



## A Review on Chronotherapy, A Time Programmed Drug Delivery

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### ABSTRACT

All humans biological process is synchronized by biological or circadian rhythm. This concept helps in the emergence of chronotherapy; that means in our body the drug delivery is coordinated with the circadian rhythm. This technology is used to deliver drugs depends upon the rhythmic pattern of particular disease at a specific time. It's otherwise called as pulsatile drug delivery system. It is characterized by delivering drugs, immediately after a predetermined lag time within a short span of time. Chronotherapy is the coordination of treatment of a disease condition and circadian rhythm. Various diseases like Hypertension, Diabetes, Peptic ulcer, Asthma etc. show circadian variations. So a therapeutic system that coordinate the drug delivery in compliance with the circadian rhythm during periods of increased risk is highly required. According to the maximal clinical manifestation of the disease, the chronotherapeutic formulations deliver the therapeutic agent as a burst. The basic concepts of chronomodulated drug delivery system, biological rhythm, disease requiring chronotropic system and recent technologies for chronotherapy were mainly focused on this review.

**Keywords:** Chronomodulated drug delivery system, Biological rhythm, Chronopharmaceutical technologies.

### INTRODUCTION

Instead of new drug discovery the development of an effective drug formulations with already existing therapeutic agents is one of the major goal of pharmaceutical research and development. Among other route of administration oral route is the preferable one, because of its patient compliance and safety. Designing of drug delivery systems are mainly focusing on sustained, variable and constant release of drug and also targeting it into the specific diseased organ/site. But in some cases the time specific drug release is required instead of the conventional drug delivery. It is known that cure of a disease condition is depends upon the nature of drug, the time and drug administration.<sup>3</sup>

Circadian rhythm regulates many process in our body like metabolism, behaviour, sleep pattern, production of hormone, physiological process etc. This rhythm of body clock is called biological clock. Compared to prescribing the medication at specific time schedule throughout the full day to maintain a constant drug concentration in the blood. It is better to maintain a relation between biological rhythm of disease and the release pattern of drug<sup>3,6</sup> and this relation is very useful in clinical practice, leads to the chronotherapy. Chronotherapy is the coordination of treatment and circadian rhythm.

In chronobiology, Chrono and biology means time and science of life respectively. So, the chronobiology deals with the biological mechanism of a disease related to the biological rhythm of human body including functions like body temperature, pulse rate, blood pressure, renal function, gastric pH, hormone secretion.<sup>7</sup>

Chronopharmaceutics is related to formulation and characterization of system that delivers therapeutic agent at a time according to the necessity of the drug for the cure of disease. In chronotherapy when the dosage form is administered the drug will not come out at first instead of it is only delivered as a burst to the site after a lag phase and this pattern of drug release is termed as pulsatile drug release.

Chronotherapeutic systems is mainly for delivering the therapeutic concentration of drug as a burst during the maximal clinical manifestation of the ailment. There by efficacy of the drug can maximise and the side effects of the drugs can be minimised.<sup>4</sup>

#### Biological Rhythm (Circadian Rhythm)

Biological rhythms are patterns of behaviour and physiology that follows a daily cycle. It mainly responds to day and night cycle of organism's external environment. For example, awake during the daytime and sleep at night time. There are mainly 2 types of biological rhythm, endogenous and exogenous. Organisms have their own endogenous rhythms and it is controlled by themselves. E.g. Human body temperature. External factors like changes in season, day and night are because of exogenous rhythm. Depending upon internal and external sources, biological rhythms can be classified into circadian rhythm, Ultradian rhythm and infradian rhythm.<sup>2</sup>

#### Circadian Rhythm

Franz Halberg introduced the word circadian rhythm from Latin word "circa" (about) and "dies" (day). It is basically a cycle between sleepiness and alertness at regular interval



that is running in the background of brain. It is also called sleep wake cycle/ 24hr internal clock. <sup>2</sup>

### Ultradian rhythm

It is an endogenous rhythm that happens on a shorter time period than circadian rhythm but frequency is high. Examples of this rhythm are blood circulation, blinking, hormonal secretion. <sup>4</sup>

### Infradian rhythm

It is longer than circadian rhythm. its frequency is less than 28hrs. Examples are menstruation or seasonal rhythm.

### Molecular level of circadian rhythm

Both hypothalamus and pineal gland consist of paired suprachiasmatic nuclei (SCN) and It controls our circadian rhythm. In our brain and peripheral tissues some other circadian oscillators are present along with SCN. One of the important factor that synchronised SCN is environmental signals like light. <sup>1</sup> Light signals are received by photo receptor cell present in retina and transmit to neurons of SCN through retino hypothalamic tract and outputs modulated through feedback/ feed through effect. In all cells there will gene expression but some of them influences the rhythmic activity, they are called as clock genes like PER I, PER II, BMALI, CRY and cyclic secretions of melatonin also keeps rhythmicity. <sup>5</sup>

### Chronotherapeutic technology

Chronotherapeutic technology consist of a core which contains plug and a polymer barrier layer which control the discharge of drug from the core. The chronotherapeutic technology can be broadly classified according to the techniques used.

- Time controlled chronotropic systems.
- Stimuli induced pulsatile drug delivery systems.
  - a) Thermo-responsive system
  - b) Chemical stimuli induced system
- Externally regulated pulsatile drug delivery systems.
  - a) Electro-responsive system
  - b) Micro electro mechanical system
  - c) Magnetically induced system

### Time controlled chronotropic system

In this system, after a predetermined lag phase, a burst release of drug within short time period. At the time of lag phase the drug is not released. This system classified into both single and multiparticulate system and also available as immediate release and pulse release type. The following are the subclasses of this system.

### Time controlled chronotherapeutic system based on capsule

Capsular system consists of a capsule body which is made of an insoluble material. This capsule body enclose the

drug and sealed with a swellable and biodegradable polymer plug. The drug usually fabricated into multiparticulates form having a polymeric membrane. The release of drug from the multiparticulates depends upon the composition and thickness of the coating material. <sup>4</sup> After a predetermined lag time the drug is released from the capsule body. The swelling strength of plug controls the lag time. Plug is usually made of hydrophilic polymers like Hydroxyl propyl cellulose, Poly ethylene oxide, Poly vinyl acetate. The swelling or erosion of the plug occurs the releasing of drug from the capsule body. Pulsincap mainly contains a hydrogel plug and a capsule body and when reaches the fluid the plug swells and pushes itself from the capsule body and thus the drug released. <sup>1</sup>

### Time controlled reservoir system with rupturable polymer coating

In this systems rupturable polymer layer is used for drug core coating and top water insoluble membrane which is semi permeable. The drug core contains both swelling agent and drug. When water enters the system creates a hydrostatic pressure developed and this leads to the breaking of polymer layer and drug release. Usually swelling agents, effervescent agents which produce gas or osmogens produce the pressure required for the polymer rupturing.<sup>4</sup> Swelling agent usually used are superdisintegrants like carboxy methylcellulose, sodium starch glycollate, L-hydroxy propyl cellulose and polymers like polyacrylic acid, polyethylene glycol etc. <sup>1</sup> The lag phase of system affected by the permeation rate of water and coating's mechanical strength.<sup>4</sup> There was a complete release of drug from this, unaffected by pH of the surrounding environment and drug solubility. If the water insoluble coating is not ruptured by the swelling agents, then there will be no drug release, the best lag time reported is approximately 4 hours and the flexibility in the release is limited. For controlling the drug release, along with insoluble polymeric coating pH affected water soluble polymer can be used. so that at high intestinal pH, polymer starts to dissolve leads to breaking of membrane after a lag time which is predetermined. Either diffusion or dissolution cause drug release, that is affected by drug's nature. Increase in concentration of osmotic agents leads to rapid release.<sup>4</sup>

### Time controlled reservoir system with eroding or soluble polymer coating

These are another type reservoir system having a polymer barrier which dissolves or erodes and causes the release of drug from the reservoir following a time lag. The thickness and viscosity of polymer barrier like HPMC controls the time lag. <sup>1</sup> in this system the drug reservoir is coated with HPMC and a top layer which is enteric coated. From gastric media enteric coat safeguard the system and then dissolves in intestine. Since the drug delivery mechanism in this is dissolution so the high drug solubility is essential relative to the dose. <sup>4</sup>



### **Pulsatile system based on change in membrane permeability**

Due to the existence of counter ions of the media surrounding the system, change in permeability of the polymer layer coat helps in drug release. It is beneficial for achieving a sigmoidal release model, timed release and colon drug delivery. The physicochemical properties of the therapeutic agent and its interaction with polymer determines the change in polymer permeability and thereby release profile of the system.<sup>4</sup>

### **Time controlled floating low density pulsatile system**

These are the system having low density, floating which retain inside the stomach and not affected by the gastric environment like gastric emptying time and pH. They may be either single system like floating tablets or multiparticulate system like beads, granules, pellets, microspheres with gastric retention capability. They are helpful for drugs either absorbed via the stomach or local delivery in stomach. It can also use for deliver the drug in intestine by crosslinking of the polymers makes them insoluble in the acid controls the drug release.<sup>4</sup>

### **Stimuli induced chromomodulated drug delivery system**

Based on the physicochemical process that occurs in our body these systems are created. That is in this case, induction of certain physicochemical process helps in the drug release. Biological stimuli like pH, temperature of site, release of some hormones, enzymes, biomolecules etc. make the polymers undergo phase transition i.e. swelling and deswelling.<sup>4</sup>

### **Thermoresponsive system**

Due to the presence of pyrogens or pathogens the human body temperature changes from normal temperature. This deviation is the drug releasing stimulus. These systems made of thermo responsive polymers that is polymer having properties like thermally reversible transition, glass transition, swelling change of network and crystalline melting.<sup>2</sup> The mainly available thermo responsive polymers include PDEA, Pluronic, poly (methyl vinyl ether), PNVC, Tetronics.<sup>4</sup>

### **Chemical stimuli induced system**

Different types of devices are available based on chemical stimuli such as glucose dependent insulin release device, Inflammation induced system, pH sensitive system and intelligent gels that release drug responding to concentration of antibody. For e.g. in Diabetes Mellitus case glucose concentration increase in the blood rhythmically, requires the insulin injection at that correct time. So systems which respond to the glucose concentration have developed. This system contains pH sensitive hydrogel with immobilised enzyme glucose oxidase in it. When the glucose concentration rises in blood, glucose oxidase convert glucose into gluconic acid. So system's pH changes and polymer swelling and thereby drug release.<sup>2</sup>

### **pH sensitive system**

In this systems mechanism are done by using pH dependent polymer. They have a reliable and predictable drug release pattern. The main advantage of this system is that we can make the drug deliver site specific as per the pH of the surrounding environment.<sup>4</sup> Usually pH sensitive system contains 2 components. One is fast release type while the other is pulse release component which make the drug release in accordance with pH. The drug release at specific area can be designed by choosing the pH responsive polymer. For example, cellulose acetate phthalate (enteric coating), polyacrylates etc.<sup>2</sup>

### **Enzyme catalysed system**

They are usually developed for specific delivery in colon and the release rate depends on the degradation of polymeric membrane by the colonic microflora secreted enzymes. So, it helps in target drug delivery.<sup>4</sup>

### **Inflammation induced system**

Physical or chemical stress cause inflammation. During inflammation hydroxyl radicals produced from inflammation responsive cells and this act as stimulus.<sup>2</sup> Inflammation responsive system use hyaluronic acid, specially hydrolysed by free radicals present at inflammatory area. So, it is used to treat inflammatory conditions like Rheumatoid arthritis by using NSAID incorporated into these systems.<sup>4</sup>

### **Externally regulated chromomodulated drug delivery system**

Here some triggering stimuli like electric effect, irradiation, ultrasound, magnetic forces etc. helps in drug release. On applying these external forces, conductors present in system that sense the force, get sensitized and triggered the release of therapeutic agent from system. When the external stimuli stop the drug's release also get stopped.

### **Electro responsive system**

They are prepared using polyelectrolytes polymers having high amount electrolyte groups that get ionise and bear charges based on the pH value. So they are pH responsive and also get influenced by electric field. This field is used as an external stimulus and the drug release can be controlled by the direction and time of electric impulse. The electro responsive polymer gel deswells or bend due to the electric field. Examples of electro responsive natural polysaccharides include, Agarose, Chondroitin Sulphate, Hyaluronic Acid, Calcium Alginate etc. synthetic polymers include acrylates and methacrylate derivatives. In hydrogel the drug is dispersed and implanted subcutaneously. When the release of drug is necessary an electro conducting patch and gel is applied on skin, an electrode is connected to the patch and electrical impulse is applied.<sup>2</sup>

### **Magnetically release induced system**

This approach involves the blending the materials with magnetic power like Cobalt, Magnetite, Nickel, Iron etc. to



elastic polymer. Drug is bound to magnetic material. Due to the application of oscillating magnetic field on the system, polymer swelling occurs which help the drug release. This is very effective method for localized drug delivery.<sup>2</sup>

### Ultrasonically modulated system

The rate of drug release in this system is modulated by ultrasound. They are made up with either non erodible or bio erodible polymers. At the time exposed to ultrasound, erosion of bio erodible polymer occurs and in a controlled manner the drug release occurs. Polymers which are bioerodible include Polyglycolide, Polylactide and their copolymer with sebacic acid. The drug release extend can be controlled by the regulating the intensity, frequency and ultrasound cycle applied.<sup>1</sup>

### Chronotherapeutics and diseases

The symptoms and occurrence of many medical conditions depends on circadian rhythm. so the disease treatment can have done in accordance with circadian rhythm that is chronotherapy. Chronotherapy helps in the management of different medical conditions like Asthma, Hypertension, Cholesterol, Peptic Ulcer, Rheumatoid Arthritis, Cardiovascular Disease etc.

### Chronotherapy of cardiovascular disease

During cardiovascular disease like Acute Myocardial Infraction, Myocardial Ischemia, Ventricular Tachycardia etc. circadian variations can occur.<sup>1</sup> Based on these variations chronotherapy helps in the prevention or treatment of above mentioned cardiovascular disease. Physiological determinants like heart rate, platelet aggregation and release of catecholamine which itself change circular and exogenous factors like anxiety, physical activity, mental stress etc. affects the rhythmic variations in cardiovascular disease. By chronotherapeutic formulations the cardiovascular diseases can be treat in accordance with the occurrence of the symptoms and severity of disease that is when the drug is utmost needed. Therefore, dose dumping can be minimised.<sup>5</sup>

### Chronotherapy of Asthma

Symptoms of asthma get worsen at sometimes of day because of circadian variation. Asthma get worsen during night and dawn than the other time.<sup>1</sup> The accurate cause of asthma at sleep are not well known even though some clarification of this are reclining position, internal triggers, high allergen exposure etc. The level of cortisol which cause inflammation in the airway will be peak at awakening period and low during midnight, the concentration of histamine which is a broncho constrictor will be peak during 4 am. So great bronchoconstriction will be occurring at that time. Chronotherapy of asthma mainly focus for getting maximum effect from bronchodilator drugs during the dawn hours.<sup>5</sup> The main focus in asthma treatment is to maintain undisturbed sleep and a steady lung function. The chronotherapy of asthma with beta 2-agonists and oral corticosteroids is well suited.

Chronotherapy with once-daily at evening time using theophylline helps to attain the above mentioned goals by increasing the level of theophylline in blood levels during night and in the awakening time, when the drug is highly needed.

### Chronotherapy of diabetes

Circadian variation influences the hormone insulin and it's counter controlling hormone like glucagon. The level of glucagon increases in blood during the mid-night. In non-diabetic this process is counter act by raising the level of insulin secretion. So the glucose blood level can be managed. But in the patients with type I diabetes (insulin deficiency diabetes) and type II diabetes (liver does not respond to insulin), the glucose level in blood increases during morning adversely.<sup>10</sup> Along with the main physiological stimulus i.e. food intake triggers the insulin secretion; the biological rhythm also influences insulin secretion time. The main goal of insulin chronotherapy is to deliver insulin as occurs in normal persons in accordance to the need.<sup>5</sup>

### Chronotherapy of Hypercholesterolemia

The hepatic cholesterol synthesis is also affected by circadian rhythm. The synthesis of cholesterol is higher at night than daytime and the maximal production shows in early morning that is 12 hrs after the supper. So it is more advantageous to take evening dose of HMG-CoA reductase inhibitors than dose take in morning.<sup>5</sup>

### Chronotherapy of Cancer

A molecular clock is present in each single cell which control the cellular proliferation over 24 hr through circadian rhythm. It also controls the division of cancer cells.<sup>1</sup> Antineoplastic can effect on both normal and tumor cells. So the cancer treatment should be precise to tumour cells and should not harm the normal cells. The difference in circadian rhythm related to normal cells and tumour cells influence the susceptibility of cells to drugs. Due to differentiation in the susceptibility rhythms of tumor cells and normal cells, the correct timing of therapy will reduce unintended toxicity to host body. Ultimately management of tumour will be better.<sup>5</sup>

### Chronotherapy of Rheumatoid Arthritis

Usually the Rheumatoid arthritis signs such as pain and stiffness of joints are more severe at the morning time. The dose scheduling of the NSAIDs like Ketoprofen, Ibuprofen once daily in accordance with the severity of the pain optimise the therapeutic effect and minimise the side effect of drug.<sup>1</sup>

### Chronotherapy of peptic ulcer

The patients with peptic ulcer usually experience high degree of pain at midnight and at dawn.<sup>5</sup> Typically the ache is because of the stomach emptying, high acid secretion.



Once daily administration of H2 antagonist at night is highly effective, enhance the healing of ulcer.<sup>9</sup>

### Chronotherapy of Hypertension

Hypertension or high blood pressure is a medical condition which is chronic because of the elevated systemic arterial blood pressure. For cardio vascular diseases, hypertension is one of big risk factor. In both normotensive and hypertensive patients, the heart rate and blood pressure are higher during morning hours (4.00 am to 6.00 am) than remaining times of the day. The lowering of sympathetic output occurs during night time when individual asleep is the reason for this. Therefore, antihypertensive agents in such cases typically needed during the dawn hours. So chronomodulated system can provide better leads.<sup>11</sup>

### Certain chronopharmaceutical technologies recently available

#### OROS® technology

This technology protects the drug from enzymatic and chemical degradation in gastro intestinal tract (GIT) and timing of drug deliver is uninfluenced by the GIT contents. This type of systems delivers bolus drug dose in a site specific or time specific manner to GIT.<sup>3</sup> This is an osmotic system which consist of two-layer tablet system, one layer composed of therapeutic agent while the next with osmotically active agent and the system is covered using a semipermeable membrane with drilled orifice on it for drug delivery. Water enter via the semipermeable membrane into osmotic agent during the exposure of system to aqueous medium. Hydration of osmotic agent causes the expansion and the force created helps in the drug release through the orifice.<sup>5</sup>

#### CEREFORM® technology

This technology produces microspheres having constant size and shape. The microspheres produced are almost perfectly spherical in shape and size of those ranges 150-180µm and also with high drug holding capacity. In this technology therapeutic agents or biodegradable polysaccharides are put through fusion of Thermal Gradients, Temperature, Mechanical forces and Flow rate during processing. The produced microspheres can formulate into different dosage forms like Suspension, Tablets, Capsules, Effervescent tablets and Sachets.<sup>5</sup>

#### CONTINR® technology

Technology involves combining hydrophilic polymer with therapeutic agent using a polar solvent as a hydrating agent and aliphatic alcohol as a fixating agent. Solvating/ hydrating the polymer with a polar solvent and then reacting the hydrated polymer directly with aliphatic alcohol, a molecular coordination complex is formed. This complex is of uniform porosity and can design as a matrix in controlled release formulations.<sup>5</sup> CONTINR® technology helps in controlling the quantity of drug released to blood stream and thereby reduce the dosing frequency every day.<sup>3</sup>

### DIFFUCAPS® technology

This multiparticulate system is to provide two drug blend in accordance to the biological rhythm. The profiles of drug release are achieved by layering active agent onto a neutral/inert core like crystals, sugar spheres or granules next coated by a rate controlling functional membrane. The coating materials used can be water soluble or water insoluble, pH dependent or independent in accordance to drug. One or more type drug containing particles with different drug release profiles can be filled in hard gelatin capsule. So a combination release profile can be achieved. We can customise any combination of release profile such as sustained release, pulsatile release or immediate release as per the specific needs of the product.<sup>5</sup>

The solubility of insoluble drugs in GIT can be improved using this technology. For this beads with cover of alkaline or organic buffer make drug soluble by producing an optimal pH microenvironment for agents showing bad solubility in intestine that is pH greater than 8.0. The first FDA approved chronotropic system contains propranolol that is Innopran R XL for the control of hypertension has been prepared by using this technology.<sup>3</sup>

### CHRONOTOPIC® technology

This technology can provide different drug release profile like time dependent, delayed in addition colon specific release.<sup>3</sup> Basically a core with drug covered with a rate controlling polymer. The polymer can be a hydrophilic polymer usually HPMC which becomes a glassy rubber transition when it gets exposed to aqueous fluid. Then through the glassy gel layer drug get released either by diffusion or erosion. The viscosity grade of the polymer used and the thickness of polymer coat formed determines the time drug release start and lag time. The application of acid resistant film onto the drug polymer core can protect them from gastric environment and allows colon specific delivery. The film helps the system to maintain them intact till the time it reaches the intestinal environment.<sup>5</sup>

### CODAS® technology

Chronotherapeutics Oral Drug Absorption System or CODAS is a technology which consist of a core loaded with drug and multi-layered membrane surrounding the core, which hold the drug release up to 5 hrs.<sup>3,5</sup> Both water insoluble and soluble polymers can use as rate controlling multi-layered membrane. The water soluble polymer dissolves slowly when come in exposure with GI fluid and pores are formed on the coat membrane. Then by diffusion of drug through the pores the drug get release. The polymer used which is water insoluble un nature perform as a barrier for maintain the drug release controlled. It is developed for dosing at bedtime which maintain a higher drug concentration in plasma during awakening morning hours.<sup>5</sup>

### TIMERx® technology

A hydrogel based system be made up of gums like xantham and locust bean which are blended along with dextrose



forms a matrix. The technique used for preparing TIMERx<sup>®</sup> matrix is wet granulation method and then coated using compression coating technique.<sup>5</sup> Due to the exposure of water, the components of matrix undergo physical interaction produce a strong binding gel and afterwards the drug releases. The drug release rate can be managed by rate of water permeation from GIT into TIMERx<sup>®</sup> gum matrix.<sup>3</sup>

## CONCLUSION

Conventional dosage forms that are available now do not effectively treat disease conditions with chronobiological pathophysiology. Chronotherapeutic drug delivery system (CDDS) developed with sigmoidal drug release solves this problem because these systems can release the drug according to the circadian rhythm. Many kinds of techniques can utilise to design a chronomodulated system like system induced by stimuli, external stimuli dependent system and time specific release system. This system helpful for various disease like asthma, cardiovascular disease, hypertension, diabetes etc. which follow circadian variation. Various CDDS are currently in research and some are already available in the market. Chronotherapeutic system surely have a bright future.

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