Drug delivery by oral route is preferred due to the ease of administration and painless approach. To be effective systemically, orally administered drugs must resist the gastrointestinal tract environment and get absorbed into the blood stream without undergoing any change. The rate and extent of drug absorption have an impact on therapeutic availability of the drug which has direct correlation with the therapeutic activity in terms of onset of action, duration of action, and intensity of therapeutic response. Hence, adequate absorption and sufficient therapeutic concentration in the blood is essential to exhibit intended pharmacological effect of an active ingredient. Factors that affect absorption of drugs should be considered for the design of suitable formulation strategy to be adopted. Absorption of drugs is governed by physicochemical properties, physiological barriers, and patient related factors.

1.1. Pharmaceutical factors affecting absorption

Solubility and permeability of an active ingredient are important for maximum therapeutic efficacy which in turn depends on the physicochemical properties like, molecular weight, particle size, polymorphism, log P (Partition coefficient), pKa (Dissociation constant), hydrogen bond count (sum of donors and acceptors), and polar surface area. Advanced in vitro screening methods such as combinatorial chemistry has led to the emergence of many potential chemical components with marked therapeutic activity. Among them about 40% of active ingredients are, however, poorly water soluble due to which their absorption is dissolution rate limited (Dahan and Hoffman, 2007). To understand physicochemical properties and to predict the absorption of poorly soluble drug molecules, drugs are classified based on their solubility, permeability and partition coefficient. According to Biopharmaceutics Classification Systems (BCS), drug substances are classified based on aqueous solubility and permeability. A drug substance is considered to be highly soluble when the maximum daily dose is soluble in 250 mL of aqueous media over the pH range of 1-7.5 and a drug substance considered to be highly permeable when >85% of the administered dose is absorbed (Shargel et al., 2005). Lipinski’s rule of five, on the other hand, provides basis in predicting the extent of absorption. The drug substance with more than 5 H-bond donors, more than 10 H-bond acceptors, molecular weight > 500 and log P > 5 is considered poorly permeable (O'Driscoll et al., 2008). Both these classification, inspite of having limitations, are
helpful in predicting drug bioavailability and in designing of suitable formulation by which pharmacokinetic profile can be improved for a particular drug.

1.2. Physiological barriers in systemic absorption of drugs
Dissolution of a poorly soluble drug from its dosage form may be limited due to a limited volume of intestinal juices and variations in pH of gastrointestinal fluids (Lobenberg and Amidon, 2000). Existence of solubilized drug in unionized form depends on the pH of gastrointestinal fluid at the absorption site. Permeability of solubilized drug in unionized form through the lipid bilayer is the prime requirement for drug absorption. Drug transport across lipid bilayer is a complex process due to the differences in membrane polarity and hydrophobicity. Intestinal permeability also depends on molecular size, polar vander wall surface area and lipophilicity of the drug (Martinez and Amidon, 2002).

Transport of the drug across the enterocyte can be divided into active, passive and specialized transport (carrier mediated and endocytosis). This may takes place via transcellular or paracellular route. The efflux transporters (Permeability glycoproteins, p-gp) present in the intestinal wall efflux the absorbed drug thereby reduces its systemic absorption (Lobenberg and Amidon, 2000). Though the intestinal tract is richly supplied with both blood and lymph, drugs preferentially get absorbed into the portal blood due to high fluid flow in the portal blood. Portal circulation transports the drugs to metabolically active liver where the enzymes metabolize the drug hence reducing the systemic absorption (Yanez et al., 2011). Drugs having log P>5, on the other hand, are transported directly to the lymph avoiding the first pass metabolism. Furthermore, gastric emptying time and intestinal transit time are important parameters that influence drug absorption.

Poor oral bioavailability resulting from poor solubility of an active ingredient in the pH range of gastrointestinal fluids is a major problem with newer drug molecules. For such drugs, dose is increased to attain the therapeutic drug concentration in the blood which may lead to undesirable effects (Chakraborty et al., 2009; Kawabata et al., 2011).

1.3. Drug delivery strategies/ formulation approaches to improve the absorption
Design of a successful oral dosage form (with improved solubility and permeability at the absorption site) for a particular compound depends on better understanding of the
physicochemical and biopharmaceutical properties and limitations of each drug delivery design. Various approaches are adopted by formulation scientists to avoid dose escalation viz., particle size reduction, nanocrystals, formation of salts, cocrystal formation, amorphous formulations, cyclodextrin complexation, pH modification, lipid based formulations and prodrug approach. Each of these methods have advantages as well as limitations and hence the selection of a particular approach is an important step in increasing their bioavailability (Shah et al., 2008; Kawabata et al., 2011).

Delivery of poor water soluble drugs using lipid based vehicles is a new and recent approach. Enhanced solubility of hydrophobic drugs in lipid excipients and improved pharmacokinetic parameters when administered along with food, especially fatty meal is the basis to design lipid based dosage forms (Pouton, 1997).

Enhanced bioavailability of drugs with fatty meal is explained by one of the following reasons such as stimulation of bile flow and pancreatic secretions by the administered lipid which promotes drug solubilization, delay in the gastric emptying thereby increasing the drug residence time in the gastrointestinal tract (GIT) for its absorption, altered gastrointestinal pH, enhanced lymphatic transport because of which first pass extraction of drug is prevented, increased intestinal wall permeability and reduced efflux of drug as lipids (anionic phospholipids) have inhibitory effect on efflux transporters (Chakraborty et al., 2009).

Though many lipid based formulations such as liposomes, solid lipid nanoparticles, self dispersing tablets, solid solutions exist, self micro emulsifying formulations are receiving more attention because of their stability, self dispersing nature, ease of preparation, and scale up.

Self emulsifying systems are one among the lipid based delivery systems that have gained more attention to deliver hydrophobic drugs efficiently. These systems produce emulsions, microemulsions (ME) upon dilution with water depending upon the nature of the oil, surfactant concentration and oil/surfactant ratio (Gershanik et al., 2000). Self Microemulsifying Drug Delivery Systems (SMEDDS) are isotropic mixtures of oil and surfactants and produce microemulsions upon dilution with the droplets in nano size range.

The formation of microemulsion from SMEDDS upon exposure to the aqueous media is instantaneous and can be produced even with motility of GIT. As SMEDDS are non-aqueous pre concentrates of microemulsions, these are stable and suitable for the drugs
that undergo chemical and enzymatic degradation in GIT as the drug is presented in the form of oil droplets. Improved solubilization of drug by presenting in nano sized droplets, reduced first pass extraction by promoting lymphatic transport, improved permeability with reduced efflux of drug contribute together for enhanced bioavailability of drugs by this approach.

Hypertension, one of the cardiovascular diseases, is most common with present life style conditions. Sustained increase in blood pressure i.e. > 140/90 mm Hg can be considered as hypertension and may lead to cardiovascular diseases necessitating medical attention. In addition to cardiovascular diseases, complications of raised blood pressure include heart failure, peripheral vascular disease, renal impairment, retinal hemorrhage and visual impairment. Antihypertensive drugs act either by reducing cardiac output or by reducing total peripheral resistance. Angiotensin II blockers mediate their action through blocking angiotensin II, which is a potent vasoconstrictor (Hoffman, 2006).

Candesartan cilexetil, an esterified prodrug of candesartan has long lasting and insurmountable effect on angiotensin II receptor (Rang et al., 2007; Abib et al., 2011). Since candesartan suffers from poor oral absorption, ester prodrug was synthesized. The therapeutic action of candesartan cilexetil depends upon generation of active metabolite. The prodrug undergoes rapid and complete hydrolysis and gets converted to candesartan during gastrointestinal absorption (Gleiter et al., 2004). Clinical effective dose of candesartan cilexetil ranges between 8-32 mg/day. Candesartan cilexetil significantly reduces diastolic, systolic and mean arterial pressures without affecting cardiac output, heart rate or stroke volume. Incomplete absorption from the gastrointestinal membrane due to low solubility across the physiological pH range resulted in less bioavailability (14%) (Moffat et al., 2004).

Eprosartan mesylate is a non-peptide, non-biphenyl and non-tetrazole angiotensin II receptor antagonist. Metabolic activation is not required for eprosartan to produce effective AT₁ receptor antagonism. It is an effective blood pressure lowering agent and possesses unique actions. It is far effective in inhibiting sympathetic nervous system activity that has clinical relevance as increased sympathetic nervous system activity causes systolic hypertension which is found in the elderly (Zoumpoulakis et al., 2002). Systolic hypertension is considered as significant factor for cardiovascular diseases and eprosartan significantly reduces pressor response to sympathetic nervous system activity. Thus eprosartan can be effectively used for isolated systolic hypertension found in the
elderly. Single oral doses of eprosartan from 10 mg to 400 mg have been shown to inhibit the vasopressor, renal vasoconstrictive and aldosterone secretory effects of infused angiotensin II with complete inhibition evident at doses of 350 mg and above. However, the bioavailability of eprosartan is low (13%) due to its pH dependent aqueous solubility and incomplete oral absorption (Tenero et al., 1998).

The major problem associated with oral delivery of these drugs is low oral bioavailability due to poor aqueous solubility by which their absorption is dissolution rate limited. Alternate formulation strategies need to be investigated to avoid dissolution rate limited absorption. Novel drug delivery approaches are required to provide bioavailable dosage forms for enhanced therapeutic profile of such drugs.

Immediate release formulations deliver the drug with a rapid rate to provide sufficient therapeutic concentration in the blood. SMEDDS, one such novel immediate release formulations, is an effective and promising approach to achieve rapid drug release with improved therapeutic profile.

1.4. Objectives

The general objective was to improve the bioavailability of candesartan cilexetil and eprosartan mesylate that show dissolution rate limited absorption using microemulsion technology.

The specific aims are;

- To develop and validate analytical and bioanalytical method for the estimation of candesartan cilexetil and eprosartan mesylate using HPLC.
- To construct pseudo ternary phase diagrams for candesartan cilexetil and eprosartan mesylate with selected lipid based vehicles.
- To formulate and evaluate self microemulsifying drug delivery systems for candesartan cilexetil and eprosartan mesylate.
- To carry out pharmacokinetic evaluation of the optimized formulations.
- To carry out the stability studies of the optimized formulations.