CHAPTER 5

DISCUSSION OF RESULTS
In the present work, studies were undertaken for the design and development of oral controlled release matrix tablets of anti-anginal drug verapamil hydrochloride and anti-hypertensive drug losartan potassium. Controlled release drug delivery systems have received much attention in the past two decades with numerous technologically sophisticated products on the market place. Such advancements have come about by simultaneous convergence of many factors, including the discovery of novel polymers, formulation optimization, better drug understanding of physiological constraints, prohibitive cost of developing new drug entities and the introduction of biotechnology and biopharmaceutics in drug product design. The major benefits of these products lie in the optimization of drug input rate into systemic circulation in order to achieve an appropriate pharmacodynamic response. This in turn should add to product safety and reduce the extent and incidence of major adverse drug reactions due to a more strict control of blood levels. Furthermore, with less frequent dosing, it is speculated that this should improve patient compliance and possibly maximize the drug product efficacy in therapeutics.

Verapamil hydrochloride is a calcium channel blocker widely used drug in the therapy of angina pectoris and hypertension. The drug is highly soluble in distilled water, chloroform and methanol. It is rapidly absorbed after oral administration but has low bioavailability after oral administration {66, 67} which is due to high first pass hepatic metabolism. The elimination half life of verapamil hydrochloride is 3 to 5 hours.

Losartan potassium is an angiotensin II inhibitor and vasoconstrictor which is widely used in the treatment of variant hypertension and
stimulates smooth muscle proliferation. It is freely soluble in distilled water, methanol and insoluble in chloroform.

Losartan potassium is well absorbed after oral administration but its availability is only 33% in systemic circulation and the bioavailability varies between individuals. The low bioavailability after oral administration is due to its first pass hepatic metabolism (68, 69). It has elimination half life of 1-3 hrs.

Based on these physicochemical and biopharmaceutical properties, Verapamil hydrochloride and losartan potassium were selected as drug candidates for developing controlled release matrix tablet formulations.

Analytical methods used for the estimation of verapamil hydrochloride and losartan potassium were simple sensitive UV spectrophotometric methods. These spectrophotometric methods were adopted for the estimation of verapamil hydrochloride and losartan potassium in the matrix tablets and in the in vitro dissolution studies. The Beers law obeyed in the concentration range of 0-50µg/ml for verapamil hydrochloride and 0-5µg/ml for losartan potassium. In vivo pharmacokinetic studies of verapamil hydrochloride and losartan potassium were carried in rabbits. The verapamil hydrochloride and losartan potassium concentration in the rabbit plasma was estimated by RP HPLC method (167). These methods were found to be suitable for determining the plasma concentrations of the drugs.

Controlled release formulations for verapamil hydrochloride and losartan potassium were prepared by direct compression method using Elite 10 station mini press. The direct compression process used for the
preparation of matrix tablets was found to be ideal and is easy to reproduce. Polymers such as poly(ethylene oxides) [Polyox WSR 301 & Polyox WSR 303], ethyl cellulose, Polymethacrylates [Eudragit S 100 & Eudragit L 100], xanthan gum, guar gum, karaya gum and sodium alginate were used in the preparation of matrix tablets as controlled release polymers and exhibited good flow properties. These polymers were found to be ideal for the preparation of controlled release matrix tablets. One hundred and two matrix tablet formulations were prepared with verapamil hydrochloride and losartan potassium by employing various polymers at different concentrations (Table no’s 4.6 to 4.25). As PEO’s are hydrophilic, the involvement of water or moisture makes the wet granulation process highly problematic. Therefore a dry process that produces acceptable powder characteristics and does not intervene with drug release characteristics is desirable. Hence the dry process such as direct compression technique was employed in the present investigation for the preparation of controlled release matrix tablets. All the batches of matrix tablets were evaluated for the physical parameters such as weight uniformity, hardness, friability and drug content uniformity.

All the matrix tablets were evaluated for weight uniformity. The weights of the prepared tablets are given in the tables no’s 4.26 to 4.31. The weight ranges of all the matrix tablets were uniform and were within the IP limits. Hardness of the tablets was evaluated by using Monsanto hardness tester. The hardness of all batches of matrix tablets was found to be uniform and the values are given in the tables 4.26 to 4.31. Friability test for matrix tablets were performed to determine the ability of tablets to withstand
abrasion during packing and transportation. The test was carried out in Roche Friabilator. Surface damages to the tablets were found to be negligible and the friability loss values were within the IP limits. The drug content for the prepared matrix tablets of verapamil hydrochloride and losartan potassium were evaluated by UV spectrophotometric method. The drug content in all the matrix tablet formulations for verapamil hydrochloride contained was as per USP specifications. For the losartan potassium matrix tablets the drug content values were within the claimed limits and the drug content values for all the formulations were given in the tables 4.26 to 4.31.

FTIR spectral studies were performed on some selected matrix tablets of verapamil hydrochloride and losartan potassium to study any drug excipients interactions. FTIR spectral studies were performed on BRUKER FTIR spectrophotometer using potassium bromide pellets. FTIR spectra of pure drugs of verapamil hydrochloride and losartan potassium were taken initially to check the basic functional groups present in them. The spectra of verapamil hydrochloride and losartan potassium pure drugs and various matrix tablet formulations were shown in Fig: 4.1 to 4.24 respectively.

The spectra of Verapamil hydrochloride exhibited principle peaks at wave numbers of 2961 cm$^{-1}$ (C-H Stretching), 2236 cm$^{-1}$ (C≡N Stretching), 1593 cm$^{-1}$ (C≡N Stretching), 1518 cm$^{-1}$ (C=C Aromatic Stretching) and 1260 cm$^{-1}$ (C-O Stretching). The spectra of matrix tablet formulations exhibited all the principle peaks present in the verapamil hydrochloride pure drug.

The spectra of losartan potassium exhibited principle peaks at wave numbers of 3292 cm$^{-1}$ (O-H Stretching), 2908 cm$^{-1}$ (C-H Stretching), 1606 cm$^{-1}$ (C≡N Stretching), 1593 cm$^{-1}$ (C=C Stretching) and 767 cm$^{-1}$ (C-Cl
The spectra of matrix tablet formulations exhibited all the principle peaks present in the losartan potassium pure drug.

The spectral studies of both verapamil hydrochloride and losartan potassium matrix tablet formulations exhibited no more changes in the principle peaks and all the peaks were observed at specific wave numbers as that of their respective pure drugs. Thus these studies indicated that there were no major interactions between the drug, polymers and diluents incorporated in the matrix tablets.

Verapamil hydrochloride release from the matrix tablets contained POLYOX WSR 301, POLYOX WSR 303 were performed in pH 1.2 acidic medium for 2 hrs followed by pH 7.4 phosphate medium for remaining period up to 24 hrs. Losartan potassium release from the matrix tablets were performed in pH 1.2 acidic medium for 2 hrs and followed by pH 6.8 phosphate medium for 24 hrs. From the In vitro dissolution studies it was also observed that the high molecular weight poly (ethylene oxide) i.e. POLYOX WSR 303, effectively controlled the release rate of the drugs for an extended period of time than the low molecular weight POLYOX WSR 301. This was due to their high molecular weight poly (ethylene oxides) such as POLYOX WSR 303 have slow swelling rates, where the release rate of the drug will be slow when compared with the low molecular weight poly(ethylene oxides)\(^\text{147}\).

The effect of hydrophilic and hydrophobic diluents on the drug release was studied. The diluents selected were lactose, microcrystalline cellulose, dicalcium phosphate, and starch 1500. The drug release from the matrix tablets containing lactose as diluent was rapid when compared to the other
diluents such as microcrystalline cellulose, DCP and starch 1500 (Table 4.33, 4.39 & 4.47, 4.52). This was due to hydrophilic nature of the lactose than other diluents, which resulted in faster penetration of dissolution media i.e. easier penetration of dissolution medium into the tablet matrix, which lead to weaker gel strength, higher erosion of gel layer and therefore faster drug release from the matrix. Insoluble but weakly swellable fillers such as MCC and DCP remained with in the gel structure and resulted in the slow release rate of the drugs. Hence MCC and DCP as insoluble diluents provided the slower rate of drug release. These excipients have minimum swelling property which had contributed to the swollen matrix for PEO and retarded the penetration of dissolution medium. Reports indicated that MCC has strong tablet binding properties which decrease the tablet porosity (171). `This nature of MCC is also responsible for the extended drug release from the matrix tablets. The formulations containing starch 1500 which is slightly soluble filler, the drug release from the matrix tablets were extended up to 18 hrs (Table 4.33, 4.39 & 4.46, 4.52) . This was due to the diluent retarded the easier penetration of dissolution medium into matrix and thus prevented the polymer matrix erosion. The swelling nature of starch 1500 upon exposure to dissolution medium resulted in the formation of a gel layer which controlled the release rate of verapamil hydrochloride and losartan potassium from matrix tablets. The matrix tablet formulations FVH3, FVH6, FVH9, FVH12, FLP3, FLP6, FLP9, and FLP12 extended the drug release up to 18 hrs. 

The influence of binary polymeric systems on the drug release was evaluated. The matrix tablets were formulated using combinations of both
hydrophilic and hydrophobic polymers. For this hydrophilic PEO and hydrophobic eudragits and ethyl cellulose were used in the formulation of matrix tablets (Tables 4.8, 4.13, 4.14, 4.23). Combinations of synthetic and natural polymers were also used in preparing the matrix tablets to study their influence on controlled release of drug. Combinations of PEO with various natural gums like xanthan gum, karaya gum, guar gum and sodium alginate were used (Tables 4.9, 4.10, 4.14, 4.15, 4.19, 4.20, 4.24 & 4.25) in the matrix tablet formulations.

The swelling behavior of selected matrix tablet formulations (formulations containing natural gums) was studied. The swelling behavior indicates the rate at which the matrix tablet absorbs water from dissolution media and swells. The water uptake and swelling started slowly and continued for 12 hours. Constant and prolonged release of drug will occur in such situation because of increase in diffusion path length due to swelling of the matrix. The formulation containing xanthan gum and guar gum exhibited a high degree of swelling when compared with the formulations containing karaya gum and sodium alginate. Hence the drug release was extended for prolonged time for the formulation containing xanthan and guar gum. The tablets appeared swollen from the beginning and a viscous gel layer was formed when they came into the contact with the dissolution medium.

The drug release from the matrix tablets containing PEO and eudragits (FVH15 -18, FVH41-44 & FLP15-18, FLP41-44) showed linear drug release over a period of 18 hrs (Table 4.35, 4.40 & 4.48, 4.53). The initial burst release of the drug was not observed in these formulations. This
was due to the presence of insoluble eudragit in the matrix which retarded the faster drug diffusion due to the formation of a rigid matrix. The gel structures formed around the matrix tablets were rigid when compared with the formulations containing PEO and natural gums. The ‘n’ value obtained from the peppas plots (Tables 4.59 – 4.61 & 4.65 – 4.67) for these 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 these matrix tablets containing verapamil hydrochloride and losartan potassium.

The drug release from the matrix tablets containing PEO and ethyl cellulose (FVH13, FVH14, FVH39, FVH40 & FLP13, FLP14, FLP39, and FLP40) was extended over a period of 20 hrs (Tables 4.59 – 4.61 & 4.65 – 4.67). The presence of hydrophobic ethyl cellulose in the matrix prevented the rapid gel formation. Since ethyl cellulose is a hydrophobic polymer it cannot swell similar to that of PEO and thus retarded the rapid drug diffusion from the matrix. The ‘n’ value obtained from the peppas plots (Tables 4.59 – 4.61 & 4.65 – 4.67) for these formulations were in the range of 0.5 to 0.89. These values indicated that the drug release is by both diffusion and matrix erosion mechanisms for these matrix tablets containing verapamil hydrochloride and losartan potassium.

The drug release form the tablets containing PEO and xanthan gum (Formulations FVH23, FVH24, FVH49, FVH50 & FLP23, FLP24, FLP49, FLP50) showed controlled release from 10 to 22 hrs (Table 4.37, 4.42 & 4.50, 4.55) than the formulations containing combination of PEO and various gums like guar gum, karaya gum and sodium alginate. This is due
to high degree of swelling and slow erosion due to polymer relaxation for xanthan gum than other gums which has been observed from the swelling index studies. The drug release from the tablets containing PEO, karaya gum and guar gum (Formulations FVH19, FVH20, FVH25, FVH26, FVH45, FVH46, FVH51, FVH52 & FLP21, FLP22, FLP25, FLP26, FLP45, FLP46, FLP51, FLP52) was extended up to 18 hrs (Tables 4.36-4.37, 4.41-4.42 & 4.49-4.50, 4.54 – 4.55). It was also observed that increase in the concentration of gums, the drug release was extended. This is due the hydrophilic nature of the poly (ethylene oxide) and gums. These tablets showed greater water uptake which resulted in the formation of highly viscous gel layer around the tablet. The formed gel layer resulted in the longer diffusional path length, there by retarding the drug diffusion. The ‘n’ value obtained from the peppas plots (Tables 4.59 – 4.61 & 4.65 – 4.67) for these 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 these matrix tablets containing verapamil hydrochloride and losartan potassium.

A different drug release profile was observed from the matrix tablets containing PEO and sodium alginate (Formulations FVH21, FVH22, FVH47, FVH48 & FLP19, FLP20, FLP47, and FLP48). Initial burst release of the drug in the acidic media was not observed which was also observed for the formulations containing eudragits. This was due to the hydrophilic polymer sodium alginate is an anionic linear polysaccharide which is insoluble at acidic pH (172). Hence in the acidic media the PEO in the tablet matrix hydrated to form gel layer on the tablet surface, but the sodium alginate
retarded the matrix tablet to swell. They remain insoluble and retarded the rapid drug diffusion. And hence the initial burst release of the drug was not observed (Tables 4.36, 4.41 & 4.49, 4.54). The ‘n’ value obtained from the peppas plots (Tables 4.59 – 4.61 & 4.65 – 4.67) for these 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 these matrix tablets containing verapamil hydrochloride and losartan potassium.

It was also observed that an increasing in the PEO content, the drug release rate from the matrix tablets was decreased. The correlation coefficient values calculated for the first order plots for the matrix tablet formulations were linear, which indicated the drug release from the matrix tablet formulations followed first order kinetics (Table 4.56 - 4.58 & 4.62 – 4.64).

The dissolution profiles of verapamil hydrochloride matrix tablet formulations were compared with marketed controlled release formulation of verapamil hydrochloride (ISOPTIN SR, 120 mg). The difference factor and similarity factor were calculated for these matrix tablet formulations. The difference factor $f_1$ values were in the range of 7 – 58 and similarity factor $f_2$ values were in the range of 19 – 79. The formulations FVH3, FVH7, FVH8, FVH10, FVH24, FVH25, FVH28, FVH29, FVH31, FVH32, FVH34, FVH36, FVH38, FVH41, FVH42, FVH44, FVH46 and FVH52 showed the similarity factor values above 50, indicated that the release profiles for these formulations were similar to that of marketed formulation.

The in vivo pharmacokinetic parameters for the optimized matrix tablets containing verapamil were performed in white rabbits. The
formulations FVH12 and FVH14 were selected for in vivo studies. The results showed that verapamil hydrochloride administered as plain drug alone reached peak plasma concentration of 994.67 ng/ml after 1 hr of administration. The matrix tablets prepared 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 after administration of tablets. The results proved that prolonged release even after 24 hrs clearly showed that drug was released slowly within a narrow range for prolonged period of time (Table 4.69 & 4.70). In vivo pharmacokinetic studies on verapamil hydrochloride matrix tablets showed prolonged release and were be able to sustain the therapeutic effect over a prolonged period of time up to 24 hrs.

The in vivo pharmacokinetic parameters for the optimized matrix tablets containing losartan potassium were performed in white rabbits. The formulations FLP 9 and FLP 14 were selected for in vivo studies. The results showed that losartan potassium administered as plain drug alone reached peak plasma concentration of 220 ng/ml after 1 hr of administration. The matrix tablets prepared reached after 6 hrs and 8hrs 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 after administration of tablets. The results proved that prolonged release even after 24 hrs clearly showed that drug was released slowly within a narrow range for prolonged period of time (Table 4.73 & 4.74). In vivo pharmacokinetic studies on losartan potassium matrix tablets showed prolonged release and were be able to sustain the therapeutic effect over a prolonged period of time up to 24 hrs.
The formulations which showed good in vitro performance were subjected to accelerated stability studies. These studies were carried out by investigating the effect of temperature on the physical properties of the tablets and on drug release from the matrix as per ICH guidelines. Formulations FVH3, FVH6, FVH9, FVH12, FVH14, FVH16, FVH18, FVH20, FVH24 and FVH26 for verapamil hydrochloride and formulations FLP3, FLP6, FLP9, FLP12, FLP14, FLP16, FLP18, FLP20, FLP24 and FLP26 for losartan potassium were subjected to accelerated stability studies.

The results of these studies were given in tables 4.71 TO 4.86. The results indicated that there was no visible and physical changes observed in the matrix tablets after storage. It was also observed that there was no significant change in drug release from the matrix tablets. The slow and controlled drug release characteristics of the matrix tablets remained unaltered. Thus the drug release characteristics of controlled release matrix tablets designed were found to be quite stable.