CHAPTER - 1

INTRODUCTION
1.1 - GENERAL INTRODUCTION

This program supports research aimed at the design and development of novel anti-lipidemic agents and studies in the synthetic approaches for the known APIs i.e., Montelukast sodium, Olanzapine and Diltiazem hydrochloride that are suitable for industrial application. Therefore, the present thesis work is oriented towards both academic research and industrial research.

With this objective, it has been planned to work on novel compounds, which are expected to act as anti-lipidemic agents; and to work on various novel and/or improved synthetic approaches of APIs namely Montelukast sodium, Olanzapine and Diltiazem hydrochloride those are proven to have very high market potential in their respective therapeutic categories as seen from their worldwide sales and worldwide consumption. Therefore, it is advantageous if novel and/or improved processes are evolved to provide simple and commercially viable synthetic processes of these APIs.

Chapter-1 deals with the general introduction and pharmacological importance of: (i) anti-lipidemic agents as statins; since statin class of compounds are being successful for more than 4 decades in reducing cholesterol in serum, which leads to the risk reduction for the cardiovascular disease; (ii) an anti-asthmatic drug Montelukast sodium, which is a highly successful drug in the area of asthma and allergy (with
worldwide sales of ~ 6496.2 million US dollars and a worldwide consumption of 27,441.5 kgs by June 2011); (iii) an anti-psychotic drug Olanzapine, which is a very successful drug for treating the indications associated with Bipolar I disorder related to acute manic or mixed episodes and schizophrenia (with worldwide sales of ~ 6545.9 million US dollars and a worldwide consumption of 10,774.3 kgs by June 2011); and (iv) an anti-hypertensive drug Diltiazem hydrochloride, which is a very successful drug for treating hypertension (with worldwide sales of ~ 1186.8 million US dollars and a worldwide consumption of 408,931.9 kgs by June 2011) (Source for worldwide sales & consumption: Newport Premium database by Thomson Reuters).

Chapter-2 deals with synthesis and characterization of novel anti-lipidemic agents by introduction of more hydrophilic scaffolds into the statin compounds by linking the pharmacophore ‘dihydroxy heptanoic acid moiety’ with more hydrophilic scaffolds to result in compounds, which are expected to act as better anti-lipidemic agents as statin compounds especially as HMG-CoA reductase inhibitors and expected to improve the level of hepato selectivity and expected to reduce the risk of adverse effects such as diarrhoea, abdominal pain, constipation, flatulence etc.

Chapter-3 deals with two novel synthetic approaches for the preparation of Montelukast sodium via novel intermediates. It also deals
with identification, synthesis and characterization of related substances i.e., impurities in Montelukast sodium \((25)\) obtained from the process of the present work. Out of these impurities few are novel intermediates of the present work and few others are known impurities of Montelukast sodium. It further deals with study on polymorphism of Montelukast sodium \((25)\) and its intermediates.

Chapter-4 deals with two novel approaches for the synthesis of Olanzapine \((69)\). It also deals with an improved, scalable, cost effective and impurity controlling process for the manufacture of Olanzapine that was exclusively developed with the intention to use the resulting Olanzapine API for early entry into some of the European countries (e.g., Spain) and Canada as these countries does not have patent protection for Olanzapine as product. In these countries, only process claims are present in the respective compound patents. It also deals with identification, synthesis and characterization of related substances i.e., impurities in Olanzapine of the present work.

Chapter-5 deals with simplified, scalable and cost effective process for the manufacture of Diltiazem hydrochloride \((88)\), which is an improvement over the known processes. It also deals with identification, synthesis and characterization of known impurities of Diltiazem hydrochloride obtained in the process of the present work.
1.2 - NOVEL ANTI-LIPIDEMIC AGENTS

1.2.1 - Drug Discovery and Anti-lipidemic agents

Anti-lipidemic agents are basic drugs for prevention of cardiovascular diseases and have been now in use for more than 4 decades. Anti-lipidemic agents are categorized into various types like (i) Niacin, (ii) Fibrates ((fenofibrate [Tricor®], gemfibrozil [Lopid®], clofibrate [Atromid-S®], bezafibrate), (iii) Resins that bind bile Acid (colestipol [Colestid®] and cholestyramine [Questran®]) and (iv) HMG CoA Reductase Inhibitors (“statins”). The first class of drugs with an established efficacy in lipid-lowering phenomenon in humans was 3-hydroxy-3-methyl glutaryl coenzyme A (HMG CoA) reductase inhibitors (statins). ¹

1.2.2 - HMG CoA Reductase Inhibitors

During 1950s through 1960s, it was evident that a major factor of risk for the advancement of coronary heart disease, was increased levels of cholesterol in plasma. This encouraged to focusing on research for few drugs that could reduce levels of cholesterol in plasma. A possible method was the reduction of biosynthesis of cholesterol. The enzyme in the pathway of biosynthesis of cholesterol that is rate-limiting, is 3-hydroxy-3-methyl glutaryl CoA (HMG-CoA) reductase and it is a natural target. HMG-CoA reductase inhibiting drug candidates, which are called as HMG-CoA reductase inhibitors (or "statins") are used to reduce
cholesterol in serum as a method of risk reduction for the cardiovascular disease.²

High concentrations of cholesterol (hypercholesterolemia) and/or lipid (hyperlipidemia) in the circulatory system are conditions known to be associated with many diseases, including, but not limited to, arteriosclerosis, atherosclerosis, stroke, coronary heart disease, peripheral vascular disease, diabetes and high blood pressure. It has been established that lowering low density lipoprotein (LDL) cholesterol concentration in the blood or also increasing the high density lipoprotein (HDL) cholesterol concentration in relation to the concentration of LDL cholesterol concentration in the blood is beneficial for protecting against diseases associated with high blood concentrations of cholesterol and/or lipids.

HMG-CoA reductase inhibiting drugs (Statins) play significant role in inhibition of biosynthesis of cholesterol involving the stimulation of the receptor arbitrated by the reduction of the LDL (bad cholesterol). Various statins behave differently to affect the increase of HDL (good cholesterol). However, most of them are able to reduce the levels of triglycerides only to some extent but not fully.³⁴⁵ The list of statins include rosuvastatin (brand name-Crestor; marked by AstraZeneca), lovastatin⁷⁸ (brand name-Mevacor; marketed by Merck), atorvastatin⁹¹⁰ (brand name-Lipitor; marketed by Pfizer), pravastatin¹¹¹² (brand name-Pravachol; marketed by...
BMS), fluvastatin\textsuperscript{13} (brand name-Lescol; marketed by Novartis), pitavastatin\textsuperscript{14,15} (brand name-Livalo), and simvastatin\textsuperscript{16,17} (brand name-Zocor, marketed by Merck).

![Fig. 1.1]

**1.2.3 - The Statin Pharmacophore**

The statins are contesting antagonists of 3-hydroxy-3-methyl glutaryl coenzyme A. All statins contain two particular scaffolds, a heptanoic acid chain with a hydroxy group and a ring system with lipophilic (non-polar) substituents. All the active statins consist of a functional group of a free acid that is similar to the free COOH of 3-hydroxy-3-methyl glutaryl coenzyme A. Few of the statin compounds that contain carboxylic acid group in the form of a lactone i.e., cyclic ester are considered to be the prodrugs. Such statins, which are prodrugs are Lovastatin and Simvastatin and contain a 3,5-dihydroxy heptanoic acid unit cyclized
into a cyclic lactone. Cyclic lactone is required to be hydrolysed to a carboxylate anion form in order to become active. Therefore all such statin prodrugs undergo hydrolysis in vivo to form the corresponding hydroxy carboxylic acid chain and inhibit HMG-CoA reductase formed in liver. HMG-CoA reductase enzyme is the rate-limiting factor for the conversion of 3-hydroxy-3-methyl glutaryl coenzyme A to Mevalonic acid irreversibly for the synthesis of cholesterol. Out of various statins available, three statins i.e., Lovastatin, Simvastatin & Pravastatin originate from fungi (Aspergillus terreus and Monascus rubber) (simvastatin and pravastatin are chemical modifications of lovastatin). These statins are called as type 1 statins. Lovastatin and Simvastatin are in the form of lactones as discussed above, which are inactive and should be metabolized by hydrolysis into the corresponding active hydroxy carboxylic acid forms for the inhibition of HMG-CoA reductase.

Few other fully synthetic statins have a very heavily substituted scaffolds linked to the HMG-like moiety and are referred as type 2 statins. Some of these type 2 statins are Fluvastatin, Atorvastatin and Rosuvastatin. One of the major differences between structural scaffolds of the type 1 and type 2 statins is the presence of fluorophenyl group of type 2 statins in place of the butyryl group of type 1 statins.

The pharmacophore of a typical statin would bind to an active site that is same as HMG-CoA substrate and would be responsible for the
inhibition of HMGR enzyme. The said inhibition of HMGR is a stereo-selective inhibition and therefore it is required that the statins have \((3R, 5R)\) configuration.\(^{19}\) The HMG CoA reductase inhibitor's ring structure would bind to HMGR enzyme. The ring structures involved in HMG CoA reductase inhibition, which are clinically useful include partially reduced pyrrole (atorvastatin), naphthalene (pravastatin, lovastatin, and simvastatin), pyrimidine (rosuvastatin) and Indole (fluvastatin).

**Fig. 1.2**

Statin pharmacophore and its structural relationship with HMG CoA

**Fig. 1.3**

Methyl butyric acid ester functionality of Lovastatin
1.2.4 - Statins – Advantages of hydrophilicity of scaffolds linked to the HMG-like moiety

Lipophilicity factor in the statins is found to play an important role because the hepato selectivity of the statins is directly proportional to the lipophilicity associated with them. The more is the lipophilicity of the statin, the higher are the levels of contact in non-hepatic tissues. On the other hand, the statins with hydrophilic scaffolds possess more hepato selective nature. Such difference in the hepato selectivity is because of the fact that statins with lipophilic groups apathetically and non-discriminatively scatter into both of the hepatocyte and non-hepatocyte. Whereas, the statins with groups possessing hydrophilic nature depend highly on rapid transport into hepatocyte to endeavor their effects.\textsuperscript{20,22} Higher level of hepato selectivity is found to result in diminished risk of adverse effects such as diarrhoea, abdominal pain, constipation, flatulence etc.\textsuperscript{21} It has been found that the organic anion transporting
polypeptide (OATP) is very important for the hepatic ingestion of statins containing hydrophilic groups such as pravastatin and rosuvastatin.\textsuperscript{20,22} OATP is conveyed in the tissue of liver on the hepatocytes basolateral membrane and is found to be a key contributor for the low level of IC\textsubscript{50} value in hepatocytes for rosuvastatin. Out of the various statins that were in the market, Cerivastatin was the statin containing most lipophilic moiety. It was associated with the highest level of serious adverse effects because of its tendency to inhibit proliferation of vascular smooth muscle and hence, it was removed from the market voluntarily by the manufacturer.\textsuperscript{20}

In view of the importance of hydrophilicity of statins discussed above, it was an endeavour to invent new HMG-CoA reductase inhibitors, which are easier to synthesize and ensured that all the newly invented inhibitors are retained with key pharmacophore of the statin compounds by embedding the more polar scaffolds to the ‘dihydroxy heptanoic acid moiety’ when compared to most of the existing statins depicted in Fig. 1.1. Hence, said novel compounds are considered to possess more hydrophilicity to be useful as better anti-lipidemic agents especially as HMG-CoA reductase inhibitors, which are expected to improve the level of hepatocyte selectivity and reduce the risk of adverse effects such as diarrhoea, abdominal pain, constipation, flatulence etc.
1.3 - MONTELUKAST SODIUM

Cysteinyl leukotrienes are significant mediators for asthma, and reduction of its effects signifies the remarkable breakthrough in the area of asthma. The asthma drugs are mainly divided into four varieties. They are Leukotriene antagonists, Anti-Ige medications, Anti-Inflammatory drugs and Bronchodilators. When a patient is found to be asthmatic, the patient will be generally given one or more asthma drugs to cure or control asthmatic symptoms on a long term perspective.

Leukotrienes are synthesized from arachidonic acid, a normal constituent of the phospholipid bilayer, which is liberated by the action of phospholipases in responses to various stimuli. Leukotrienes are formed by the activation of 5-lipoxygenase (5-LO) enzyme on arachidonic acid to form an unstable intermediate, 5-hydroperoxyeicosatetraenoic acid (5-HPETE) which is converted to epoxide leukotriene LTA4. 5-LO is a member of a family of lipoxygenases, and is an iron-containing enzyme consisting of 673 amino acids, which is dependent on Ca+++, adenosine triphosphate and several cofactors for maximal activity. 5-LO translocates from the cytosol to the nuclear cell membrane to initiate leukotriene biosynthesis. 5-HPETE is formed through the action of 5-LO and the 5-lipoxygenase-activating protein (FLAP), a nuclear membrane protein to which 5-LO binds to make a stable complex.
LTA4 is the pivotal intermediate from which all other leukotrienes are synthesized. LTA4 hydrolase is a zinc containing cytosolic metalloproteinase possessing intrinsic aminopeptidase activity, with considerable homology to the aminopeptidase N family of enzymes. LTA4 enzymatic activity can be inhibited by metallohydrolase inhibitors, such as bestatin. LTA4 is unstable and may be hydrolysed to the dihydroxyacid LTB4 by LTA4 hydrolase, or glutathione is incorporated to form the peptidoleukotriene LTC4 by the enzyme LTC4 synthase. LTC4 synthase has been recognized as an 18 kDa integral microsomal membrane protein and has recently been cloned. The nucleotide and deduced amino acid sequences of its complementary deoxyribonucleic acid (cDNA) show no significant homology to glutathione S transferases but share amino acid identity with FLAP. Interestingly, MK-886, a FLAP inhibitor, inhibits LTC4 synthase activity.

The subsequent conversion of LTC4 to LTD4, a cysteinyl glycinyl derivative, is via the action of a-glutamyl transpeptidase. LTD4 is further metabolized to the cysteinyl derivative, LTE4, by the action of a dipeptidase. Leukotrienes are rapidly metabolized and removed from the circulation. Peptidoleukotrienes undergo oxidation, resulting in biliary and urinary elimination of biologically less active and inactive metabolites. LTE4 is an important urinary metabolite that can be used to monitor the production of leukotrienes in man.
Leukotriene receptors are of two classes, those for the dihydroxy-leukotrienes, LTB4, termed BLT receptors, and those for cysteinyl leukotrienes, CysLT receptors, according to the recent International Union of Pharmacology (IUPHAR) receptor nomenclature. Specific membrane CysLT receptors have been described, using functional receptor assays on isolated smooth muscle preparations and receptor ligand-binding studies in mammalian lung tissues. Although few synthetic agonists for CysLT receptors now exist, many antagonists have been produced. Two broad subgroups of Cys LT receptors have been recognized, those blocked by known antagonists (Cys-LT1-receptors) and those that are resistant to blockage (Cys-LT2-receptors). One recent antagonist appears to have activity both for Cys-LT1- receptors and Cys-
LT2-receptors. In human airway smooth muscle, LTC4, LTD4 and LTE4 all activate a Cys-LT1-receptor, although a subclass of Cys-LT1-receptor may be activated specifically by LTE4 alone. In human pulmonary vasculature, a Cys-LT2-receptor has been identified. Cys-LT1-receptor is likely to be G-protein-coupled, leading to calcium mobilization on activation.

Early compounds in the development of receptor antagonists were relatively weak in activity. The first leukotriene receptor antagonist of the hydroxyacetophenone class described was FPL-55712, which exhibited poor bioavailability and a short half-life. Other compounds within the same class, e.g. LY 171883, L-649,923, and YM-16638, were synthesized, but did not possess sufficient potency to act effectively as an LTD4 receptor antagonist. In addition to having no effect on allergen-induced responses, L-649,923 was poorly-tolerated, with a high incidence of gastrointestinal effects.

The newer generation of leukotriene antagonists, such as ICI 204,219 (or Accolate), the quinolones MK-571 and RG-12,525, ONO-1078 (prankulast) and SK&F 104,353 are more promising. SK&F 104,353 has little oral activity and has been studied via the inhaled route. These compounds are at least 200 fold more potent than earlier leukotriene antagonists in [3H]-LTD4 binding assays. The efficacy and safety of potent leukotriene receptor antagonists against leukotriene-induced
bronchoconstriction in normals and asthmatics has been shown in several studies. ICI 204,219, at a single oral dose of 40 mg, shifted the LTD4-induced bronchoconstriction doseresponse curve by 100-fold and provided significant antagonism for at least 24 h in normal subjects, with no apparent side-effects. MK-571 provided a shift of greater than 88 fold in asthmatic patients. The introduction of these potent antagonists has been critical in defining the role of LTD4 in bronchial asthma.24

The sodium salt of Montelukast (25) is a leukotriene receptor antagonist (LTD4). It is useful in treatment of asthma, inflammation, allergies, angina, cerebral spasm, glomerular nephritis, hepatitis, endotoxemia, uveitis and allograft rejection.25

In view of the importance of leukotriene receptor antagonists (LTD4) enumerated above and the market potential of Montelukast sodium (25) as evident from its worldwide sales and worldwide consumption, while certain processes for preparation of Montelukast sodium were reported in literature as discussed in Chapter-3, there is a continuing need for new processes for the preparation of Montelukast and its salts more specifically Montelukast sodium (25). Therefore, the objective of the present work is to study novel synthetic approaches to provide cost effective, eco-friendly process for the preparation of Montelukast sodium (25), which is well suited for commercial scale up.
1.4 - OLANZAPINE

Schizophrenia is a disorder related to psychosis characterized by symptoms that significantly impair functioning and that involves disturbances in form and concept of thought, mood, behavior, sense of self and relationship to the external world. Schizophrenia affects the nearly 1% of population.55

Mood or bipolar disorder is a psychiatric diagnosis that defines a group of mood disorders defined by the presence of one or more episodes of abnormally increased energy levels, cognition, and mood with or without one or more depressive episodes.56

1.4.1 - Therapeutic agents for treatment of schizophrenia and bipolar I disorders:

Initial attempts were made to specifically treat schizophrenia disorders with chlorpromazine and, then, with other medications, like haloperidol which became the standard drug for schizophrenia. Treatment of schizophrenia with haloperidol was moderately effective against positive symptoms, but its use was limited by the lack of efficacy against negative symptoms. Later developed atypical anti-psychotics for example risperidone and clozapine for the same treatment, showed some efficacy on negative symptoms.55

Potency of Olanzapine is greater than clozapine in blocking serotonin 5HT2 and dopamine D2 receptors, and its ability to block serotonin 5HT2
and dopamine D2 receptors indicates its possible usefulness as an anti-psychotic drug.\textsuperscript{57}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{olanzapine_clozapine.png}
\caption{Olanzapine and Clozapine.}
\end{figure}

1.4.2 - Mechanism of action of atypical anti-psychotics:

5 types of Dopamine receptors in human beings are known. Out of which, type 1 & 5 are termed as “D\textsubscript{1} like receptor” since these two are similar in structure and drug sensitivity. Type 2, 3 & 4 are called as ‘D\textsubscript{2} like receptor” because they are similar in structure. D\textsubscript{2}, D\textsubscript{3} and D\textsubscript{4} receptors have different sensitivities towards the antipsychotic drugs.

The below given figure-1.6 displays the conc. of antipsychotic drugs which block D\textsubscript{2} receptors in vitro are identical to the concentration identified in the fluid in spine or water in plasma of patients, whose symptoms are controlled by anti-psychotics.\textsuperscript{58}
Atypical anti-psychotics for instance olanzapine shows antipsychotic activity only at doses which occupy 65% or more of D2-receptors, which is similar to the action of haloperidol.59

5-HT2A Occupancy: Olanzapine shows higher affinity for 5-HT2A receptor than D2 receptor in vitro.

**Fig. 1.7:** Relation between threshold for clinical response and occupancy of D2 and serotonin 5-HT2 receptors for atypical antipsychotic olanzapine (1).
In view of the importance of Olanzapine (69) in drug therapy as enumerated above and also in view of its market potential as evident from its worldwide sales and worldwide consumption; it is the objective of the present work to study on efficient, cost-effective and alternative synthetic approaches for the preparation of Olanzapine (69) to overcome the limitations of the reported synthetic approaches.

1.5 - DILTIAZEM HYDROCHLORIDE

1.5.1 - Treatment of blood pressure elevation: 69

Increased blood pressure treatment with suitable drugs should be determined by cardiovascular adverse phenomenon risk. Safety, effectiveness, indication, contra-indication, less side effects, drug-drug interactions dictate the drug to be taken by the individual patients. Many patients shall require many drugs for reducing their blood pressure to their normal level. The main drugs classified into antihypertensive drugs are effective equally for lowering blood pressure. However, beta blockers are not recommended any more when patients are treated for their blood pressure for the first line treatment.

Healthy lifestyle of patients having increased blood pressure may be advantageous for reduction of alcohol and salt, weight loss and exercise, but is not sufficient. This leaves them at risks of coronary heart disease,
stroke and/or renal failure. Drug treatment should be planned up on confirmation of high blood pressure by perfect measurements frequently.

Treatment of increased blood pressure should also take into account the risk of cardiovascular or myocardial infarction or heart stroke for a usual 5 years of time period. An absolute risk calculator may be used to confirm who is going to be benefited from the treatment.

Treatment of increased blood pressure is suggested for patients having:

i. blood pressure - 180 mmHg or higher - systolic

ii. blood pressure - 110 mmHg or higher - diastolic

iii. blood pressure - 160 mmHg or higher - systolic and 70 mmHg or less - diastolic.

The following associated conditions of the patients require urgent treatment. Those are heart stroke or myocardial infarction, or proof of end-organ damage like hypertrophy of left ventricle and/or microalbuminuria.

1.5.2 - Starting drug therapy:

After concluding to start drug treatment, picking of a drug for hypertension for a patient depends on age and the coupled clinical conditions or damage of end-organ. If the patient is suffering from
diseases other than hypertension, it leads to favourability or limitation in the use of classes of drugs and their interactions. Drugs for hypertension have efficacy similar in various classes. In patients not complicated, it is suggested to begin with a diuretic, an (ACE) inhibitor, ARB or CCB. As first-line treatment, 2 β blockers are no more suggested for patients not complicated with hypertension as the statistical data show that they show risk of heart stroke and diabetes compared to other drugs.

1.5.3 - Blood pressure – Target:

In patients not complicated, the target hypertension must, if tolerated, be ≤140/90 mm-Hg. In patients complicated with damage of end organ or diabetes conditions, the target is < 130/80 mm-Hg, and in proteinuria patients it must be < 125/75 mm-Hg (>1 g a day).

Reaching blood pressure recommended is vital for starting treatment. If it is failed to arrive at the same, it may keep patients at significant residual adverse risk.

Treatment starts with drug selected at lowest possible dose with a revisit in six weeks. If it is not tolerated well or not effective drug, the drug is to be changed to a varied class. If still not achieved, additional lesser dose of a drug from a different pharmacological class is to be preferred instead of giving original drug at higher dose.
When to start drug treatment for hypertension

**Fig. 1.8**

In the above figure BP means blood pressure, SBP means systolic blood pressure and DBP diastolic blood pressure.⁶⁹
1.5.4 - Diltiazem hydrochloride - Mechanism of Action: 69

The exact mechanism of action for anti-anginal activity are not yet very clearly described so far. However, it is believed that the following are the two ways of mechanism of action which Cardizem acts.

**Angina because of coronary artery spasm.**

Cardizem is proven to dilate coronary arteries potently by epicardial dilation and subendocardial dilation. Cardizem inhibits spontaneous coronary artery spasm and ergonovine induced coronary artery spasm effectively.

**Angina - Exertional**

Production of increases of exercise tolerance has been shown by Cardizem, probably because of the ability to reduce MOD. This is reached by heart-rate reduction and systemic blood pressure at below maximal and maximal workloads in exercise.

Diltiazem hydrochloride (Cardizem®) has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reduction in heart rate and systemic blood pressure at submaximal and maximal exercise workloads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the
configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Many synthetic approaches were reported in literature for the preparation of Diltiazem or its intermediates including asymmetric synthetic approaches. Some of those reported synthetic approaches were discussed in chapter-5.

In view of the importance of Diltiazem hydrochloride (88) in drug therapy as enumerated above and also in view of its market potential as evident from its worldwide sales and worldwide consumption; the present work has an objective to develop an improved process for the preparation of Diltiazem hydrochloride (88) by modifying the conditions of the reported synthetic procedures, replacing costly reagents and solvents with simple and cost effective reagents, which are available commercially and are inexpensive on commercial scale; and by simplifying the steps to produce cost competitive Diltiazem hydrochloride (88) API when compared to reported synthetic procedures.