparticles were observed to improve the pharmacokinetic characteristics and *in-vivo*, showing minimal organ toxicity. Prepared nanoparticles were found to be safe and effective drug carriers for targeted cancer therapy.

Similarly, GSH-responsive Cetuximab-anchored Chitosan/Vitamin-E succinate conjugate-based hybrid nanoparticles were prepared, showing sub-200 nm size, cationic surface charge, and redox-responsive drug release. These nanoparticles exhibited superior cytotoxicity, enhanced cellular uptake, and reduced mitochondrial membrane potential compared to free CBT. *In vivo* studies indicated better performance of the nanoparticles, with improved pharmacokinetic parameters and reduced toxicity. Tumor regression analysis and survival studies further confirmed the efficacy of these nanoparticles. However, the variability in tumor microenvironments poses a challenge for the

translational potential of such systems, necessitating further research to optimize their response to a broader range of redox stimuli.

Additionally, nanoparticles-loaded microneedle for localized drug delivery was also investigated for breast cancer therapy. The HA-OA/CS-OA nanoparticles exhibited a size of approximately 125.5 nm and were homogenous and stable. Surface characterization confirmed the presence of Cmab as targeting ligand on nanoparticles surface, and the drug release studies indicated pH-responsive behavior. In vitro studies demonstrated enhanced cytotoxicity and cellular uptake, leading to significant mitochondrial membrane potential decline and higher G2/M phase cell cycle arrest, as compared to pure drug. The microneedles provided excellent skin insertion and drug permeation capabilities, resulting in a substantial reduction in tumor volume and increased median survival in DMBA-induced tumor-bearing rats. Despite the promising results, challenges such as the need for longer microneedles and higher needle density for human application remain for consideration. Continued research and optimization are essential to fully realize the potential of microneedle technology in breast cancer management.

In conclusion, the advancements in nanoparticle-based drug delivery systems, including formulations developed as part of this thesis, i.e., HA-stabilized CS nanoparticles, GSH-responsive hybrid nanoparticles, and microneedle-mediated localized delivery, have shown significant potential in improving targeted cancer therapy. These systems offer high drug entrapment, controlled drug release, higher cytotoxicity and reduced systemic toxicity. However, further research is needed to address the challenges and optimize these technologies for clinical application. The promising results from these studies pave the way for the development of effective and safe targeted drug delivery platforms for cancer treatment

7.1 Future perspective

Recent advancements like multiplex immunohistochemistry, single-cell sequencing, organoid models, and 3D-tumor models have given us a better understanding of the microenvironments of various tumors in recent years. The past two decades have also seen a paradigm shift towards developing treatment regimens with multiple therapeutics where, along with chemotherapeutics, components modulating or disrupting the tumor microenvironment have been used. Combining such regimens with tumor microenvironment-responsive nano-sized platforms has shown immense potential in preclinical settings with improved and precise targeted therapy and reduced systemic toxicity. Also, recent strides in genomics and proteomics, advances in tumor microenvironment modulations, and improved real-time imaging capabilities have enabled the development of effective and personalized tumor microenvironment-responsive nanomedicine with real-time response monitoring capabilities.

These advancements in nanomedicine, cancer biology, and the tumor microenvironment, and the surge in clinical trials on regimens that take into account the characteristics of tumor microenvironment targeted therapies offer hope for tumor microenvironment responsive targeted and personalized nanomedicine in the future. Furthermore, taking into account the extensive ongoing studies in the fields of material sciences, 3D-printing, immunology, and other aforementioned fields, their integration and interdisciplinary collaboration promise avenues for tailored and personalized cancer treatment technologies in the future, allowing for better targeting of specific tumor types and patient profiles while simultaneously improving the efficacy of cancer treatments while minimizing side effects