1.0 INTRODUCTION

1.1 Cardiovascular diseases:

Cardiovascular diseases (CVDs) are one of the leading life threatening diseases of the world and are also responsible for placing a great burden on our national healthcare services. CVDs occupy the number one position in the morbidity and mortality statistics in most industrialized countries of the world. The two leading causes of death, coronary heart disease (CHD) and stroke are currently responsible for 12 million deaths (22% of the 55 million total). Seven million deaths are due to CHD, five million to stroke and other six million are due to other causes of CVDs. The pattern will change in 2020 with CHD and stroke remaining the two leading causes of death and together will be one of the leading causes of disability adjusted life years lost (DALY's). By 2020, CVDs are expected to account for seven out of every ten deaths in the developing countries compared with less than half this value today. In 2005, the estimated direct and indirect treatment cost of CVDs is $393.5 billion. Projections suggest that in India, hypertension will increase from 16.3 to 19.4% between 1995 and 2025.

Atherosclerotic vascular disease (ASVD) is responsible for nearly 75% of all deaths from CVDs, and it is the leading cause of death for both men and women in India. Elevated cholesterol, specifically cholesterol contained in low-density-lipoprotein (LDL) particles, is an important risk factor for the development of ASVD. Despite multiple randomized trials showing that a reduction in an elevated LDL level lowers cardiovascular morbidity and mortality, most patients with high LDL levels remain unidentified or untreated.

Cardiac heart failure (CHF) is also one of the most common causes of death and disability in industrialized nations and is among the syndromes most commonly encountered in clinical practice. CHF is a progressive syndrome resulting from the heart's inability to adequately perfuse and oxygenate peripheral tissues. This syndrome is manifested by symptoms of fatigue, dyspnea and congestion. Chronic heart failure is associated with worsening ventricular dysfunction and pathologic ventricular remodeling, resulting in adverse hemodynamic changes. The diagnosis of heart failure carries a risk of mortality comparable to that of the major malignancies. Patients with newly diagnosed CHF have an average 5 year survival.

Presently, the cardiovascular diseases such as ASVD and CHF are treated by statins and β-blockers respectively.

Loop diuretics e.g. furosemide, angiotensin-converting enzyme inhibitors e.g. captopril, β-blockers e.g. Carvedilol, Organic nitrates e.g. isosorbide mononitrate have been used to treat CHF. Out of above listed classes of drugs, beneficial effects of β-blockers have been documented for several decades. Recent clinical trials showed that β-blockers markedly reduce mortality and reduce left ventricular function in CHF patients. Carvedilol is indicated in the treatment of mild to moderate congestive heart failure in combination with other agents (e.g., digitalis, diuretics and ACE inhibitors) and also used in the management of essential hypertension. The treatment is mostly accomplished by orally administered conventional drug delivery systems (tablets) of Carvedilol, which suffers from certain disadvantages like poor bioavailability and extensive first pass metabolism.

Statins have become the first-line agents for primary and secondary prevention of CHD in patients with elevated LDL levels because of their effectiveness, tolerability and safety. The statins work by blocking enzyme HMG-CoA reductase which assists in the manufacture of cholesterol. The available statins (in order of labeling by the U.S. Food and Drug Administration) include lovastatin, Pravastatin sodium, simvastatin, fluvastatin, atorvastatin and cerivastatin. The treatment is mostly accomplished by orally administered conventional drug delivery systems (tablets) of Pravastatin sodium, which suffers from certain disadvantages like poor bioavailability and extensive first pass metabolism.

1.2 Brief Profile of Carvedilol:

Carvedilol is a lipophilic, nonselective β-adrenergic blocking agent. On oral administration, it is extensively absorbed but its **oral bioavailability is 25%** because of substantial hepatic first pass metabolism. Carvedilol is used for the treatment of mild to moderate heart failure of ischemic or cardiomyopathic origin, alone or in conjunction with other agents. It is also indicated for management of essential hypertension. But its conventional dosage form (tablets, 6.250 mg/three times a day) suffers from certain **disadvantages** such as,

1. Low oral bioavailability.
2. Extensive hepatic first pass metabolism.
3. Less patient compliance because of higher frequency of administration.

1.3 Brief profile of Pravastatin sodium:

Pravastatin sodium is most effective and best tolerated agent for treating ASVD. Pravastatin sodium has attracted considerable attention because of its potential to prevent cardiovascular disease by retarding the accelerated atherosclerosis which is important factor for coronary

heart disease in hyperlipoproteinemic individuals. It is hydrophilic and orally administered as β-hydroxy acid sodium salt form with 34% percent of the oral dose being absorbed. There is extensive first pass metabolism (up to 70%), as a consequence of which its **oral bioavailability is only 17%.** Its metabolites do not contribute to its therapeutic activity.

In ASVD, the therapy once initiated, usually lasts life long or for years; therefore precise treatment coupled with exact delivery system is required. But when Pravastatin sodium is administered as conventional dosage form (tablets, 10 mg/once a day) it suffers from certain **disadvantages** such as,

1. Low oral bioavailability.
2. Unstable at acidic pH.
3. Reduction of absorption in presence of food.
4. Incomplete absorption through GIT.
5. Extensive first pass metabolism.
6. Higher cost of therapy due to wastage of drug through GIT.
7. Increase in liver load to metabolize the drug because therapy lasts for years.

The **logical way** of overcoming above listed drawbacks of Carvedilol and Pravastatin sodium is by administering Carvedilol and Pravastatin sodium in drug delivery systems capable of bypassing first pass effect, improving bioavailability and providing sustained release to achieve maximum therapeutic benefits.

Buccoadhesive drug delivery offers certain distinct and specific advantages over other mucosal routes and delivery systems,

1.4 Specific advantages of buccal route and buccoadhesive formulations:

1) Bypasses hepatic first pass metabolism.
2) Greater bioavailability and reduction in dosage.
3) Consistent and continuous supply of tissue, therefore rapid absorption.
4) Ability to readily manipulate experimental conditions.
5) Offers safe environment.
6) Virtual lack of langerhans cells makes it tolerant to potential allergens.
7) Facilitates intimate contact of the formulation with the underlying absorption surface.
8) Allows modification of tissue permeability for the absorption of macromolecules.
9) Decrease in overall use of medical resources.
10) Improved disease management.

11) Assurance of sustained release from the dosage form.

1.5 Aims & Objectives:

The main objective of the present investigations was to prepare and evaluate buccoadhesive formulations of Carvedilol and Pravastatin sodium aimed at reducing drawbacks of conventional formulations.

The main **benefits** envisaged from above studies are:

1. Improved oral bioavailability.
2. Avoidance of first pass metabolism.
3. Sustained release effect.
4. Reduced dose and frequency of administration.
5. Improved patient compliance.
6. Effective disease management.

It is envisaged that the proposed delivery system will **overcome first pass metabolism** and wastage of drug through gastrointestinal tract which will result in **increased bioavailability.** It is expected to provide sustained release of Carvedilol and Pravastatin sodium which will reduce the frequency of administration of conventional dosage form and will improve patient compliance. Delivery system will help to keep **effective control** over hyperlipidemia, coronary heart disease, atherosclerotic vascular disease and cardiac heart failure by **improving absorption & bioavailability** of Carvedilol and Pravastatin sodium. It will also **reduce the dose** of administration. Ultimately it will result in improved disease management.

1.6 Hypothesis

Drugs having inherent drawbacks related to poor bioavailability due to first pass metabolism can be effectively delivered by buccal route as a buccoadhesive formulation to improve its bioavailability to considerable extent.

1.7 Proposed Plan of Work:

1. Preformulation studies and compatibility testing of actives and polymers.
2. Formulation of buccoadhesive systems

   Carvedilol: core-in-cup tablets, bilayer patches, bilayer tablets formulated with microspheres.

   Pravastatin sodium: core-in-cup tablets, bilayer patches.
3. Optimization of process and formulation variables.

4. *In vitro* characterization and evaluation of formulated buccoadhesive systems.
5. Pharmacokinetic studies of the optimized formulation.
6. Histological studies.
7. *In vivo* acceptability testing.
8. Pharmacodynamic studies.