Objectives
OBJECTIVES
1. To develop novel multidrug formulations for poorly bioavailable drugs and to improve their bioavailability with selective controlled release of drug at desired site in GIT and immediate release of the drug in GIT to achieve desired pharmacokinetic and therapeutic profile.
2. To develop following analytical profiles for the developed formulations.
   a. UV method development.
   b. HPLC method development.
   c. Absorbance
   d. Optical rotation.
   e. Refractive index.
   f. pH.
   g. Conductance
3. To optimize the developed novel formulations by studying the release profile of each drug in the formulation employing analytical methods from the developed analytical profiles.
4. To carry out short term stability studies on the prepared tablets.
5. To study in vitro and in vivo evaluation for the formulations.
   a. Tablet dimensions
   b. Tablet hardness.
   c. Tablet friability.
   d. Tablet weight variation test.
   e. Tablet content uniformity.
   f. Floating characteristics.
   g. Tablet in vitro dissolution.
   h. DSC studies.
   i. IR studies.
   j. In vivo x-ray studies.
RATIONAL OF THE THESIS
RATIONAL BEHIND COMBINATION OF ANTIHYPERTENSIVE AND ANTIHYPERLIPIDEMIC DRUGS (TREATMENT)

Dyslipidemia is a term often used to describe a group of syndromes or conditions involving imbalances or extremes in blood lipid levels. Generally, the term encompasses hyperlipidemia and hypercholesterolemia and other lipid disorders, and may also include conditions such as metabolic syndrome, of which hyperlipidemia and/or hypercholesterolemia are hallmarks. Many of these conditions put a patient at greater risk for coronary artery disease, heart attack and stroke. Such cerebrovascular and cardiovascular events are leading cause of death in many countries. Therefore, there is a great need for methods for treatment of lipid disorders, especially those which predispose a patient to cardiovascular problems such as myocardial infarction, anginal conditions, stroke, and coronary artery diseases etc.

Hypertension and hypercholesterolemia frequently coexist and may require concomitant drug treatment. The efficacy and safety profile of Lovastatin given in the presence of antihypertensive medication was evaluated using patient subgroups identified in the expanded clinical evaluation of Lovastatin study. The treatment of hypertension coexisting with hyperlipidemia is always subjected to various kinds of drugs, like ACEI, Ca-channel blockers, β-blockers etc. Control over the blood pressure was effectively achieved in combination therapy than individual therapy. In U.S., ever large clinical trials were conducted viz-antihypertensive and lipid -lowering treatment to prevent heart attack trials (ALLHAT). Several studies suggest that hypertension and hyperlipidemia may have additive or may have synergistic effects.

Since the first trial landmark showed that statins decrease the risk of coronary events and total mortality in patients after myocardial infarction, these drugs have become the cornerstone of prevention therapy. Statins have proven record in the secondary prevention of coronary heart disease. Furthermore, statins have been shown to exert varying degree of pleiotropic effect, which may stabilize vulnerable atherosclerotic plaques. A compelling body of evidence from randomized controlled trials demonstrates that high dose, potent statin therapy initiated immediately after an acute coronary event can significantly reduce early as well as longer term morbidity and mortality. Furthermore, high-dose, potent statin therapy displays a reasonable safety profile. National guidelines now recommended that in patients with ACS, statin therapy should be initiated in hospital prior to discharge, irrespective to baseline low density lipoprotein cholesterol level, to improve clinical outcomes. Every effort should be made to ensure all eligible patients with ACS are initiated and maintain on statin therapy.

Rubin et al undertook a study to determine the relative efficacy of antihypertensive and cholesterol-lowering therapy in ameliorating progressive renal injury in nephrotic serum nephritis in rat, a model characterized by both hypertension and hyperlipidemia. Rats were treated with, Lovastatin alone, Antihypertensive alone and Lovastatin – Antihypertensive combination for reduction in increased blood pressure to normal and hyperlipidemic condition. The results of the study showed that, Lovastatin alone had no effect on blood pressure. Antihypertensive therapy significantly lowered blood pressure. Combination therapy significantly lowered blood pressure. At 16 weeks, blood pressure averaged 118±2mm of Hg in Antihypertensive group and 111 ±3mm of Hg in combination therapy of Lovastatin and Antihypertensive drugs. Lovastatin significantly lowered serum cholesterol (16 weeks values; 2.02±0.41mmol/L) whereas, combination therapy lowered serum cholesterol (16weeks values; 2.09±0.52 mmol/L). Antihypertensive therapy had no significant effect. This finding suggests a combination therapy for the treatment of hypertension and hyperlipidemia. In a clinical trial study, in a ten subject study, co-administration of diltiazem (120 mg b.i.d.) with Lovastatin resulted in 3-4 times increase in mean Lovastatin AUC and Cmax versus
Lovastatin alone. Diltiazem plasma levels were not significantly affected by Lovastatin. The clinical trial indicates the need of combination of Antihypertensive and Antihyperlipidemic treatment.

The combination of elevated blood pressure and hyperlipidemia creates a synergistic increased risk of cardiovascular disease. The potential effects of Antihypertensive drugs on serum lipids must be considered in treated patients who are both hypertensive and hyperlipidemic. Patients with CHD and hypertension need aggressive cholesterol lowering therapy and careful lowering of blood pressure. β-blocker may be needed for patients with CHD for Antianginal effects and secondary prevention of myocardial infarction. Antihyperlipidemic treatment may slow the progression of atherosclerosis and possibly induce plaque regression. The primary prevention trial demonstrated that a reduction of both blood pressure and cholesterol is needed to reduce cardiovascular morbidity. A VA based trial of the effects of six different antihypertensive drugs found no major adverse effects on lipids and lipoprotein after 1 year of therapy with Atenolol, Captopril, Clonidine, and Diltiazem.

A retrospective, nonrandomized analysis published in American journal of cardiology evaluated the effect of initiating statins or beta blocker treatment early in the course of heart failure developed during acute myocardial infarction compared with the effect of neither or both treatments. Early initiations of statin or beta blocker alone was associated with improved event-free survival and the benefit of the combined treatment were additive. Compared with no treatment, statin treatment alone reduced the risk of dying by 26.1 percent, beta-blocker alone yielded a decrease of 30.6 percent and the combination of statins and beta blockers cut mortality by 48.3 percent.

Beta blockers reduce the risk of death, non-fatal recurrent myocardial infarction and sudden cardiac death and are recommended in national guidelines. Study of 46,000 survivors of myocardial infarction with asthma and chronic obstructive pulmonary disease reported a 40% reduction in total mortality in patients treated with blockers and benefits for the patients aged over 80 years and those with heart failures.

The combination therapy also has the benefits like—

i) Fixed-dose pharmaceutical products, which contain two or more active ingredients in a single dosage form, also reduce the number of prescriptions and thus administrative cost to the manufacturer (packaging cost) and costs to the end user in terms of (co-pays). Reducing the complexity of drug regimen also increase patient compliance and thereby can also increase effectiveness of combination therapy therefore may be tremendous benefit.
REFERENCES:
1. US Patent No. 60/580,734.
5. www.fda.gov/cardiazem SR_PT.