CHAPTER 1

INTRODUCTION

1.1 BACKGROUND

Hypertension is defined as an elevated Blood Pressure (BP), which is a major risk factor that predisposes one to cardiovascular disorders and is responsible for most of the morbidity and mortality (Kannel 2000, 2004). Nowadays, patients are considered hypertensive if their BP reaches or exceeds 90/140mmHg (European Society of Hypertension 2003). High BP affects about 20% of the world's adult population and is a serious condition that can lead to coronary heart disease, heart failure, stroke, kidney failure and other health problems (Richard 2011).

The Renin-angiotensin system (RAS) plays an important role in cardiovascular homeostasis and in the pathophysiology of hypertension (Goodfriend et al 1996). Angiotensin II is the key effector peptide produced by the RAS. The Angiotensin II receptor Type 1 (AT$_1$) appears to mediate most of the cardiovascular effects of the renin-angiotensin cascade. Angiotensin II Receptor Blockers (ARBs) are the newest drug class for the treatment of hypertension. The ARBs have a more direct mechanism of action for affecting the RAS than Angiotensin Converting Enzyme Inhibitors (ACEIs) (Messerli et al 1996). Inhibition of the RAS is an attractive approach for treatment of hypertension and heart failure. Candesartan Cilexetil (CC) is a prodrug of Candesartan which is potent and highly selective ARB that has distinctive receptor-binding properties (Reif et al 1998). However, CC exhibited low oral bioavailability due to its poor aqueous solubility.
Several clinical studies have disclosed that CC administration is safe and effective for the treatment of hypertension, heart failure, renal disease and diabetes mellitus. In addition, CC can be used alone or in combination with other antihypertensive agents (Ross and Papademetriou 2004). The drug CC lowers BP in a dose dependent manner and it maintains its antihypertensive effect over long-term treatment. The recommended daily dose in the management of hypertension is 4 to 8 mg twice or once a day (Atacand 1998, Nekkanti et al 2010). The elimination half-life of candesartan is about 5-9 h. It blocks the receptors AT1 thereby decreasing the BP levels (Nekkanti et al 2010a). Following oral administration, the drug CC is absorbed in Gastrointestinal Tract (GIT) and rapidly bioactivated to its active metabolite candesartan. From the active metabolite, only 20 to 30% are metabolized in the liver by cytochrome P450 isoenzyme, especially CYP2C9 and the rest 70 to 80% are excreted in an unchanged form. The drug CC showed very poor solubility within the physiological pH range that could result in incomplete intestinal absorption and very low systemic exposure leads to very poor bioavailability (15%) (Nekkanti et al 2009, 2010). Therefore, it is vital to find a new approach to enhance the oral bioavailability of CC. To facilitate this approach, Solid Lipid Microparticles (SLM) were designed to improve its bioavailability and the prepared SLM were further used to formulate controlled release compressed tablets and floating tablets.

1.2 GASTROINTESTINAL ABSORPTION

Absorption is defined by the rate at which the drug leaves the site of administration and the extent (bioavailability) to which it occurs. The absorption of a drug is dependent on the anatomy and physiology of the GIT, physiochemical properties of drug such as solubility, particle size, chemical form and the type of dosage formulation. Most drugs are absorbed by passive diffusion in the GIT, where the rate of absorption is proportional to the drug concentration gradient across the barrier. Alternatively, drugs can be absorbed by a combination of passive and active transport that can increase or decrease
the absorption depending on their location and whether they are influx or efflux transporters.

1.3 ORAL ADMINISTRATION

The oral route for delivery of pharmaceuticals is the most widely used and accepted. Moreover, oral route is the most convenient way for administration of drugs as it offers greatest degree of patient compliance. Oral drug delivery accounts for more than 50% share of the global drug delivery market and the sales of oral formulations is expected to reach $56.7 billion in 2012 for the US alone (Preshita et al 2012). Thus, development of orally effective novel drugs and technologies are mainstay of pharmaceutical research. The oral administration is very effective for drugs with high solubility and gastrointestinal permeability, the development of efficient oral delivery of poorly aqueous soluble drugs are very challenging. First pass metabolism of a drug can occur in the GIT and liver, prior to the drug reaching systemic circulation, resulting in a decreased bioavailability (Preshita et al 2012).

Oral drug delivery system can be differentiated as follows;

i) Modified release: Drug release occurs only after some time following administration to a specific target in the body. This system has been developed to optimize the bioavailability of the drug and to improve the pharmacokinetic profiles of active pharmaceutical ingredients.

ii) Immediate release: Drug is released immediately following administration and rapid adsorption has leads to the fluctuations in the plasma drug concentration.

Modified release also defined as “the dosage forms for which the drug release characteristics of time course or location are chosen to
accomplish therapeutic objectives not offered by the conventional dosage forms” (USP 2009). Modified release systems can be further classified as delayed release and extended release. Extended release systems allow the drug to be released over prolonged time periods. It can be achieved using sustained or controlled release dosage forms (Jones 2008).

Drug concentration at the site of activity within the body is compared between 4 injections of immediate release at 6 h intervals and single dose of controlled release formulation (Figure 1.1). The more fluctuations in drug plasma levels are observed in immediate release formulation. Whereas, the controlled release formulation is provided steadier levels drug plasma concentration.

Figure 1.1 Comparative plasma drug profile for immediate release and a zero order controlled release formulation

1.3.1 Controlled Release Drug Delivery System (CRDDS)

Controlled release technology is usually evolved with matrix or membrane technology. The objective behind the development of oral
controlled release formulations is to achieve constant release rate of the entrapped drug. On the basis of this concept, the zero order osmotic delivery system used in procardia XL became one of the top 10 bestselling medicines in the past century. From that point of time, the industry has seen a number of innovative oral controlled release dosage forms patented at a rapid pace (Nandita and Sudip 2003).

1.3.1.1 Advantages

**Patient compliance:** This can be achieved by administering once daily controlled release dosage form for reducing the dose, frequency of administration, toxicity and to maintain a steady state drug plasma concentration.

**Reduced 'see-saw' fluctuation:** Administration of drug with a conventional dosage form often results in ‘see-saw’ pattern of drug concentration in the systemic circulation and tissue compartments. These fluctuations depend upon drug kinetics such as the rate of absorption, distribution, elimination and dosing intervals. The 'see-saw' or 'peak and valley' pattern is more striking in case of drugs with biological half life less than 4 h. A well designed CRDDS can significantly reduce the frequency of drug dosing and also maintain a steadier drug concentration in blood circulation and target tissues.

**Reduced total dose:** CRDDS have repeatedly shown effective in control of the disease by utilizing less amount of the drug, thereby reducing the systemic and local side effects.

1.3.1.2 Disadvantages

**Dose dumping:** Dose dumping is a phenomenon where relatively large quantities of drug in a controlled release formulation is released rapidly,
introducing potential toxic quantities of the drug into the systemic circulation. Dose dumping can lead to fatality in case of potent drug which indicate a narrow therapeutic index.

**Less flexibility in accurate dose adjustment:** Dose adjustments are simpler in case of conventional dosage forms e.g. tablet can be divided into two fractions. On the contrary, dose adjustment appears to be much more complicated since property of the controlled release dosage form may get lost, if the dosage form gets fractured.

### 1.4 SOLID DISPERSION

Solid dispersion technique has been widely used to improve the solubility, dissolution rate and oral absorption of poor water soluble drugs (Suhagia et al 2006). In this technique, drug is dispersed in a biologically inert matrix to enhance oral bioavailability (Hasegawa et al 2005). It has many advantages for the poorly soluble and highly permeable drugs, which was categorized into Biopharmaceutical Classification System-II (BCS-II). Even though there are many ways to increase the aqueous solubility of poorly soluble compounds, including micronization and salt formation, solid dispersion is a viable method to improve the drug solubility. For many compounds, decreasing the particle size may not lead to a significant or adequate increase in bioavailability. Salt formation may also be problematic particularly with neutral compounds and weak acids. In solid dispersion the drug may be present in the amorphous state which offers an attractive means of increasing the solubility thus, potentially increasing the oral bioavailability of poorly soluble compounds (Figure 1.2) (Pikal et al 1978, Pouton 2006).
1.4.1 Advantages of Solid Dispersion

1.4.1.1 Particles with reduced size

Solid dispersion also called as molecular dispersion represents the least state on particle size reduction and after carrier dissolution the drug is molecularly dispersed in the dissolution medium. In which the drug release is achieved by creating a mixture of poorly water soluble drug and highly soluble carriers lead to the formation of high surface area, which results in increased dissolution rate and consequently improve bioavailability (Leuner and Dressman 2000, Kang et al 2004).

1.4.1.2 Particles with improved wettability

A strong contribution to the enhancement of drug solubility is related to the drug wettability improvement. It was observed that even carriers without any surface activity like urea or with surface activity such as bile salts and cholic acid improved drug wettability. Additionally, carriers can influence drug dissolution profile by direct dissolution or co-solvent effects. Hence, improved wetting may lead to reduced agglomeration and increased surface area (Pikal et al 1978).
1.4.1.3 Particles with high porosity

Particles in solid dispersion are found to have a higher degree of porosity. Increase in the degree of porosity depends on the carrier properties. Solid dispersion containing linear polymers produced larger and more porous particles than those containing reticular polymers. Increased pores particles resulted higher dissolution rate. The increased porosity of particles also hastens the drug release profile (Jain et al 2006).

1.4.1.4 Drugs in amorphous state

Poor water soluble crystalline drugs modified into amorphous state results in increased solubility. The enhancement of drug release can usually be achieved using the drugs in amorphous state and no energy is needed to break up the crystal lattice during the dissolution process. In this method, drugs are surviving as supersaturated solutions after system dissolution and it is speculated that drugs precipitate to metastable polymorphic form with higher solubility than that of the crystal form (Lloyd et al 1999, Pokharkar et al 2006, Dhirendra 2009).

1.4.2 Disadvantages of Solid Dispersion

The limitations of this technology are laborious, expensive methods of preparation and the amorphous nature may undergo crystallization due to mechanical stress, temperature and humidity (Mooter et al 2006).

1.4.3 Solid Dispersion by Fusion Method

The fusion method is also referred as the melt method. Sekiguchi and Obi (1961) were the first to use the melting method, which includes melting of the drug within the carrier followed by cooling and pulverization of the obtained product. Several processes such as solidification on Petri
dishes at room temperature, ice bath agitation, stainless steel thin layer spreading followed by a cold draught, spreading on plates placed over dry ice, immersion in liquid nitrogen were used. After cooling, the mixture must be pulverized. The fusion process is technically less difficult method of preparing dispersions provided the drug and carrier are miscible in the molten state. However, the use of high temperatures can degrade several drugs by melting process, which can be a limitation of this method (Greenhalgh et al 1999, Damian et al 2002).

1.4.4 Characterization of Solid Dispersion

A variety of techniques such as X-ray Diffraction (XRD), Differential Scanning Calorimetry (DSC), Scanning Electron Microscopy (SEM) and Fourier Transform Infrared (FTIR) spectroscopy have been used to identify the crystal form in a wide selection of dosage forms, including tablets, ointments, microsphere suppositories and capsules (Newman and Byrn 2003).

1.5 SOLID LIPID MICROPARTICLES

This drug delivery system is an innovative and appealing way to deliver drugs and bioactive compounds in a controlled fashion. It consists of particles (dimensional range microns) composed of a solid hydrophobic fat matrix in which the active drug compound is dissolved or dispersed (Cortesi et al 2002). SLM is usually prepared by different methods which including hot melt emulsification (Reithmeier et al 2001), solvent evaporation (Reithmeier et al 2001a), high pressure homogenization (Jaspart et al 2005), membrane emulsification (Doria et al 2009) and spray cooling/congealing (Passerini et al 2010).
In the present study, it has been decided to focus on SLM, a non-polymeric microcarriers constituted of lipid materials. From the literatures it was observed that extensive work has not been carried out with lipophilic excipients. Moreover, this kind of drug carrier provides many advantages. SLM can be considered as physicochemically stable (Trotta et al 2005), allowing a large-scale production at a relative low production cost (Cortesi et al 2002, Jaspart et al 2005).

1.5.1 Lipophilic Excipients

Over the last decade there has been a growing interest in lipid-based formulations to deliver challenging compounds such as lipophilic drugs. The unique characteristics of lipid-excipients as well as Lipid-Based Drug Delivery Systems (LBDDS) have presented many challenges to pharmaceutical research in all stages of drug development. Excipients are considered as inert substances that would be used mainly as diluents, fillers, binders, lubricants, coating agent and solvents in the manufacture of drug products (Chen 2008). Advances in pharmaceutical science and technology have facilitated the availability of a wide range of novel excipients. Most of the LBDDS use lipid vehicles or excipients to solubilize the hydrophobic drugs within the dosage form matrix. The lipids can also be digested and dispersed in the GIT (Kaukonen et al 2004).

Lipophilic drugs have poor bioavailability when administered orally as solid dosage form. It is mainly due to slow and incomplete drug dissolution in the GIT. The principal objective for a lipophilic drug is to achieve a formulation where the drug is dissolved in the lipophilic excipients and this is diluted by the surrounding physiological fluid once present in the GIT. During this dilution stage, the lipophilic drug may remain in the physiological solutions and may form a liquid dispersion which improves the bioavailability (Stuchlk and Stanislav 2001).
1.5.2 Mechanisms of Lipid-Based Formulations and Effects of Lipid-Based Excipients

The physical state of a lipophilic drug is important for the *in vivo* performance of any oral dosage form because the drug is generally solubilized in LBDDS. This is a crucial advantage for the delivery of lipophilic drugs, but it is not enough if solubilization capacity is lost upon aqueous dilution and dispersion. Further, LBDDS delivers a drug in solubilized form and maintains adequate solubilization during the gastrointestinal passage. Presence of the lipid-based excipients often increases drug solubility during *in vivo* and can foster supersaturation that is often sufficient for drug absorption (Kuentz 2012). There are three mechanisms by which lipids and lipophilic excipients can improve the bioavailability after oral administration such as,

- Alteration of the composition and character of gastrointestinal milieu
- Interaction with enterocyte-based transport and influence on drug uptake and efflux

Many lipid-based excipients such as glycerides, fatty acids, ionic and non-ionic surfactants are known permeability enhancers (Aungst et al 1993). The permeability enhancing effects may due to increased membrane fluidity or opening of tight junctions by excipients. Another mechanism of permeability enhancement is the interaction with efflux transporters. Substrates are expected to have increased permeability when the efflux pump is inhibited by excipients. Excipients with inhibiting effects on efflux pumps were found in the group of medium-chain glycerides, polyethylene glycols, polysorbates, polyethoxylated castor oil or block copolymers of the type
pluronic (Bogman et al 2003). Since, there are several mechanisms involved, it is challenging to predict the resulting biopharmaceutical effect of lipid-based excipients or formulations. In most cases, lipid-based systems exhibit positive effects on absorption of lipophilic drugs. These excipients demonstrate several mechanisms by which drug absorption is promoted (Kuentz 2012). Therefore, the present work is focused on lipid-based drug delivery using lipophilic excipients such as fatty alcohol, fatty acids, hydrogenated castor oil and polar wax.

1.6 FLOATING DRUG DELIVERY SYSTEM (FDDS)

FDDS is one of the gastroretentive dosage forms, which could prolong Gastric retention time (GRT) to obtain sufficient drug bioavailability (Arora et al 2005). FDDS is desirable for drugs with an absorption window in the stomach or in the upper small intestine (Singh and Kim 2000, Sato et al 2004, Talukder and Fissihi 2004). Prolonged gastric retention enhances bioavailability, improves solubility for drugs that are less soluble in a high pH environment and reduces drug waste (Palin 1985, Cargill et al 1988, Fix et al 1993).

The FDDS have a density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach. This leads to an increase in the GRT and better control over fluctuations in the plasma drug concentration (Whitehead et al 1998). In this context CC is a suitable drug for making controlled release floating tablets since it is absorbed in the GIT, where it is bioactivated by ester hydrolysis at the ester link converted to a active candesartan (McClellan and Goa 1998). The drug CC is also suitable for fusion method of solid dispersion due to its temperature insensitive and poor solubility in water. Designing of
floating dosage forms mainly include the single and multiple unit systems (Yang and Fassihi 1996).

1.6.1 Single Unit Dosage Form

Single unit dosage forms are easiest to develop but suffer from the risk of losing their effects too early due to their emptying from the stomach. Moreover, they may cause high variability in bioavailability and local irritation due to large amount of drug delivered at a particular site of the GIT (Whitehead et al 1998). Single unit formulations are associated with problems such as sticking together or being obstructed in the GIT which may have a potential danger of producing irritation.

1.6.2 Multiple Unit Dosage Form

Main purpose of designing multiple unit dosage form is developing a reliable formulation that has all the advantages over the single unit dosage form. In recent years, multiparticulate dosage form as matrix or coated pellets or micro particles have gained popularity for variety of reasons.

1.6.3 Classification of FDDS

FDDS are divided into effervescent and non-effervescent system, based on the mechanism of buoyancy.

Effervescent FDDS is further classified into

- Volatile liquid containing systems
- Gas generating system
Non-effervescent FDDS is also classified into
- Colloidal gel barrier systems
- Micro porous compartment system
- Alginate beads
- Hollow microspheres/microballons

1.6.3.1 Effervescent FDDS

This approach is based on the formation of Carbon Dioxide (CO₂) gas. Various effervescent compounds like sodium carbonate, calcium carbonate, tartaric acid and citric acid are utilized in this system. The CO₂ generating components may be mixed with the tablet matrix components, producing a single layered tablet (Hasim and Li 1987). The formulations when in contact with the acidic gastric contents, CO₂ is liberated and gets entrapped in swollen hydrocolloids (Sangekar 1987, Singh and Kim 2000). This produces an upward motion of the dosage form and maintains its buoyancy. A decrease in specific gravity causes the dosage form to float on the chime. Moreover, floating capsules by filling with a mixture of sodium alginate and sodium bicarbonate were shown to float during in vitro tests as a result of the generation of CO₂ that was trapped in the hydrating gel network on exposure to an acidic environment (Stockwell et al 1986).

1.6.4 Advantages of FDDS

- Administration of prolonged release floating dosage forms like tablets or capsules result in dissolution of the drug in the gastric fluid. They get dissolved in the gastric fluid and would be available for absorption in the small intestine after emptying of the stomach contents. Hence it is expected that a drug will be
fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine

- The gastroretentive systems are beneficial for drugs meant for local action in the stomach like antacids
- When there is a vigorous intestinal movement and a short transit time, which might occur in certain type of diarrhea, poor absorption is expected. In such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response

1.6.5 Limitation of FDDS

- It is not feasible for those drugs have solubility or stability problem in the GIT
- This system needs a high level of fluid in the stomach for drug delivery to float
- Some drugs present in the FDDS causes irritation to gastric mucosa

1.7 ANALYTICAL METHOD DEVELOPMENT AND VALIDATION

Analytical method development and validation play important roles in the discovery, development and manufacture of pharmaceuticals. The efficient development and validation of analytical methods are critical elements in the development of pharmaceuticals. Moreover, these processes are used by quality control laboratory to ensure the identity, potency, purity and performance of the drug products. Developing dissolution methods to poor soluble compounds have been consistent challenges for the pharmaceutical scientists. Due to inherently slow dissolution, poorly soluble
compounds are good candidates for developing *in vitro*/*in vivo* correlations. Further, intestinal permeability is high and drug dissolution is the controlling mechanism for the release of drug from the dosage form (ICH 2000). Drug absorption from a dosage form after oral administration depends on the release of the drug from the pharmaceutical formulation, dissolution and its solubilisation under physiological conditions and the permeability across the GIT. Due to the critical nature of drug release and permeability, *in vitro* dissolution may be relevant to the prediction of *in vivo* performance (Amidon et al 1995, Emami 2006).

Analytical method validation is the process to confirm that the analytical procedure employed for a specific test is suitable for its intended use. Food and Drug Administration (FDA) regulations such as Good Manufacturing Practice (GMP), Good Laboratories Practice (GLP), Good Clinical Practice (GCP) and quality standard of International Organization for Standardization (ISO 17025) require validation of analytical method before and during routine use (PDR 2009). Method validation is defined as the process of proving scientific studies, through an analytical method is acceptable for its intended use. Regulatory guidance for method validation is provided by USP (FDA 2000). Recent guidelines for methods development and validation for new non-compendial test methods is provided by FDA draft document (USP 2009) which covered the parameters of precision, accuracy, linearity, ruggedness, robustness, specificity, limit of quantitation and limit of detection.

Over the past decade, several published literatures reported that there is no validated method for dissolution and moreover no official monograph available for CC. Therefore, the present study covered, separate development and validation of new analytical methods for assay and
dissolution of CC by Reversed-Phase High Performance Liquid Chromatographic method (RP-HPLC).

1.8 RATIONALE OF THE STUDY

High Blood Pressure (HBP) is a serious condition that can lead to Cardiovascular Diseases (CVD) morbidity and mortality. There are several existing antihypertensive agents available for the management of HBP, majority of them having several untoward effects. The other important issue is patient non-compliance, which is common with any conventional dosage forms (Iosif and Jean 2005). Thus, management of HBP with the conventional dosage forms of the existing antihypertensive agents are challenging to the clinicians. These problems can be overcome by developing the modified release product of the existing molecules wherein (i) untoward effects can be minimized by lowering the peak plasma concentration coupled with better control of HBP by maintenance of more or less constant drug blood level and (ii) patient compliance can be improved by reducing the frequency of administration. Hence, the current study was designed to make controlled release formulation of CC.

The drug CC is a non-peptide selective blocker of the angiotensin II receptor subtype 1 is prescribed twice or once daily with total daily doses ranging from 8 to 32 mg for systolic heart failure, and the minimum starting dose is 2 mg. Following oral administration, CC showed low solubility across the physiological pH range is reported to result in incomplete absorption from the GIT and hence is reported to have an oral bioavailability of about 15% (Nekkanti et al 2010). Therefore, still it was a real problem to improve the intestinal absorption and oral bioavailability of CC. To overcome of this snag the present work was designed to formulate SLM of CC in controlled release drug delivery and floating controlled release tablets. Based on the dose calculation, the dose was fixed as 8 mg of Candesartan cilexetil in controlled
release dosage form and the formulation was designed to release 2 mg as initial dose and 6 mg as loading maintenance dose, which minimize the dose frequency, improved drug bioavailability and maintain the drug release over 24 h in the predetermined release manner.

The poor aqueous solubility of a drug leads to less solubilisation in the gastrointestinal fluids, low or variable bioavailability and poor in vitro/in vivo correlation. Lipids and lipophilic excipients are having a significant positive effect on the absorption of poorly soluble drugs after oral delivery. It alters the composition and character of gastrointestinal milieu and the stimulation of bile salts secretion caused emulsification of poorly soluble drug in the gastrointestinal fluid, thus enhances its in vivo solubility (Porter et al 2007). The lipophilic excipients are useful in dissolution enhancement as well as in controlled release formulations (Jaspart et al 2005). Hence, the present study was designed to use lipophilic excipients as carrier to improve the CC bioavailability. The formulations were designed to make controlled release SLM using lipophilic excipients to improve the drug bioavailability. To improve the patient compliance and ensure the drug release profile up to 24 h, the prepared SLM were further formulated into controlled release compressed tablets and floating tablets.

1.9 OBJECTIVES

The objectives of the present study were to develop and investigate controlled release solid lipid microparticles of CC to improve the bioavailability, reduce the dose and frequency of drug administration. Particular goals were:

i) Development and validation of RP-HPLC methods for estimation of drug content and in vitro release of CC.
i) Preparation and characterization of controlled release solid lipid microparticles of CC using various lipophilic excipients.

ii) Formulation and evaluation of controlled release compressed tablets of CC using formulated solid lipid microparticles.

iii) Preparation and *in vitro* characterization of floating tablets using the gas generation principle for CC.

iv) Drug release kinetics studies and mechanisms for the fabricated formulations of compressed tablets and floating tablets of CC.

v) Stability studies for the selected formulations of controlled release compressed tablets and floating tablets.

1.10 REVIEW OF LITERATURE

Marja et al (2002) formulated controlled release polar lipid microparticles of felodipine with various erodable lipophilic excipients like fats and waxes by spray chilling method. The prepared microparticles were characterised and concluded that the degree of felodipine crystallinity and tablet disintegration played a major role on the drug release rate than the matrix lipophilicity. The felodipine release rate was extremely slow from the least lipophilic cetyl alcohol and stearic acid tablets, less than 15% was released after 4 h, and equally low dissolution rate was obtained from the glycercyl palmitostearate tablets. Felodipine was released markedly faster from the most lipophilic but easily disintegrating carnauba wax tablets, 50% was dissolved after 4 h. Hydrogenated castor oil contained tablets showed less *in vitro* release though disintegrated easily. From the results, it was concluded that felodipine was released markedly faster from most lipophilic excipients.
Mamoru et al (2006) investigated the influence of sodium bicarbonate on the physicochemical properties of controlled release Hot Melt Extruded (HME) tablets containing Eudragit L100-55 and Eudragit L100. Acetohydroxamic acid and chlorpheniramine maleate were used as model drugs. Sodium bicarbonate was incorporated into the tablet formulations and the drug release properties and buoyancy in media for HME tablets and directly compressed tablets were investigated. The HME tablets prepared from the powder blend containing both Eudragit L100-55 and sodium bicarbonate exhibited sustained release properties and the tablets floated on the surface of the media for 24 h. The cross-sectional morphology of the HME tablets showed a porous structure since CO\textsubscript{2} gas was generated due to the thermal decomposition of sodium bicarbonate in the softened acrylic polymers at elevated temperature during the extrusion process. In contrast, all directly compressed tablets prepared in this study showed no buoyancy and rapid drug release in the dissolution media. The drug release rate from floating HME tablets was controlled by both the incorporation of Eudragit L100-55 into the matrix tablet and the diameter of the die used in the extrusion equipment. The drug release profiles and buoyancy of the floating HME tablets were stable when stored at 40 °C/75% RH for 3 months.

Amal et al (2007) prepared Testosterone (TS) SLM for transdermal drug delivery using various types and concentrations of fatty materials, namely glyceryl monostearate, glyceryl distearate, stearic acid and glyceryl behenate by emulsion melt homogenization method. The prepared microparticles were examined and \textit{in vitro} release study was performed for 24h. The results indicated that the type of lipid affected the morphology and particle size of SLM. Rheological studies and DSC examination revealed that the microparticles showed plastic flow characteristics and existed in amorphous form respectively. Almost all the SLM formulations followed Fick’s law than Higuchi model as indicated by the higher values of
coefficient of determination. It seemed that the release and transport of TS were affected not only by the concentration of lipid but also by the type of lipid used in the formulation. The choice of the type and lipid concentration can affect the final physicochemical and release characteristics of SLM formulation.

Rao et al (2007) have developed an isocratic reversed-phase liquid chromatographic method for quantitative determination of CC, both in bulk drug and in pharmaceutical dosage forms. Chromatographic separation was made on a 250 mm × 4.6 mm, 5 µ particle, cyano column with a 50:50 (v/v) mixture of phosphate buffer, pH 3.0 using acetonitrile as mobile phase at wavelength 210nm. Resolution of CC and six potential impurities was greater than two for all pairs of compounds. The drug was subjected to different stress conditions namely hydrolysis, oxidation, photolysis etc and the major product obtained as a result of basic hydrolysis was different from that produced by acid hydrolysis and aqueous hydrolysis. The stress samples were assayed and were found to be 99.6% and the method was validated. Quantitative analysis of CC and related substances in both bulk drug and pharmaceutical dosage forms is precise, accurate and specific.

Dalpiaz et al (2008) prepared SLM loaded with adenosine A<sub>1</sub> receptor agonist N<sup>6</sup>-Cyclopentyladenosine (CPA). The microparticles were produced by the conventional hot emulsion technique, using different lipids carriers (tristearin, glyceryl behenate and stearic acid) and hydrogenated phosphatidylcholine as the surfactant. The controlled release of CPA was achieved only with stearic acid microparticles. These SLM were characterized by release studies, SEM and X-ray Powder Diffraction (XRPD) analysis. The obtained particles showed proper features in terms of morphology and size distribution (3.2-10.3 µm). CPA presents remarkable challenges for
sustained release delivery systems with stearic acid used microparticles with greater stability.

Garg and Gupta (2009) formulated and evaluated acyclovir floating tablets for prolongation of gastric residence time. Floating effervescent tablets were formulated using various materials like Hydroxypropyl Methylcellulose (HPMC) K4M, K15M, psyllium husk, crospovidone, microcrystalline cellulose, gas generating agent like sodium bicarbonate, citric acid and were evaluated for floating properties, swelling characteristics and in vitro drug release studies. Floating non-effervescent tablets were formulated by polypropylene foam powder and different matrix forming polymers like HPMC K4M, Carbopol 934P, sodium alginate and xanthan gum. In vitro drug release studies were carried out and drug release kinetics was evaluated using the linear regression method found to follow both the Higuchi and the Korsmeyer-Peppas equation.

Gokce et al (2009) prepared metronidazole lipophilic matrix tablets with Cutina (hydrogenated castor oil), stearic acid, Compritol (glyceryl behenate) and Precirol (glycerol palmitostearate) in two different shapes namely cylinder and hexagonal. They investigated the influence of the lipid excipients and geometric shape on the release behaviour of metronidazole and the influence of tablet Surface Area/Volume (SA/V) ratio on drug release from controlled release matrix tablets. In vitro release test was performed, where stearic acid showed the highest release rates for both geometric shapes reflecting the highest surface area and the lowest SA/V ratio. Also, Higuchi kinetic constants obtained with hexagonal tablets were higher than the cylinder tablets. Like the type of lipid matrix, the geometry of the tablets also influence on the diffusion and release kinetics. This showed that surface area and volume ratio may be used as parameters for the evaluation of the drug release profile.
Mezzena et al. (2009) prepared budesonide SLM system containing oil in water emulsification followed by spray drying process. The SLM were studied and compared to conventional spray-dried crystalline and amorphous budesonide samples. The particle size distributions of the amorphous, crystalline, and SLM were found to be similar by laser diffraction study. On the other hand, the microparticles morphology was more irregular than the spray-dried drug samples. It is thermal response suggested polymorphic transition and melting of the lipid, glyceryl behenate (at ~48 °C and ~72 °C). No peaks were observed for budesonide melting or crystallisation, suggesting that the budesonide was incorporated into the matrix. In vitro dissolution of the formulations was studied using a flow through model and curves analysed using difference/similarity factors and fitted using the Higuchi model. Regression analysis were observed for amorphous, crystalline, and the solid lipid microparticles, respectively. Based on the observations, amorphous budesonide showed increased rate of dissolution when compared with crystalline budesonide.

Nekkanti et al. (2009) developed candesartan nanoparticles by wet bead milling technique and the solid-state properties of CC before and after milling were evaluated by XRPD and DSC analysis. The nanosuspensions (milled) were converted into solid intermediate by spray drying process and were characterized, indicated no phase transitions. The spray dried nanoparticles were blended with excipients for tableting. The rate and extent of drug dissolution in physiologically relevant dissolution medium for tablet formulation incorporating drug nanoparticles was significantly higher as compared to commercial tablet formulation. The results from in vitro studies indicated significant increase in the rate of drug dissolution in physiologically relevant dissolution medium.
Patel et al (2009) formulated verapamil HCl to increase the gastric retention time of the dosage form and to control its release. HPMC, Carbopol and xanthan gum were incorporated for gel-forming properties and effervescent mixture (sodium bicarbonate and anhydrous citric acid) were incorporated for buoyancy. *In vitro* drug release studies were performed and drug release kinetics was evaluated using the linear regression method. The optimized formula composed of 3:2 of HPMC K4M to xanthan gum showed 95.39% drug release in 24 h *in vitro*, while the buoyancy lag time was 36.2 s and the tablet remained buoyant for >24 h, which followed zero-order and non-Fickian drug release mechanism. Optimized intragastric floating tablet showed no significant change in physical appearance, drug content, total buoyancy time, or *in vitro* release pattern after storage at 40 °C/75% relative humidity for 3 months.

Nekkanti et al (2010) developed and characterized Self-Microemulsifying Drug Delivery System (SMEDDS) of CC for hard gelatin capsules. Four formulations were made using mixtures of oils, surfactants, and co-surfactants in different proportions. The self-microemulsification properties, zeta potential and droplet size of these formulations were studied upon dilution with water. The dissolution characteristics of SMEDDS filled into hard gelatin capsules was investigated and compared with liquid formulation and commercial formulation to ascertain the impact on self-emulsifying properties following conversion. The results revealed that solid intermediates showed comparable rate and extent of drug dissolution in a discriminating dissolution medium as liquid SMEDDS indicating that the self-emulsifying properties of SMEDDS were unaffected following conversion.

Shah et al (2010) developed and optimized a controlled release multiunit floating system of gatifloxacin using Gelucire 39/01, and Gelucire
Gatifloxacin lipid granules were prepared by the melt granulation technique and evaluated for \textit{in vitro} floating and drug release. Ethylcellulose was taken as release rate modifier. The moderate amount of Gelucire 39/01 and ethyl cellulose provides desired release of gatifloxacin from a floating system. The temperature sensitivity studies for the prepared formulations at 40°C/75% relative humidity for 3 months showed no significant changes during \textit{in vitro} drug release pattern. These studies indicated that the hydrophobic lipid Gelucire 39/01 can be considered an effective carrier for design of a multiunit floating drug delivery system for gatifloxacin.

Uhumwangho et al (2010) investigated drug release profile of Gastroretentive Drug Delivery System (GDDS) of diltiazem hydrochloride prepared with a hydrophilic polymer HPMC, hydrophobic polymer ethylcellulose and a waxy material carnauba wax. Formulations were either prepared alone with the individual polymer or admixed with carnauba wax, sodium bicarbonate 30% was incorporated as gas generating agent. Formulations contained carnauba wax was prepared by melt granulation technique. Drug release profile was compared with a commercial formulation of the drug. \textit{In vitro} buoyancy and \textit{in vitro} release studies were performed and the \textit{in vitro} release results further subjected to analysis four mathematic models such as zero order, first order, Higuchi and Korsmeyer-Peppas equations. Formulations prepared with carnauba wax showed more than 96% drug release for 12 h. Diltiazem drug release from the formulations showed Fickian diffusion mechanism.

Wadher et al (2010) designed oral sustained release metformin hydrochloride tablet formulation using lipophilic waxes such as hydrogenated castor oil, stearic acid and glyceryl monostearate either alone or their combinations. The \textit{in vitro} dissolution study was carried out using USP 22
apparatus I, basket method. The drug release kinetics demonstrated that hydrogenated castor oil sustained the release of metformin greater than stearic acid and glycercy monostearate when used alone. Combination of hydrogenated castor oil with stearic acid (1:1) sustained the drug release greater than hydrogenated castor oil with glycercy monostearate and stearic acid with glycercy monostearate combinations. Kinetic modeling of in vitro dissolution profiles revealed that metformin release ranges from diffusion controlled or Fickian transport to anomalous type or non-Fickian transport mechanisms. Applying Korsmeyer equation to in vitro drug release data indicated that diffusion along with erosion could be the mechanism of drug release.

Someshwar et al (2011) prepared tizanidine hydrochloride effervescent floating matrix tablets to prolong the gastric residence time in order to overcome its low bioavailability (34-40%). Tablets were prepared by direct compression method, using various viscosity grades of HPMC K4M, K15M and K100M and were evaluated for various physical parameters and floating properties. Further, in vitro drug release characteristics were studied for 12 h. Drug release from effervescent floating matrix tablets remain sustained over 12 h with buoyant properties. Based on the release kinetics, all formulations best fitted the first order model, Higuchi and non-Fickian as the mechanism of drug release.

Shah et al (2011) prepared ofloxacin controlled release matrix tablets by wet granulation technique to investigate the potential of ethylcellulose ether derivatives as a matrix material. Formulations using different types and grades of ethocel were prepared in different ratios. In vitro drug release studies were carried out using phosphate buffer (pH 7.4). A comparative study was performed between the tested ofloxacin-ethocel formulations and a standard reference obtained from the local market.
Dissimilarity factor (f1) and similarity factor (f2) were applied to the formulations for the checking of dissimilarities and similarities between the tested formulations and reference standard.

Based on the above furnished literatures, it was concluded that there was no work carried out in SLM of CC. Hence, our research focuses on the development of SLM to improve the CC bioavailability with reduced dose and frequency of administration.