3) Objective:

Raised blood pressure is a common and quantitatively important cardiovascular risk factor. Over 50% of over 65’s in industrialised countries may be considered to have hypertension\(^1\). The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) and European Society of Hypertension (ESH) guidelines recommend that therapy with more than one antihypertensive agent be considered in patients with systolic blood pressure (SBP) more than 20 mm Hg or DBP more than 10 mm Hg above goal and among patients at high cardiovascular risk, as determined by elevated BP level and the presence of other risk factors. Combination drug therapy is recommended for treatment of hypertension to allow medications of different mechanism of action to complement each other and together effectively lower blood pressure at lower than maximum doses of each.

The rationale for combination therapy is to encourage the use of lower doses of drug to reduce the patient’s blood pressure to goal to minimize dose dependent side effects and adverse reactions. When smaller doses of medication with different mechanism of action are combined synergistic or additive effects on blood pressure are achieved and dose dependent side effects are minimized.

National Harris interactive survey for hypertension, in the United States revealed that out of 90% patients taking medication only 50% to 60% were involved in some form of lifestyle change to control BP. Thus majority of patients with hypertension rely on medication for the control of their BP. More recent clinical trials suggest that the approach of using monotherapy for the control of hypertension is not likely to be successful in most patients and especially in those with some comorbidity (eg. DM, heart failure\(^{15}\)).

Amlodipine is a prototype second generation dihydropyridine calcium channel blocker that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. It has a longer duration of action (ie) half life of 40 hours and the initial effects are cumulative over many days and more over for patient compliance in case of anti-angina patients, a rapid onset of action is necessary for immediate pain relief. Hence Amlodipine can be given as a single immediate release dose. Amlodipine can be safely combined with ß blockers, ACE inhibitors, thiazides and nitrates.

Metoprolol is selective ß1 receptor blocker devoid of ISA. It effectively inhibits the inotropic and chronotropic responses of isoprenaline and it’s potency in this regard is equal to propanolol.
It reduces plasma rennin activity in hypertensives. It also reduces mortality in postinfract patients. It has half life of 3 to 4 hours in fast hydroxylator and about 7 hour in slow hydroxylators. Hence to improve its therapeutic efficacy and patient compliance the formulation of metoprolol succinate as sustained release is necessary for chronic use. Non-dihydropyridine CCB’s, such as verapamil and diltiazem, should be avoided in combination with β- blockers due to the risk of symptomatic bradycardia and atrioventricular block. Dihydropyridine CCB’s have however been shown to be effective with β- blockers and are another therapeutic option in low dose combination. β- Blockers suppress renin secretion which potentiates the vasodilatory properties of CCB’s and this theoretical advantage is supported by data combining felodipine plus metoprolol. This combination appears to have an additive effect on blood pressure.

Metoprolol can prevent the potential reflex tachycardia caused by Amlodipine; Amlodipine can counteract decrease in cardiac output caused by Metoprolol. Thus both Metoprolol and Amlodipine have different complimentary mechanisms of actions resulting in synergistic anti-hypertensive activity. Based on these observations, bilayer matrix tablets comprising Metoprolol Succinate extended release layer and Amlodipine Besilate immediate release layer were prepared.

The proposed study relates to development of a dosage form which can be administered orally containing two antihypertensive drug in combination. The dosage form will be a unit solid dosage form i.e. a bilayer tablet containing two layers. One layer containing a calcium channel blocker and the other containing beta blocker.