CHAPTER 6

SUMMARY AND CONCLUSIONS
Oral controlled drug delivery systems have received much attention of the researchers. The rationale for developing a controlled release formulation is to enhance its therapeutic benefits, reducing its side effects and improving the management of diseased condition. A number of strategies have been developed to obtain controlled release of the drug in the body. These include a simple matrix tablet to more technologically sophisticated products which are introduced to the market place.

Studies have been carried out for developing controlled release matrix tablet formulations of verapamil hydrochloride and losartan potassium by using polymeric materials like polyox WSR 301, polyox WSR 303, eudragits, xanthan gum, guar gum, karaya gum and sodium alginate. These were selected as matrix forming polymers for controlled release as these were reported to have matrix forming properties.

Studies were undertaken to investigate the influence of poly (ethylene oxides) level and type on the controlled release of the drugs from matrix tablets by in vitro methods. The influence of nature of fillers in the matrix tablets on drug release rate and mechanism was studied. Studies were undertaken to evaluate the influence of binary polymeric systems on the controlled release of the drugs from the matrix tablets.

The prepared matrix tablets were evaluated for weight uniformity, hardness, friability and drug content. The matrix tablets were then evaluated by in vitro dissolution studies. Studies on swelling behavior of the matrix tablets were carried out for formulations containing natural polymers to evaluate the influence of changes in matrix and gel structure on the drug release.
The selected matrix tablets of verapamil hydrochloride and losartan potassium were subjected to *in vivo* pharmacokinetic studies. Rabbits were used as animal model for the study. The pharmacokinetic parameters such as $c_{\text{max}}$, $t_{\text{max}}$, $t_{1/2}$, MRT and AUC $\text{AUC}_{0-t}$ $\text{AUMC}_{(0-t)}$ were estimated from plasma concentrations of the drug versus time profiles. The serum concentrations of the drug were determined by HPLC method.

Selected formulations of verapamil hydrochloride and losartan potassium were subjected to accelerated stability studies. The formulations were stored at $40^\circ\text{C} \pm 2^\circ\text{C}$, $75\% \pm 5\%$ RH for 6 months. During the accelerated storage condition the tablets were evaluated for physical parameters such as weight uniformity, hardness, friability, drug content and for drug release before and after storage.

**The following conclusions were drawn from the results:**

1. Verapamil hydrochloride and losartan potassium are freely water soluble drugs found to be suitable for formulating as controlled release matrix tablets with POLYOX WSR 301 and POLYOX WSR 303 by direct compression process.

2. The direct compression process employed for the preparation of matrix tablets were found suitable with the drugs and all the polymers used.

3. The physical parameters evaluated for the matrix tablet formulations such as weight uniformity, hardness, friability and drug content were uniform and were with in the IP limits.
4. Weight uniformity of matrix tablet formulations were uniform in all the cases and were maintained within I.P specified limits.

5. Hardness of all the matrix tablet formulations was found to be within the range of $6.5 \pm 0.5$ Kg/cm². Friability loss was negligible, less than 0.20% for all the matrix formulations.

6. Drug content was evaluated for all the matrix tablet formulations and found to be uniform. Drug content for the matrix tablet formulations was found to be within the specified range for verapamil hydrochloride extended release tablets USP.

7. FTIR spectral studies of selected formulations of verapamil hydrochloride and losartan potassium exhibited no major interactions between the drug, polymer and diluents.

8. The matrix tablets containing POLYOX WSR 301 extended the release of verapamil hydrochloride and losartan potassium up to 12 hrs. The drug release from these matrix tablets followed anomalous transport mechanism. As the concentration of the polymers increased, the drug release was extended. Formulations FVH28, FVH29, FVH31, FVH32, FVH36, FVH38, FVH40, FVH42, FVH44, FVH46, FVH48, FVH52, FLP28, FLP29, FLP32, FLP34, FLP36, FLP38, FLP40, FLP42, FLP44 and FLP52 were found to extend the linear drug release up to 12 hrs.
9. The drug release from the matrix tablets containing POLYOX WSR 303 was extended up to 22 hrs. Drug release from the tablets depended up on the polymer concentration, polymer combinations and type of diluents used. Drug release form these matrix tablets followed anomalous transport mechanism. Formulations FVH6, FVH9, FVH12, FVH14, FVH18, FVH20, FVH22, FVH24, FVH26, FLP2, FLP3, FLP6, FLP9, FLP12, FLP14, FLP16, FLP18, FLP20, FLP22, FLP24 and FLP26 were found to extend the linear drug release upto 22 hrs.

10. Diluents such as microcrystalline cellulose, dicalcium phosphate, starch 1500 have high influence on extending the drug release over a prolonged period of time. The order of delay in drug release in presence of diluents in the matrix tablet formulations were Starch 1500 > DCP > MCC > Lactose.

11. Binary polymeric systems used for the preparation of the matrix tablets for verapamil hydrochloride and losartan potassium had influence on extending the drug release. Among the binary polymeric systems used for the preparation of matrix tablets, combination of poly (ethylene oxide) (Polyox WSR 303) and ethyl cellulose, eudragits, xanthan gum, guar gum, karaya gum extended the drug release for a period of 18 to 22 hrs. Formulations FVH12, FVH14, FVH20, FVH24, FVH26, FLP14, FLP18, FLP20, FLP22, FLP24, and FLP26 showed prolonged release for a period of 18-22 hrs.
12. Log percentage drug undissolved versus time plots for first order release rate constant of all the prepared matrix tablets were found to be linear with $R^2$ values of 0.91-0.97.

13. Amount of drug release versus square root of time plots for all the matrix tablet formulations were linear which indicated that the drug release from the matrix tablet formulations is by diffusion process.

14. The ‘n’ value obtained from the peppas plots (Tables 4.44 – 4.45 & 4.48 – 4.49) for the matrix tablet formulations were in the range of 0.5 to 0.89. These values indicated that the drug release is by both diffusion and matrix relaxation mechanisms for the matrix tablets containing verapamil hydrochloride and losartan potassium.

15. Pharmacokinetic evaluation verapamil hydrochloride pure drug and selected prepared matrix tablets were carried out in rabbits which indicated the rapid absorption of verapamil oral solution. Verapamil hydrochloride administered as pure drug form alone reaches highest plasma concentration 994.67 ng/ml after 1 hr of administration. The peak plasma concentrations for test tablet formulations reached after 4 hrs of administration and also the maximum concentration reached is 679 ng/ml and 662 ng/ml for FVH12 and for FVH14 respectively.
16. Pharmacokinetic evaluation of losartan potassium pure drug and selected prepared matrix tablets were carried out in rabbits indicated the rapid absorption of losartan potassium oral solution. Losartan potassium administered as pure drug form alone reaches highest plasma concentration of 220 ng/ml after 1 hr of administration. The peak plasma concentrations for test tablet formulations reached after 4 hrs of administration and also the maximum concentration reached is 186.67 ng/ml and 194.00 ng/ml for FLP 9 and for FLP 14 respectively.

17. No significant changes were observed in the physical characteristics and in the drug release profiles of selected matrix tablet formulations of verapamil hydrochloride and losartan potassium after storing them at accelerated storage conditions.

**Future Scope:** *In vivo* pharmacokinetic study proved that the losartan potassium from test tablets showed prolonged release and may be able to sustain the therapeutic effect. This can be further proved by pharmacodynamic study.