Chapter 2

AIMS AND OBJECTIVES

Cardiovascular diseases are one of the major public health issues results from elevated blood pressure. Though various groups of blood pressure lowering medicines are available, beta blockers (Prichard et al., 2001; Khan and McAlister, 2006) or calcium channel blockers (Freedman and Waters, 1987; Godfraind, 1994) are the first choice for the primary management of hypertension because of their long history of proven safety and efficacy (Heidenreich et al., 1999; Psaty et al., 2003).

Among the various beta blockers, nebivolol has been widely used because of its unique pharmacologic properties relative to other beta blockers. Nebivolol has more beta adrenoceptor selectivity (Bundkirchen et al., 2003; Baker, 2010) and has direct dilating effects on blood vessels. It has the ability to maintain blood pressure under control and minimization of cardiovascular disease during long-term therapy for the hypertension, which lasts much longer than that of other antihypertensive beta blockers (Ignarro, 2008; Tran Quang et al., 2009; Kamp et al., 2010).

Similarly, calcium channel blocker, felodipine is also used for the treatment of systemic arterial hypertension (Saltiel et al., 1988). It has more vasoselective activity (Ljung, 1985) with lower negative inotropic effects. The greater vascular selectivity provides therapeutic benefits in patients with left ventricular dysfunction. Felodipine acts on the myocardium reducing heart rate and myocardial contractility.

Both nebivolol and felodipine have poor aqueous solubility, and poor oral bioavailability. They belong to BCS Class II drugs. Poor and variable bioavailability requires 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 achieve better therapeutic outcome it is required to maintain the effective drug concentration in blood for longer period of time.

For maintaining the required therapeutic level of drug throughout the treatment period, in the present study an attempt has been made to develop oral sustained release delivery system of nebivolol and felodipine with the help of nanoparticulate technology using two polymers Eudragit® RS100 and poly (D, L-lactic-co-glycolic acid) or (PLGA).
In order to achieve the above aim, the present study was designed with the following objectives:

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

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

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


5. To perform *in vivo* evaluation of the most acceptable nanoparticulate systems toxicity, bioavailability and antihypertensive activity.
PLAN OF THE WORK

1. Selection of drugs and polymers is based on literature review. The drugs should have stable analytical profile in UV and HPLC method.

2. Compatibility studies between the drugs and polymers using DSC and FTIR.

3. Optimization of the process variables.

4. Preparation, characterization and in vitro evaluation of nebivolol nanoparticles using Eudragit® RS100.

5. Optimization of process variables.

6. Preparation, characterization and in vitro evaluation of nebivolol nanoparticles using PLGA.

7. In vivo studies (toxicity, bioavailability and antihypertensive activity) of selected nebivolol nanoparticle systems.


9. Preparation, characterization and in vitro evaluation of felodipine loaded nanoparticles using Eudragit® RS100.


11. Preparation, characterization and in vitro evaluation of felodipine loaded nanoparticles using PLGA.

12. In vivo studies (toxicity, bioavailability and antihypertensive activity) of selected felodipine loaded nanoparticulate systems.

13. Stability studies of selected drug loaded nanoparticles.