AN UPDATE ON CHRONOTHERAPEUTIC DRUG DELIVERY SYSTEMS

R. Santosh Kumar¹, G.V.Radha¹, K. Lakshmi Deepthi² and P. Sujitha³
¹GITAM Institute of Pharmacy, GITAM University, Rushikonda, Visakhapatnam-45.
²Sri Venkateswara College of Pharmacy, Etcherla, Srikakulam.
³SrinivasaRao College of Pharmacy, P.M.Palem, Visakhapatnam-41.

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ABSTRACT
Chronotherapeutics refers to a treatment method in which in vivo drug availability is timed to match rhythms of disease in order to optimize therapeutic outcomes and minimize side effects. It is also known as pulsatile drug delivery system and it focuses on the release of a drug at particular time and at a particular site in order to maintain constant blood levels of a particular drug. The specific time that patients take their medication is very important as it has significant impact on success of treatment. If symptoms of a disease display circadian variation, drug release should also vary over time. Drug pharmacokinetics can also be time dependent; therefore, variations both in a disease state and in drug plasma concentration need to be taken into consideration in developing drug delivery systems intended for the treatment of disease with adequate dose at appropriate time. These drug delivery systems are designed to release the drug within a short period of time, immediately after a predetermined lag time. Chronotropic systems are promising drug delivery systems in asthma, peptic-ulcer, cardiovascular diseases, arthritis, attention-deficit syndrome in children and hypercholestremia e.t.c. Approaches like capsular systems, systems with different type of barrier coatings, stimuli sensitive pulsatile systems and externally regulated systems are summarized in this article. This article mainly focuses on diseases requiring chronotropic systems, approaches to design them, recent technologies for chronotherapy.

Corresponding author
R. Santosh Kumar
GITAM Institute of Pharmacy,
GITAM University, Rushikonda,
Visakhapatnam-45.
radasantosh@rediffmail.com

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INTRODUCTION

The leaves of certain trees open during day and close at night, showing a clear rhythmicity. Circadian rhythms of behavior in mammals are known to be robust and precise. The efficacy and toxicity of many drugs depends upon the relationship between the dosing schedule and the 24 hour rhythms of biochemical, physiological and behavioral processes. Also several drugs cause alterations to 24 hours rhythms leading to illness and altered homeostatic regulation. Alteration in biological rhythm is also a novel concept of adverse effects, which can be minimized by optimizing the dosing schedule.

Traditionally, drug delivery was only concerned with drug absorption which should be predictable from gut or site of injection. Besides this, second generation drug delivery was meant to achieve perfection in continuous and constant rate delivery of bioactive agents.

Since living organisms do not show “zero order” requirement or response to drugs and they are predictable resonating dynamic systems, so they require different amounts of drug at predictably different time within circadian cycle which will maximize desired and minimize undesired drug effects.

Hence Rationale behind Developing Chronotropic Systems is :

(a) Treatment of diseases in which circadian rhythms play important role in their pathophysiology (chronopharmacotherapy).
(b) Minimize the degradation of drugs in upper gastrointestinal tract (proteins and peptides).
(c) For programmed delivery of hormones (since continuous release dosage forms may lead to disturbance in normal feedback mechanism of body as well as development of resistance may also take place).
(d) For delivery of those drugs which develop biological tolerance (e.g. nitroglycerines) or undergo extensive first pass metabolism and also that are targeted to specific site of gastrointestinal tract e.g. colon.

Chronotropic systems are based on the concept of chronopharmaceutics in which there is a transient release of certain amount of drug within a short period of time immediately after a predetermined off-release period.

Concept of Chronotherapy and Chronopharmaceutics:

Chronopharmaceutics includes pharmaceutical application of “Chronobiology” in drug delivery. Chronobiology is the study of biological rhythms and their responses to other metabolic functions of body.

There are three types of mechanical rhythms in our body:

Circadian Rhythms
Ultradian Rhythms
Infradian Rhythms

(a) Circadian Rhythms:

The term “circadian” was obtained from Latin words “circa” meaning “about” and “dies” meaning “day”. Oscillations in our body that are completed within 24 hours are termed as circadian rhythms.

(b) Ultradian Rhythms:

Oscillations that are completed in a shorter duration of less than 24 hours are termed as ultradian rhythms (more than one cycle per day).

(c) Infradian Rhythms:

Oscillations that are completed in more than 24 hours are termed as infradian rhythms (less than one cycle per day).

For development of a chronotropic or pulsatile drug delivery system, thorough knowledge of pathogenesis of disease and role of circadian rhythm in its pathophysiology is required. Hence these systems are generally designed for the diseases having enough scientific background to justify their need for chronotropic systems as compared to conventional drug delivery systems.

Diseases such as:

- Bronchial asthma.
- Myocardial infarction.
- Angina pectoris.
- Rheumatic disease.
- Ulcer.
- Diabetes.
- Attention deficit syndrome.
- Hypercholesteremia.
- Hypertension.
- Epilepsy.
- Alzheimer’s disease.
- Parkinson’s disease.
Bronchial Asthma:
It has been estimated that symptoms of asthma occur 50 to 100 times more often at night than during the day\textsuperscript{4}. Many circadian-dependent factors appear to contribute to the worsening of nocturnal asthmatic symptoms. For example, cortisol (an anti-inflammatory substance) levels were highest at the time of awakening and lowest in the middle of the night, and histamine (a mediator of broncho constriction) concentrations peaked at a level that coincided with the greatest degree of broncho constriction at 4:00 am\textsuperscript{5}. A research finding also reveals that theophylline absorption is slower at night\textsuperscript{6}. The enhanced understanding of the chronobiological impact upon the pathophysiology of asthma, and the pharmacology and pharmacokinetics of the drugs used in its management, have led to new approaches to disease management and enhanced patient care.

Ulcer:
Generally gastric acid secretion is highest in the evening in duodenal ulcer patients and decreases in the early morning\textsuperscript{7,9}. One group of authors studied incidence of ulcer perforation for daily (circadian), weekly (circaseptan) and yearly (circannual) time effects\textsuperscript{10}. A circadian rhythm has been found overall that was reproducible and fairly stable across seasons, decades, and days of the week. Duodenal perforations showed highest incidence in the afternoon, while gastric perforations showed a major peak around noon and a secondary peak near midnight. For duodenal ulcer perforation, the circannual pattern was characterized by a 6-month rhythm, with significantly higher incidence in May-June-July and in November-December in most subgroups. A circaseptan rhythm was not found, but there was a significantly higher incidence on Thursday-Friday as compared to Sunday-Monday.

Epilepsy:
The circadian rhythm may also take a significant role in seizures of some types of epilepsy\textsuperscript{11}. The influence of the biological clock on seizure of some partial seizures has been found in some experimental animal models. The methodology for measurement of the circadian rhythm in humans is also investigated. Behavioral chronobiology provides the detection of probable new regulation processes concerning the central mechanisms of epilepsy\textsuperscript{12} Because of this fact, the circadian psychophysiological patterns of epilepsy show dynamic biological systems which recommend some intermodulating endogenous processes between observation and seizure susceptibility. Furthermore, such chronobiologic studies applied to epileptic behavior suggest the development of new heuristic aspects in the field of comparative psychophysiology.

Diabetes:
In case of type I diabetes, circadian rhythms of insulin requirement and action are of clinical importance\textsuperscript{13}. Generally, insulin is released in pulsatile fashion but sometimes it is irregular. Insulin can show cyclic rhythmicity of 8-30 min, which can conclude optimal action. The basal mode of insulin release acts on B cell in both stimulatory and inhibitory fashions. Target cell sensitivity to insulin action and hyperglycemia may be impaired by stress hormones, cortisol, epinephrine and growth hormone. Partly intrinsic rhythmicity, dehydration and prolonged insulin withdrawal may induce a secondary feed-back signal on insulin release which can help to raise blood glucose levels. The modulators of insulin release and action are secreted in a circadian fashion and secondarily impress the mode of insulin release. So, any difference between a daily maximum and minimum in plasma insulin concentration besides i

Hypercholestremia:
A circadian rhythm is seen in the synthesis of cholesterol, which is generally higher during night time than day light. Sometimes it varies according to individuals. The maximal production occurs early in the morning, i.e., 12 h after last meal. Studies with HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase inhibitors have suggested that evening dosing was more effective than morning dosing. The activity of rate limiting enzyme HMG-CoA is higher in the night time\textsuperscript{14} but the diurnal variations occur due to periodicity or degradation of this regulatory enzyme.

Alzheimer’s Disease:
Change of circadian rhythm is also seen in patients with Alzheimer's disease\textsuperscript{15} Individuals with Alzheimer's show less diurnal motor activity, a higher percentage of nocturnal activity, lower inter day stability of motor activity, and a later activity acrophase (time of peak) than normal healthy individuals. Alzheimer's disease leads to pathological changes in the suprachiasmatic nucleus and thus it disrupts circadian rhythms of the brain's function. The core body temperature is also higher in patients with this disease. The circadian abnormalities are seen together with cognitive and functional deterioration in this disease. No other change has been evaluated.

Parkinson’s Disease:
Autonomic dysfunction seen in Parkinson's disease discloses many alterations in circadian rhythm of blood pressure, amplified diurnal blood pressure variability and postprandial hypotension\textsuperscript{16} But, existence of circadian rhythm in this disease has not been evaluated. Clinical data have shown daily fluctuation of motor activity pattern, but the effect of the phase of the disease and the subsequent roles of drugs are difficult to estimate.
Cardiovascular Therapy:
The differences in patterns of illness between day and night for cardiovascular disorders such as hypertension, angina, heart attack, sudden cardiac death and stroke have been documented\textsuperscript{17}. Medications have been formulated, and dosing schedules established, in an attempt to provide appropriate concentration of a drug in the target area of the body when the drug is most Needed\textsuperscript{17}. For example, it has often been found that the blood pressure of a hypertensive patient increases rapidly in the morning after awakening, typically peaks in the middle to late time of the day, decreases in the evening, and is lowest while the patient sleeps at night\textsuperscript{17}. It may also be important to recognize that the risk of heart attack appears to be greatest during the early morning hours after awakening. Currently, there are antihypertensive products in the market that are chronotherapeutic medications with novel drug delivery systems, releasing drug during the vulnerable period of 6 am to noon upon administration of medications at 10 pm.

<table>
<thead>
<tr>
<th>Table: 1.1 Some Chronotherapeutic Antihypertensive Products.</th>
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<td><strong>Product</strong></td>
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<td>InnoPran XL</td>
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<td>Cardizem LA</td>
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<td>Verelan PM</td>
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<td>Covera HS</td>
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Antihypertensive Drugs:
For example, with cardiovascular drugs such as nifedipine, oral nitrates and propranolol, plasma peak concentration is twice as high and time to reach peak concentration is shorter after morning dosing compared with evening dosing\textsuperscript{18}. Such a variation was not detected when sustained release dosage forms of nifedipine and isosorbide mononitrate were used. The underlying mechanisms of their chronopharmacokinetic pattern involve a faster gastric emptying time and a greater gastrointestinal perfusion in the morning. Shiga et al documented that atenolol, in contrast to propranolol, is not absorbed more rapidly after morning administration compared with post-evening administration\textsuperscript{19}. This confirms that the absorption rate of a lipophilic, but not hydrophilic, drug is faster after morning dosing\textsuperscript{20}.

Anti-inflammatory Drugs:
Studies on NSAIDs, e.g., indomethacin and ketoprofen, have also shown that these drugs have a greater rate and/or extent of bioavailability when they are given in the morning than when they are given in the evening. Markedly higher ketoprofen plasma peaks were observed after administration at 07:00 than after administration at other times\textsuperscript{21}. Earlier and higher peak concentrations were obtained when indomethacin was given at 07:00 or 11:00 than at other times of the day or night\textsuperscript{22}. Better morning absorption has also been observed with controlled release indomethacin and ketoprofen formulations \textsuperscript{23}, \textsuperscript{24}. The clinical relevance of such variations is that high plasma concentrations correlate with high incidence of adverse effects. It has been suggested that morning absorption for these drugs is better than night-time absorption. Greater blood flow of the gastrointestinal tract in the morning than in the evening may explain this phenomenon. Circadian changes in renal function, plasma protein binding or hepatic blood flow could also explain temporal variation in drug plasma levels. Many variables are known to influence pharmacokinetics.

Aggravations of asthmatic attacks occur in early morning or after midnight due to low lung function promoted by circadian changes at that time. Also cardiovascular diseases like angina, hypertension, myocardial infraction and stroke etc are more prone in early morning. Circadian changes also contribute in lipid metabolism in patients as well as in normal subjects, leading to complication in cholesterol synthesis in patients\textsuperscript{25}. Role of circadian changes in glucose level and insulin synthesis has been extensively studied. Peptic ulcer also favors the nocturnal acid break through due to circadian variation. In case of rheumatoid arthritis, level of C – reactive protein increases early morning leading to enhanced pain and inflammation.

Designing of Chronotropic Systems:
Numerous methodologies have been developed to design chronotropic systems to achieve desired drug-release profile in a pulsatile fashion.

Timed-release/time-dependent Chronotropic Systems:
- Reservoir systems with rupturable polymer coating.
- Capsular systems.
- Chronotropic systems dependent on changed membrane permeability.
- Reservoir systems with soluble/eroding polymer coating.
- Low density/floating systems.

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Stimuli Dependent Systems (pulsatile drug delivery systems):
- Temperature sensitive pulsed-release delivery systems.
- Inflammation induced systems.
- Enzyme dependent pulsatile-release systems.
- Glucose concentration dependent insulin release systems.
- Intelligent gels responding to antibody concentration.
- pH sensitive pulsatile drug delivery systems.

Timed-release/time-dependent Chronotropic Systems:
These types of systems show a burst release of drug immediately after a predetermined lag time. Depending on methodologies applied to design them, these systems can be further classified into following subtypes:

Reservoir Systems with Rupturable Polymer Coating:
These systems may be either single unit or multi particulate reservoir systems with outer rupturable barrier. Upon entry of water within the systems, a hydrostatic pressure develops which leads to rupturing of surrounding polymeric layer resulting drug release from the core of system. Pressure build-up required to rupture the coating can be achieved by using swelling agents, gas producing effervescent agents or osmogens. Rate of water permeation and mechanical resistance of the outer membrane are major factors affecting the lag time. Drug release mechanism is based on either diffusion or dissolution according to the nature of drug. Ueda et al. discovered time controlled explosion systems for water insoluble drugs in both single as well as multiple unit dosage forms.26-29. Both types of dosage forms contain a core of drug plus osmotic agent and super disintegrants. Finally the cores are coated with a protective polymeric rupturable layer and a top water insoluble semipermeable layer, which is the rate controlling membrane for influx of water into osmotic core. Different type of release pattern can be obtained in different types of dosage forms, for instance in case of tablets, drug is released quickly after the explosion of outer membrane while in case of pellets or granules, drug is released with zero order pattern after a definite lag time because of the time variance of the explosion of the outer membrane. In each bead or granule, drug release is time controlled by the rupturing of external water insoluble membrane caused by explosive swelling effect of the swelling agents. The lag time increases with increasing coating level and higher amount of talc and plasticizer in coating. Drug release from time controlled explosion systems was found to be complete, independent of environmental pH and drug solubility. But there is a drawback of failing to release drug if swelling agents fail to rupture the water insoluble coating and having limited flexibility in the release pattern. In order to attain a better control over release pattern, water soluble polymer (mainly pH dependent) can be incorporated in insoluble polymeric membrane so that at elevated pH of small intestine, polymer starts dissolving leading to weakening of membrane after a predetermined lag time. By variation in coat thickness as well as proportion of soluble and insoluble material in the coating, the lag time before drug release can be prolonged with better control and reliability and eventual disintegration of coating ensuring release of drug.30 Diclofenac sodium pulsatile release pellets were prepared by extrusion-spheronisation technology and coated in a mini fluidized bed spray coater with swelling material as the inner coating swelling layer and ethyl cellulose aqueous dispersion as the outer coating controlled layer. The lag time for pulse delivery of diclofenac was found to be good agreement between in vitro and in vivo.

Capsular Systems:
Capsular systems are mainly consisted of an insoluble capsule body and swellable and degradable plugs made of approved substances. The lag time is controlled by plug, which is pushed away by swelling or erosion and drug is released as a pulse from the insoluble capsule i.e. “Pulsincap”. A swellable hydrogel seals the drug contents into the capsule body. Upon coming in contact of dissolution medium, the hydrogel plug swells and after a lag time, the plug pushes itself outside the capsule and rapidly releases the drug. Hydrophilic polymers are generally used for plugs like hydroxypropylcellulose, polyvinyl-acetate, and polyethylene-oxide etc. The swelling strength of plug decides the lag time. Many of the drugs have been formulated in form of pulsincap systems for hypertension, angina, peptic ulcer etc. Gohel and Sumitra developed a system wherein weighed quantity of dicalcium phosphate was filled into the capsule body followed by drug (Diltiazem HCl). Weighed amount of the hydrophilic swellable polymers such as HPMC or guar gum was placed on top and compressed lightly using a rod to form a compact plug. To simplify this technology the hydrogel plug has been replaced by an erodible tablet, which has a tight fit in the capsule. To prevent the entry of fluid during the release process it erodes away from the mouth of capsule.
Chronotropic Systems Dependent on Changed Membrane Permeability:

Drug release in such type of systems is achieved by change in permeability of polymeric coating layer in presence of certain counter ions of surrounding media. Narisawa et al developed a device capable of pulsed-release depending on the change in diffusion properties of Eudragit RS. They studied and justified that cores of theophylline coated with Eudragit RS show very slow release in pure water but release rate increases significantly when the microcapsules are immersed in an organic acid solution containing succinic acid, glutaric acid, tartaric acid, malic acid or citric acid. The above phenomena occurs due to higher hydration of film containing quaternary ammonium groups in the polymer chain and that is not affected by succinic acid, suggesting that the quaternary ammonium groups of Eudragit RS are essential to produce unique drug release profile. The release profile of systems based on permeability changes depend strongly on physicochemical properties of the drug and its interaction with membrane. Therefore, with this system a pulsatile release profile may be obtained for some particular drug molecules in a specific formulation but cannot be generally applied to all drugs.

Reservoir Systems with Soluble/eroding Polymer Coating:

This class of reservoir type pulsatile systems posses a barrier layer, which dissolves or erodes after a specific lag time followed by burst release of drug from the reservoir core. In these types of systems, the lag time prior to drug release is controlled by thickness of coating layer. A chronotropic system which consists of a drug containing core layered with HPMC and a to player of enteric coating, the lag time before drug release will be dependent upon the thickness and viscosity grade of HPMC layer. Since drug release mechanism in these types of systems is dissolution, that’s why, a high degree of drug solubility relative to dose of drug is essential for rapid release of drug after the lag period. Various grades of hydroxyl propyl methyl cellulose and Eudragit (acrylate) polymers have been studied to in an attempt to deliver drugs to various sites in gastrointestinal tract due to their solubility and eroding properties. Formulations dependent on slow dissolution behavior of high viscosity polymers was described by Gazzaniga et al. by formulation of mini tablets of drug substance which is coated with a high viscosity polymer (HPMC 40000) and an outer enteric coating. The outer film protects the system from fluids in the stomach and dissolves upon entering in small intestine. HPMC layer delays the drug release for 3-4 hours when the system is transported through small intestine.

Low density/floating Systems:

Nowadays floating dosage forms are gaining importance as technological drug delivery systems with gastro-retentive behavior, offering several advantages in drug delivery. Like treatment of gastrointestinal disorders such as gastro-esophageal reflux, improved drug absorption (because of increased GRT) , ease of administration and better patient compliance. These systems are comprised of low density/floating pulsatile dosage forms which are retained in stomach for long time (4-12 hours) and not affected by variation in gastric pH, local environment or gastric emptying rate. These dosage forms may be either single unit (floating tablets) or multiparticulates (beads, pellets, granules, microspheres) with capability of gastro-retention. These systems are specifically beneficial for drugs, either absorbed from the stomach or requiring local delivery in stomach. Generally polysaccharides are widely accepted in gastroretentive delivery systems because of their simplicity to formulate the drug delivery system and achieve the desired drug release profile. Badave et al developed hollow calcium pectinate beads for floating pulsatile release of diclofenac sodium intended for chronotherapy.

A multiparticulate floating pulsatile drug delivery system was developed using porous calcium silicate (Fluorite RE) and sodium alginate for time and site specific drug release of meloxicam for chronopharmacotherapy of rheumatoid arthritis. Meloxicam was adsorbed on the Fluorite RE by fast evaporation of solvent from drug solution containing dispersed Fluorite. Drug adsorbed fluoxetine powder was used to prepare calcium alginate beads by ionotropic gelation method. The floating time for this system was controlled by density of beads and hydrophobic character of drug. To overcome limitations of various approaches for imparting buoyancy hollow/porous calcium pectinate beads were prepared by simple process of acid base reaction during ionotropic cross linking. The floating beads provide two- phase release pattern with initial lag time during floating in acidic medium followed by rapid pulse release in phosphate buffer. These drug delivery systems show distinct behavior from other approaches in chronotherapy with desired low drug release in acidic medium, reduced time consumption due to single step process and also overcame the limitations of process variable caused by multiple formulation steps.
Stimuli Dependent Systems (pulsatile drug delivery systems):

Such systems are novel drug delivery approaches meant for targeted drug delivery at specific site due to induction of certain physiochemical stimuli at target site. Release of certain enzymes, hormones, antibodies, pH of the site, temperature of the site, presence of certain cells, and concentration of biomolecules (glucose, neurotransmitters, inflammatory mediators) act as stimuli to trigger the release of drug from these types of drug delivery systems.

Temperature Sensitive Pulsed- Release Delivery Systems:

Physiological temperature of various types of cells inside the body is not same due to their different metabolic functions. Certain cells posses some what different temperature (either higher or lower) with respect to other cells like tumor cells, in which cellular temperature is raised due to their higher metabolic rate. For targeting tumors, a pulsatile drug delivery system can be designed by utilizing thermo-responsive hydrogel system. As the name suggests, these polymers undergo swelling/deswelling phenomena in response to temperature change (at different metabolic rates of tumors cells) which modulates drug release from these systems. Y.H Bae. et al developed indomethacin pulsatile drug delivery system in temperature range of 200C -300C by using reversible swelling properties of copolymers of N-isopropyl acrylamide and butylacrylamide. Kataoka.et.al developed the thermo-sensitive polymeric micelles as drug carrier to treat cancer.

Inflammation Induced Systems:

Any physical or chemical stress (injury, fracture etc), which may lead to inflammation, acts as a stimulus (due to hydroxyl radicals produced from inflammation responsive cells).In favor of this Yui and coworkers et.al designed and developed inflammation responsive pulsatile drug delivery system which responded to hydroxyl radicals and degraded in a limited manner. They utilized hyaluronic acid which is specifically hydrolyzed by hyaluronidase or free radicals present at inflammatory site abundantly rather than normal tissue. Hence it became possible to treat patient with inflammatory diseases like rheumatoid arthritis, using NSAIDS incorporated into hyaluronic acid gels as a new implantable drug delivery system.

Enzyme Dependent Pulsatile-Release Systems:

Such systems are generally developed for colonic delivery of drug since release rate of drug is dependent upon the catalysis of polymeric membrane by enzymes secreted by colonic microflora. Therefore these systems are more specific for targeting, independent of pH variations along the gastrointestinal tract. Numerous natural polysaccharides such as chondroitin sulphate, pectin, dextran, guar gum etc have been investigated for their potential in designing colon specific drug delivery. The use of polysaccharides for coating purposes has been tried with limited success. Most of the non starch polysaccharides suffer from the drawback of lacking good film forming properties. Also they tend to swell in gastrointestinal tract and become porous resulting in early release of drug. Chronotherapy of rheumatoid arthritis has been tried by utilizing these polymers to deliver NSAIDS in colon after a lag time of 4-6hours to relieve pain in early morning. Also pulsatile delivery of 5-aminosalicylic acid has been attempted in case of irritable bowel syndrome.

Glucose Concentration Dependent Insulin Release Systems:

It was depicted earlierly that there is an increase in blood glucose concentration rhythmically in Diabetes-mellitus Type1. Several systems were developed which responded to changes in glucose concentration. One such stimuli induced system includes pH sensitive hydrogel containing glucose-oxidase enzyme immobilized in hydrogel. As the blood concentration of glucose rises, glucose-oxidase converts glucose into gluconic acid, which changes the pH of system. Due to change in pH, swelling of polymer takes place and this result into insulin release. Insulin decreases the blood glucose level and consequently the gluconic acid level also declines and system turns to deswelling and hence decreasing the insulin release. Examples of pH sensitive polymers include n, n-dimethyl amino ethyl methacrylate, chitosan, polyol etc. Okan et.al developed the system based on the fact that boronic acid moiety forms reversible bonds with polyol compounds including glucose. They used water soluble copolymers containing phenyl boronic acid side chains which showed formation of a reversible complex gels with polyol compounds such as PVA. Such complexes are dissociated after the addition of glucose in a concentration dependent manner.

Intelligent Gels Responding to Antibody Concentration:

Resistance as well as tolerance towards antibiotic concentration is a common phenomenon shown by microbes in many of the infectious diseases. Hence in order to kill all microbes, both multiplying as well as in dormant phase, a pulsatile release of antibiotic is desired. Novel kind of gels have been developed the respond to change in antibiotic concentration to alter their swelling/deswelling characteristics. Utilizing the difference in association constants between polymerized antibody and naturally derived antibody towards specific antigens reversible gel swelling/deswelling and drug permeation changes occur.
pH Sensitive Pulsatile Drug Delivery Systems:

pH dependent polymers are widely accepted and most versatile approach to achieve a desired lag time before drug release in a chronotropic system. Either single unit or multiparticulate dosage forms, they show reliable and predictable drug release profile. These systems take the advantage of fact that there exists different pH environment at different parts of gastrointestinal tract. Hence utilizing pH dependent polymers, targeting at specific site of gastrointestinal tract is possible as well as a desired lag time can be achieved due to dependency of polymer solubility only at a particular pH of gastrointestinal tract. Generally pH dependent polymers include copolymers of methacrylic acid (various grades of Eudragit), phthalates, carboxymethylcellulose e.t.c. these polymers are utilized for enteric coating to protect the drug from degradation in upper G.I.T and attain drug release at specific part of intestine (according to solubility of polymer at particular pH and specific site of intestine) after a predetermined lag time. A number of chronotropic systems have been developed and marketed for chronotherapy utilizing pH dependent polymers for asthma, angina, rheumatoid arthritis, cancer, diabetes and ulcer etc. Akhgari et.al studied on the optimum ratio of eudragitL100 and Eudragit S1000 for colonic delivery of indomethacin pellets for chronotherapy of rheumatoid arthritis. In a study Gupta et.al attempted to exploit various grades of Eudragit soluble at pH more than 7 to achieve colonic delivery of 5-aminosalisylic acid for treatment of irritable bowel syndrome. Also colon targeted chronotropic systems of theophylline, diltiazem, verapamil, budesonide, nitroglycerine etc have been formulated to treat asthma, angina and hypertension.

Dosage Form Development:

Multi-Layered Tablets or Capsules:

Such systems are generally time controlled rupturable pulsatile drug delivery systems either in form of hard gelatin capsules or tablets. In case of capsules, drug filled in capsule-body is either for single pulse or multi-pulse release (in form of multi particulates) which is coated over with a swelling layer followed by an external water insoluble semi permeable polymeric coating. Upon water ingress the swelling layer swells to attain a threshold hydrodynamic pressure required to rupture the outer coating and allowing the release of contents in surrounding medium. The time required by swelling layer to rupture outer coating serves the purpose of desired lag time required in chronotherapy of disease. The tablets are manufactured and coated on the same principle as that of double coated gelatin capsules.

Press Coated Tablets:

These are timed release formulations, simple to manufacture, comprised of an inner core that contains an active pharmaceutical ingredient and excipients surrounded by an outer layer that dissolves or disintegrates slowly to produce the lag time. The core is placed between two layers of polymer and directly compressed by flat punches of tableting machine. Surrounding polymeric layers protect the drug from release before the desired lag time, hence effective delivery in chronotherapy as it allows the drug release at the point in circadian cycle when clinical signs develop and increase. Drugs that treat cardiovascular disease (nifedipine, nitrendipine, amlodipine, diltiazem etc) and asthma (theophylline, budesonide) had been attempted to formulate such dosage forms. Sawada et al. prepared timed release compression coated tablets of nifedipine for chronotherapy of angina and compared its invitro-invivo release profile with sustained release formulation.

Core-cup-Tablets:

The system consists of three different components, a core tablet containing the active ingredient, an impermeable outer shell and a top cover layer-barrier that should be removed at predetermined time. Ideally, the drug should be released after a complete removal of the top cover layer, with the lag time being controlled by the characteristic properties of the material in the top cover. The impermeable coating cup consisted of cellulose acetate propionate and the top cover layer of hydrophilic swellable materials such as polyethylene oxide, sodium alginate or sodium carboxymethylcellulose. The system releases the drug after a certain lag time generally due to the erosion of top cover layer. The quantity of material, its characteristics (viscosity, swelling, gel layer thickness) and the drug solubility was found to modify lag time and drug release. The lag time increases when quantity of top layer increases, whereas drug release decreases.
Multiparticulate Systems:
Such systems have been designed on the basis of various methodologies of designing pulsatile drug delivery system discussed earlier (like time controlled, stimuli induced or externally regulated pulsatile drug delivery systems). Various types of multiparticulate dosage forms are: Pellets, microsponges, microspheres, granules, nanoparticles and Beads etc. Multiparticulate dosage forms are gaining much more importance over single unit dosage forms due to their potential advantages over single unit dosage forms. The potential benefits include increased bioavailability, predictable, reproducible, and generally short gastric residence time; no risk of dose dumping; reduced risk of local irritation; and flexibility to blend pellets with different compositions or release patterns. Because of their smaller particle size, these systems are capable of passing through gastrointestinal tract easily, leading to less inter- and intra-subject variability. A no. of multiparticulate pulsatile drug delivery systems has been developed for chronotherapy. For instance, colonic delivery of theophylline in form of microspheres and coated pellets for nocturnal asthma, formulation of pellets and microspheres of NSAIDS (indomethacin, ibuprofen, flurbiprofen, meloxicam, aceclofenac, diclofenac) for chronotherapy of rheumatoid arthritis and floating beads of alginates encapsulating the active drug component in core, have been attempted to deliver many of the drugs which are absorbed in upper gastrointestinal tract. Numerous advanced technologies have been developed in designing of pulsatile release multiparticulate dosage forms and many of them are FDA approved and being marketed.

Pulsincap Systems:
These are the well designed pulsatile release drug delivery systems capable of releasing drug at a predetermined time. Drug formulation is contained within the insoluble capsule body which is sealed by means of a hydrogel plug. On oral administration the water soluble capsule cap dissolves in the gastric juices and hydrogel plug swells. At a controlled and predetermined time point after the ingestion, the swollen plug is ejected from the pulsincap dosage form after which the encapsulated dosage formulation is then released. To simplify this technology, the hydrogel plug has been replaced by an erodible tablet, which has a tight fit in capsule to prevent the entry of fluid. During the release process it erodes away from the mouth of capsule. The effect of various parameters such as type and weight of swellable polymer, type of hydrophilic polymers used in erodible tablet formulation and erodible tablet weight was investigated in order to characterize the lag time and drug release profiles.
Infusion Pumps:

These are externally and internally controlled, pre-programmed systems and sensitive to modulated enzymatic or hydrolytic degradation, pH, magnetic fields, ultrasound, electric fields, temperature, light and mechanical stimulation. Infusion pumps recently in the market that have been referred as “chronomodulating infusion pumps” for drug delivery application include the “Melodie”, "Programmable-Synchronomed”, “Panomat V5 infusion”, and the “Rhythmic Pumps”. The portable pumps are usually characterized by a light weigh (300–500 g) for easyportability and precision in drug delivery. In case of insulin therapy, implantable infusion pumps containing a reservoir of insulin may be surgically placed within the subcutaneous tissue of the abdomen in the left upper or lower quadrant (above or below the belt). A catheter leads from the pump through the muscle layers into the peritoneal cavity, where it floats freely, and insulin delivery is by the intraperitoneal route. The insulin reservoir is refilled once a month or every 3 months at a physician’s office by inserting a needle through the skin into the pump (a local anesthetic is first used). Doses adjustments are made by the patient (within ranges established by the physician) using radiotelemetry and an electronic device that is held over the pump. Their advantages include the fact that the peritoneum provides a large, well-vascularized surface area, and absorption is faster by this route than after subcutaneous injection (better insulin gradient), improved glycemic control and a reduction in the frequency of hypoglycemic episodes. Possible drawbacks of this approach include eventual formation of fibrous tissue pocket and local skin erosion. Catheter blockade which can reduce insulin delivery, are the most common problems with implantable pumps. However, these pumps have been effectively used in the chronotherapy of several diseases such as cancer and diabetes.

Chronomodulating-Microchips:

Micro-fabrication technology is an alternative method to achieve pulsatile or chronopharmaceutical drug release. Santini et.al. reported a solid-state silicon microchip that can provide controlled release of single or multiple chemical substances on demand46. The release mechanism was based on the electrochemical dissolution of thin anode membranes covering microreservoirs filled with chemicals in solid, liquid or gel form. This technology has the potential to be used in the design of chronotropic drug delivery systems with a better control over drug release kinetic in order to match biological requirement over a versatile period of time.

Chronotherapy of Hypertension:

Hypertension is a chronic medical condition in which the systemic arterial blood pressure (BP) is elevated. It is present in over 90% of all patients with cardiovascular disease (CVD) and affects nearly 74 million individuals in the United States. This condition is a major risk factor for stroke, myocardial infarction, heart failure, arterial aneurysm, and chronic kidney failure. The chronic elevation of BP is a silent disorder in that its progression occurs largely asymptomatically. However, its impact is deafening, causing CVD, end-organ damage, which eventually leads to shortened life expectancy. Simple relationship between high BP and CVD that is heavily influenced by our behavior and what we eat is also conditioned by the time of day. Hence, circadian rhythm is a significant input into the regulation of BP 47-49.

Chronobiology of Hypertension:

Chronobiology is a branch of science that objectively explores and quantifies mechanisms of biological time structure including important rhythmic manifestations of life right from molecular level of living being, unicellular organism to complex organism such as human being. Technologic and scientific advancements in the last 30 years have allowed a greater understanding of the chronobiology of BP and also a detailed analysis of a patient BP risk profile. Research studies over the last few decades have revealed some important findings regarding the typical 24-hour BP profile. One of the strongest among these findings is the ability of the night: day ratio of systolic BP to more accurately predict risk for CV events compared with office BP 50.
Heart rate (HR) and BP have distinct circadian rhythms in both normotensive and hypertensive persons. The BP and HR in both normotensive and hypertensive patients are higher during the morning hours (04:00–06:00 h) than any other time of the day due to a decrease in sympathetic output occurring at night while the individual is asleep. Upon waking, the systolic blood pressure (SBP) rises rapidly by 20–25 mmHg and diastolic blood pressure (DBP) by 10–15. A schematic representation of the change in BP during a 24-hr period is shown in Figure 1. However, different forms of hypertension may exhibit different circadian patterns. In normotension as well as in hypertension, there is a general night drop in BP, whereas in secondary hypertension caused by any of the following conditions such as renal disease, gestation, Cushing’s disease, the rhythm in BP is abolished or even reversed with highest values at night in about 70% of the cases. Ghergel et al. represented the extent of the drop in BP during the night in the region of 10–20%. However, approximately two thirds of the world’s population presents with a BP drop of this magnitude during the night and they are known as dippers. The remaining one third present with a BP drop of < 10% and are known as nondippers.

Prolonged exposure to a higher BP level seen in non-dippers, contributes to an increase in CVD such as myocardial infarctions, angina and strokes during the early hours of the morning. Douglas reported that there is a 40% higher risk of a heart attack, a 29% increased risk of cardiac death and a 49% increased risk of stroke between 06:00 am and 12:00 noon. Conversely, vasospasms in Prinzmetal angina and congestive heart failure symptoms are common during sleep. Since then, an impressive evidence base has occurred regarding the prognostic value of Ambulatory blood pressure monitoring (ABPM), in both treated and non treated. However, night time BP and stratification by dipping status appear even more closely related to prediction of stroke, myocardial infarction, and incident chronic heart failure. Some authors, who first described optic nerve ischemia associated with low BP at night, hypothesized that the reduction in blood flow below a critical level plays a role in the multifactorial pathogenesis of anterior optic neuropathy and glaucomatous neuropathy. Anterior ischemic optic neuropathy is not the only potential collateral damage occurring from excessive lowering of BP at night; a higher rate of cerebral lacunae has also been reported in extreme dippers. The incidence of thrombotic and hemorrhagic stroke is greatest in the morning around the time of commencing diurnal activity. Ischemic events, chest pain, and ST-segment depression of angina are strongest during the initial three to four hours of daytime. The manifestation of ST-segment elevation in Prinzmetal’s angina is most frequent during the middle to latter half of the nighttime. Within the past 10 years, special bedtime tablet and capsule BP-lowering medications have been introduced that proportion the drug level in synchrony with the day-night pattern of systolic and diastolic BP in primary hypertension. The occurrences of coronary infarction as well as of angina pectoris attacks and of pathologic electrocardiography (ECG) - recordings are unevenly distributed over the 24-hour span of a day with a predominant peak in the early morning hours. Moreover, subtypes of a disease entity such as forms of vasospastic and stable angina pectoris or of primary and secondary hypertension may exhibit pronouncedly different 24-hour patterns in their symptoms.

![Fig: 1.7 Schematic representation of the change in BP in a patient with untreated hypertension. The dotted lines represent the normal limit for ambulatory systolic and diastolic BP. The green zone indicates the sleeping period.](image)

With each day, the human body experiences a reproducible rhythm in behaviour, waking in the morning and sleeping in the evening a circadian rhythm. This is a consequence of the brain “resting” and “waking” as evidenced by changes in electrical activity. Moreover, in human hypertension, there are significant deviations to this rhythm in BP. Recent evidence suggested that the genetic components of the circadian clock exert a key and fundamental role in the regulation of BP. The time at which antihypertensives are actually administered, chronotherapy, also impacts BP control.

**Chronotherapy and Chronopharmacology:**

The term chronotherapy is defined as medical treatment administered according to a schedule that corresponds to a person’s daily, monthly, seasonal, or yearly biological clock or the treatment of a sleep disorder by altering an individual’s sleeping and waking times and resetting his or her biological clock. On the other hand, chronopharmacology investigates the effects/side effects of drugs upon temporal changes in biological functions or symptoms of a disease as well as drug effects as function of biologic timing. The treatment of hypertension includes various types of drugs such as diuretics, β- and α-adrenoceptor blocking drugs, calcium channel blockers, converting enzyme inhibitors, and others that differ in their sites of action.
**β-Adrenoceptor Antagonists:**

The main steps in the mechanisms regulating the BP are circadian phase-dependent showed that β adrenoceptor antagonists do not affect or reduce or even abolish the rhythmic pattern in BP. In general, however, there is a tendency for β- adrenoceptor antagonists to predominately reduce daytime BP levels and not to greatly affect nighttime values, being less/not effective in reducing the early morning rise in BP. Consistently, decreases in HR by β-adrenoceptor antagonists are more pronounced during day time hours. In healthy subjects, a cross-over study with propranolol similarly showed a more pronounced decrease in HR and BP during daytime hours than at night. Interestingly, the agent with partial agonist activity, pindolol, even increase HR at night. Clinical data indicate that β-adrenoceptor mediated regulation of BP dominates during daytime hours and is of less or minor importance during the night and the early morning hours. This correlates well with the circadian rhythm in sympathetic tone as indicated by the rhythm in plasma noradrenaline and cAMP.

**Calcium Channel Blockers:**

In primary hypertensives, 3 times daily dosing of non retarded verapamil did not greatly change the BP profile, however, less effective at night. A single morning dose of a sustained-release verapamil showed a good 24-hour BP control. Dihydropyridine derivatives [DHP] differing in pharmacokinetics, seem to reduce BP to a varying degree during day and night, drug formulation and dosing interval may play an additional role. In eight studies in essential hypertensives using a cross-over design, DHP did not differently affect the 24-hour BP profile after once morning or once evening dosing. Most interestingly, the greatly disturbed BP profile in secondary hypertensives due to renal failure was only normalized after evening but not after morning dosing of isradipine.

In primary hypertension, antihypertensive drugs should be given at early morning hours, whereas in secondary hypertension it will be necessary to add an evening dose. Some studies have shown that different cardiovascular active compounds such as propranolol oral nitrates and nifedipine showed higher peak drug concentrations [Cmax] and/or a shorter time-to-peak concentration [tmax] after morning than evening oral drug dosing, at least when non-retarded formulations were used. In the case of retard formulation of IS-5-MN (Elantan® long sustained release) and nifedipine, no circadian phase-dependency in their pharmacokinetics were found. For chronopharmacodynamics of calcium channel blockers (CCB) several trials have investigated the differential effects of morning vs. evening administration of CCB, including amlopidine, cilnidipine, diltiazem, isradipine, nifedipine, nisoldipine, and nitrendipine in diurnally active subjects. A sustained-release formulation of diltiazem was found to be more effective in controlling the 24-hour BP mean when administered at night, while also reducing the diurnal/nocturnal BP ratio towards a more non dipper profile. In some cases, evening administration of these medications resulted in a more marked effect on nocturnal BP and a significant modification of the circadian BP profile.

**Angiotensin-converting Enzyme Inhibitors (ACEI):**

Angiotensin-converting enzyme inhibitors (ACEI) clinical studies demonstrated a different effect of the ACEI benazepril, enalapril, perindopril, quinapril, ramipril, spirapril, and trandolapril when dosed in the morning vs. the evening. Kuroda et al. investigated the effects of the long-acting lipophilic ACEI trandolapril when ingested just before going to bed or in the morning in 30 hypertensive patients. Bedtime administration of the medication was found to be safe and effective means of controlling morning BP in hypertensive patients without the induction of excessive BP reduction nocturnally. The fixed combination of captopril and hydrochlorothiazide was slightly more effective in reducing nocturnal BP when administered in the evening. More recently, Hermida et al. investigated the administration-time-dependent efficacy of spirapril, an ACEI recommended for once-daily administration because of its extended duration of action due to its long elimination half-life of about 40h. They studied 100 patients with grade 1–2 essential hypertensions randomly assigned to receive 6 mg/ day spirapril as a monotherapy, either upon awakening in the morning or at bedtime at night. The efficacy of spirapril was slightly higher with morning dosing, 10.3 and 8.3 mm Hg reduction in the 24-hour mean SBP and DBP, respectively, as compared with bedtime dosing, 8.5 and 5.2 mm Hg reduction in SBP and DBP, respectively. Morning administration of spirapril, was significantly more effective than bedtime administration in reducing the diurnal BP mean and is significantly less effective in controlling nocturnal BP. Accordingly, the diurnal/nocturnal BP ratio was significantly reduced with spirapril ingestion on awakening and significantly increased with spirapril ingestion at bedtime.

**α-Adrenoceptor Antagonists:**

α-adrenoceptor antagonist’s effectively reduces peripheral resistance in the early hours in the morning than at other times of the day and night. Indeed, a single night time dose of the α-blocker doxazosin reduces both SBP and DBP throughout day and night, but its greatest effect is exerted early in the morning. Interestingly, the peak effect of doxazosin following night time dosing occurs later than predicted based upon its pharmacokinetics (PK). Circadian-stage dependency in the dose – response relationship was detected for nifedipine, enalapril, and propranolol.
A recent study explored the administration-time dependent effects of the new doxazosin gastrointestinal therapeutic system (GITS) formulation. In this study, 91 subjects were involved with stage 1 or 2 essential hypertension. Thirty-nine (39) patients had been previously untreated and received the single doxazosin GITS formulation (monotherapy group), while the remaining 52 patients had been treated with two antihypertensive medications with inadequate control of their hypertension (polytherapy group). The subjects of the monotherapy and polytherapy groups were randomly assigned to ingest the daily 4 mg/day dose of doxazosin GITS, either upon awakening or at bedtime, for 3 months. Daily ingestion of doxazosin GITS upon awakening caused only a small and nonstatistically significant BP reduction, because of unavailability of drug effect on nocturnal BP. In contrast, daily ingestion of the new doxazosin GITS formulation at bedtime resulted in a statistically significant BP reduction (P<0.05), mainly of the nocturnal BP. In summary, doxazosin GITS ingested daily upon awakening failed to provide full 24-hour therapeutic coverage, while bedtime dosing, resulted in a significant reduction of BP throughout the 24 h, whether ingested alone as a monotherapy or as part of a combination polytherapy. In a recent study, Calvo et al. evaluated the effects of nebivolol on the 24-hour BP profile of 67 hypertensive patients who received 5 mg/day of the drug on awakening. The effects of nebivolol were significantly greater on the diurnal than nocturnal mean SBP and DBP, resulting in a significant reduction of their diurnal/nocturnal ratios. The efficacy of nebivolol was comparable independent of its dosing time, 13.0 and 11.3 mm Hg reduction in the 24-hour mean SBP and DBP with nebivolol ingested upon awakening; 12.8 and 10.3 mm Hg reduction in the 24-hour mean SBP and DBP with nebivolol ingested at bedtime. At both treatment times, efficacy was more pronounced on the diurnal than nocturnal BP, although differences between the diurnal and nocturnal BP reduction were greater with the morning dosing schedule. Accordingly, there was a significant reduction in diurnal/ nocturnal BP ratio when nebivolol was administered upon awakening, but not at bedtime. The prevalence of nondipping was doubled with the morning nebivolol dosing schedule and remained unchanged with the bedtime nebivolol dosing schedule. These results thus suggested that the optimum dosing time for nebivolol is at bedtime. This ingestion-time schedule, avoids loss in drug efficacy during the 24-hour dosing interval and even the undesired reduction in the diurnal/nocturnal BP ratio that is associated with increased patient cardiovascular risk.

Angiotensin II receptor Blockers:

Angiotensin II receptor blockers (ARB) selectively and specifically antagonize the action of angiotensin II, a potent vasoconstrictor impacting BP regulation. ARBs are becoming increasingly popular for the treatment of hypertension because they are effective and well tolerated. A recent study used 48-hour ABPM to assess the antihypertensive efficacy of the ARB valsartan when ingested by stage 1 or 2 essential hypertension patients for 3 months as a monotherapy, either in the morning upon awakening from night time sleep or at bedtime. The highly significant BP reduction after treatment with the 160 mg/day dose of valsartan was similar for both treatment times. A 17.0 and 11.3 mm Hg reduction in the 24-hour mean SBP and DBP with morning administration as well as 14.6 and 11.4 mm Hg reduction in the 24-hour mean SBP and DBP with bedtime administration was observed by the researchers. Valsartan administration at bedtime has resulted in a highly significant average increase by 6% in the diurnal/nocturnal BP ratio, corresponding to a 73% relative reduction in the number of nondipper patients. In another study, Morgan et al. involved 100 elderly patients with grade 1–2 essential hypertension who were randomly assigned to receive the 160 mg/day dose of valsartan as a monotherapy, either upon morning awakening or at bedtime at night. There was a significant BP reduction after 3 months of valsartan treatment, irrespective of dosing time. The reduction was slightly greater with bedtime dosing, 15.3 and 9.2 mm Hg reduction in the 24-hour mean SBP and DBP than with morning dosing, 12.3 and 6.3 mm Hg reduction in the 24-hour mean SBP and DBP. The diurnal/nocturnal BP ratio was unchanged in the group ingesting valsartan upon awakening (~1.0 and ~0.3 for SBP and DBP; p>0.195). This ratio significantly increased (6.6 and 5.4 for SBP and DBP; p<0.001) when valsartan was ingested at bedtime. The reduction of the nocturnal mean was doubled in the group that routinely ingested valsartan at bedtime as compared with the group that did so in the morning (p<0.001). In the second trial, Hermida et al. used a similar design to investigate the administration-time-dependent effects on BP of the same dose of valsartan (160 mg/day) in a selected population of 148 nondipper hypertensive patients. The significant BP reduction after 3 months of valsartan treatment(p<0.001) was similar for both dosing times (13.1 and 8.5 mm Hg reduction in the 24-hour mean SBP and DBP with morning administration; 14.7 and 10.3 mm Hg reduction in the 24-hour mean SBP and DBP with bedtime administration; p<0.126 for the treatment-time effect). The diurnal/nocturnal BP ratio was significantly increased only when valsartan was administered before bedtime, which resulted in 75% of the patients in this group reverting to dipper status. Other classes of antihypertensive medications have rarely been studied in relation to possible circadian variation of effects. In the first, trial investigating the administration-time-dependent effects of a loop diuretic, Hermida et al. studied 90 hypertensive patients randomly assigned to receive 5 mg/day of torasemide as a monotherapy ingested either upon awakening in the morning or at bedtime at night. The efficacy of torasemide treatment was significantly greater with dosing at bedtime (12.9 and 8.9 mm Hg reduction in the 24-hour mean SBP and DBP) as compared with dosing upon awakening (6.1 and 3.2 mm Hg reduction in the 24-hour mean SBP and DBP; p<0.004 between groups).

Chronotherapy in Resistant Hypertension:

Patients with resistant hypertension are at a greater risk for stroke, renal insufficiency, and morbid cardiovascular events than are patients whose BP is well controlled by pharmacotherapies. Results of the studies on the chronotherapy of resistant hypertension summarized by these researchers revealed the importance of dosing time with combination therapy.
Some Antihypertensive Chronotherapeutically Designed Market Medications:

There are some chronotherapeutically-designed market medications for the treatment of hypertension. The calcium channel blocker (CCB) controlled-onset, extended-release (COER)-verapamil was the first special drug delivery tablet medication specifically designed for the chronotherapy of hypertension (and stable angina pectoris)133, 134. COER-verapamil (USA: Covera HSTM; other markets: ChronoveraTM) was approved in the United States by the Food and Drug Administration (FDA) in 1999 for marketing by the then Searle Pharmaceutical Company. The drug-delivery technology of this tablet medication delays the release of verapamil for approximately 4–5 h following its recommended bedtime ingestion. Medication is released thereafter so the highest blood concentration is achieved in the morning around the time of awakening, generally between 6 and 10 a.m., with an elevated level sustained throughout diurnal activity. Chronotherapeutic oral drug absorption system (CODAS)-verapamil is a second special drug-delivery-based CCB chronotherapy of hypertension. CODASverapamil (Verelan PMTM; Schwarz Pharma) was approved by the FDA in 1999. Release of verapamil from the polymer-coated beads of this capsule medication following recommended bedtime ingestion is delayed for approximately 4 h. Medication is then dispersed in an increasing amount so that peak blood concentration is achieved in the morning, between 6 and 10 a.m., Graded-release long-acting diltiazem (Cardizem LA, Biovail Pharmaceuticals) was approved by the FDA in 2003 for once daily dosing either in the morning or evening. Multiple-dose studies show ingestion of the 360 mg dose of this special drug-delivery form of diltiazem at 10 pm results in the desired PK profile for a chronotherapy of essential hypertension135. Trough blood diltiazem concentration occurs during nighttime sleep at 2 a.m. due to the retarded and slow release of medication following dosing, peak concentration occurs during the morning between 10 a.m. and 12 noon, and an effective drug level is maintained during the remainder of the 24-hour dosing interval. The antagonist propranolol chronotherapy (Innopro XLTM, Reliant Pharmaceuticals) was approved in 2003 by the FDA. The summary of the few marketed chronotherapeutic formulations are presented in Table

<table>
<thead>
<tr>
<th>GENERIC NAMES</th>
<th>BRAND NAMES</th>
<th>MANUFACTURER</th>
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<tbody>
<tr>
<td>Verapamil HCL</td>
<td>Covera-HS® Extended release tablets</td>
<td>Searle Pharmaceutical</td>
</tr>
<tr>
<td>Verapamil HCL</td>
<td>Verelan® PM Extended release capsules</td>
<td>Schwarz Pharma</td>
</tr>
<tr>
<td>Diltiazem HCL</td>
<td>Cardizem® LA</td>
<td>Biovail Pharmaceutical</td>
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<tr>
<td>Propranolol HCL</td>
<td>Innopran® XL</td>
<td>Reliant Pharmaceutical</td>
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<tr>
<td>Diltiazem HCL</td>
<td>CartiaXT</td>
<td>Andrx Laboratories</td>
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Advances in Pulsatile Drug Delivery:

Chronotropic systems are one of the interesting novel drug delivery systems emerging for chronotherapy due to advanced technologies and desired therapeutic application. Among these, multiparticulate systems (beads, pellets, microspheres etc) are gaining more importance than single unit systems due to their potential benefits over them. Various pulsatile technologies have been developed on the basis of approaches discussed previously. These include:

- CODOS technology.
- OROS technology.
- TIMERx technology.
- CONTIN technology.
- DIFFUCAPS technology.
- CEFORM technology.
- Three Dimensional Printing (Their Form Technology).
- PULSYS™ technology.

CODOS Technology:

Term CODOS stands for “Chronotherapeutic Oral Drug Absorption System”, which is a multiparticulate system designed for bedtime drug dosing, incorporating a 4–5 h delay in drug delivery. This delay is introduced by the level of non-enteric release-controlling polymer applied to 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 drug. The rate of release is essentially independent of pH, posture and food. The nighttime dosing regimen of (CODAS-Verapamil) was not associated with excessive BP reductions during the sleeping hours. The CODAS-verapamil extended release capsules (Verelan PM) as chronotropic drug delivery systems actually provided enhanced BP reduction during the morning period when compared with other time intervals of the 24-h dosing period.
OROS Technology:
OROS technology is based on osmotic mechanism to provide pre-programmed, controlled drug delivery to the gastrointestinal tract. Osmotic systems utilize the principle of osmotic pressure for the delivery of drugs. Drug release from these systems is independent of pH and other physiological parameter to a large extent and it is possible to modulate the release characteristic by optimizing the properties of drug and system. The dosage form comprises a wall that defines a compartment. The active drug is housed in a reservoir, surrounded by a semi-permeable membrane/wall (e.g. cellulose esters, cellulose ethers and cellulose ester-ethers) and formulated into a tablet. The tablet is divided into two layers, an active drug layer and a layer of osmotically active agents (e.g. polyethylene oxide). Water from the gastrointestinal tract diffuses through the membrane at a controlled rate into the tablet core, causing 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, Delayed Push-Pull System, also known as controlled onset extended release (COER) was used to design Covera, a novel anti-hypertensive product. It actually enabled delayed, overnight release of verapamil to prevent the potentially dangerous surge in BP that can occur in the early morning.

TIMERX Technology:
The TIMERx technology (hydrophilic system) has been developed by utilizing time dependent natural polymers obtained primarily from xanthan and locust bean gums mixed with dextrose. Physical interaction between these components leads to the formation of strong binding gel in the presence of water. Drug release is controlled by the rate of water penetration from the gastrointestinal tract into the TIMERx gum matrix, which expands to form a gel and subsequently releases the active drug substance. This system can precisely control the release of the active drug substance in a tablet by varying the proportion of the gums, together with the third component, the tablet coating and the tablet manufacturing process.

CONTIN Technology:
This technology utilizes the concept of molecular coordination complexes formed between a cellulose polymer and a non-polar solid aliphatic alcohol optionally substituted with an aliphatic group by solvating the polymer with a volatile polar solvent and reacting the solvated cellulose polymer directly with the aliphatic alcohol, preferably as a melt. This complex serves as matrix in controlled release formulations since it has a uniform porosity (semipermeable matrices). This technology has concretely enabled the development of tablet forms of sustained-release aminophylline, theophylline, morphine, and other drugs. Research suggested that evening administration of Uniphyl (anhydrous theophylline) tablets represented a rational dosing schedule for patients with asthma who often exhibit increased bronchoconstriction in the morning. Patients demonstrated improved pulmonary function in the morning compared with use of twice-daily theophylline when once-daily Uniphyl was administered in the evening. Thus, evening administration of once-daily theophylline may block the morning dip in lung function commonly seen. CONTIN technology provides for closer control over the amount of drug released to the bloodstream, and benefits patients in terms of reducing the number of doses they need to take every day, providing more effective control of disease particularly at night.

DIFFUCAPS Technology:
DIFFUCAPS technology is the most popular and versatile approach for chronotherapy for delivering drugs into the body in a circadian release fashion. It is comprised of multiparticulate one or more populations of drug-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 3–5 h. The active core of the dosage form may comprise an inert particle or an acidic or alkaline buffer crystal (e.g. cellulose ethers), which is coated with a film-forming formulation and preferably a water-soluble film forming composition (e.g. hydroxypropylmethylcellulose, polyvinylpyrrolidone) to form a water-soluble/dispersible particle. The active core may be prepared by granulating and milling and/or by extrusion and spheronization of API. Such a chronotropic drug delivery system is designed to provide a plasma concentration-time profile, which varies according to physiological need during the day, i.e. mimicking the circadian rhythm and severity/manifestation of a cardiovascular disease, predicted based on pharmacokinetic and pharmacodynamic considerations and in vitro/in vivo correlations. This technology has been used to formulate the first and recently FDA approved propranolol containing chronotropic system (InnopranR XL) for the management of hypertension.

Fig:1.8 Diagrammatic Representation of Multiparticulate Drug Release Mechanism in “DIFFUCAPS Technology”.

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**CEFORM Technology:**

CEFORM technology applies several mechanical forces which allow the production of uniformly sized and shaped microspheres of pharmaceutical compounds. The basic methodology applied in designing of such chronotropic system is based on “melt-spinning technology”, which involves subjecting of biodegradable polymer / bioactive agents to the combination of temperature, thermal gradients, mechanical forces, flow, and flow rates during processing. The microspheres obtained are almost perfectly spherical, having a diameter that is typically 150–180 μm, and allow for high drug content. The microspheres can be used in a wide variety of dosage forms, including tablets, capsules, suspensions, effervescent tablets, and sachets. The microspheres may be coated for controlled release either with an enteric coating or combined into a fast/slow release combination. This technology has been actually used to develop “Cardizem LA”, 1-day Diltiazem formulation as chronotropic systems.

**Three Dimensional Printing (Their Form Technology):**

It is a fully integrated computer-aided development and manufacturing process. Products may be designed on a computer screen as three-dimensional models before actual implementation of their preparation process. This versatile technology may found potential application in chronopharmaceutics in the future. Three dimensional printing (3DP) is a novel technique used in the fabrication of complex oral dosage delivery pharmaceuticals based on solid free form fabrication methods. It is possible to engineer devices with complicated internal geometries, varying densities, diffusivities, and chemicals. Different Types of complex oral drug delivery devices have been fabricated using the 3DP process: immediate-extended release tablets, pulse release, break away tablets, and dual pulsatory tablets. The enteric dual pulsatory tablets were constructed of one continuous enteric excipient phase into which diclofenac sodium was printed into two separated areas. These samples showed two pulses of release during in vitro with a lag time between pulses of about 4 hr. This technology is the basis of the “Their Form technology”. The latter is a micro-fabrication process that works in a manner very similar to an “ink-jet” printer.

**PULSYS Technology:**

PULSYSTM technology, pioneered by Middle Brook™ (previously Advancis) Pharmaceuticals, Inc., could be considered a significant step forward in improving current antibiotics treatment regimens. From the very start, the company faced numerous setbacks and challenges before its once-daily amoxicillin (775 mg) product, Moxatag, based on PULSYSTM technology (was approved by the US FDA on 24 January 2008); it was set to enter the market on 16 March 2009. Moxatag is an extended-release tablet for the treatment of adults and pediatric patients aged ≥ 12 years with pharyngitis and/or tonsillitis secondary to Streptococcus pyogenes (commonly referred to as ‘strep throat’). The PULSYSTM technology of delivering drug in parallel concomitant pulses corrected the flaws in traditional anti-infective therapy, which relied on single, strong and immediate drug doses that – rather than killing microbes – tend to trigger defensive dormancy in bacteria; studies have shown that antibiotics are most effective against actively growing bacteria. However, traditional anti-infective therapy methods, which focus on immediate-release doses, prompt bacteria to enter a dormant state, in which they may survive the drug. Exposing the bacteria to rapid antibiotic pulses within the first hours of initial dosing was found to have the potential to cripple the natural defense mechanisms of bacteria, eliminating them more efficiently and effectively than conventional anti-infective therapy regimens.

![Image of pulsatile chronotherapeutic formulations](image-url)

**Fig: 1.8 Scalable Pulsatile Chronotherapeutic Formulations consisted of a Capsule Containing Tablets with Different Coating Layers Adjusting Precisely the Time of Felodipine release.**
CONCLUSION

Besides lots of experimental and theoretical development, chronotherapy is still in stage of infancy. Market constraints and increasing demand of such drug delivery systems demonstrate the clinical relevance of chronopharmaceutics; hence chronotropic systems are an emerging approach to drug delivery. Chronopharmaceutics assures improved patient outcome and optimized disease management in the future. Dependence of response over human action to trigger the drug release is the major drawback associated with these systems. Hence an ideal chronotropic system should be self regulating, taken any time and should take environmental factors in account (e.g. awake – sleep, light – dark, activity – rest status). For example, the human body is comprised of molecules, hence the availability of molecular nanotechnology that facilitate self-regulation of chronotropic systems based on body immune system and disease state will permit dramatic progress in human medical services. Moreover, the circadian clock of the suprachiasmatic nucleus (SCN) is thought to drive daily rhythms of behavior by secreting factors that act locally within the hypothalamus. The overall success of chronopharmaceutics will depend on the successful integration of knowledge from future advances in development timing, system biology and nano medicine. The selection of the appropriate chronopharmaceutical technology should take into considerations the application range (e.g. targeted drugs of different physiochemical properties), the ease of manufacturing, the cost-effectiveness, and the flexibility in the pharmacokinetic profile. Pulsatile drug delivery systems are smart and efficient dosage forms satisfying needs of patients and offering interesting options for intelligent life cycle management. In near future due to more advancement of technology, the hurdles in manufacturing and processing steps will be overcome and a number of patients will be greatly benefited by these systems.

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Conflicts of Interests

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<table>
<thead>
<tr>
<th>No.</th>
<th>Drug</th>
<th>Category</th>
<th>Pharmacological Properties</th>
<th>Encapsulation Method</th>
<th>Polymer Used</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Carvedi lol.</td>
<td>Non-Selective and Adrenergic antagonist.</td>
<td>Carvedi lol which have no intrinsic sympathomimmetic activity widely used to treat essential Hypertension and Anginapectoris. Due to its short biological half life (7-10 hrs) and low dose (6.25-25mg) coupled with good colonic absorption make it an ideal candidate for colon targeting.</td>
<td>Emulsion solvent diffusion technique. Emulsion cross linking method.</td>
<td>Chitosan. Eudragit S-100</td>
<td>Ec3 formulation was found to be the best formulation. It showed that 3.98% of drug was released in initial 4 hours from the capsule.</td>
</tr>
<tr>
<td>4</td>
<td>Diltiazem hydrochloride.</td>
<td>Benzothiazepine calcium channel antagonist.</td>
<td>Diltiazem hydrochloride exhibits high solubility and hence it would be possible to minimize drug release from coated pellets below pH7.0 and effectively release the drug at colonic pH only with higher coat loads(15-20% weight gain).</td>
<td>Aqueous extrusion spherionisation. Automatic coating pan.</td>
<td>MCC, PVPK30. Triethyl citrate, Eudragit S100.</td>
<td>MCC was a key ingredient for effective aqueous spheronization. The pellets DH4 was found to be the best formulation as minimum drug was released below pH7.0 and at the same time release the entire content(83.29%) at the colonic Ph.</td>
</tr>
<tr>
<td>5</td>
<td>Diltiazem hydrochloride</td>
<td>Benzothiazepine calcium channel antagonist.</td>
<td>The basic idea behind the dosage from development is to investigate effect of coating design on lagtime and drug release from directly compressed time controlled release tablet.</td>
<td>Direct compression method. Compression coating.</td>
<td>AVICEL pH 102, Cross carmellose sodium.</td>
<td>The system is capable in delaying drug release for a programmable period of time to attain drug release 6-8 hrs after an evening dose taken at approx 10:00 pm. Water uptake studies showed that the plain gellable polymers such as klucel HF/ klucel HFX have higher water uptake capacity as compared with Eudragit RSPO. KLUCEL HF gave a lag time of 7hrs and complete release in 8.5hrs. The present study conclusively demonstrate the feasibility of effectively encapsulating Lornoxicam into natural polymers to from potential; chronomodulated drug delivery system.</td>
</tr>
<tr>
<td>6</td>
<td>Lornoxicam.</td>
<td>NSAID.</td>
<td>Being a weak acidic drug it is well absorbed in the lower GIT and has a short biological half life of 3-5hrs and hence Loxnoxicam is used to prolong its duration of action and reduce the frequency of usage and minimize its irritant effect on the stomach.</td>
<td>Suspension polymerization method. Emulsification solvent evaporation method. Emulsification method.</td>
<td>Gelatin, Sodium CMC, Chitosan.</td>
<td>HPMC showed excellent time-delayed release of the drug by way of an optimal lay period in both acidic and basic environment.</td>
</tr>
</tbody>
</table>
8. Salbutamol sulphate. Selective β-2 receptor blocker. It is capable of releasing the drug in a pulsatile fashion and is aimed to have a lag time of 6hrs.

9. Theophylline. Bronchodilator. Theophylline was selected as a drug candidate considering its short half life (7-9hrs), good oral bioavailability (96%) and good colonic absorption.

10. Toreosedime. Pyridine sulfonylurea type loop diuretic. Toreosedime was selected since the symptoms of Hypertension are more prevalent during the early hours of morning and therefore to obtain the predetermined lag time of 6hrs, after which the drug is released.

11. Terbutaline sulphate. A Potent β-2 receptor stimulant. To develop delayed capsules device since the drug has been effective for preventing time related occurrence of Asthma.

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