Review Of Literature
2.1 BACKGROUND
Plants and animals have characteristic rhythms historically. In fourth century BC, Alexander the Great’s scribe Androsthenes noted that the leaves of certain trees opened during the day and closed at night showing a clear rhythmicity. In 1729, the French astronomer Jean Jacques d’Ortous deMairan conducted the first known experiment on biological rhythms (Pittendrigh et al., 1993). Since then, it has been proven that insects use photoperiodic information to bring their growth and dormant periods into harmony with seasons (Adkisson et al., 1966). The relationship between the dosing schedule and the 24 h rhythms of biochemical, physiological and behavioral processes also affect the effectiveness and toxicity of many drugs. A large number of texts have shown the basis behind chronotherapy (Smolensky and D’Alonzo, 1988; Redferm and Lemmer, 1997; Hrushesky et al., 1991). Circadian rhythms of behavior in mammals are known to be present (Krammer et al., 2001). The concept of chronopharmaceutics is to bridge the gap between the existing concept of chronobiology (Munger and Kenney, 2000; Hrushesky, 2001), chronopharmacology (Ritschel and Forusz, 1994; Auvil-Novak, 1999; Lemmer, 1997; White and LaRocca, 2002), chronopharmacokinetics (Lemmer and Bruguerolle, 1994; Smolensky et al., 1987), and chronotherapeutics (Anwar and White, 1998; Carter, 1998; Glasser, 1999; Poirier et al., 1999).

2.2 CIRCADIAN TIME STRUCTURE
One means of illustrating the human circadian time structure is to depict the peak time of 24 h rhythms on a clock-like diagram that shown in Fig. 2.1 (Smolensky and Bing, 1997). The circadian rhythm (CR) of white blood cell (WBC), thyroid stimulating hormone (TSH), growth hormone (GH), melatonin, prolactin, atrial natriuretic peptide (ANP), eosinophil and lymphocytes in blood peaks between bedtimes and early hours of sleep. CR in the blood level of adrenocorticotropic hormone (ACTH), follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone, cortisol, catecholamine, rennin activity, aldosterone and angiotensin peak near the end of night time sleep and start of
day time activity. CR of hemoglobin and serum iron peak around mid-day and total serum proteins and forced expiratory volume peak in the afternoon.

It is also evident from the Fig. 2.1 that CR of body temperature, respiratory rate and level of insulin, cholesterol and triglycerides peak late in the afternoon while those of urine production, forearm blood flow, neutrophils, basal gastric acid production and calcitonin gene related peptide (a vasodilator) peak early night span. Together, the phasing (peak time) of these and numerous other 24 h rhythms in biological processes make up the circadian time structure of human beings. This gives rise to day-night pattern in disease activity, with the potential for varying in time requirements for pharmacotherapy, as well as administration-time differences in the kinetics and dynamics of medications.

![Human Circadian Time Structure](image-url)

**Fig. 2.1: Human circadian time structure (Smolensky and Bing, 1997)**
2.3 CIRCADIAN RHYTHM AND DISEASES

Chronobiological studies have established circadian rhythm for almost all body functions, eg. heart rate, blood pressure (BP), body temperature, plasma concentration of various hormones, gastric pH and renal functions. It has become evident that rhythmic processes are important for treatment of human diseases (Fig. 2.2).

Different attributes of the cardiovascular system (e.g. BP, heart rate, cardiac output) are subject to circadian rhythms. The circadian pattern of BP has been well recorded (Fig. 2.3) (Millar-Craig, 1978; Drayer et al., 1985). BP is at its lowest during the sleep cycle and rises sharply during the early morning awakening period.

Fig. 2.2: Diseases displaying circadian rhythm (Smolensky and Portaluppi, 1999)
Fig. 2.3: Pathophysiologic changes accompanying the morning surge (Millar-Crag et al., 1978)

Most patients with essential hypertension have circadian rhythm of BP similar to normotensive persons, although hypertensive patients have comparatively higher shift in the BP profile (Drayer et al., 1985). Capillary resistance and vascular reactivity are higher in the morning and decrease later in the day. Platelet aggregability is increased and fibrinolytic activity is decreased in the morning, leading to a state of relative hypercoagulability of the blood (Fig. 2.4) (Tofler et al., 1987; Lemmer, 1992; Mismetti et al., 1995; Anwar and White, 1998).
It was showed that taking account of circadian in the treatment of cardiovascular diseases may lead to the reduction of adverse cardiac events (Tofler et al., 1987; Muller, 1989).

Many studies have shown an increase in the incidence of early morning myocardial infarction, sudden cardiac death, stroke and episodes of ischemia (Muller, 1989).

**Duodenal ulcer:** Gastric acid secretion is highest at night (Moore and Englert Jr, 1970; Cloud and Offen, 1992) while gastric motility and emptying are slower at night recommending slow walk after dinner. These have important implications in the pharmacokinetics of orally administered drugs. At night time, when gastric motility and emptying are slower, drug disintegration, dissolution and absorption may be slower (Sanders and Moore, 1992). In peptic ulcer patients, gastric acid secretion is highest during the night. Suppression of nocturnal acid is an important factor in ulcer healing. Therefore, for duodenal ulcer, once daily dose of H₂ antagonists at bedtime is recommended dosage regimen (Humphries and Root, 1991; Cloud and Offen, 1992).

The role of circadian rhythms of **asthma** indicates that airway resistance increases progressively at night in asthmatic patients (Martin and Banks-Schlegel, 1998). Circadian changes are also seen in normal lung function, which reduces in the early morning hours.
This fall in lung function is particularly obvious in people with asthma. Because bronchoconstriction and exacerbation of symptoms vary with circadian pattern so asthma is well appropriate for chronotherapy. Chronotherapies have been studied for asthma with oral corticosteroids, theophylline, and β2-agonists (Arkinstall, 1988; Kraft and Martin, 1995; Martin and Banks-Schlegel, 1998).

Patients with **rheumatoid arthritis** have a circadian rhythm in the plasma concentration of C-reactive protein (Herold and Gunther, 1987) and interleukin-6 (Arvidson et al., 1994). Many of drugs used to treat rheumatic diseases have varying therapeutic and toxic effects according to the time of administration (Vener and Reddy, 1992). The chronotherapeutics of pain was extensively reviewed (Auvil-Novak, 1999). Patients with osteoarthritis are prone to have less pain in the morning and more at night, while those with rheumatoid arthritis have pain that usually at its peak in the morning and decreases throughout the day. Chronotherapy for all forms of arthritis using NSAIDs should be administered in such a manner that the highest blood levels of the drug match with peak pain. For osteoarthritic patients, the optimal time for a drug such as ibuprofen would be around noon or mid afternoon. The same drug would be more effective for people with rheumatoid arthritis when taken after the evening food.

The work done by Haus et al., 1972 on **leukemic** mice demonstrated that the circadian chemotherapy timing significantly affects drug toxicity patterns, tumor response quality and the survival of patients with cancer. Human and animal studies suggested that chemotherapy may be more effective and less toxic, if cancer drugs are administered at carefully selected times that take advantage of tumor cell cycles while less toxic to normal cells (Hrushesky, 1985; Hrushesky and Bjarnason, 1993; Wood and Hrushesky, 1996). The blood flow to tumors and tumor growth rate are each up to three fold greater during each daily activity phase of the circadian cycle than during the daily rest phase (Hori et al., 1996). The chronotherapeutic approach for cancer may add improvements in current cancer treatment strategies and in the development of new anticancer drugs (Levi, 2001).
Synthesis of cholesterol in liver follows circadian pattern (Mayer, 1976; Hulcher et al., 1985). It has been recommended through a study conducted by Stein et al., 1998 that evening dosing schedule of HMG CoA reductase inhibitors was more effective than morning dosing for the treatment of hypercholesterolemia. Since, there is a large variation in plasma mevalonate concentrations among individuals. Therefore cholesterol synthesis is normally higher during the night than daytime. However, the maximal production occurs early in the morning, i.e. 12 h after the last meal (Goff et al., 2001).

Elaborate studies have been carried out to investigate circadian variations of glucose and insulin in diabetic patients (Rigas et al., 1968; Malherbe et al., 1969; Castillo et al., 1983; Verrillo, 1984; Cincotta and Meier, 1984; Waldhausl, 1989). The aim of insulin therapy is to take off the normal physiologic pattern of endogenous insulin secretion in healthy individuals as well as secretion after meal. Exogenously administered insulin to diabetic patients inhibits hepatic glucose production (Hirsch, 1999).

Circadian studies also showed that chronobiology permits the development of new theoretical concepts in the field of neurological science (Poirel and Ennaji, 1991; Poirel and Ennaji, 2000). Circadian rhythm of noradrenaline in adrenergic nerve terminals in the brain region (Ziegler et al., 1976) and human sleep, its duration and organization (Czeisler et al., 1980) are well known facts. A chronopharmaceutical formulation against insomnia that addresses the entire oscillatory cycle of human sleeping process may prove a boon in the field of neuroscience.

2.4 CHRONOPHARMACEUTICS

It is imperative to know the concepts of chronobiology and pharmaceutics prior to be familiar with chronopharmaceutics. Chronobiology is the study of biological rhythms and their mechanisms. Biological rhythms are defined by a number of characteristics (Smolensky and D’Alonzo, 1988). The term ‘circadian’ was derived from the Latin term circa, meaning about, and dies, meaning day. Oscillations which are of shorter duration (more than one cycle per 24 h) are ‘ultradian’. Oscillations which are longer than 24 h (less than one cycle per 24 h) are ‘infradian’ rhythms. Ultradian, circadian, and infradian
rhythms coexist in biologic systems (Smolensky and D’Alonzo, 1988). Simply, a drug delivery means to get absorbed a drug predictably from the site of application. A modified drug delivery system delivers the bioactive agents continuously at a constant rate (zero-order). However, living organisms are not ‘zero-order’ in their response to drugs. They are rhythmically varied systems, which require different amount of drug at different times within the circadian cycle in order to maximize desired and minimize undesired drug effects (Hrushesky, 2001). Chronopharmaceutics is a branch of pharmaceutics devoted to the design and evaluation of drug delivery systems that release a bioactive agent at a rhythm that ideally matches the biological requirement of a given disease therapy. Ideally, chronopharmaceutical drug delivery systems (ChrDDS) should embody time-controlled and site-specific drug delivery systems (Bussemer, 2001).

2.5 CHRONOPHARMACEUTICAL DRUG DELIVERY SYSTEMS

The category of controlled release formulations can be divided into subgroup of rate controlled release, delayed release and pulsed release formulations. Delayed release formulations include time-controlled release and site-specific dosage forms. When constant drug plasma level need to be avoided, as in chronopharmacotherapy, time controlled or pulsed release formulations are preferable, especially in the treatment of early morning symptoms. So that peak plasma concentration is obtained at optimal time and number of dosage per day can be reduced. Saturable first pass metabolism and tolerance development can also be avoided.

Various technologies to develop time-controlled drug delivery systems have been extensively studied in the past. Currently key technologies in chronopharmaceutics includes: Physicochemical modification of the active pharmaceutical ingredient (API), CONTIN®, TIMERx, OROS®, CODAS®, DIFFUCAPS®, CEFORM®, chronomodulating infusion pumps, three dimensional printing, controlled release erodible polymer and controlled release microchip strategies.

Through **physico-chemical modification of the API** approach, the physicochemical properties (e.g. solubility, partition coefficient, membrane permeability etc.) of the drug
are modified to attain the chronopharmaceutical objective. Antiulcer agents (H₂ receptor antagonists) (Humphries et al., 1991) and antihyperlipidemic statins (HMG-CoA reductase inhibitors) (Stein et al., 1998) are examples which have been formulated for chronotherapy. Lovastatin (m.p. 174.5°C) has been converted to simvastatin (m.p. 135-138°C) by introducing a methyl group. Physicochemical modifications affect Tₘₐₓ that increases from 2 to 4 h for lovastatin and simvastatin, respectively.

Lovastatin may be modified to simvastatin in the liver. Thus, prodrug approach may also be used to obtain a ChrDDS of improved solubility of active form (Mahley and Bersot, 2001).

In CONTIN technology, the complex between a cellulose polymer and a non-polar solid aliphatic alcohol is used as a matrix in controlled release formulations since it has a uniform porosity. This technology has been used for the development of tablet forms of sustained-release aminophylline, theophylline and morphine. Asthmatic patient’s exhibit increased bronchoconstriction in the early morning. Thus, evening administration of once-daily theophylline may block the morning dip in lung functions (Leslie, 1986).

The TIMERₓᴿ (Hydrophilic system) technology combines xanthan, locust bean gum and dextrose. The physical interactions between these components form a strong, binding gel in the presence of water. Drug release is controlled by the rate of water penetration from the gastrointestinal tract into the TIMERₓᴿ gum matrix, which expands to form a gel and subsequently releases the active drug substance. This system can be prepared in a tablet dosage form. A clinical trial of a chronotherapeutic formulation containing a bioactive agent (AD 121) is being tested against rheumatoid arthritis. This technology has been utilized earlier in the development of an oral, CR opioid analgesic oxymorphone (Endo/Penwest, 2003).

OROSᴿ technology is based on osmotic pressure to provide pre-determined drug delivery to the gastrointestinal tract (Jao et al., 1992). In this, the drug is placed in a reservoir, surrounded by a semi-permeable membrane made up of cellulose esters or cellulose ethers in the form of tablet. The tablet is divided into two layers, an active drug layer and a layer of osmotically active agents e.g. polyethylene oxide and sodium
chloride. When water from the gastrointestinal tract diffuses through the membrane at a controlled rate into the tablet core, it causes the drug to be released in solution or suspension at a predetermined rate. This creates a 'pump' effect that pushes the active drug through a hole in the tablet. This technology, especially the OROS\textsuperscript{R} Delayed Push–Pull System, also known as controlled onset extended release (COER) was used to design Covera- HS\textsuperscript{R}, a novel antihypertensive product. It actually enabled delayed release of verapamil to prevent the surge in BP that can occur in the early morning (White \textit{et al.}, 1997, Glasser, 1999).

The Chronotherapeutic Oral Drug Absorption System (CODAS\textsuperscript{R}) is a multiparticulate system which is intended for bedtime drug dosing, incorporating a 4-5 h delay in drug delivery. This delay in drug delivery was obtained by using non-enteric release-controlling polymers onto drug loaded beads. The release controlling polymer is a combination of water soluble and water insoluble polymers. As water from the gastrointestinal tract comes into contact with the polymer coated beads, the water soluble polymer slowly dissolves and the drug diffuses through the resulting pores in the coating. The water insoluble polymer continues to act as a barrier, maintaining the controlled release of verapamil (Prisant \textit{et al.}, 2000). The rate of release is essentially independent of pH, posture and food. The nighttime dosing regimen of (CODAS\textsuperscript{R}-verapamil) was not associated with excessive BP reductions during the sleeping hours. The CODAS\textsuperscript{R}-verapamil extended release capsules (Verelan\textsuperscript{R} PM) as ChrDDS actually provided enhanced BP reduction during the morning period when compared with other time intervals of the 24 h dosing period (Smith \textit{et al.}, 2001).

DIFFUCAPS\textsuperscript{R} technology comprises of drug-containing particles (beads, pellets, granules etc.) in a unit dosage form such as a capsule for delivering drugs into the body in a circadian fashion. Each bead population exhibits a pre-designed rapid or sustained release profile with or without a predetermined lag time of 3-5 h. The active core part may comprise an inert particle which is coated with a drug containing water-soluble film made up of hydroxypropyl methylcellulose (HPMC) or polyvinyl pyrrolidone (PVP). Such a ChrDDS is considered to provide a plasma concentration-time profile, which
varies according to physiological need during the day i.e. mimicking the circadian rhythm of cardiovascular diseases. This technology has been used to formulate the FDA approved propranolol-containing ChrDDS (Innopran\textsuperscript{R} XL) for the management of hypertension (FDA, 2003).

The CEFORM\textsuperscript{R} technology is used to prepare microspheres by combining the drug and polymer along with physical parameters such as temperature, thermal gradients, mechanical forces, flow and flow rates via a melt-spinning process. The CEFORM\textsuperscript{R} technology allows the production of uniformly sized and shaped microspheres. The microspheres can be used in various types of dosage forms such as tablets, capsules and effervescent tablets. The microspheres may be coated for controlled release with an enteric coating or fast/slow releasing polymer combinations. This technology has been actually used to develop Cardizem\textsuperscript{R} LA, once a day diltiazem formulation as ChrDDS (Verma and Sanjay, 2001).

Chronomodulating infusion pumps work based on enzymatic or hydrolytic degradation, pH, magnetic fields, ultrasound, electric fields and temperature. Thus they can be controlled externally and internally (Sershen and West, 2002). These pumps have been effectively used in the chronotherapy of a number of diseases such as cancer and diabetes (Levi \textit{et al}., 1997; Pickup and Williams, 2000).

Oral drug delivery systems may be prepared by utilizing \textbf{three-dimensional printing\textsuperscript{R} (3DP) technique}. A device can be framed with complicated internal geometries, varying densities, diffusivities, and chemicals (Katstra \textit{et al}., 2000). Various oral drug delivery systems such as immediate, extended release tablets, pulse release and dual pulsatory tablets have been prepared using the 3DP process. The enteric dual pulsatory tablets were made up of one continuous enteric excipient phase into which diclofenac sodium was printed into two separated areas. These samples showed two pulses of release during \textit{in vitro} with a lag time between pulses of about 4 h (Rowe \textit{et al}., 2000).

Different dosage forms such as tablets, capsules and microparticles have been prepared using \textbf{controlled release erodible polymers} for ChrDDS applications. A chronopharmaceutical capsule drug delivery system has been reported by Ross \textit{et al}.,
2000. The drug formulation is sealed inside the insoluble capsule body by an erodible tablet that is composed of an insoluble (e.g. dibasic calcium phosphate) and gel-forming (e.g. hydroxypropyl methylcellulose) excipient. The time-delayed release of a model drug (propranolol HCl) evaluated through in vitro dissolution study depends on both the composition and weight of erodible tablet. Programmable pulsatile release has been achieved from a capsule device over a 2-12 h period.

A microchip of solid-state silicon provides controlled release of active substances on demand using micro fabrication technology (Santini et al., 1999). The release mechanism was based on the electrochemical dissolution of thin anode membranes covering microreservoirs filled with chemicals in solid, liquid or gel form. Initially a pulsatile release studies of poly(L-lactic acid), radiolabelled dextran, human growth hormone or heparin in vitro was carried out using gold and saline as model electrode material and release medium respectively (Richards et al., 2003). This technology has the potential to be used in the design of ChrDDS with a better control to match biological requirement over a period of time.

**2.6 PRESS-COATED TIMED RELEASE TABLETS**

![Diagram of press-coated core tablet]

**Fig. 2.5: Design of press-coated core tablet**

Press-coating of dosage forms has a long history. Interest in press-coated tablets became widespread between 1950s and 1960s. Press-coated formulations can be used to protect
hygroscopic, light sensitive, oxygen labile or acid labile drugs to separate incompatible drugs from each other or to achieve sustained release (Ritschel et al., 1990).

To achieve time-controlled delivery a press-coated formulation containing a swellable core and a less water permeable coat has been developed whereas core contained drug and disintegrating agent. The outer shell delays commencement of drug release. A melted blend of hydrogenated castor oil and polyethylene glycol 600 has been used for coating. Lag times depend on the composition of the blend used for coating (Ishino et al., 1992).

In recent years, various controlled release, especially time controlled release drug delivery systems based on compression-coating technology have been studied. Mostly such formulations release drug after a lag phase. Such press-coated formulations comprised of the inner core containing the drug and the outer core is made of different types of polymers. The outer barrier controlling drug release can be either swellable or erodible. Lag time can be varied by changing the barrier formulation or the coating thickness (Conte et al., 1992, 1993).

A time-controlled explosion system (TES) was developed. TES has a four layered spherical structure, which consists of inert core, drug, swelling agent and water insoluble polymer membrane. TES is characterized by a rapid drug release with a precisely programmed lag time i.e. expansion of the swelling agent by water penetrating through the outer membrane, destruction of the membrane by stress due to swelling force and subsequent rapid drug release. TES was designed using metoprolol and polystyrene balls as a model drug and core particles, respectively. The release profile of the metoprolol from the system was not affected by the pH of the dissolution media. Lag time was controlled by the thickness of the outer EC membrane, thus, a combination of TES particles possessing different lag times could offer desired release profile of the metoprolol (Ueda et al., 1994).

Intermittent release can also be achieved by incorporating one portion of a drug in the core and the other in the coat. Press-coating is relatively simple and cheap technique. Compression-coating can involve direct compression of both the core and the coat, obviating needs for separate coating process and use of coating solutions. Materials such
as hydrophilic cellulose derivative can be used. Compression is easy on laboratory scale while for large scale manufacture, special equipment is needed. The major drawbacks of the technique are that relatively large amounts of the coating materials are needed and it is difficult to position the core part correctly (Gazzaniga et al., 1994).

A formulation comprising diltiazem hydrochloride has been developed which was intended for the treatment of time-related symptoms of ischaemic heart disease and hypertension. The tablet consisted of a drug containing core and a coat formed by compressing hydroxyethyl cellulose. Diltiazem was rapidly released after a lag of several hours. Lag time could be controlled primarily by changing the thickness of the outer polymer shell (Matsuo et al., 1995).

The influence of critical formulation and processing variables on scale up of oral extended-release dosage forms, using hydrophilic polymer hydroxypropyl methylcellulose (methocel K100LV) was studied. Results showed that the percent metoprolol release was found to be significantly reduced by an increase in polymer level from 10 to 50%. Increase in lactose level was found to increase lag period. The effects of magnesium stearate and lubricant blend time were not found to be statistically significant (Rekhi et al., 1999).

Pharmaceutical composition in the form of a sustained release coated tablet having an inner core and an outer coating. Inner core comprising of pseudoephedrine sulphate and other excipients while outer coat comprising of HPMC and HPC along with drug. This was claimed for the effective treatment of sinusitis and sinus headache, generally exemplified by discomfort, pain, pressure and dizziness (Chris et al., 1999).

Press-coated tablets containing diltiazem hydrochloride in the core tablet and coated with hydroxypropyl cellulose (HPC) as the outer shell, were developed for investigating HPC applicability as timed-release tablets with a predetermined lag time and subsequent rapid drug release phase. The results indicated that tablets with the timed release function could be prepared and that the lag times were prolonged as the viscosity of HPC and the amount of the outer shell were increased (Fukui et al., 2000a).
Enteric coated timed release press-coated tablets were formulated by coating enteric polymer on timed-release press-coated tablets composed of an outer shell of hydroxypropyl cellulose and core tablet containing diltiazem. The results indicated that tablets showed acid resistance and time-released functions on in vitro dissolution tests and applicability in the field of chronopharmacotherapy (Fukui et al., 2000b). Pulsatile release tablets could suppress release of diltiazem hydrochloride in stomach and release it in intestine rapidly after a predetermined lag time of about 3 h. Ethylcellulose/Eudragit L were employed for film coating of the tablets. It was concluded that the lag time \(t_{10\%}\) was prolonged with an increase of the coating level, whereas the drug release rate was almost constant, irrespective of the coating level (Fan et al., 2001). An attempt was made to achieve chronopharmacotherapy for asthma, press-coated tablets which contained aminophylline in the core part with low substituted hydroxyl propyl cellulose (L-HPC) and coated with microcrystalline cellulose (Avicel PH-102) and polyethylene glycol (PEG). Their applicability as timed release (delayed release) and subsequent rapid drug release phase was investigated. These results suggested that the press-coated aminophylline tablets offers promising chronotherapy for asthma (Watanabe et al., 2002).

It was claimed that a unit dosage form formulation such as a capsule delivered drug into the body in a circadian fashion. It comprised of one or more populations of propranolol-containing particles (beads, pellets, granules etc.). Each bead population exhibits a pre-designed rapid or sustained release profile with or without a predetermined lag time of 3 to 5 h. This drug delivery system was designed to provide a plasma concentration-time profile according to pathophysiological condition during the day, i.e. mimicking the circadian rhythm and severity/manifestations of cardiovascular diseases, predicted based on pharmacokinetic and pharmacodynamic considerations and in vitro-in vivo correlation (Percel et al., 2002).

Bioavailability of compression coated tablets was improved by changing composition of the core part of compression coated tablets. The effect of their composition in compression coated tablet on in vivo pharmacokinetics was investigated. The results
showed that adding excipients with high water solubility to the core results in a greater core erosion ratio and reported formulation with a large core erosion ratio can significantly increase in vivo drug release from compression-coated tablets, leading to increased acetaminophen absorption from the lower GI tract (Sawada et al., 2003).

Polymer matrix tablet containing a core of drug was designed for obtaining a time-controlled release profile characterized by an initial phase of lag time followed by a zero order kinetics. The spherical central core was formed by a solid dispersion of the drug in hydrophilic polymer PEG 4000, which enabled an improvement of drug dissolution properties. Eudragit RS 100 mixed with sodium chloride and Emdex (channeling agent) and it was used as inert polymeric matrix for the core coating. Lag time increased with reduction of the particle size of channeling agent because of smaller pores formed by its dissolution (Gonzalez-Rodriguez et al., 2003).

Time and pH dependent colon specific drug delivery systems (CDDS) for orally administered diclofenac sodium (DS) and 5-aminosalicylic acid (5-ASA) were investigated. DS tablets and 5-ASA pellets were coated by EC and methacrylic acid copolymers (eudragit L100 and S100), respectively. Results showed that release profile of time-dependent coated tablets were not influenced by pH of the dissolution medium, but the lag time of drug release was primarily controlled by the thickness of the coating layer. It was concluded that two types of CDDS, prepared by mean of the regular coating technique, were able to achieve site-specific drug delivery targeting at colon following oral administration and provide a promising strategy to release the drug in lower gastrointestinal region (Cheng et al., 2004).

Dry coated tablets of diclofenac sodium containing ethylcellulose (EC) with optimal lag time were designed. Whole layer of the outer shell of tablets were prepared by employing different ratios of coarse (167.5µm) and fine particles (<6 µm) of EC. It influenced the release behavior of the diclofenac sodium from dry-coated tablets. The results indicated that diclofenac sodium released from all the dry coated tablets exhibited an initial lag period, followed by rapid drug release. When the lower layer in the outer shell was composed of EC powder (coarse) and the upper layer was formulated by mixing different
weight ratios of coarse and fine powders of EC, the drug release also exhibited a time controlled disruption behavior (Lin et al., 2004).

Tablets consisting of cores coated with two layers of swelling and erodible coatings was prepared and evaluated for pulsatile behaviour. Cores containing buflomedil HCl as model drug were prepared by direct compression and were then coated sequentially by an inner swelling layer containing a superdisintegrant (cross carmellose sodium) and an outer rupturable layer of EC. The results showed that the lag time of the tablets decreased with increasing amount of microcrystalline cellulose in the core and increased with increasing thickness of both swelling layer and rupturable ethylcellulose coating. It was concluded that the lag time of the system could be modified by several factors such as core composition, level of swelling layer and rupturable coating and addition of magnesium stearate to rupturable layer (Sungthongjeen et al., 2004).

A delayed release oral solid dosage form, comprising a core containing drug and xanthan gum and locust bean gum as compression coating material was claimed by Anand et al., 2004. The compression coating material delayed the release of drug from dosage form.

Pharmacokinetics of an immediate release, a controlled release and two pulse dosage form of metoprolol tartrate in dogs were studied. Metoprolol was chosen as a model drug because of its high solubility and high permeability pattern throughout the GI tract. The dosage forms were administered to four dogs and the plasma levels were measured using LC-MS/MS. The comparison of the plasma level-time curves of the dosage forms showed significant difference in the drug plasma levels. The pulsatile drug delivery capsules caused two defined $C_{\text{max}}$ values and offer a promising way for chronopharmacotherapy if the time of administration and pulse time are adjusted to the circadian pattern (Lobenberg et al., 2005).

Modified release press-coated tablets of venlafaxine hydrochloride were prepared using hydroxypropyl methylcellulose K4M and hydroxypropyl methylcellulose K100M as release modifier in core and coat, respectively. A $3^2$ full factorial design was adopted for optimization. The drug to polymer ratio in core and coat were chosen as independent
variables. The drug release in the first hour and drug release rate between 1 and 12 h were chosen as dependent variables. The kinetics of drug release was best explained by Korsmeyer-Peppas model and followed anomalous non-Fickian diffusion (Gohel, 2008). The gastric retentive and chronopharmacologic drug delivery tablets were prepared by press-coated techniques. The effects of formulation and techniques of coating layer on release characteristics of the drug were investigated by dissolution testing. The mechanism of drug release was proved by erosion test. The lag-time was prolonged with the increase of the ratio of HPMC/carrageenan and the amount of matrix material in coating layer. Coating layer erosion and tablet core swelling were involved in the mechanism of drug release (Zhang et al., 2009).

The practicability of a pulse-echo ultrasonic approach developed for the real-time quality monitoring of dry-coated tablets in the tablet press during compaction was evaluated. It was demonstrated that the reflection of an ultrasonic pulse generated by a transducer embedded in a die or a punch from the coat-core interface can be acquired by the same transducer (Liu et al., 2011).

2.7 OVERVIEW OF DRUGS

2.7.1 METOPROLOL TARTRATE

The effect of critical variables of scale-up on the performance of an extended release tablet of metoprolol tartrate prepared by using methocel K100 was evaluated. Variables studied were filler ratio (Lactose: dicalcium phosphate (50:50), polymer level (15/32.5/50%), magnesium stearate level (1/1.5/2%), lubricant blend time (2/6/10 min) and compression force (400/600/800 kg). Increased level of dicalcium phosphate and compression force was found to significantly reduce the percentage release (Q) of the drug. Increased level of lactose was found to increase Q (Rekhi et al., 1999).

The effect of once daily metoprolol succinate CR/XL on mortality, hospitalization and tolerability in patients with severe heart failure was analyzed. The study showed that patients with severe heart failure showed reduction in hospitalization for worsening heart
failure with metoprolol CR/XL treatment as compared to those of included in the total studies (Goldstein et al., 2000).

Peak plasma level produced by metoprolol 200 mg CR/XL was compared to those of 50 mg immediate release. Metoprolol CR/XL 200 mg was associated with a more pronounced suppression of heart rate than metoprolol 50 mg. It was suggested that patients can safely be switched from multiple dosing to a once daily-dose dose of metoprolol CR/XL (Anderson et al., 2001).

Bioadhesive sodium alginate microspheres of metoprolol tartrate for intranasal systemic delivery were prepared to avoid the first-pass effect and to obtain improved therapeutic efficacy in the treatment of hypertension and angina pectoris. The formulation variables were drug loading, polymer concentration, cross-linking agent concentration and cross-linking time. The microspheres were evaluated for particle size, incorporation efficiency, swelling ability, *in vitro* bioadhesion, *in vitro* drug release and *in vivo* performance in rabbits. Kinetic assessment of *in vitro* data indicated matrix-diffusion controlled drug delivery. Concentration of polymer and crosslinking agent and crosslinking time affected the drug release profiles significantly. *In vivo* studies indicated significantly improved therapeutic efficacy of MT from microspheres as compared with oral and nasal administration of drug solution (Rajnikanth et al., 2003).

A study was carried out to investigate the effect of food on relative bioavailability of rapidly dissolving drugs from immediate release dosage forms, thereby supporting the hypothesis that rapidly dissolving immediate release solid oral products containing a BCS class I drug (metoprolol tartrate) are likely to be bioequivalent under fed conditions (Yu, et al., 2004).

The effect of metoprolol on cardiac functions in children with heart failure was assessed. Randomized double-blind placebo controlled clinical trial was performed in children with heart failure due to left ventricle volume overload structural heart disease. Metoprolol caused improvement of cardiac systolic and diastolic function in children with heart failure due to cardiac defect. Therefore, metoprolol was recommended in patients with
heart failure who have not been controlled adequately by therapy of an inotrope, a diuretic and a vasodilator agent (Ghader and Abaskhanian, 2009). Renal function was estimated with glomerular filtration rate (eGFR) using the simplified modification of diet in renal disease (MDRD) equation in patients from the metoprolol CR/XL controlled randomized intervention trial in chronic HF (MERIT-HF). Renal function as estimated by eGFR was a powerful predictor of death and hospitalization from worsening HF. Metoprolol CR/XL was as effective in reducing death and hospitalization for worsening HF in patients with eGFR < 45 as in those with eGFR > 60 (Ghali et al., 2009).

A study was carried out to investigate the effects of metoprolol on structural and functional characteristics of left ventricle, cerebral circulation, microcirculation, lipid spectrum, rheologic and viscous properties of blood in patients with grade II-III hypertensive disease and metabolic syndrome. Patients were given metoprolol (100-150 mg/day) and indapamide (1.5 mg/day) for 6 months. Metoprolol was shown to be metabolically inert and its benefits were confirmed for the treatment of hypertensive diseases with metabolic syndrome (Markova et al., 2010).

Hypertension is one of the main determinants of cardiovascular morbidity and mortality in patients with aortic coarctation (CoA). Comparison of the effects of candesartan and metoprolol on blood pressure, large artery stiffness and neurohormonal status in hypertensive patients after repair of CoA were carried out. Metoprolol proved better antihypertensive than candesartan. It was concluded that neurohormonal outcome did not support a significant role for the renin-angiotensin system in the causative mechanism of hypertension after CoA (Moltzer, 2010).

Sustained-release matrix tablets were prepared by using eudragit RL and RS. The influence of process temperature, matrix composition, drug load, plasticizer level and salt form of metoprolol tartrate, fumarate and succinate on ease of processing and drug release was evaluated. Formulations composed of eudragit RL and metoprolol tartrate showed the fastest drug release, substituting part of eudragit RL by RS resulted in slower drug release. All formulations showed first-order release kinetics. Adding triethyl citrate
enhanced the processability but adversely affected long-term stability. Solubility parameter assessment, thermal analysis and X-ray diffraction demonstrated the formation of a solid solution immediately after production, in which H-bonds were formed between metoprolol and eudragit as evidenced by near-infrared spectroscopy. However, high drug loadings of metoprolol succinate and metoprolol fumarate showed a tendency to recrystallize during storage. The in vivo performance of injection-moulded tablets was strongly dependent upon drug loading (Quinten et al., 2012).

One study was carried out to determine whether control of aggressive heart rate (HR) in patients with both chronic atrial fibrillation (AF) and heart failure (HF) is associated with improved outcomes. HR control is one of the mainstays in management of patients with AF. However, rate control can be challenging in patients with HF. This study was designed as an interventional clinical trial, using patients with chronic AF and left ventricular systolic dysfunction. Aggressive HR control was difficult in this group of patients with chronic AF and HF due to patient intolerance of increasing doses of β-blockade, and not associated with improved outcomes. Further studies are needed to establish guidelines for target HR in patients with chronic AF who also have significant HF (Silvet et al., 2012).

Randomized controlled trials have demonstrated the efficacy of selected β-blockers (metoprolol tartrate and atenolol) for preventing cardiovascular events in patients following myocardial infarction (MI) or with heart failure (HF). Using electronic medical record and health plan data from the cardiovascular research network hypertension registry incident of MI, HF and stroke were compared in patients who used new β-blocker between 2000 and 2009. Patients had no history of cardiovascular disease and had not previously filled a prescription for a β-blocker. There were no statistically significant differences in incident cardiovascular events between atenolol and metoprolol tartrate users with hypertension. Such analysis may be useful for determining comparative effectiveness of drugs that are unlikely to be resolved by randomized trials (Parker et al., 2012).
2.7.2 CARVEDILOL

Comparison of the effects of carvedilol and metoprolol on clinical outcome was carried out. In a multicentre, double-blind, and randomized parallel group trial, 1511 patients with chronic heart failure treated with carvedilol (target dose 25 mg twice daily) and 1518 patients were treated with metoprolol (metoprolol tartrate, target dose 50 mg twice daily). The reduction of all cause mortality was consistent across predefined subgroups. Incidence of side effects and drug withdrawals did not differ significantly between the two study groups. Results suggested that carvedilol extends life span as compared with metoprolol (Poole-Wilson et al., 2003).

To test the clinical usefulness of chronotherapy with a β-blocker, evening carvedilol administration was added to first-line antihypertensive therapy in patients with essential hypertension showing a morning blood pressure surge. Patients with hypertension (12 men and 5 women) were treated with first line antihypertensive drugs for 4 weeks and then underwent 24 h ambulatory blood pressure monitoring. After 4 weeks, ambulatory blood pressure, diastolic blood pressure and pulse rate were reassessed by 24 h monitoring. Evening carvedilol administration significantly suppressed the morning increase in systolic pressure and pulse rate while morning administration lacked significant anti-surge effect. The addition of chronotherapy with carvedilol may be an effective way to suppress morning surges of hypertension (Koga et al., 2005).

Left ventricular ejection fraction (LVEF) is an important measure of ventricular function in the evaluation of heart failure. Immediate-release carvedilol twice daily has been shown to improve LVEF in subjects with ischemic and non ischemic chronic heart failure. A once-daily formulation, controlled-release carvedilol, is expected to improve quality of care through improved adherence as a result of the reduced frequency of dosing. This multicentre, randomized, double-blind study in subjects with stable chronic heart failure were compared the change in LVEF in patients receiving carvedilol immediate release with those receiving carvedilol controlled release. Based on its equivalent pharmacokinetic/pharmacodynamic profile, it was hypothesized that
carvedilol controlled release improved LVEF as great extent as carvedilol immediate release (Greenberg et al., 2006).

A study was conducted to investigate the utilization of xanthan-grafted copolymer (XG) of acrylamide (AAm) as a controlled release matrix for antihypertensive drugs such as atenolol and carvedilol. Tablets were prepared from plain XG, its grafted copolymer with AAm, and other excipients by incorporating atenolol and carvedilol, which have different physico-chemical properties. Effects of grafting ratio, drug loading and other excipients on the release kinetics were evaluated for both the class of drugs. The nature of drug transport through matrix tablets followed the non-Fickian (anomalous) trend. A significant difference in the release rate of atenolol from the tablets prepared from XG and the grafted copolymer were observed (Mundargi et al., 2007).

To improve the solubility and dissolution rate of carvedilol, a ternary complex was formed with β-cyclodextrin and citric acid to formulate mouth-dissolving tablets. The prepared complexes were characterized by fourier transform infra red spectroscopy (FTIR), differential scanning calorimetry (DSC), powder X-ray diffractometry, scanning electron microscopy (SEM) and complexation efficiency. The complex obtained by the spray drying method resulted in highest complexation efficiency and a 110-fold increase in the solubility of carvedilol. The mouth-dissolving tablets formulated using the spray dried complex with suitable excipients showed 100% dissolution within five min. (Pokharkar et al., 2009).

In hypertension, extended-release carvedilol resulted in lower triglycerides, insulin and C-peptide levels compared with extended-release metoprolol. Similar effects were observed in high-risk subgroups. Both treatments were well tolerated. This differential metabolic profile could be useful in determining antihypertensive treatment options (Fonarow et al., 2009).

A better metabolic profile could be achieved with newer third generation vasodilating beta-blockers, such as carvedilol and nebivolol. Vasodilating action of carvedilol and nebivolol, due to alpha1-blocking effect and release of nitric oxide, respectively, showed
the lack of adverse metabolic effects of these beta-blockers that could also be used in hypertensive patients with metabolic syndrome (Carella et al., 2010).

The designed transdermal drug delivery system (TDDS) of carvedilol and hydrochlorothiazide produced therapeutically effective plasma concentrations of the cardiovascular agents up to a range of 60 to 72 h (in different volunteers with a mean of 66 h). It can be concluded that the system meets the intended goal of at least 2 day management of stage II hypertension with application of a single transdermal patch, hence improving patient compliance over the inconvenience seen with frequent oral administration (Agrawal et al., 2010).

A formulation was developed as liquid self-nano-emulsifying drug delivery systems (SNEDDS) to enhance the bioavailability of carvedilol by facilitating its transport via lymphatic circulation. SNEDDS systems released the drug by non-Fickian mechanism. The TEM imaging of the optimized formulation assured the uniform shape and nano size of the system. Accelerated studies of the optimized formulation indicated high stability of the formulation upto 6 months. So, SNEDDS has potential for enhance the oral bioavailability of BCS class II drugs (Singh et al., 2011).

It has been shown that oxidative stress may play an important role in the development of atherosclerosis and carvedilol reducing oxidative stress. It was assessed that carvedilol may reduce the severity of atherosclerosis in apolipoprotein E (apoE)-deficient mice in addition to its hemodynamic effects. The accumulation of macrophages and expression of CD4 (+) and CD8 (+) cells in the lesions were decreased by the treatment of the drugs, of which carvedilol was the most effective. In addition, carvedilol reduced superoxide production in aortic walls detected by ethidium staining. The heart rates in the treated groups were decreased by 4%-12% compared with the control group, with carvedilol showed highest suppression of heart rate. Carvedilol may suppress atherosclerosis via reducing superoxide production, in addition to the hemodynamic modifications in this animal model (Shimada et al., 2012).

β-Blockers are a standard treatment regime for the acute myocardial infarction, heart failure and patients at risk for coronary events. All β-blockers are not the same in
properties such as lipophilicity, metabolic profile, receptor inhibition, hemodynamics, tolerability and antioxidant/anti-inflammatory effects. A comparative analysis of the clinical efficacy of metoprolol, atenolol and carvedilol showed superiority of carvedilol over other β1-blockers (Di Nicolantonio and Hackam, 2012).

2.8 LITERATURE REVIEW OF POLYMERS
Compressed coated tablets by using theophylline and HPC were prepared. Effects of the viscosity grades of the polymer, the mixing ratios of two polymers with different viscosity grades and the polymer contents in the tablets on release patterns of theophylline were examined in vitro. It has been showed that release rate was decreased with increasing viscosity and polymer contents in the tablets. A low but sustained level of theophylline in saliva was observed after oral administration of sustained-release tablets to five human volunteers, indicating in vivo sustaining efficiency of tablets (Nakano et al., 1983).

It was found that drug release from ethylcellulose and HPMC (90:10) coated pellets significantly increased with decreasing molecular weight of the ethylcellulose. This could be explained by the decreasing mechanical stability of the polymeric films, facilitating the formation of cracks within the film coatings through which the drug can rapidly diffuse out. Thus, the permeability of a polymeric controlled release film coating can strongly depend on the mechanical pressure which with it is exposed (Rowe, 1986).

A release pattern with two pulses was obtained from a three layer tablet consisting of two drug containing layers, separated by a drug free gellable polymeric barrier layer. The three-layer tablet was coated on three sides with an impermeable coating of ethylcellulose and the top side of the tablet remained uncoated. Upon contact with dissolution fluids, the initial dose incorporated into the top layer was released rapidly from the uncoated surface of the tablet. The second pulse was obtained from the bottom layer after the gelled barrier layer (HPMC) had been eroded and dissolved (Conte et al., 1989).

The permeability of KCl through films containing ethylcellulose and HPMC as a function of a defined applied tensile stress was measured. Films containing 24% w/w HPMC (or
less) became permeable to KCl only under the influence of an applied tensile stress. With increasing HPMC content the tensile stress required to induce film permeability decreased (Hjartstam et al., 1990).

The utility of micronized HPC-L as an insoluble swellable matrix carrier for sustained release tablets was investigated, using procainamide hydrochloride, theophylline and indomethacin. The amount of water-soluble fraction and the degree of aggregation of HPC-L particles in water increased with decreases in particle size. The mechanism of formation of non-disintegrating matrix tablets by micronized HPC-L was discussed on the basis of fast hydration and gel formation due to loss of the fibrous structural integrity of the cellular polymer. The results suggested that the drug release from directly compressed HPC-L matrices was affected not only by polymer swelling but also by the drug solubility and the amount of soluble fraction in the matrices (Nakagami et al., 1991).

The TIME CLOCK® system enabled fast and complete release of a drug after a predetermined lag time. A tablet containing the drug molecule and bulking agents was formulated. This core was coated with a hydrophobic dispersion of carnauba wax, bees wax, poly oxyethylene sorbitan monooleate and HPMC in water. The lag time could be proportionally modulated by altering the thickness of the coating. In vitro results indicated rapid release after a certain lag for the TIME CLOCK® system with the hydrophobic coating. This approach may also be used to control the release onset time. Furthermore, drug release is independent of normal physiological conditions, such as pH, digestive state and anatomical position at the time of release. This approach could be applicable for implant systems as well as for oral systems (Pozzi et al., 1994).

A pharmaceutical implant adapted to rupture at a predetermined period of time after implantation containing a biologically active material, at least one water soluble excipient and a polymer film coating. A film coating comprising a mixture of ethylcellulose and a copolymer of glycolic and lactic acids is used. As ethylcellulose is an insoluble polymer, when the polylactic glycolic acid (PLGA) polymer in the film hydrolyzes, the film becomes porous and allows release of the drug. The rate of hydrolysis of the PLGA
depends on the ratio of lactic acid to glycolic acid in the polymer (Barr and Thiel, 1997). The Pulsincap® system consisted of a water insoluble capsule body, which is filled with the drug formulation. The capsule was closed at the open end with a swellable hydrogel plug. The dimensions and the position of the plug could control the lag time prior to drug release. In order to ensure rapid release of the drug, effervescent agents or disintegrants can be included in the drug formulation, in particular with water-insoluble drugs. This system was coated with an enteric layer, which dissolved upon reaching the higher pH region of the small intestine. This system comprised insoluble capsules and plugs. The plugs consisted either of swellable materials, which are coated with insoluble but permeable polymers (e.g. polymethacrylates), or of erodible substances such as HPMC, polyvinyl alcohol, polyethylene oxide (Krogel and Bodmeier, 1997).

A reservoir-type time controlled pulsatile release system was based on rupturable coating. The drug was released from a core after the rupture of a surrounding polymer layer, caused by a pressure build-up within the system. The pressure necessary to rupture the coating can be achieved with gas producing effervescent excipients, inner osmotic pressure or swelling agents. An effervescent mixture of citric acid and sodium bicarbonate was incorporated in the core of a tablet, which was coated with ethylcellulose. The development of carbon dioxide after water penetration into the core resulted in release of the core materials after rupture of the coat, which was generally dependent on the mechanical properties of the coating layer, the weak and nonflexible ethylcellulose film ruptured sufficiently when compared with more flexible films. The lag time prior to release prolonged with increasing coating level and increasing hardness of the core tablet (Krogel and Bodmeier, 1999).

The chronotopic system is an oral dosage form that is designed to achieve time controlled delivery. The chronotopic system consisted of drug containing core layered with HPMC, optionally coated with an outer enteric coating. The lag time prior to drug release was controlled by the thickness and the viscosity grade of the HPMC layer. This system has been developed keeping in view of interaction between gastro-intestinal fluids and the coating polymer, which causes time or site controlled release (Maroni et al., 2005).
Pure ethylcellulose films are poorly permeable for many substances and can result in very low release rates for certain drugs from coated dosage forms, if the film coatings are completely formed and remain intact upon exposure to the release media. To increase the permeability of the polymeric membranes, different amounts of a water-soluble polyvinyl alcohol-polyethylene glycol (PVA-PEG) graft copolymer were added to aqueous ethylcellulose dispersion (Aquacoat ECD). The presence of only low percentage of this hydrophilic copolymer significantly increased the water uptake efficiency, dry weight loss and drug permeability of the films. In contrast to HPMC, the PVA-PEG graft copolymer does not cause flocculation of the colloidal coating dispersion. The transport of water as well as drug theophylline through the polymeric networks was primarily controlled by pure diffusion. A pH-independent drug release rate was obtained from drug-loaded pellets by simply varying the content of PVA-PEG graft copolymer. An appropriate curing step after coating was required, but the investigated curing conditions (differing in time and relative humidity) resulted in very similar drug release patterns, indicating that stable film structure was achieved (Siepmann et al., 2007).

A novel programmed drug delivery system was developed which contained a water-soluble cap, impermeable capsule body, and two multilayered tablets. Sodium alginate and hydroxypropyl methylcellulose (HPMC E5) were chosen as the drug modulating barrier material. The lag time was controlled by adjusting ratio of sodium alginate and lactose, between the first two pulsatile release patterns. Linear relationship was observed between the polymer ratio and the lag time. Through adjusting the ratio of HPMC E5/lactose, lag time between the second and the third pulse could be successfully modulated. The results revealed that pulsatile drug release for three times daily could be obtained from these tablets in capsule system (Li et al., 2008).

It was attempted to characterize the influence of core and coating formulations on the release profiles to establish in vitro-in vivo correlations of pulsatile pattern for a pulsatile drug delivery system activated by membrane rupture based on three core tablet formulations (A-core: HPMC 50+4000 cps, B-core: E10M, and C-core: K100M) coated with various thicknesses of a semipermeable ethylcellulose membrane plasticized with
HPMC 606 at different ratios with/without adding various amounts of water to dissolve it in the coating solution. Results showed that drug release from the three kinds of core tablets in deionized water increased with an increasing stirring rate and decreased with an increasing viscosity grade of HPMC used in the core formulations. Results further demonstrated that a slightly slower release rate in pH 1.2 solution and a faster release rate in pH 6.8 buffer than that in deionized water were observed for the A-core and B-core tablets, with the former being slower than the latter. However, similar release rates in the three kinds of media were observed for C-core tablets, but they were slower than those for the A and B-core tablets. Dissolution of coated tablets showed that the controlling membrane was ruptured by osmotic pressure and swelling which activated drug release with a lag time. The lag time was not influenced by the pH value of the release medium or by the rotation speeds. The lag time increased with a higher coating level, but decreased with the addition of the hydrophilic plasticizer, Pharmacoat 606, and of the water amount in the coating solution. Results of the three pilot crossover studies for the exemplified pulsatile systems indicated that the lag time for the in vivo plasma profile was well correlated with that determined from the in vitro release profile in pH 1.2 solution and the in vivo release rate was better reflected by that performed in pH 6.8 buffer (Lin et al., 2008).