CHAPTER 6

Summary & Conclusion

The sustained release tablets of enalapril maleate were prepared successfully using HPMC polymer of different viscosity. According to in vitro release studies, the release rate was decreased with increasing viscosity and amount of polymer. The results of the study clearly demonstrated that HPMC matrix tablet formulation is an effective and promising drug delivery system for once daily administration of Enalapril maleate. The analysis of the release profiles in the light of distinct kinetic models (zero order, first order, Higuchi, Korsmeyer Peppas and Hixon Crowell) led to the conclusion that, the drug release characteristics from HPMC polymer matrices follows Higuchi square root time kinetics and the mechanism of drug release was both diffusion and erosion.

The in vivo study was conducted which showed no dose dumping with modified release formulation of Enalapril Maleate. The modified release formulation was successful in modifying (delaying / lowering) rate and extent of drug release in-vivo. Drug intake after food slowed down the rate and extent of drug release compared to fasted state. These observations successfully supported our objective of the study.

Our primary aim was also to demonstrate the steady plasma concentration of single dose Enalapril modified release product so as to counter act the morning hypertension. The RAS is activated in the morning and could contribute to morning BP surge and increases cardiovascular risk. In addition to the reduction in the morning BP level, if morning activation of tissue RAS could be suppressed effectively, it could theoretically lead to increased protection against hypertensive target-organ damage and cardiovascular events in hypertensive patients. In regard to this our Single dose of Enalapril Maleate modified release product provided plasma drug concentrations (especially for Enalaprilat) above MEC (10 ng/mL) for periods up to 24 hours.
Chapter 6: Summary & Conclusion

The modified formulation provided adequate therapeutic drug concentration in the plasma during early morning hours (between 2:00 AM to 8:00AM), which could be beneficial in reduction of morning BP surge. This action to reduce the morning hypertension is of unmet need as it increases the patient compliance towards the therapy.

The development of a predictive and reliable IVIVC model is a complex process. To investigate, the evaluation of Enalapril maleate in-vitro profile demonstrated by comparison of dissolution profile, model-dependent approaches and similarity factor (f2-test) method. Wagner-Nelson deconvolution, and convolution were used for in-vivo evaluation. Level A correlation could not be applied straight forwardly as common time scaling to all the formulation is not possible. A time scaling is existing but is formulation dependent.

Level C results revealed good correlations between in vitro drug release and in vivo AUC and Cmax. Level C IVIVC also exhibited a strong linear IVIVC between Cmax and percent drug dissolved at 4 hours. That means that based on dissolution we can predict both AUC and Cmax and can adjust our formulation based on the IVIVC. In conclusion, the current work indicates that level C IVIVC for a Enalapril maleate.

Based on data from the literature, it is evident that current IVIVC studies have focused more on the development and validation of level C IVIVC which gives more useful information on the relationship between in vitro release and in vivo AUC and Cmax from dosage form. Levels A and C IVIVCs have been evaluated for several purposes in formulation development, for example, to select the appropriate excipients and optimize the manufacturing processes, for quality control purposes and for characterizing the release patterns of newly formulated sustain release products relative to the references. Present regulatory guidelines for IVIVC is only applicable to oral sustain release dosage forms. Also, it is possible that the IVIVC can still be explored to provide a greater understanding of the factors influencing clinical quality.

This research attempts to elucidate some of the general principles involved in the construction of IVIVC. Before the commencement of model building, it was important to consider the factors that may contribute to the in vitro and in vivo performance of the drug compounds. Since by definition the IVIVC is a mathematical model, various algebraic, calculi and statistical methods
were employed in its development. Once a reliable IVIVC model was developed, it could serve as regulatory guidance for pharmaceutical industry. With justified modifications, its applications can be expanded to include more dosage forms beside oral dosage forms. An in vitro dissolution test can replace absorption studies during the pre-approval process, to develop a desirable formulation, and to ensure batch-to-batch bioequivalence. It could also be extremely useful in performing possible post-approval changes in the formulation scale-up or changes in the drug substance or excipients supplier.