THE CLOCK WHICH TIMES US - CHRONOBIOLOGY, CHRONOPHARMACOLOGY AND CHRONOTHERAPEUTICS – NEXT FRONTIER IN OPTIMIZING DRUG THERAPY

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ABSTRACT
Chronobiology is the branch of science which examines periodic phenomenon in living organisms and their adaptation to biological rhythm. These biological rhythms can be yearly, monthly, daily or more frequent. Daily (24hr) rhythms are called as circadian rhythms. Chronopharmacology is one of the disciplines which take into account the influence of time. It is concerned with the effects of drug upon the timing of biological events and rhythms and the relation of biological timing and endogenous periodicities to the effect of drugs. It further deals with chronotherapeutics, chronokinetics, and chronotoxicity. The circadian rhythms in mammals are maintained and regulated by the master clock in brain called as Supra chiasmatic nucleus (SCN) present in hypothalamus. Circadian rhythms deals with the cyclic changes occurring in day and night which depends on absence and presence of light. When the light falls on the retina, the light sensitive ganglion cells act as receptors and sends signals to SCN through retinohypothalamic tracts. SCN either directly by influencing pineal gland which releases melatonin or indirectly by influencing autonomic nervous system regulates different physiological activities. Biological rhythms are observed in different physiological organ systems like urinary, gastrointestinal tract, hepatic system, cardiovascular system and endocrine system. Circadian rhythms are also exhibited by many diseases. Some drugs show
difference in absorption (A), distribution (D), metabolism (M) and excretion (E) in relation to
time. The study which deals with the temporary changes in ADME and takes into account the
influence of time of administration on these different processes is called as
chronopharmacokinetics or chronokinetics. The present review focuses on the chronobiology,
chronopharmacology, chronokinetics of different drugs and their applications in treating
different diseases i.e chronotherapeutics. It also focuses on different techniques involved in
formulation of drugs undergoing chronopharmacokinetics.

KEYWORDS: circadian rhythms, suprachiasmatic nucleus, chronopharmacology,
chronopharmacokinetics, chronotherapeutics, pulsatile drug delivery system.

INTRODUCTION
The functions of all living creatures are influenced by change with time, resulting in
biological rhythms. Time change occurs at each functional level of an organism, from
molecular to whole body interactions. These rhythms can be yearly (circannual), monthly,
daily (circadian) or more frequent (pulsatile). These are genetically predetermined (biological
clock) but can be influenced and modulated by environmental factors (time-trigger).
Chronobiology is the branch of science which examines periodic phenomena in living
organisms and their adaptation to biological rhythms.

In medicine 3 disciplines take into account the influence of time.
- Chronophysiology
- Chrono pathology
- Chrono pharmacology

Chronopharmacology is the branch of chronobiology concerned with the effects of drug upon
the timing of biological events and rhythms and the relation of biological timing and
endogenous periodicities to the effect of drugs.

When a drug is administered the pharmacological action of the drug can be predicted based
on the body circadian rhythm.

It is possible to explain all the functions of the body as a function of time. In the same way as
sleep – awake, feed hunger, joy depression are regulated by the living clocks, the maximum
efficacy and minimum toxicity of a drug can be achieved if it is administered at appropriate
time i.e right drug in the right form at right dose at right time.\(^\text{[1]}\) So the given drug acts
synergistically with biological clock. Pharmacology is based on circadian rhythms which are important in medicine. A circadian clock in the brain coordinates daily physiological cycle.

**Chrono pharmacology further deals with**\(^2\)

- Chronotherapeutics
- Chronokinetic
- Chronesthesia
- Chronergy
- Chronotoxicity

![Chronopharmacology and its branches.](image)

**Fig. 1: Chronopharmacology and its branches.**

Chrono therapeutics: Knowledge of day-night and other prediction in time variations in the symptoms intensity and risk of acute exacerbation of disease coupled with evidence of circadian rhythms in the kinetics, effects and safety of medications constitutes the rationale for new pharmacologic approach to treatment. It deals with increase of the efficiency and safety of medications by proportioning their concentrations during the 24hrs in synchrony with biological rhythm determinants of disease.

Chrono pharmacokinetics: It deals with the study of temporary changes in absorption (A), distribution (D), metabolism (M), excretion (E) and thus takes into account the influence of time of administration on these different steps.

Temporal changes in drug absorption from GIT occurs due to circadian variations in gastric acid secretion and pH, motility, gastric emptying time, gastrointestinal blood flow, plasma protein binding and drug distribution and drug metabolism (temporal variations in enzyme
activity, hepatic blood flow and in renal drug excretion or due to variations in glomerular filtration, renal blood flow, urinary pH and tubular reabsorption.

**Chronesthesia:** It deals with circadian or other systemic changes in the susceptibility and sensitivity of the target system to a drug.

** Chronergy:** It deals with rhythmic difference in effects of drug on the organism as a whole which includes both desired and undesired effects.

**Chrono toxicology:** It is an aspect of chronodynamics; it refers specifically to dosing time i.e rhythm – dependent differences in the manifestations and severity of adverse effects and thus intolerance of patients to medication.

The term circadian comes from Latin word circa means ‘about’ and dian means ‘day’. Circadian rhythms are most important type of biological rhythms and are most significant for humans and animals. They play an important role in maintaining body temperature, heart rate, blood pressure, organ blood flow, pulmonary and kidney functions as well as for concentration of neurotransmitters, hormones, enzymes, electrolytes and glucose.

Study of rhythms is important for pharmacotherapy.

Chronotherapy coordinate drug delivery with human biological rhythms and holds huge promise in areas of pain management and treatment of asthma, heart diseases and cancer.

**MECHANISM OF CIRCADIAN RHYTHMS**

Circadian clock present in brain coordinates daily physiological cycle like

- Sleep wake cycle
- Digestion and temperature
- Hormones etc.

Internal biological clock synchronises with environmental conditions. In mammals, the circadian clock resides in two clusters of nerve cells called the suprachiasmatic nuclei (SCN), which are located in a region at the base of the brain called the anterior hypothalamus. Information on day light or its limitation by artificial illumination is received by retina cells and project via the retinohypothalamic tract into the SCN in the hypothalamus. Special light
sensitive ganglion cells act in the retina as brightness receptors and send appropriate information useful for the regulation of circadian rhythms.

SCN uses its connection with the autonomic nervous system for its time of day message by setting the sensitivity of endocrine glands (thyroid, adrenal, and ovary) or by directly controlling on endocrine output of pineal gland (i.e. melatonin synthesis).\[4\]

Circadian rhythms are also reflected in the robustly rhythmic behavioral and physiological outputs, such as feeding, sleep-wakefulness, hormone secretion and metabolic homeostasis.

![Fig 2: Supra chiasmatic nuclei (SCN) and pineal gland location.](image1)

**Fig 2: Supra chiasmatic nuclei (SCN) and pineal gland location.**

**Fig 3: Mechanism of biological rhythms**

**BIOLOGICAL RHYTHMS OBSERVED IN VARIOUS BIOLOGICAL SYSTEMS**

1. Urinary system

Diurnal or circadian variations in urine volume, electrolyte excretion, uroflow, micturition frequency, volume per void, and urine and osmole output rates have been extensively studied.\[5, 6\] For example, water and electrolyte excretion is significantly low during the sleep phase compared with active daytime in healthy.
2. Gastrointestinal system

The gastrointestinal motility, intraluminal pH, blood flow to stomach and enzymatic action are not the only factors that influence the gastrointestinal absorption of the drug. It also depends on circadian rhythms and it is influenced by time of the day. Biological rhythms are responsible for daily food intake; the period of hunger and satiety is controlled by the central pacemaker, SCN. It has been found that clocks in the GIT are responsible for the periodic activity (PA) of its various segments and transit along the GIT; they are localized in special interstitial cells, with unstable membrane potentials located between the longitudinal and circular muscle layers. The rhythm of slow waves is controlled in various segments of the GIT: in the stomach (about 3 cycles per min), in the duodenum (12 cycles per min), in the jejunum and ileum (from 7 to 10 cycles per min), and in the colon (12 cycles per min).

3. Hepatic system

- Circadian regulation plays a large role in liver metabolism, as glucose, bile acids, lipids and cholesterol are all subject to timed circadian control.

- In normal humans, blood glucose and insulin levels in response to an oral glucose load vary over 24 h, with lower glucose response and higher insulin levels occurring in the morning, regardless of fasting duration, resulting in increased glucose tolerance in the morning compared to evening.[7, 8]

- Leptin, a hormone which is secreted by the white adipose tissue displays a circadian rhythm. It regulates the sensation of hunger by binding to the receptors in the hypothalamus as well as those which are present on liver. Obesity is caused due to increase in the levels of leptin. Usually leptin is at its peak in the night than in the morning.[9]

4. Cardiovascular system

Cardiovascular activities show circadian rhythm and cardiac electrophysiological properties change diurnally and enable the cardiovascular system adapt to rest, exercise cycles. Blood pressures are highest in afternoon and decrease in evening and attain lowest values at nights which are due to circadian rhythms in nervous and endocrine system. Myocardial infarction occurs frequently in morning as a result of several physiological and biochemical conditions.[10]
5. Hormones

A variety of hormones, including melatonin, cortisol, thyroid stimulating hormone (TSH), and prolactin (PRL), vary across the 24-hour day and are highly regulated by the circadian and sleep-wake cycles. Evidence suggests that these hormones, as well as other physiological rhythms like body temperature, play a role in sleep organization and can also be affected by sleep itself (or lack thereof).

Fig 4: Hormones and different physiological activities showing circadian rhythms

Fig: 5 Physiological activities during day and night.

DISEASES EXHIBITING CIRCADIAN RHYTHMS

1. Allergic Rhinitis

Allergic rhinitis is associated with symptoms like sleep disturbances, daytime somnolence and fatigue. These symptoms can interfere with sleep quality. The nasal congestion which causes sleep-disordered breathing is responsible for rhinitis related sleep disorders. The severity of nasal decongestion is thought to be worst during night and in the early morning.\(^{11}\)
2. Bronchial asthma
Airway hyperresponsiveness and decreased lung function are exaggerated during night time and in the early morning. This is due to circadian changes in the neurotransmitters like epinephrine, AMP, Histamine and other inflammatory mediators, cortisol, vagal tone, body temperature, lower airway secretions favours nocturnal bronchoconstriction. [12]

3. Arthritis
Clinical signs and symptoms in arthritis depend on the time of day. The symptoms of arthritis such as joint stiffness and pain are more prominent in the early morning. This is due to the diurnal rhythmicity exhibited by the production of proinflammatory cytokines which are at peak during night and early morning at the time when cortisol (anti-inflammatory) is lowest and melatonin (proinflammatory) is highest. Sex hormones also play a role in circadian rhythms of arthritis. The symptoms are common in luteal phase when the production of estrogen and progesterone is higher than in the follicular phase. [13]

4. Angina pectoris and Myocardial infarction
A number of physiological functions exhibit diurnal variations including Blood pressure, heart rate, coronary blood flow, platelet function, blood coagulability and fibrinolytic activity. The systemic BP and heart rate are increased in the early morning and therefore the oxygen demand of the heart is augmented. This can lead to sudden cardiac death.

5. Peptic ulcer disease
Stomach acid secretion is 2-3 times greater between 22:00 and 02:00 than in the day. In addition, eating and drinking immediately stimulates stomach acid production. Daytime heartburn symptoms arise from meal-triggered acid secretion, while nighttime ones result from the circadian rhythm of stomach acid production that peaks at night. Peptic ulcer disease exhibits 24 hour as well as weekly and annual cycles. [14]

6. Stroke
The incidence of stroke is in similarity with other cardiovascular events showing high incidence rate in the early morning after awakening and lowest incidence during nocturnal sleep.

This typical diurnal variation has been found in number of cardiovascular diseases like myocardial infarction, stroke (thrombotic or intracerebral or subarachnoid haemorrhage), angina (stable, unstable, or silent) and sudden death.
Morning awakening is accompanied by an abrupt increase in sympathetic nervous system activity (as central mechanism) that results in an increase in blood pressure and heart rate, as well as platelet aggregability, and a reduction in fibrinolytic activity. These simultaneous changes cause vasoconstriction, an increase in wall resistance and thrombogenesis and can lead to stroke.

Table 1: Diseases displaying biological rhythms.

<table>
<thead>
<tr>
<th>S.No</th>
<th>DISEASE</th>
<th>CIRCADIAN RHYTHMCITY (Higher incidence during)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Allergic rhinitis</td>
<td>Early morning upon awakening</td>
</tr>
<tr>
<td>2</td>
<td>Bronchial asthma</td>
<td>At night during sleep</td>
</tr>
<tr>
<td>3</td>
<td>Arthritis</td>
<td>Early morning and in the middle or latter portion of the day</td>
</tr>
<tr>
<td>4</td>
<td>Angina pectoris</td>
<td>Early morning</td>
</tr>
<tr>
<td>5</td>
<td>Myocardial Infarction</td>
<td>Early morning</td>
</tr>
<tr>
<td>6</td>
<td>Peptic ulcer disease</td>
<td>At night mostly during 22:00 to 2 am</td>
</tr>
<tr>
<td>7</td>
<td>Stroke</td>
<td>Early morning</td>
</tr>
</tbody>
</table>

DRUGS UNDERGOING CHRONOKINETICS

1. Antibiotics

The important aspects of chronokinetics of antibiotics are

- Antibiotics show temporal variations in their pharmacokinetics in a 24hr cycle.
- The efficacy of antibiotics is determined by the time at which the concentration is greater than minimum inhibitory concentration.
- It not only increases the efficacy but also decreases the toxicity of antibiotics.

Examples

- Aminoglycosides: the renal toxicity of aminoglycosides like amikacin and gentamicin can be reduced by giving the drug as a single daily injection when the patients are active i.e at day time or in the activity period. \[15\]
- Cephalosporins: the toxicity of ceftriaxone is decreased by administering it at night as its total clearance value is highest during night and lowest during day time.
- Floroquinolones: the elimination of ciprofloxacin was found to be greater when the drug is administered at 10am than wen it was administered at 10pm.
- Ampicillin: the renal and biliary clearance of ampicillin was greater at day time (activity period) than at night time.

2. Anti hypertensive drugs

- The rhythms in the blood pressure and heart rate depend on the time of the day. The kinetics of antihypertensive drugs also varies with the time of the day. The \( C_{\text{max}} \) was higher
and $t_{\text{max}}$ was shorter when the drug was administered in the morning than in the evening. This is applicable to different lipophilic drugs like nifedipine, propanolol, verapamil etc.

- Angiotensin converting enzyme inhibitors (ACEIs) are found to be safe when are administered at bed time when compared to morning.
- Atenolol (hydrophilic drug) is not absorbed rapidly after morning administration.

3. **Anti epileptic drugs**
Valproic acid: $C_{\text{max}}$ was found to be higher, $t_{\text{max}}$ was shorter and absorption rate constant $k_a$ was higher in morning than in the evening. \[16\]

4. **Anti inflammatory drugs**
They have greater rate and extent of bioavailability when administered in the morning than in the evening. Ex: indomethacin, ketoprofen.

5. **Anti migraine drugs**
$C_{\text{max}}$ of Sumatriptan, drug of choice for migraine was higher when the drug was administered durin morning 7 am than after 7pm administration. \[17\]

6. **Anti cancer drugs**
The renal toxicity of cisplatin was significantly reduced by evening administration rather than morning.

5-Floro uracil is intracellularly catabolised by an enzyme dehydropyrimidine dehydrogenase. The activity of this enzyme increases by 40% during midnight. Therefore the drug is highly tolerable when administered between 00:00 to 4 am. \[18\]

7. **Anti hyperlipidemic drugs**
Cholesterol synthesis takes place in the presence of hydroxyl methyl glutaryl Co enzyme A reductase (HMGCoA reductase). More cholesterol is synthesized in the evening than in the morning. Therefore anti hyperlipidemic drugs like HMGCo A reductase inhibitors should be administered in evening for increased efficacy except atorvastatin which has a longer half life.

8. **Opioid analgesics**
Stronger analgesic effects of tramadol and dihydrocodeine were observed when they were administered in the evening to relieve painful stimulus.
morphine was found to be highest peak plasma concentration at 9:00 am and least was found at 3:00 am.

Mepiridene was shown to be effective with the morning dose than the evening dose.

9. Heparin
The significant inhibition of blood coagulation by heparin was more pronounced at night. Even if it is given at constant infusion rate, risk of bleeding varies with hour of the day.

10. Topical steroids
The anti-inflammatory action of steroids is found to be maximum in afternoon.

11. Local anesthetics
Amide type local anesthetics like lidocane, ropivacaine, mepivacaine and betoxyzaine were highly effective when are applied around 3:00pm the plasma levels of lidocaine were higher in the evening than any other time of the day.

12. General anesthetics
- Barbiturates
Barbiturates like pentobarbital was highly effective when administered during the dark phase. This is because GABA ergic activity is highly pronounced during night time.

- Benzodiazepines
The elimination half life of midazolam was found to be shortest at 14:00 hrs and is longest at 2:00 h. BZds like ketamine, etomidate, propolol are efficacious during night than during the day time.

13. Anti psychotic drugs
Chlorpromazine produces maximum sedative effect when administered at midnight and maximum anti psychotic effect when administered immediately after awakening.

Haloperidol shows both sedative and antipsychotic effect when administered in the evening.

APPLICATIONS OF CHRONOPHARMACOLOGY IN TREATING VARIOUS DISEASES – CHRONOTHERAPEUTICS
It refers to the treatment in which the invivo drug availability is timed to match the rhythms of the disease in order to optimize therapeutic outcomes and minimize the toxicity.
Chronotherapeutics is found to be useful in

1. **Allergic rhinitis**
   As rhinitis is worst in the morning and evening, non sedative anti histaminic drugs are administered before bedtime to control the exacerbations during sleep. Oral corticosteroid therapy can be given in the morning for severe allergic rhinitis.

2. **Bronchial asthma**
   - The risk of asthma is more pronounced during night and in the early morning. Therefore, sustained release formulation of theophylline is given at night time. It increases the efficacy of the drug, decreases its toxicity and also helps in avoiding multiple doses.
   - High nocturnal cholinergic activity due to vagus nerve hyperactivity can be prevented by using cholinergic antagonist like Ipratropium bromide during night time.
   - Corticosteroids should be administered during day time around 5:30pm so as to maximize their efficacy.
   - Leukotriene receptor antagonist zileuton should be administered in night as LTB4 concentration was found to maximum during night time.

3. **Peptic ulcer disease**
   As the maximal acid secretion, peptic ulcer disease pain, perforation of ulcers are maximum at night time, H2 receptor blockers like rantidine, famotidine are preferentially given at evening time.

4. **Arthritis**
   The symptoms of Rheumatoid arthritis are worse in the morning while that of osteo arthritis are worse in night and less in the morning. Therefore NSAIDs like ibuprofen, ketoprofe and indomethacin are given at night in rheumatoid arthritis patients while are administered in the morning in osteo arthritis patients. \[^{19}\]

5. **Cardio vascular disorders**
   - The blood pressure is usually 20% high immediately after awakening due to increased physical activity, increased catecholamine activity, increased platelet aggregation, increased vascular tone, increased thrombolytic activity.\[^{20}\] Therefore new COER Verapamil (Controlled onset extended release) is used in hypertension. It is formulated such that when it is taken at bedtime and it dissolves slowly and exerts its peak effect between 5 am and noon. There is also no dip in blood pressure during night.
• ACEIs like Ramipril and doxazosin are given at bed time rather than morning.

6. Diabetes mellitus

Morning hyperglycemia is common in patients with diabetes mellitus.

This can be explained by two phenomena

a) Dawn phenomenon
b) Somogyi phenomenon

a) Dawn phenomenon

Recurring abnormally high glucose levels in the morning before breakfast is known as dawn phenomenon. It occurs mostly between 3 am to 5 am. This is due to increase in growth hormone secretion \(^{[21]}\) which has hyperglycemic properties during sleep. \(^{[22]}\)

b) Somogyi phenomenon

It is also called as rebound hyperglycemia phenomenon. It refers to blood sugar being high in the morning, after having been low (hypoglycemia). Hyperglycemia after hypoglycemia is a result of the insulin-antagonistic action of some hormones, especially those belonging to the hypothalamic-pituitary-adrenal axis. It is mainly caused by too much or long acting insulin. Because of insulin the glucose levels will be low at night or bed time, but later because of increase in growth hormone, cortisol and catecholamine levels during bed time causing hyperglycemia. \(^{[23]}\)

Therefore controlled release insulin (insulin pumps) should be preferred or should be taken at the time when there are more chances of hyperglycemia. Care should be taken so that insulin should not peak at the wrong time or in the middle of the night.

7. Oral contraceptives

Female sex hormones exhibit monthly cycle and oral contraceptives are prescribed as per menstrual cycle.

8. Cancer

Normal cells and tumor cells exhibit different biological rhythms. The tumor cells are fast growing at around 2 am and slow growing at 10 pm.
The drugs are prescribed based on

- The duration of the phase of cell cycle
- Rate of cell proliferation

a. Colorectal cancer

Oxaliplatin is administered at daytime whereas 5-Floruracil at night.

b. Breast cancer

Treatment of these solid tumors is preferred during later half of the menstrual cycle as there is more clearance rate than early half of the cycle. Progesterone released in the later half cycle inhibits the enzymes which are responsible for the spread of cancer.

Cyclophosphamide toxicity was lower during the night and cure rate was higher. This means that it is possible to optimize the therapeutic index by carefully selecting the time of administration.[24]

NEW TECHNIQUES BASED ON TIME CONTROLLED DRUG DELIVERY SYSTEM.

The chronotherapy of a medication can be accomplished either by administering in the appropriate timing of the conventionally formulated tablets and capsules or by using special techniques in special drug delivery system to synchronize drug concentration to the biological rhythms. New tools and formulation procedures or pumps with constant programmable delivery rates now make it possible to deliver a drug at definite time or during a definite span of time at controlled rate.

The focus is on developing and commercializing PDDS (Pulsatile drug delivery system). The technologies developed are

1. Spheroidal oral drug absorption system (SODAS)

It is based on production of controlled release beads and is characterized by its inherent flexibility enabling the production of dosage forms that respond directly to individual drug candidate needs. We can even provide drug release profiles which includes immediate release of drug followed by sustained release to give fast onset of action maintained till 24 hrs. [25]
2. Chrotherapeutic oral drug absorption system (CODAS)

It is multiparticular system formulated in the form of beads. They are designed such that there is predetermined delay in drug delivery. This delay is achieved by introducing a level of release controlling polymer applied to drug loaded beads. The release controlling polymer is a combination of both water soluble and water insoluble polymers. When the drug is administered, initially the water soluble polymer dissolves and releases the drug whereas the water insoluble polymer serves as a barrier for the drug release. After a certain delay, the water insoluble polymer releases the drug. When taken at bedtime, this controlled onset extended release delivery system enables a maximum plasma concentration in the morning hours when blood pressure is high.\textsuperscript{[26]}

3. Programmable oral drug absorption system (PRODAS)

It is a technique in which a number of controlled release mini tablets are incorporated in to a single hard gelatine capsule. These formulations can be immediate release or delayed release or controlled release. Minitablets can vary in size depending on the amount of release of drug required at different sites.\textsuperscript{[27, 28]}

4. OROS Technology

This technology is based on osmotic mechanism which aids in preprogrammed controlled drug delivery in gastro intestinal tract. The drug release through this system is independent of pH, and other physiological parameters. This system is composed of two compartments – the drug vessel and osmotic engine cap. The drug vessel is made up of water impermeable ethylene- co-vinyl acetate copolymer. It incorporates drug in one or more layers. One or more layers will be accomplishing drug molecules along with a suspending agent or osmogen, whereas the other layers are called as push layers. The osmotic engine cap is made up of proprietary water-permeable blends of polycaprolactone and flux enhancers. In aqueous medium, the water permeates into the osmotic engine cap via the osmotic membrane or rate controlled membrane. Hydration of the cap causes the cap to expand and thereby it exerts force on the drug vessel to release the drug. The two compartments separate from each other by sliding apart and exposing the drug to the fluid medium.\textsuperscript{[26]}

5. Diffucaps

It is the most popular and versatile system which can be used in chronotherapy. This system is designed in 3 compartments. It has Drug-containing cores by drug-layering on inert particles, customized release beads coated with immediate release particles along with rate
controlling polymers or waxes, a hard gelatin or hydroxyl methyl cellulose capsule which incorporates polymer coated diffucaps (beads). The beads contain a layer of organic acid or an alkaline buffer which directs the drug solubility by creating an optimal pH environment. Beads also contain a solid solution of drug and crystallization inhibitor so as to improve the bioavailability and maintain the drug in its amorphous form. \(^{[26]}\)

6. **Continr technology**

This technique reduces the number of doses of medication to be taken in a day and also closely monitors the amount of drug release into the blood stream increasing its efficacy and decreasing the adverse effects. In this technique, the cellulose polymer is solvated by using volatile polar solvent. This solvated cellulose polymer is reacted directly with aliphatic alcohol as a melt. This constitutes the formation of molecular coordination complex, a matrix with uniform porosity thereby facilitating controlled release of drug molecules. Aminophylline and theophylline are drugs which have been formulated through this technology.\(^{[29]}\)

7. **Chronomodulatory infusion pump**

This technique involves externally and internally pre programmed controlled systems across a range of technologies and systems that are sensitive to modulated enzymatic or hydrolytic degradation, pH, magnetic field, ultra sound, electronic field, temperature, light and mechanical stimulation.\(^{[30, 31]}\)

8. **Time Rx technology or hydrophilic system**

Zero order kinetics is possible with this system. It is hydrogel based controlled release system. It manipulates different molecular interactions and thereby can provide different release kinetics. It involves combining xantham and locust bean gums mixed with dextrose. The resultant interaction between these gums leads to the formation of a short binding gel in the presence of water. Drug release is controlled by the rate of water penetration from the GIT into the timer X gum matrix which expands to form a gel facilitating controlled release.\(^{[30]}\)

**Classification of oral pulsatile system**

**Pulsatile system can be classified into**

1. Single unit system
2. Multiple unit system
1. Single unit system
It is formulated as capsule based on osmosis based systems. It is designed by coating the systems either with eroding or soluble or rupturable coating. These are sub classified as capsule based systems, osmotic systems delivering systems with rupturable coating.

Capsule based system
In this the lag time is controlled by a plug which gets pushed away by swelling or erosion and the drug is released as a pulse from the insoluble capsule body. Pulsing cap was developed by R.P Schever institutional corporation. US. It consists of water insoluble capsule enclosing the drug reservoir. A swelable hydrogel plug was used to seal the drug contents into the capsule body.

Osmotic drug delivery systems
This system uses osmotic pressure for controlled drug delivery using osmogens. The tablet has a rigid water-permeable jacket with one or more laser drilled small holes. As the tablet passes through the body, the osmotic pressure of water entering the tablet pushes the active drug through the opening in the tablet.

2. Multiple unit system
In multiple units pulsatile release is induced by changing membrane permeability or by coating with rupturable membrane.

Mechanism of action
When the capsule comes in contact with dissolution fluid it swells and after long time i.e. lags time the plug pushed itself outside the capsule and releases the drug.

CONCLUSION
The Major objective of this study is to know the role of biological clock and chronopharmacology to human health and diseases and to monitor rhythmic markers such as clock genes which may be useful to choose the most appropriate time of day for administration of drug that may be increase therapeutic effects and reduce side effects.

REFERENCES


