Chapter 6

SUMMARY AND DISCUSSION

High blood pressure is a major public health related problem globally. The increase in blood pressure is considered to be a major risk factor in the development of cardiovascular complications (Kearney et al., 2005; Ong et al., 2007). Cardiovascular diseases (CVD) are the leading cause of death worldwide, accounting for an estimated 14 million deaths in 1990 and projected to cause 25 million deaths in 2020. High blood pressure affects more than 1 billion people worldwide and among these more than 72 million people are from United States. Hypertension is also a public health problem in developing countries like India. Estimates from the global burden of diseases suggest that by the year of 2020, India will have more individuals with CVD than other region in the world. The relationship between blood pressure and risk of CVD is continuous, consistent and independent of other risk factor. One of the most dreaded and a common complication of long-standing hypertension is atherosclerosis. The blood pressure is not only causes the myocardium to change structurally but also leads to impaired cardiac function. Stroke and encephalopathy are potential complications of long-standing hypertension. Stroke risk increases with proportional elevation in blood pressure – both systolic and diastolic. Controlling blood pressure is a major strategy in the reduction of stroke incidence. Kidney failure is another complication of long-standing hypertension. Hypertension is at times the primary cause of renal failure, but even if it is not, its presence increases the rate of kidney damage.

The treatment of hypertension has become a challenge with the finding that even small reductions in blood pressure can significantly reduce the risk of morbidity and mortality. Nebivolol, a beta blocker and felodipine, a calcium channel blocker have been widely used for the treatment of blood pressure. Both nebivolol and felodipine belong to BCS Class II drugs and have poor aqueous solubility and poor oral bioavailability. Poor and variable bioavailability along with low biological half life require frequent dosing which leads to more fluctuation of drug concentration in the blood. This frequent dosing leads to poor patient compliance and poor therapeutic outcome. In order to improve patient compliance through reducing the number of doses per day, to maintain a uniform drug concentration throughout the therapy, and to reduce side effects of drugs, sustained released formulations are advisable. In the present study it was attempted to develop oral sustained release delivery system of nebivolol and felodipine exploring nanoparticulate technology using two polymers Eudragit® RS100 and poly (D, L-lactic-co-glycolic acid) or (PLGA).
The objectives of the present study were:

6. To identify the polymers based on the compatibility study.

7. To develop the polymeric nanoparticles of nebivolol and felodipine using the identified polymers following solvent evaporation technique.

8. To characterize the developed polymeric nanoparticles for particle size, Zeta potential, size distribution and surface morphology


10. To perform in vivo evaluation of the most acceptable formulation for toxicity, bioavailability and antihypertensive activity.

The drug-polymer compatibility study was conducted with 1:1 physical mixtures using DSC and FTIR spectroscopy. The DSC thermograms showed no appreciable interaction. The FTIR spectroscopy results confirmed the preservation of all the functional groups of drug and excipients indicating no interaction. Based on the compatibility results, PLGA (50:50) and Eudragit RS 100 were selected for developing nanoparticulate systems for nebivolol and felodipine.

Modified solvent evaporation technique involving sonication, homogenization and mechanical stirring were used for preparing nanoparticles. A series of nanoparticle sustained release systems were prepared: Nebivolol nanoparticles with Eudragit® RS100 (8 formulations) and Nebivolol nanoparticles with PLGA (50:50) (6 formulations). The formulated nanoparticles were evaluated for particle size and size distribution, entrapment efficiency and surface morphology. Based on the particle size, entrapment efficiency the formulation NNP6 (Nebivolol-Eudragit® RS100) and formulation NP2 (Nebivolol-PLGA 50:50) were selected for further in vitro and in vivo study. The in vitro study showed the slow release of the drug from the nanoparticles and improved permeability. The toxicity study showed no mortality and no significant changes in biochemical parameters at a dose of 240 mg/Kg indicating reasonable level of safety. The improved bioavailability and antihypertensive activity of both the formulations were observed when compared with pure nebivolol.

Similarly, felodipine loaded nanoparticles were also prepared using Eudragit® RS100 (7 formulations) and PLGA 50:50 (7 formulations). The modified solvent evaporation technique was used for preparing the nanoparticles. The prepared nanoparticles were evaluated for
particle size and size distribution, entrapment efficiency and surface morphology. Based on the particle size and entrapment efficiency the formulation FEN3 (Felodipinel-Eudragit® RS100) and formulation FP7 (Felodipine-PLGA 50:50) were selected for further in vitro and in vivo study. The in vitro studies showed the prolongation of drug release and improve permeability from the nanoparticulate systems. Both the formulations (FEN3 and FP7) were reasonably safe up to the dose level of 240 mg/kg after single dose oral administration. The formulations were able to improve the bioavailability and antihypertensive activity when compared with pure felodipine.