CHAPTER-IV

SUMMARY AND CONCLUSIONS
4.1 SUMMARY

The aim of the present study was to develop a nanoparticulate tablet dosage form for poorly soluble drugs such as Candesartan cilexetil and Camptothecin analog to increase their saturation solubility and dissolution rate for enhancing oral bioavailability.

The primary and secondary stabilizers selected were able to produce stable nanosuspensions for conversion to solid intermediates required for solid dosage form processing. The key property of granules is their recovery, i.e., their ability to reconstitute into nanometer-sized particles when dispersed in an aqueous medium or physiologically relevant media. The particle size distribution of nanosuspensions and granules following re-dispersion in an aqueous medium indicated complete recovery.

The DSC thermograms and X-ray diffraction spectra showed no solid-state transitions indicating that the drug crystallinity was maintained upon milling. The scanning electron micrographs of ‘as-is’ drug and drug nanoparticles illustrate the recrystallization of water soluble carrier around the drug creates a highly hydrophilic environment preventing particle interaction and aggregation.

The saturation solubility of drug nanoparticles of Candesartan cilexetil and Camptothecin analog was significantly higher than jet-milled microparticles and ‘as-is’ drug at all pH conditions. These results clearly demonstrate that reduction in particle size to sub-micron or nanometer range affects saturation solubility that may result in enhancement of dissolution rate.
The dissolution rate from tablet formulations incorporating drug nanoparticles of Candesartan was significantly higher as compared to the marketed product (Candelong®). Since no commercial oral dosage form is available for the Camptothecin analog the drug release was compared with micronized drug formulation in a discriminating dissolution media. The results indicated that the amount of drug released from tablet formulation incorporating drug nanoparticles was significantly higher as compared to micronized drug formulation.

Systemic exposure studies of Candesartan nanosuspension in male Wistar rats following oral administration showed a significant enhancement in the rate and extent of drug absorption. There was a 2.5-fold increase in the extent of drug absorption based on area under the plasma concentration - time curve (AUC\(_{0-t}\)) and a 1.7-fold increase in the rate of absorption based on maximum or peak plasma concentration (C\(_{\text{max}}\)) and, significant reduction in the time required to reach maximum plasma concentration (T\(_{\text{max}}\)) when compared to the micronized suspension.

Following peroral administration of Camptothecin analog, there was a 7.3-fold increase in area under the plasma concentration - time curve (AUC\(_{0-t}\)) and, a 7.2-fold increase in maximum plasma concentration (C\(_{\text{max}}\)) for the nanoparticle formulation as compared to the suspension containing the micronized drug. The increase in rate and extent of absorption for the nanoparticle formulations could be attributed to the increase in the rate and extent of drug dissolution in the gastrointestinal (GI) tract.
The stability study results of Candesartan cilexetil and Camptothecin analog demonstrated that the tablet physical properties and dissolution performance were unaffected upon storage indicating a stable drug product.

4.2 CONCLUSION

[1] The results from these studies demonstrated that wet bead milling process coupled with Spray Drying or Spray Granulation is a viable approach for developing a tablet dosage form of Candesartan cilexetil and Camptothecin analog with enhanced solubility and dissolution. Enhancing solubility and dissolution rate of poorly soluble compounds correlates with improved pharmacokinetic (PK) profile.

[2] Nanoparticle formulation of Candesartan cilexetil demonstrated that the approach can be used to enhance its *in-vivo* performance that may result in improved therapeutic outcome.

[3] Results from nanoparticle formulation of Camptothecin analog indicated that the approach is also useful in early stages of drug product development to overcome issues of poor solubility and low bioavailability.

[4] The formulation approach for Camptothecin analog also addressed the limitation of currently marketed product of similar therapeutic category that is only amenable for intravenous administration and has significant side effects including pain, tissue damage at injection site, hemolysis upon prolonged use.
[5] The approach herein can be extended to other BCS class II compounds (where absorption is either solubility and/or dissolution limited).

[6] The manufacturing process used is relatively simple and scalable indicating general applicability of the approach to develop oral dosage forms of poorly soluble drugs with enhanced dissolution and improved bioavailability.