

## THE PHARMA INNOVATION

# Chronopharmacology: As A Therapy for Cardiovascular Disease

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Chronopharmacology is the study of the manner & extent to which the kinetics & dynamics of medication directly affected by endogenous biological rhythm & also how the dosing time of medications affects biological timekeeping & features ( period, level, amplitude & phase ) of biological rhythms. Chronopharmacology includes chronopharmacotherapy, chronopharmacokinetics & Chronotoxicity. Chronopharmacotherapy is the investigative science that elucidates the biological rhythm dependencies of medication. It is useful to solve problems of drug optimization i.e. to enhance the desired efficiency or to reduce its undesired effects. So Chronopharmacologic approaches involve a lesser risk of errors and or false information than the conventional homeostatic approach. The effectiveness & toxicity of many drugs vary depending on dosing time associated with 24 hours rhythm of biochemical , physiological & behavioural process under the control of circadian clock such chronopharmacological phenomenon are influenced by not only the pharmacokinetics but also pharmacodynamics of medication. Now a day Chronopharmacological principle are used in the therapy of various cardiovascular diseases such as hypertension, myocardial infarction, angina pectoris, pulmonary embolism etc. blood pressure fluctuates according to the circadian pattern. Continuous monitoring of blood pressure throughout the day and night reveals a pattern with minimum values of systolic & diastolic pressure between midnight & 4 am. Early in the morning B.P begins to rise from the low levels reached during sleep. Increases in blood pressure are accompanied by increase in heart rate caused by the chemical generated by the body & delivered into the blood stream.

*Keyword:* Chronopharmacotherapy, Circadian rhythm, hypertension, myocardial rhythm

**INTRODUCTION:** Many functions of the human body vary day by day and these types of variations cause the changes in both in disease state and in plasma drug concentration<sup>[1]</sup>.

Cardiovascular functions such as heart rate and blood pressure show 24 h variation. The incidence of cardiovascular disease such as acute myocardial infarction, strokes and arrhythmia also exhibits clear diurnal oscillation since most of these disorders can induce fatal or severe outcomes. It is important to elucidate the precise mechanism of the onset of these diseases<sup>[2]</sup>. The dependence of our body functions in the certain

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diseased state depends on the circadian rhythm<sup>[1]</sup>. Circadian rhythm occurs in the certain diseased condition. The science dealing with the phenomenon of biological rhythmicity in living organism is called chronobiology. The branch dealing with the pharmacologic aspects of chronobiology is termed Chronopharmacology which may be subdivided into chronotherapy, chronopharmacokinetics & Chronotoxicity<sup>[3]</sup>.

**Circadian Phase:** The phase of circadian rhythm is defined with respect to an easily identifiable reference point of the endogenous circadian oscillation such as through of the body temperature rhythm or the onset of metabolism rhythm. Thus circadian phase shift can be determined by measuring the change in timing of the chosen phase maker from one cycle to the next. During ambulatory conditions, changes in environmental stimuli and behaviour (e.g. - Light/dark, rest/ activity and temperature) often obscure the endogenous component of the underlying circadian oscillation that is being measured. The amplitude of circadian rhythm refers to the half distance from the maximum to the minimum of the observed rhythm<sup>[4]</sup>. Circadian clocks regulate a number of key behaviours in a wide variety of organisms it also helps organism to restrict their activity to species – specific times of the day, which enable them to find food escape predators & avoid undue competition between sympatric species e.g. - in drosophila parasitism activity peaks of different species occurs at different times of the day, which significantly reduces intrinsic competitive disadvantage for the inferior competitor and such temporal portioning is achieved at least partly with the help of circadian clocks<sup>[5]</sup>. In the evening, when less light enters in the eyes, the master clock triggers production of a hormone called melatonin which makes feel drowsy & helps stay in asleep. Circadian rhythm and their sensitivity to time may change as the age of the individual person increase<sup>[6]</sup>.

Chronopharmacology is useful to solve problems of drugs optimization means to enhance the desired efficiency or to reduce its undesired effects. The chronopharmacologic approach

involves a lesser risk of errors or false information than the conventional homeostatic approach. Many seasonal psychopharmacological drugs are useful in seasonal affective disorders though diazepam has fewer adverse effects and other selected drugs like phenobarbitone and chlorpromazine also have many adverse effects because of which they are leaving the market even though their pharmacological actions are potent. The need of the hour is to design strategies to ameliorate the side effects which make them more acceptable if the pharmacology and adverse effects of these drugs is circadian time dependant, it can be modulated by altering the time of administration of drugs. Any dependence of these drugs on the circadian time may provide a clue to ameliorate the major drawback of drugs<sup>[7]</sup>.

**Chronopharmaceutics :-** It has been described as a branch of pharmaceutics devoted to the design and evaluation of drug delivery system that release a bioactive agent at a rhythm that ideally matches the biological requirement of a given disease therapy.

**Chronopharmacokinetics:** - It refers to rhythmic changes in drug bioavailability as well as excretion.

**Chronotherapeutics:** - 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 based on the observation that there is an interdependent relationship between the peak-to through rhythmic activity in disease symptoms and risk factors, pharmacologic sensitivity, and pharmacokinetics of many drugs takes into account predictable administration time dependent variation in the pharmacokinetics of drugs as well as the susceptibility due to temporal organization of physiochemical process and function of body as circadian and others rhythms<sup>[8]</sup>. One approach to increase the efficiency of pharmacotherapy is the administration of drugs at times at which they are most effective and best tolerated<sup>[9]</sup>.

**Chronopharmacotherapy:** - It is an area where the drug administration is synchronized with biological rhythms so as to maximize therapeutic effect. It involves both the investigation of drug effects as a function of biologic timing and the investigation of drug effects upon rhythm characteristics. Circadian changes in the effect of various chemical agents have been documented such as histamine, sodium salicylate, acetylcholine, halothane, prostaglandin F<sub>2</sub>alpha, reserpine, Cyproheptadine, ethanol, insulin, chlorothiazide, oxymetholone, orciprenaline and SCH 1000 (the latter being bronchodilators), Indomethacin, lignocaine, ACTH, cortisol and various synthetic corticosteroids.

#### **Advantages of Chronopharmacotherapy –**

1. It prevents an overdosing of any class of drug.
2. It makes the utilization of the drug more appropriate and thus the value of a drug is increased.
3. It reduces the unnecessary side effects of a drug and helps in caring out the treatment for only a particular or limited period of time<sup>[7]</sup>.

#### **Reason for Chronopharmacology:-**

##### **Auto induction:-**

A repetitive dose of a drug induces or increases enzymes responsible for its elimination, thereby increasing its clearance. This is called as auto induction. It is dependent on dose and concentration of the drug. It has a number of therapeutic consequences. It affects the time to achieve steady state and limits one's ability to use information from a single dose to predict kinetics after repeated dose or continuous administration. Carbamazepine shows time dependence in its disposition. The decrease in its peak concentration on repetitive oral administration that either oral bioavailability decreases or clearance increases with time.

##### **Auto inhibition:-**

It may occur during the metabolism of certain drugs. The metabolites formed from drug firstly increase in concentration and further inhibit metabolism of the parent drug. This phenomenon is called as product inhibition or allosteric inhibition or feedback inhibition.

##### **Food effects:-**

Food is the major cause of diurnal variations. Gastric emptying is slowed or delayed by food, often resulting in a decrease the absorption of drug or decrease in the peak concentration and an increase in the time of its occurrence following a single dose. It is a major cause of circadian variations in patients tending to eat more in the evening than at breakfast. When absorption is slowed by food, the input rate and concentration of drug entering in the liver are lowered, thus metabolism is lowered. Hence, a concurrent intake of heavy food and some drugs in evening reduces the bioavailability of the drug.

#### **NEED FOR CHRONOPHARMACOTHERAPY**

It is required to monitor therapy so as to limit the duration of therapy especially in cases where patients are already having compromised renal, cardiac and hepatic or any other function of the body. Any type of accumulation of drugs in these organs causes greater toxicity which may led to diminished function of the organ. Thus the chronopharmacotherapy becomes a very important part of treatment of several diseases particularly those effecting targeted body parts<sup>[10]</sup>.

#### **Chronotherapeutics clinical studies**

**overview –** Chronopharmaceutics also grants new challenges for scientists and regulators. According to FDA, chronotherapeutics clinical studies need more additional parameters which are not applied for other clinical trials including –

1. Drug administration time of the day.
2. Patient's normal habits & sleep patterns.
3. Biological factors which are time related, like seasonal disorder.

According to the 1996 American medical association review, more consideration of chronotherapy in clinical trials is highly welcomed by the whole medical community. The result of the survey showed that 75 percent of the doctors are in favour of patient's circadian or daily rhythm oriented treatment [11].

### BIOLOGICAL RHYTHMS AND RHYTHMIC COMPONENTS:-

Circadian implies approximately a day, major periodic components of biological rhythms are found around 24 hours (circadian) and 30 days (Circamensual) and one year (Circannual). Circadian rhythms are found in all the organisms, infact the existence of circadian rhythms in living organisms was first established during a detailed study of leaf movement in plants more than 200 year ago. Biological rhythms posses both an internal as well as external components. Rhythmicity has been detected for a numbers of physiological variables like pulse, temperature, blood pressure, hormonal secretion via diurnal variation in effects of insulin on blood glucose [12].

**Table-1 BIOLOGICAL RHYTHMS AND COMPONENTS:**

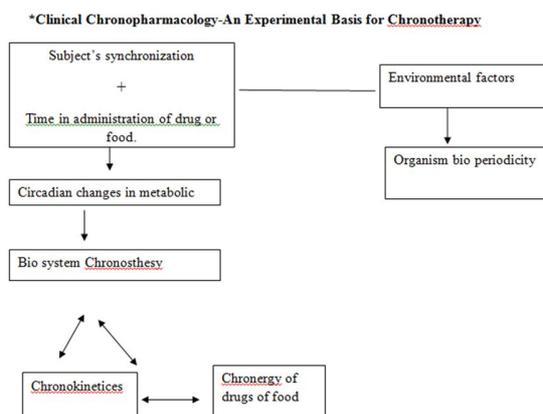
Period( $T$ )	Mark rhythmic components
Short period ( $T < 0.5$ h)	$S < T < 1$ S Pulsatile $T \sim \text{min.}$
2. Intermediate period $0.5 \text{ h} < T < 6$ days	Circadian $20 \text{ h} < T < 28 \text{ h}$ Ultradian $0.5 \text{ h} < T < 20 \text{ h}$
3. Long period	Infradian $28 \text{ h} < T < 6$ days Circamensual ( $T \sim 30$ days) Circaseptan ( $T \sim 7$ days) Circannual ( $T \sim 1$ year) [11]

Rhythmicity has been observed in the efficiency and orientation of metabolic pathways and in the sensitivity of target systems to endogenous or exogenous chemical substances. The concepts of biological temporal structure have led to the development of Chronopharmacology and its practical significance is well illustrated in the form of chronotherapy i.e. "prescribing medicine at specified clock hours so as to achieve an

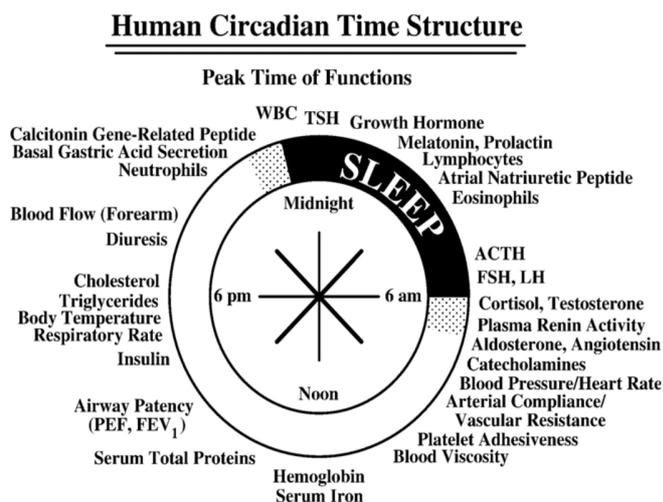
optimization of therapeutic administration". Thus Chronopharmacology involves both investigation of drugs effects as timing as well as investigation of medicines upon temporal structure, thus making it possible to enhance to desired and reduce the undesired effects of medicine.

**Chronosthesy:** - It refers to rhythmic variation detected in the systems. It also includes susceptible variations detected in parasites, bacteria, tumours.

**Chronergy-** The rhythmic changes in its effects and side effects, this depends on the Pharmacokinetics of drugs & Chronosthesy of various systems. It is also important to recognize the fact that plasma proteins undergo a circadian rhythm.



### HUMAN CIRCADIAN TIME STRUCTURE:-



The specific time that patients take their medication is very important as it has significant impact on treatment success. Optimal clinical outcome cannot be achieved if drugs plasma concentrations are constant. If symptoms of a disease display circadian variation, drugs release should also vary over time. Chronopharmaceutical drug delivery system are gaining importance in the field of pharmaceutical technology as these system deliver right dose at specific time at a specific site. Various technologies such as time- controlled, pulsed, triggered and programmed drug delivery devices have been developed and extensively studied in recent years for Chronopharmaceutical drug delivery [13]. Many functions of the human body vary considerably in a day. These variations cause changes both in disease state and in plasma drug concentrations. Human circadian rhythm is based on sleep-activity cycle, is influenced by our genetic makeup and hence, affects the body's functions day and night (24- hour period [14]. Research in the chronopharmacological field has demonstrated the importance of biological rhythms in drug therapy and this brought a new approach to the development of drug delivery systems [15].

**Circadian rhythm in the pathogenesis of CVS disease:-** From the various studies, it is formed that the many cardiovascular events including myocardial infarction, stroke and sudden death occur during the initial hours of morning activity

between 6 AM and 12 noon. And this is much higher during this period that other timing during the day. BP rises rapidly in the early morning hours, the time when most individuals wake and begin their day. This rise in BP corresponds to increased secretion of catecholamine's and increased plasma rennin activity [6]. Thus, vascular tone and total peripheral resistance increase in the morning hours, and BP rises as a result. At the same time, heart rate increases in the late morning or early afternoon [16].

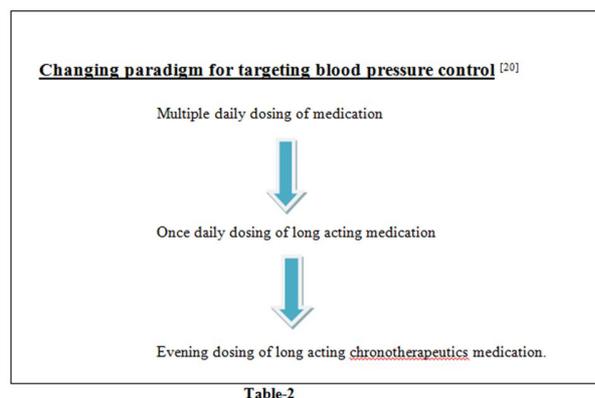
**Chronotherapy of cardiovascular diseases: -** The differences in patterns of illness between day and night for cardiovascular disorders such as hypertension, angina, heart attack, sudden cardiac death and stroke have been documented [17]. Chronotherapeutics approach gives more accurate determination of the time when patients are at highest risk and in greatest need of therapy. For example – it has often been found that the blood pressure of 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. It may also be important to recognize that the risk of heart attack appears to be greatest during the early morning hours after awakening. For instance, capillary resistance and vascular reactivity are higher in the morning and decreases later in the day. Platelet agreeability is increased and fibrnolytic activity is decreased in the morning, leading to a state of relative hyper coagulability of the blood. Blood Pressure is at its lowest during sleeping period and rises steeply during the early morning period. Many anti-hypertensive drugs do not control the early morning blood pressure, when given once daily early in the morning [13].

**VARIOUS CARDIOVASCULAR DISEASES:-**  
**Blood pressure (B.P) / Hypertension:**

Blood Pressure is well known to exhibit 24 h variation with a peak in the morning. A number

of factors influence diurnal variation of blood pressure which is internal factors such as the autonomic nervous system, vasoactive intestinal peptide, plasma cortisol, plasma rennin activity, aldosterone, plasma atrial natriuretic peptide. Both sympathetic activity and the rennin-angiotensin-aldosterone access peak in the early morning hours. In addition, b.p is affected by a variety of external factors including physical activity, emotional state, meal and sleep/wake routine. These extrinsic stimuli also affect the autonomic nervous system thus the 24 h variation in the B.P is representative of both endogenous diurnal rhythms and exogenous factors [2]. Blood pressure is characterized by a circadian rhythm, both in hypertensive and in normotensive subjects; this pattern is associates with lower B.P values during sleeping time and periods of minimal activity and higher B.P levels during wakefulness and mental and physical activity [18]. Various, researchers reported that blood pressure changed depending on whether the subjects was sleeping, resting or working. Blood pressure fluctuates throughout the day and night. The duration of the fluctuations may be short, from seconds to minutes, or long from day to night and season to season. The most easily noted and significant blood pressure variations are the diurnal changes related to the sleep-wake cycle. The pattern of blood pressure values obtained during the sleep-wake cycle from characteristic circadian rhythm. The Continuous monitoring of blood pressure throughout the day and night reveals a pattern with minimum values of systolic & diastolic pressure between midnight & 4 am. The pressure increases during waking hours remaining at a plateau for several hours & then reaching a maximum values early in the morning. This diurnal blood pressure fluctuation is altered in certain disease states, such as preeclampsia & chronic hypertension [19]. Hypertension is a common chronic condition affecting up to 35% of human adults. This condition is an important risk factor for strokes, heart attacks and other vascular & renal disease. The Pharmacological treatment of high blood pressure reduces the incidence of these complications & prolonged life.

The treatment of hypertension not only includes the usual clinical goal of reducing mean blood pressure levels, but also the normalization of the entire blood pressure circadian pattern. The predictable day-night variation in the symptoms of chronic medical conditions, risk of severe life-treating cardiovascular events & in medical conditions that are predisposing to serious disease presents the opportunity for a new i.e. chronotherapeutics treatment strategy that involves the delivery of medications so they are synchronized in time to biological need that varies according to the chronobiology of the targeted tissue. Currently available, once daily extended release antihypertensive medication provide safe & effective B.P reduction over a 24 hours during interval but their static pattern of drug release may not tailored to suit daily physiologic B.P variations. Currently chronotherapeutics calcium channel blocker is available in market for the management of certain cardiovascular disease [3].



### COMMON ONSET TIME OF CARDIOVASCULAR SYSTEM

Disease	Common onset time
Atrial fibrillation	Morning/ night
Ventricular tachycardia/fibrillation	Morning
Acute coronary syndrome	Early morning

Pulmonary embolism	Early morning
Cerebral infraction	Morning
Subarachnoid haemorrhage	Day time <sup>[20]</sup>

### Acute myocardial infraction(AMI) / pulmonary embolism(PE)

It is well known that AMI or PE frequently occurs in the early morning. A number of physiological functions exhibit diurnal variation including BP, heart rate, coronary blood flow, platelet function, blood coagulability and fibrinolytic activity. In the early morning, systemic BP & heart rate increases and augment the oxygen demand of the heart. In addition, the vascular tone of the coronary artery rises and coronary blood flow decreases in the morning. This increases in oxygen demand & decreases in oxygen supply exaggerate a mismatch of oxygen demand and supply in the morning. In addition, platelet function & blood coagulability also increases in the morning. A reduction in fibrinolytic activity resulting in a hypercoagulable state that could elicit the morning onset of thromboembolic events. Accumulating evidences suggests that the autonomic nervous system plays a major role in the circadian variation of the onset of AMI. A morning increase in the frequency of ischemic episodes is absent in diabetic patients with autonomic nervous dysfunction. Patients receiving beta-blocker do not show morning increase in the incidence of angina, AMI & sudden death. Heart rate variability which reflects sympathetic/vagal balance is also associated with the onset of ischemic episode in the chronic stable angina. Platelets are not involved in the variation of AMI or thromboembolic numbers & their aggregation activity possess circadian oscillation. Platelet activation in vivo is induced by catecholamine secreted from the sympathetic nervous system in a circadian fashion. However studies regarding platelet activation do not show clear circadian expression of any surface marker characteristic of platelet activation, therefore it is

unclear whether the internal clock system directly affects the circadian functions of platelets<sup>[21]</sup>.

### Arrhythmia:

A number of reports demonstrated the presence of circadian variation of cardiac arrhythmia. Evidences suggest that basic electrophysiological parameters have circadian variations. Atrial & ventricular refractory periods are strongly affected by the autonomic nervous system, in which sympathetic activity shortens it and parasympathetic activity elongates the period. Therefore fluctuations in the activity of autonomic nervous system within a day can be a major trigger of circadian onset of cardiac arrhythmia. Each parameter of ECG was analyzed as to whether it has diurnal variations. ECG, AV nodal function, QT interval, R&T wave voltage & QT interval have been shown to exhibit circadian variations. For the onset of cardiac arrhythmia paroxysmal atrial fibrillation is categorized into two types-

1. Vagatonic PAF- occurs at night.
2. Adrenergic PAF- occurs during day time.

There are several reports showing different results in term of peak paroxysmal supra ventricular tachycardia (PSVT) from morning to midnight. However they are consistent in that it is rare for PSVT to occur during the night time. Continuous halter monitoring of ECG revealed a 24 h variation in the occurrence of ventricular premature beats with a peak between 6 am & 12 noon. The presence of a circadian onset of VPBs depends on left ventricular function. Only patient with a left ventricular ejection fraction greater than 30 % have a circadian variation of VPBs<sup>[21]</sup>.

### RECENT TECHNIQUES OF TIME CONTROLLED PULSATILE TECHNOLOGY:

Currently pharmaceutical companies have been focused on developing and commercializing PDDS that fulfil unmet medical needs in the

treatment of various diseases. Recently developed technologies are SODAS ® technology, IPDAS ® technology, CODAS technology, CONTINR, OROSR, CEFORMR, DIFFUCAPSR, chronomodulating infusion pumps, TIMERx R and physic-chemical modification of API.

### **Spheroidal Oral Drug Absorption System (SODAS):-**

This technology is based on the production of controlled release beads and it is characterised by its inherent flexibility, enabling the production of customized dosage forms that respond directly to individual drug candidate needs. SODAS can provide a number of tailored drug release profiles, including immediate release of drug followed by sustained release to give to a fast onset of action, which is maintained for 24 hrs. An additional option is pulsatile release, where a once daily dosage form can resemble multiple daily doses by releasing drug in discrete bursts throughout the day<sup>[21]</sup>.

### **The Intestinal Protective Drug Absorption System (IPDAS):-**

This technology is a high density multiparticulates tablet technology, intended for gastrointestinal irritant compounds. The IPDAS technology is composed of numerous high density controlled release beads, which are compressed into a tablet form. Once an IPDAS tablet is ingested, it rapidly disintegrates and disperses beads containing a drug in the stomach, which subsequently pass into the duodenum and along the gastrointestinal tract in a controlled and gradual manner, independent of the feeding state. Release of the polymeric membrane and or the micro matrix of polymer / active ingredient formed in the extruded/ spheronized multiparticulates<sup>[13]</sup>.

### **Chronotherapeutics Oral Drug Absorption System (CODAS):-**

The Chronotherapeutics oral drug absorption system (CODAS) is a multiparticulate system which is designed for bedtime drug dosing, incorporating a 4-5 hrs delay in drug delivery. This delay is introduced by the level of non

enteric release – controlling polymer applied to drug loaded beads<sup>[13]</sup>. This technology was designed to release its drug component after a prolonged period of time when administered. A good example is Verelan PM, which was designed to release verapamil approximately four to five hours after ingestion. This delay is introduced by the level of release –controlling polymer applied to the drug –loaded beads. The release controlling polymer is a combination of water-soluble and water –insoluble polymers. When fluid from the gastrointestinal tract contacts the polymer coat 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 the drug. When taken at bed time, this controlled onset extended release delivery system enables a maximum Plasma concentration of verapamil in the morning hours, when blood pressure normally is high<sup>[22]</sup>.

**Continr Technology:-** In this technology, molecular coordination complexes are formed between a cellulose polymer & a non-polar aliphatic alcohol optionally substituted with a aliphatic group by solvating the polymer with a volatile polar solvent & reacting the solvated cellulose polymer directly with the aliphatic alcohol . This constitutes the complex having utility as matrix in controlled release formulations since it has a uniform porosity (Semi permeable matrix)<sup>[23]</sup>.

**Orosr Technology: -** This Technology uses an osmotic mechanism to provide pre- programmed controlled drug delivery to the git. E.g. Oros technology delayed push-pull system, also known as controlled onset extended release (COER) was used to design covera-HSR, a novel antihypertensive product<sup>[23]</sup>. The dosage form comprises a wall that defines a compartment. The active drug is housed in a reservoir, surrounded by a semi permeable membrane (e.g. cellulose esters, cellulose ethers and cellulose ester-ethers.) and formulated into a tablet which is divided into two layers, an active drug layer and a layer of

osmotically active agents for example, 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 at a predetermined rate. This creates a pump effect that pushes the active drug through a hole in the tablet. This technology (OROSR delayed push-pull k system also known as controlled onset extended release (COER) which was used to design Covera-HSR, a novel antihypertensive product. It actually enabled delayed, overnight release of verapamil to help prevent the potentially dangerous surge in BP that can occur in the early morning<sup>[13]</sup>.

**Diffu Caps Technology:-** In the Diffu caps technology, a unidosage form, such as capsule for delivering drugs into the body in a circadian release fashion, is comprising of one or more populations of drug-containing particles (beads, pellets, granules). Each bead population exhibits a pre designed rapid or sustained release profile with or without a predetermined lag time of 3-5 hours<sup>[23]</sup>. 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 an API-containing film-forming formulation and preferably a water-soluble film forming composition (e.g. HPMC, PVP) to form a water-soluble/dispersible particle. The active core may be prepared by granulating and milling or by extrusion and spheronization of polymer composition containing the API. Such a ChrDDS 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 cardiovascular diseases, predicted based on pharmacokinetic and pharmacodynamics considerations and in vitro/in vivo correlations. This technology has been used to formulate the first and recently FDA approved propranolol-containing ChrDDS (InnopranR XL) for the management of hypertension<sup>[13]</sup>.

**Ceform Technology:** - The Ceform technology allows the production of uniformly sized & shaped microspheres of pharmaceutical

compounds. This ChrDDS approach is based on 'melt-spinning' which means subjecting solid feed stock i.e. biodegradable polymer or bioactive agents combinations to the combinations of temperature, thermal gradients, mechanical forces, flow & flow rate during processing. The microsphere may be coated for controlled release either with an enteric coating or combined into a fast/flow release combination<sup>[23]</sup>.

**Physic- Chemical Modification of API:** - In this technology, a proprietary method is used to modify the physicochemical properties (e.g. - solubility, partition coefficient, membrane permeability) of API to achieve Chronopharmaceutical objectives

**Chronomodulating Infusion Pumps:-** Externally and internally controlled systems across a range of technologies including pre-programmed systems, as well as systems that are sensitive to modulated enzymatic or hydrolytic degradation, pH, magnetic fields, ultrasound, electronic field, temperature, light, & mechanical stimulation have been developed<sup>[23]</sup>.

**TIMERx Technology:-** The TIMERx Technology (hydrophilic system)<sup>[24]</sup> combines primarily Xanthan & Locust bean gums mixed with dextrose. The physical interaction between these components works to form a strong binding gel in the presence of water. Drug release is controlled by the rate of water penetration from the gastrointestinal tract into the timer x gum matrix which expands to form a gel & subsequently releases the active drug Substances<sup>[23]</sup>.

## CONCLUSION

The major objective of this article is to inform biologists, clinicians, pharmaceutical scientists and other professional about the importance of biological clocks & Chronopharmacology to human health and disease also motivate the investigator to develop new tools for the treatment of cardiovascular diseases such as cardiac arrhythmia, myocardial infarction etc. this

article also provide a new ideas to use of older or already well-established active pharmaceutical ingredients for the treatment of various diseases

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