ABSTRACT
Chronotherapy is recent advanced appropriate technology drug delivery system. The drug is delivery to particular site with the specific time. It is also recognized as chronotropic drug delivery system. It any therapy based on the timing of physiologic and pathologic activities of human body. This process in which a person’s daily activates are supposedly synchronized with a natural metabolic rhythm in a 24-hours cycle. The particular time those patients took a medication it as impact a treatment of suitable diseases. The disease symptoms circadian variations drug release to vary over time. Drug pharmacokinetics can also a time depended, variation of disease state and in plasma drug concentration. This drug delivery system designed to benefit of drug release with in short period of time, after predetermined a long time. This system is favorable drug delivery systems in circadian diseases like asthma, cardiovascular diseases, arthritis, and hypercholestremia Approaches are capsular system. Different types of barrier coated, stimuli sensitive pulsatile system and externally regulated system are synopsize in this article. These review articles focus on disease of chronotropic systems,

INTRODUCTION
The generally clear showing a rhythmic activity in plant or trees. The leaves of trees or plant opening day and closing at night time. The circadian rhythms acts in mammals are known to be absolutely healthy. The drug ability and toxicity depending on relationship between dosing of drug the 24 hours rhythms of biochemical and physiological actions. Also some drugs alternation reaction of 24 hours rhythms leading to illness and homeostatic organizing. Alternation in biological rhythm is also a novel concept of adverse effects, which can be minimized by optimizing the dosing schedule. The drug delivery was as per rule worried
with absorption should be easy to be foretell from site of injection or gout. The second generation drug delivery added to achieved perfection in continues 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 amount of drug at predictable different time within circadian cycle which will maximum desired and minimum undesired drug effects.

**Figure No. 1: Human circadian biological clock.**

**Chronobiology** is the branch of science it defined as the study of biological rhythms and there mechanisms within suitable time. “*Chrono*” means pertains to time and “*biology*” means pertains to the study or science of life.[3]

**Chronopharmacology** is the science it is chronobiological approaches to pharmalogical phenomena. The study of the manner and extent to which the kinetics and dynamic actions of drug are affected by biological rhythms and the effected of the drugs on biological rhythms.[3]

**Chronopharmacokinetic** involves the rhythm dependent difference in the absorption, distribution, metabolism and excretion of the drug. In the kinetic parameter time is constant, are influencing by different physiological functions in circadian rhythms. The changes of circadian in gastric acid secretion, gastrointestinal motility, and gastrointestinal blood flow, drug protein binding, renal blood flow and liver enzyme activity. pH can role in time depended variation of drug plasma concentration.[3]

**Chronotherapy** the investigative science that elucidates the biological rhythms dependencies of medication. The delivery of drugs in synchrony with the rhythm dependent circadian variation inherent in the human body.[3]
Chronopharmaceutics is a branch of pharmaceutics devoted to the design and evaluation of drug delivery systems that release drug to match the biological requirements of a disease therapy.[3]

There are three types of mechanical rhythms in human body.

Infradian Rhythms
Ultradian Rhythms
Circadian Rhythms

Infradian Rhythms (from the Latin “infra” meaning “under,” and “dies” meaning “day”) are rhythms that last more than 24 hours. These are repeated only every few days, weeks, months, or even once per year. Good examples are seasonal rhythms such as bird migration, lunar rhythms (which follow the phases of the moon, or about 29.5 days) and semi-lunar rhythms (about 14 days) that are associated with tidal cycles. Another example is unpredictable rhythms (aka “non-circadian rhythms” that do not have any environmental correspondence) such as a woman’s menstrual cycle.

Ultradian Rhythms (from the Latin “ultra” meaning “over,” and “dies” meaning “day”) are biological rhythms that are shorter than 24-hours. There are many physiological functions of the human body that exemplify an ultradian rhythm. These rhythms have multiple cycles in one day. An adult, for example, has an exertion and rest cycle about every two hours. Ultradian rhythms regulate physical, emotional and spiritual functions. They often last several hours and include the ingestion of food, circulation of blood, excretion of hormones, different stages of sleep and the human performance curve. These processes are built into our bodies in millions of ways. Some last merely seconds, such as the control of breathing. Some last only milliseconds, such as the majority of processes that take place in the cell on a microcirculatory level. Tidal rhythms (about 12.4 hours) are often observed in marine life, follow the transition of the tides from high to low and back and have a special function for many people living inside a surf zone.

Circadian Rhythms (from Latin “circa meaning around and “dies” meaning “day”) are rhythms that take approximately 24-hours, i.e. the human sleep/wake cycle or the leaf movements of plants. Many effects of circadian rhythms directly and immediately affect humans, therefore, they are the most extensively researched. Thus, all further explanations refer to circadian rhythms.
Treatment of chronotherapy: The coordination of biological rhythms treatment is known as chronotherapy. Each person’s body have own rhythm which are governed by the environment changes or genetically.

Chronotherapy disease given below

- Hypertension
- Bronchial asthma
- Peptic ulcer
- Arthritis
- Hypercholesterolemia
- Diabetes
- Sleep Disorders
- Epilepsy
- Cancer
- Alzheimer’s Disease
- Parkinson’s Disease

Hypertension: it is chronic disease and 1 billion people suffered from hypertension disease in world. According to physiological conditions described as early morning arise the systolic and diastolic pressure increase up to 3mmHg/hour between 4 to 8 hours A.M which is called as post-awakening. Blood pressure and heart rate higher at walking at the morning and it will being to decrease at afternoon and finally reaches to systolic and diastolic pressure at night.

Some cardiovascular drugs have their higher peak concentration twice at morning dose compared with evening dose. Several drugs a shorter time is required to reach peak concentration of the drug morning compared to evening dose. But the sustained release dosage forms showed the no such variation. The chronopharmacokinetic mechanisms involved gastrointestinal perfusion in the morning and faster gastric emptying time.

Bronchial asthma: it is chronic airway inflammation disease and more circadian variations then the other diseases with respect time. Many circadian-dependent factors appear to contribute to the worsening of nocturnal asthmatic symptoms. The chronopharmacological studies statically show that the development of asthma symptoms 50 to 100 times more at night and many types of the bronchospastic attacks in mid night to early morning from 2 to 6
A.M every day. Various chronic other agents studies have been under taken and show that intake of theophylline with in time at 3 P.M. achieves therapeutic dose at night and toxic levels during the day are avoided.[5-9]

**Peptic ulcer:** Many of the functions of the gastrointestinal tract are subjected to circadian rhythms generally gastric acid secretion is highest at night time compare to day. Gastric emptying and motility are slower at night, In the past, histamine2 antagonists were administered at regular intervals around the clock, on the basis of pharmacokinetic properties. However, because maximal acid secretion, peptic ulcer disease pain, and perforation of gastric and duodenal ulcers are more common at night, administration of these drugs at bedtime is more effective. Nocturnal administration not only reduces acid secretion more effectively but also promotes ulcer healing and reduces ulcer recurrence.[5-9]

**Arthritis:** it is can depended chronobiology pattern have been observed two types of arthritis pain they are rheumatoid and osteoarthritis. The symptoms of rheumatoid arthritis are always worse in at morning taken the long time period acting of NSAID they showed the optimizing therapeutic effects at bed time and minimized the side effects.[11] The osteoarthritis tend have more pain morning at and end mid night. Ibuprofen may be more effective at relieving pain if dug is administered at least 4 to 6 hours before the pain reaches its peak. The NSAID is more helpful for arthritis patients take the before bed time they particularly discomfort in the morning.[12]

**Hypercholesterolemia:** The synthesis of cholesterol is generally higher during night time than day light according to A circadian rhythm. 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.[13] The activity of rate limiting enzyme HMG-CoA is higher in the night time but the diurnal variations occur due to periodicity or degradation of this regulatory enzyme.

**Diabetes:** The circadian variations of glucose and insulin in diabetes have been extensively studied and their clinical importance in case of insulin substations in type 1 diabetes as been perversely discussed.[13] Insulin can show its cyclic rhythmicity of 8-30 min which can show the optimal action. The modulators of insulin release and action are secreted in a circadian pattern and impress the mode of insulin release. So difference between maximum and
minimum plasma insulin concentration has short-term rhythmicity and complex secondary circadian rhythm is variable early-morning and late-afternoon insulin resistance.[14]

**Alzheimer’s Disease:** The change of circadian rhythm is also seen in patients with Alzheimer's disease. Individuals with Alzheimer's symptoms show less diurnal motor activity and higher percentage of nocturnal activity which show the lower inter daily stability of motor activity and activity of macrophages peak time than normal healthy individuals. The core body temperature is also higher in patients and the circadian abnormalities are seen together with cognitive and functional deterioration in this disease.[14] 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.[15]

**Parkinson’s Disease:** Parkinson's disease discloses many alterations in circadian rhythm of blood pressure; amplified diurnal blood pressure variability and postprandial hypotension are due to autonomic dysfunction.[16] But existence of circadian rhythm in this disease has not been evaluated in clinical data because the daily fluctuations of motor activity pattern of the phase of the disease and the subsequent role of drugs are difficult to estimate.

**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.

**Stimuli Dependent Systems or 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 shows burst release of drug immediately after predetermined lag time. The design of methodology these systems can be further classified into several subtypes.

**Reservoir systems with bursting polymer coating**

These systems are may be single or multiparticulate reservoir systems outer layer coated with bursting polymers when the water is enter into within system up on the a hydrostatic pressure develops which leads bursting a polymeric layer that’s resulting drug release from the core of system.\(^{[17]}\) The pressure is increased required to bursting polymer coating can be achieved by swelling agents gas producing effervescent agents. The mechanical resistance of the bursting layer is major factors affecting the lag time depending on rate of water permeation. The mechanism of drug release based on either diffusion process according to the nature of drug.\(^{[18]}\) Discovered time controlled explosion systems for water in soluble drugs in both single and multiple dosage forms. 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 semi permeable 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 bursting 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.\(^{[19-25]}\) 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.\textsuperscript{[26-30]} 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 pulsed delivery of diclofenac was found to be good agreement between in vitro and in vivo.

![Schematic Diagram of Reservoir Systems with Rupturable Coating Layer.](image)

**Figure No 2: Schematic Diagram of Reservoir Systems with Rupturable Coating Layer.**

**Capsular systems:** This type of system consisted of degradable and swellable plugs and insoluble capsule body they are made of approved substances. The plug id long time controlled which is time right now a way by swelling and drug released as pulse from the insoluble capsule the polymers used for designing of the hydrogel plug.\textsuperscript{[31]} Insoluble but permeable and swellable polymers (e.g., polymethacrylates) Erodible compressed polymers (e.g., hydroxy propylmethyl cellulose, polyvinyl alcohol, Polyethylene oxide) Congealed melted polymers (e.g., saturated polyglycolated glycerides, glycercyl monooleate) Enzymatically controlled erodible polymer (e.g., pectin).\textsuperscript{[32]}

**Chronotropic systems dependent on changed membrane permeability**

In this chronotropic system drug release is depending on the permeability of membrane and polymeric coating layer in presence of counter ions in enclosing media. That device capable of pulsed release development is depending on the diffusion properties of eudragit RS. They studied and legitimize cores of theophylline coated with Eudragit RS then show the slow release in pure water and when the microcapsules are immersed organic acid solution increased the drug release rate significantly containing succinic acid, glutaric acid, tartaric acid, malic acid or citric acid.\textsuperscript{[33-34]} The phenomena take place higher hydration of film containing polymer chain in quaternary ammonium groups of eudragit RS are important to produce unique profiles of drug release. The drug release system depending on permeability changes strongly depending physiochemical properties of drug and interaction with
membrane. Therefore with this system a pulsalite release profiles may be obtained some particular drug molecules this type of formulations cannot be suitable to all drugs.

**Reservoir systems with soluble/eroding polymer coating**

This type of pulsatile reservoir system drug is enclosed in barrier layer when the dissolved polymer layer burst release of drug from a reservoir core with specific lag time. The long time drug release depending upon thickness of coating layer, which mainly consists of drug core layered with HPMC and top of enteric coating the long period drug release will be depending on the thickness and viscosity grade of HPMC layer. Since mechanism of drug release in this system is dissolution, because the drug solubility higher relative the dose of drug is essential for very quick drug release after long period. Different grades of HPMC and Eudragit polymers have been referees to in attack a drug delivery to various sites gastrointestinal tract due to 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.\(^{35}\)

![Diagram](image)

**Figure No 3:** Expected Behavior and Release Profile of Soluble/Erodible Reservoir Systems for Oral Pulsatile Delivery.

**Low density/floating systems:** Nowadays floating drug delivery is most importance technology, drug delivery depending on the gastro retentive behavior and so many advantages in drug delivery. Generally treatment of gastrointestinal disorders and improved drug absorption then better patient compliances.\(^{36}\) This system dosage forms are retained in
stomach for long time 4-12 hours and do not affected by any physiological and variations of gastric pH, local environment or gastric emptying time. The floating dosage forms are single unit dosage forms beads, pellets, granules, microspheres are mutiparticulates with ability to perform gastro retention. 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.\(^{[37]}\)

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.\(^{[38]}\) The drug of meloxicam was adsorbed on calcium solicate by solvent evaporation process and that powder was use to calcium alginate beads by ionotropic gelation method. The floating time of the system depending on the density of beads and nature of drug. To overcome limitations of various approaches for imparting elasticity of calcium pectinate beads were prepared by simple process of acid base reaction and during ionotropic cross linking method. The floating beads provide two-phase release pattern with initial long time during floating in acidic medium followed by rapid pulse release in phosphate buffer. These drug delivery systems show 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 formulations.

**Stimuli Dependent Systems or pulsatile drug delivery systems**

This system is approaches to novel drug delivery system meant drug is directly delivered to specific target site within a time. It induction of physiochemical stimuli at target site particularly drug release this type of drug delivery systems like Release of certain enzymes, hormones, antibodies, pH of the site, temperature of the site, presence of certain cells, and concentration of biomolecules.

**Temperature sensitive pulsed-release delivery systems**

In this systems the polymer undergo swelling or deswelling phase in response to the temperature with modulate drug release in swollen state. The polymer swelling activities depending body temperature according to physiological functions, in this system thermo-responsive hydrogel system have been develop for pulsatile delivery system.\(^{[39]}\)
Inflammation induced systems

On receiving physical or chemical stress like injury, fracture, more inflammation is a particular site here hydro radicals are produce from inflammation responsive cells, yui and co-workers et al, they are focused on induced of inflammatory and design drug delivery system, hear response to degraded in limited manner of hydroxyl radicals and in this system they are used hyaluronic acid with specify degraded of radicals it is dominate and rapid when HA injected at inflammatory site. Thus it possible to treatment of rheumatoid arthritis diseases and same way anti inflammatory drug incorporated HA gels as new implantable drug delivery system.

Enzyme dependent pulsatile-release systems

Such types of system are mainly developed for colonic drug delivery hears rate of drug release is dependent on catalysis of polymeric membrane by enzyme secreted by colonic microflora. In this system drug is targeted of specific site independent of pH variations in gastrointestinal tract. number of natural polysaccharides used in formulation of colon specific drug delivery and coating of purpose has been tried with limited success. Yui and coworkers et al. The main drawback of non starch polysaccharides lacking of film forming properties and also swell in gastrointestinal tract the drug release is early the rheumatoid arthritis Chronotherapy has been tried by utilizing these polymers to deliver NSAIDS in colon after a lag time of 4-6 hours to relieve pain in early morning.

Glucose concentration dependent insulin release systems

This system describe according to rhythmically glucose concentration increase in blood there requiring injection of the insulin at proper time at diabetes-mellitus type-1. so many methods are developed which are able to respond to changes in glucose concentration. Such as one system are developed includes pH sensitive hydrogel containing glucose oxidase immobilized in the hydrogel. When glucose concentration increased in blood then glucose oxidase converts glucose into gluconic acid change in pH of system. That pH inducer swelling of polymer insulin is released. Insulin by integrity of action reduced blood glucose level and consequently gluconic acid levels can decreased and turn of the deswelling therapy in insulin release. Examples of pH sensitive polymers include n, n-dimethyl amino ethyl methacrylate, chitosan, polyol e.t.c. Okan et al.
Intelligent gels responding to antibody concentration
This system are recently novel gel technology were developed responded to the change in the concentration of bio active compounds to alternate reselling or swelling nature. The observed number of kid’s bio active compound which exist in the body some assiduity given to antigen-antibody complex develop as in gel cross linking units and that interaction is very specific. 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 (survase et al 2007).

pH sensitive pulsatile drug delivery systems
This type of pulsatile drug delivery system develop a two types components one is immediate release type the second one is pulsed release hear drug is response to pH. The advantage has been taken pH depended system different pH environment parts of gastrointestinal tract by selecting the suitable polymers and drug release obtained from specific location. An given examples of pH dependent polymers includes cellulose acetate, polyacrylates and sodium carboxyl methyl cellulose. This type of polymers used as enteric coating materials so it provide drug release in small intestine (survase et al. 2007).

Dosage form development
Multi –layered tablets or capsules
Generally this systems are time controlled bursting pulsatile drug delivery systems and either in form of hard gelatin capsules or tablets. In case develop capsules, drug filled in capsule-body is either for single pulse or multi-pulse release, which is coated over with a swelling layer followed by an external water insoluble semipermeable polymeric coating. Upon water is intended into a swelling layer swells to attain a threshold hydrodynamic pressure required to bursting 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
This type of all formulation drugs releasing depending on time and manufacture is simple. It consists of two layers one is inner core and outer core inner core compressed of active pharmaceutical ingredients and outer core compressed with excipients. The role of the press coated tablet outer layer dissolve or disintegrates slowly to produce long time. The core is
placed between two outer layers or excipients layers directly compressed with a flat of tablet machine. The main role of surrounding polymers layers protect the drug from release before particular time, then chronoterapy at allow the drug release at point of circadian cycle then clinical significances develop and increase. Drugs that treat cardiovascular disease (nifedipine, nitrendipine, amlodipine, diltiazem e.t.c) 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.

![Diagram of press-coated system](image)

Fig 4: Design of the press-coated system composed of FELO/PVP 10/90 w/w (black color) and an inactive and adjusting coating layer containing different PVP/HPMC ratios (h =expected rupture area)

Core –cup-tablet

The system consists of three different components the active ingredient contain tablet core, bottom shell is impermeable layer and upper barrier is top cover layer when should be removed at suitable time. The total drug released after removed of top cover layer with in lag time, this layer controlled by depending on characteristics properties of material in top cover. The bottom layer of 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 like time controlled, stimuli induced or externally regulated pulsatile drug delivery systems.\[42\] different types of multiparticulate dosage forms are: Pellets, microsponges, microspheres, granules, nanoparticles and Beads e.t.c. Multiparticulate dosage forms are achieve much more importance over single unit dosage forms due to their potential advantages over single unit dosage forms. The potential benefits are 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 have been developed for chronotherapy.\[43\] 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, acetylsalicylic acid) for chronotherapy of rheumatoid arthritis and floating beads of alginites encapsulating the active drug component in core, have been attempted to deliver many of the drugs which are absorbed in upper gastrointestinal tract.
**Pulsincap system**

This system as well as pulsatile drug delivery system the drug release depending on a pre-determine time. The drug developing contain with the present insoluble capsule body sealed with that means of a hydrogel plug.\(^{[44]}\) When orally administrated capsule in soluble capsule cap hydrogel plug is swelling and dissolved in the gastric juices. After incorporated drug that flowed At a controlled and predetermined time point, the swollen plug is ejected from the pulsincap dosage form after which the encapsulated dosage formulation is then released. 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.\(^{[45]}\) 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-Synchronmed”, “Panomat V5 infusion”, and the “Rhythmic Pumps”. The portable pumps are usually characterized by a light weight (300–500 g) for easy portability 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**

The pulsatile or chronopharmaceutical drug release is alternative method to achieve Microfabrication technology Santini et.al. reported a solid-state silicon microchip that can provide controlled release of single or multiple chemical substances on demand. The mechanism of drug release 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 major risk factor for coronary heart diseases and stroke and frequently causes damage to the arterial blood vessels the eyes and kidneys it prolonged enlargement of heart may lead to heart failure. Common risk factors of hypertension like myocardial infarction,
heart failure, arterial aneurysm. These disorders progressive occur largely asymptomatically and Blood pressure displays appreciable predictable-in-time circadian variation. The chronotherapy of hypertension takes into account the clinically relevant features of the 24-h pattern of blood pressure, e.g. the accelerated morning rise and nighttime decline during sleep, plus potential administration circadian time determinants of the pharmacokinetics and dynamics of antihypertensive medications.\textsuperscript{[47-49]}

**Chronobiology of hypertension**

A major objective of a chronotherapy for cardiovascular diseases would be to deliver the drug in higher concentrations during time of greatest need (e.g., the early morning post-awakening period) and in lesser concentrations when the need is less (e.g., during the middle of the sleep cycle). At present, there are not enough data to know whether altering the dosing time of a conventional antihypertensive or anti-anginal therapy would achieve these objectives. Recently, the effects of the timing of the dose of a conventional antihypertensive agent on circadian blood pressure patterns.\textsuperscript{[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\textsuperscript{6-9}. 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\textsuperscript{10-13} 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 present 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 nondippers, contributes to an increase in CVD such as myocardial infarctions, angina and strokes during the early hours of the morning\textsuperscript{14-16}. 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.

Graph No 1: 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.
(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. 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 a function of biologic timing. The treatment of hypertension includes various types of drugs such as diuretics, and 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 adrenoceptor antagonists do not affect or reduce or even abolish the rhythmic. In general, 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 daytime 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.\(^{[65]}\)

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. chronopharmacodynamics of calcium channel blockers (CCB) several trials have investigated the differential effects of morning vs. evening administration of CCB, including amlodipine, 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 nondipper profile.\(^{[66]}\) 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, andtrandolapril when dosed in the morning vs. the evening. 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.\(^{[64-66]}\) The fixed combination of captopril and hydrochlorothiazide was slightly more effective in reducing nocturnal BP when administered
in the evening, 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. 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.\[66\]

**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. a single night time dose of the 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).\[64-66\] Circadian-stage dependency in the dose – response relationship was detected for nifedipine, enalapril, and propranolol.

**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.\[83\] 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.\[83\] 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.\[83\] In another study, Morgan et al\[84\] 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 al85 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 al85 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).69-72

**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 drugdelivery tablet medication specifically designed for the chronotherapy of hypertension (and stable angina pectoris).87-88 COER-verapamil (USA: Covera HST™; other markets: Chronovera™) was approved in the United States by the Food and Drug Administration (FDA) in 1996 for marketing by the then Searle
Pharmaceutical Company. The drug-delivery technology of this tablet medication delays the release of verapamil.

Table No 1: Antihypertensive Chronotherapeutically-Designed Market Medications available in the Market.

<table>
<thead>
<tr>
<th>GENERIC NAMES</th>
<th>BRAND NAMES</th>
<th>MANUFACTURER</th>
</tr>
</thead>
<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>
</tr>
<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 motivating novel drug delivery systems rising for chronotherapy due to advanced technologies and beloved therapeutic application. Among these, multiparticulate systems (beads, pellets, microspheres etc) are in advance 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 only at bedtime drug dosing, incorporating a 4–5 hr delay in drug delivery. This system 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.\cite{81}

**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. This system 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 suitable system. 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, one is active drug layer and another a layer of osmotically active agents (e.g. poly ethylene 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.\cite{80-83}

**TIMERX Technology**

The TIMERx technology also called (hydrophilic system) it has been developed by utilize time dependent the natural polymers is obtained primarily from xanthan and locust bean gums mixed with dextrose. Common Physical interaction between these components leads to the formation of strong binding gel in the presence of water. The Drug release is controlled by the rate of water dispersion 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.[82-84]

CONTIN Technology
This technology utilizes the main concept of complexes formed a molecular coordination 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 physical parameter of porosity (semipermeable matrixes). This technology has concretely enabled the development of tablet forms sustained-release of aminophylline, theophylline, morphine, and other drugs. The investigate suggested that type of dosage forms evening time administration of Uniphyl (anhydrous theophylline) tablets represented a rational dosing schedule for patients with asthma who often show signs of increased bronchoconstriction in the morning. So Patients demonstrated improved pulmonary function in the morning compared with use of twice-daily theophylline when once-daily Uniphyl was administered in the evening.83-84 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 time.

DIFFUCAPS Technology
DIFFUCAPS technology is the most popular and adaptable 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.\textsuperscript{[84-85]}

![Figure No: 7 Diagrammatic Representation of Multiparticulate Drug Release Mechanism in “DIFFUCAPS Technology”](image_url)

**CEFORM Technology**

CEFORM technology applies several motorized 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.\textsuperscript{[85]}

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

It is a fully included computer-aided development and manufacturing process. The Products may be designed based on a computer screen as three-dimensional (3D) models before actual execution 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.\[85-86\]

**PULSYS Technology**

PULSYS™ 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 PULSYS™ 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 PULSYS™ 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.\[85-88\]

**CONCLUSION**

Chronopharmaceutics assures improved patient outcome and optimized disease management in the future. The human action dependence of response to trigger the drug release is the
major problem associated with these systems. Hence an ideal chronotropic system should be dependent, 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.

ACKNOWLEDGEMENTS
We would like to take this opportunity to express my profound gratitude and deep regard to Prof.G. Devala Rao, Principal, KVSR SCOPS Vijayawada for his exemplary guidance, valuable feedback and constant encouragement throughout the duration. His valuable suggestions were of immense help throughout our writing of this review. His perceptive criticism kept us working to make this project in a much better way. We would also like to give my sincere gratitude to all the friends and colleagues who filled in the survey, without which this review compilation would be incomplete.

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