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Chronomodulated drug delivery system-A Review

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ABSTRACT

Chronobiology is the science deals with the biological mechanism of the diseases according to a time structure. The variations in the pharmacological actions of various drugs over a period of time. Putting this all together, chronotherapeutics considering the timing of drug delivery according to inherent activities of a disease over a certain period of time. With the advancement in the field of chronobiology, modern drug delivery approaches have been elevated to a new concept of chronopharmacology, that is the ability to deliver the drugs on a specific preprogrammed pattern i.e. at appropriate time and at appropriate site of action. chronopharmaceutical technology advantageous to the application range, the ease of manufacturing, the cost effectiveness and the flexibility in the pharmacokinetic profile. It also provide perfect therapy by targeting to the specific site at most appropriate time. The mechanisms are associated with the 24- hour rhythms of biochemical and physiological behavioral processes under the control of the circadian clock. Research in chronobiology described the importance of biological rhythms in drug delivery that timing of drug delivery has significant effect on treatment success. So this can be concluded that chronomodulated drug delivery system provides a solution for delivery of drugs for those disease conditions regulated by circadian rhythm. present article gives an overview of various types of chronomodulated drug delivery systems and also tries to highlights some of the recent advances being done in chronopharmaceutical drug delivery system.

Keywords: Chronopharmacokinetics, Biological rhythms, Circadian time structure, Chronopharmacotherapy, Chronotherapeutic drug delivery systems.

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INTRODUCTION[1,2,3,4]

Chronobiology is the science concerned with the biological mechanism of the diseases according to a time structure. Chronopharmacology is the science that considers the variations in the pharmacological actions of various drugs over a period of time. The review addresses the approaches to this sub-discipline, calls attention to potential disease-targets, and identifies existing technologies, hurdles and future of chropharmaceuticals. Chronopharmaceutical coupled with nanotechnology could be the future of dds, and lead to safer and more efficient disease therapy in the future.

Over the last 30 years, numerous technical advancements in biodegradable polymers, formulations and comprehensive understanding of pharmacokinetics have resulted new techniques of drug delivery. These techniques are capable of controlling the rate of drug release, sustaining the duration of therapy and/or targeting delivery of a medicinal agent to a specific organ or tissue. It is for this reason controlled or targeted drug delivery systems have been, and continue to be, receiving more and more attention. However, recently one type of drug delivery system, where delivery device is capable of releasing drug after predetermined time-delay, known as pulsatile drug delivery system has drawn the attention of scientists.

The Chronopharmaceutical Drug Delivery System (CDDS) has emerged during the last decade as a possible drug delivery system against several diseases, which may lead to the creation of a sub-disciple of pharmaceutics to be explored called 'chronopharmaceutics'. Chronopharmaceutics is 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 in real time the biological requirement of a given disease therapy. The main goal of chronotherapeutics is to match the timing of treatment with the intrinsic timing of illness. Optimum therapy is given when the right amount of drug is delivered to the correct target organ at the most appropriate time. If symptoms of a disease are varied the circadian rhythms also varied the drug release.

Definition

Chronotherapeutics: refers to the use of circadian or other rhythmic cycles of a condition's symptoms and/or of the individual being treated in the application of therapy.is the discipline concerned with the delivery of drugs according to the intrinsic activities of a disease over a certain period of time because the biochemical, physiological and pathological variations over a 24h period in humans have occurred . Different types of the rhythms affecting human body[5]**:**

Ultradian: these cycles last for a shorter than a day. E.g. 90 minutes sleep cycle[6,7].The series of events usually experienced in our day to day life shown in Figure 1.

Circadian: This word comes from Latin word "circa" means about and "dies" means day[6,7].This lasts for over 24 hours. E.g. sleeping and waking patterns.

Infradian: cycles longer than 24 hours. E.g. monthly menstruation[7].

Seasonal: such as seasonal affective disorder (SAD), this causes depression during the short days of winter in susceptible people[8] .

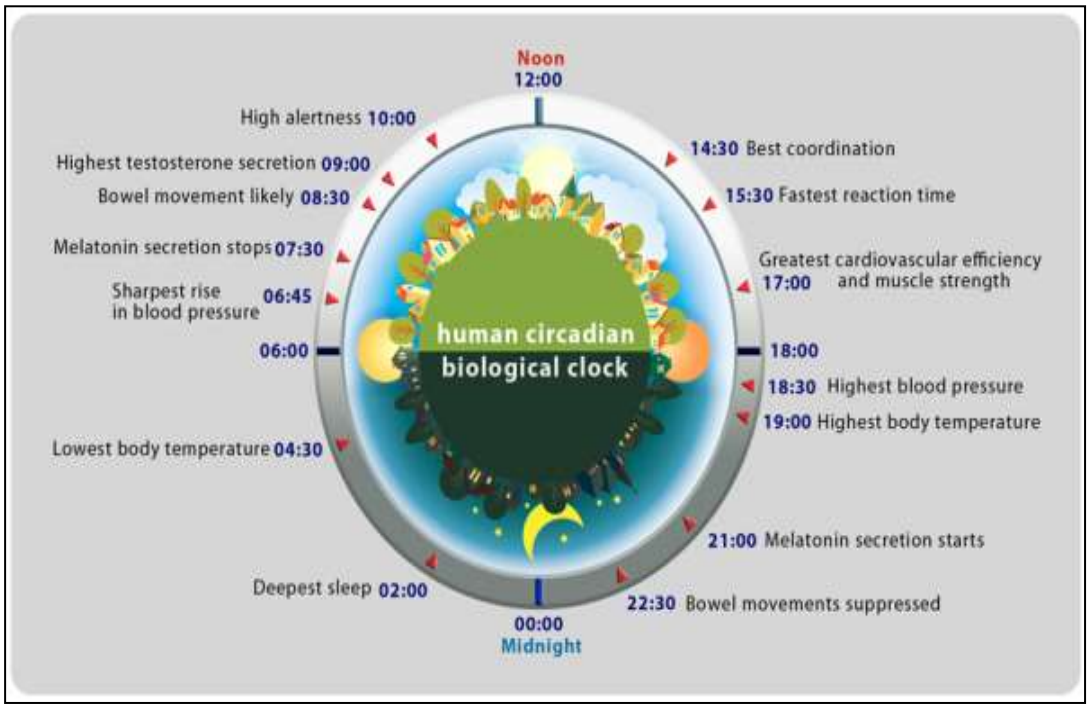

Figure 1.Human circadian biological clock[11].

ADVANTAGES AND DISADVANTAGES OF CHRDDS[4,13,19]

Advantages

i. Improves stability.
ii. Improves patient comfort and compliance.
iii. Extends patent protection, globalizes the product, and overcomes competition.
iv. Achieves a unique release pattern.
v. Predictable, reproducible, and short gastric residence time.
vi. Ease of combining pellets with different compositions or release patterns.
vii. Reduced adverse effects and improved tolerability.
viii. Less inter- and intra-subject variability.
ix. Limited risk of local irritation.
x. Flexibility in design.

xi. Improves bioavailability.

Disadvantages

i. Need of advanced technology.

ii. Large number of process variables.

iii. Medical supervision is mandatory for this therapy.

iv. LOW drug loading.

v. It develops a non 24 hours sleep wake syndrome after the treatment as the person sleeps or over 24 hours during the treatment.

vi. Multiple formulation steps.

vii. Newer equipment should be provide.

viii. Lack of manufacturing reproducibility and efficacy.

ix. Higher cost of production.

x. Trained / skilled personnel needed for manufacturing.

TECHNOLOGYS OF CHRDDS

Oros® Or Chronoset Technology

Chronset™ is a proprietary OROS® osmosis-based delivery system that reproducibly delivers a bolus drug dose, which is time dependent and in site-specific manner, to the gastrointestinal tract. The drug is kept in a reservoir surrounded by a semi permeable membrane laser, drilled with a delivery orifice, and formulated into a tablet or capsule. The tablet consist of two layer, one is drug layer and other consist of osmotically active agent. Upon contact with the GI fluid this osmotic agent changes its characteristic from a nondispensable to a dispensable viscosity. As a result drug is pushed away through the channel due to the pump effect of the osmotic agent. It is generally used in the designing of an extended release tablet[3].

DIFFUCAPS® technology

DIFFUCAPS® technology, a unit dosage form, such as a capsule is used for delivering drugs into the body in a circadian release fashion[4]. Diffucaps is a multiparticulate bead system comprised of multiple layers of drug, excipients, and functional polymer membrane to control the rate of drug release. Diffucaps beads are<1.5 mm in diameter and filled into capsules. The beads contain a layer of organic acid or alkaline buffer to control the solubility of a drug by creating an optimal pH microenvironment for drugs that exhibit poor solubility in intestinal pH, in environments with pH greater than 8.0, or in physiological fluids[10].

CHRONOTOPIC® technology

It is also described in the system with an erodible, soluble or rupturable membrane system. It is basically a drug-containing core, coated with an outer release controlling layer. Both single and multiple unit dosage forms such as tablets and capsules or minitablets and pellets have been employed as the inner drug formulation[4].

EGALET® technology

It is a delayed release form consisting of an impermeable shell with two lag plugs, enclosing a plug of active drug in the middle of the unit. After erosion of the inert plugs the drug is released **.**Time taken to erode the inert plugs determines the lag time. The shells are made of slowly biodegradable polymers (e.g., ethylcellulose) and plasticizers (e.g., cetostearyl alcohol), while the matrix of the plugs is a mixture of pharmaceutical excipients, including polymers like polyethylene oxide (PEO)[4].

CODAS® technology

Chronotherapeutical oral drug absorption system consisting of drug loaded beads that are coated with release-controlling polymer. Both water-soluble and water-insoluble polymers are used to to obtain a predetermine a lag time[13].

GeoClock® technology

Geoclock® tablets have an active drug inside an outer tablet layer consisting of a mixture of hydrophobic wax and brittle material in order to obtain a pH independent lag time prior to core drug delivery at a predetermined release rate. This dry coating approach is designed to allow the timed release of both slow relese. and immediate release active cores by releasing the inner tablet first after which time the surrounding outer shell gradually disintegrates[10.]

Diffutab Technology

The Diffutab technology incorporates a blend of waxes and hydrophilic polymers that control drug release through diffusion and erosion of a matrix tablet. It includes high drug loading capability. This technology is applies to both soluble and insoluble products[10.]

Eurandminitabs® technology

It consists of tiny (2 mm x 2 mm) cylindrical tablets coated with a functional membrane to control the rate of drug release. They contain gel-forming excipients that control the drug release rate. The tablets are filled into capsules, allowing a combination of multiple drugs and/or multiple release profiles in the same dosage form. Minitabs can be formulated as matrix tablets prior to further coating[10].

PORT® technology

The Programmable Oral Release Technologies (PORT) system is a uniquely coated, encapsulated system that can provide multiple programmed release of the drug. It contains a polymeric core coated with a semipermeable, rate-controlling polymer. Poorly soluble drugs can be coated with solubilizing agents, to ensure a uniform controlled release from the dosage form. In the capsule form the gelatin capsule is coated with a semipermeable, rate-controlling polymer. Drug mixed with an osmotic agent is kept inside the capsule shell. A water-insoluble plug is used to seal the capsule shell. Immediate release compartment can be added according to need[4].

Three-dimensional printing® (3DP) technology

Three-dimensional printing (3DP) is a novel technique based on solid freeform fabrication methods. Consist of engineer devices with complicated internal geometries, varying densities, diffusivities, and chemicals. (3DP) is a rapid prototyping (RP) technology. Prototyping involves constructing specific layers that use powder processing and liquid binding materials. Different types of complex oral drug delivery devices such as immediate-extended release tablets, pulse release, breakaway tablets, and dual pulsatory tablets fabricated using the 3DP process[12].

CEFORM® technology

This technique helps in development of microspheres of uniform size and shape. It is based on "melt spinning"[20] in which biodegradable polymer or bioactive agents combination is subjected to combination of temperature, thermal gradients, mechanical forces, flow, and flow rates during processing[4]. The microspheres can be used in tablet capsule, suspension, sachet form. It can also be coated for controlled release[14]. Biodegradable polymers/bioactive are subjected to varying temperature, thermal gradients and flow processes to produce microspheres of uniform size and shape[13].

CONTIN^{R} technology

In this technology, molecular coordination complexes are formed between a cellulose polymer and non-polar solid aliphatic alcohol, optionally substituted with an aliphatic group, by solvating the polymer with a volatile polar solvent and reacting the solvated cellulose polymer directly with the aliphatic alcohol, preferably as a melt. This constitutes the complex having utility as a matrix in controlled release formulations, as it has a uniform porosity (semi permeable matrixes), which may be varied[20]. The CONTINR technology provide benefits to patients by reducing the dose they need to take every day also provide more effective control of their disease (particularly at night), and reducing unwanted side effects control over the amount of drug released to the bloodstream[14].

TIMERx® technology

It is a hydrogel-based, controlled release oral dug delivery system acceptable to soluble and insoluble drugs. Basically it is composed polysaccharides xanthum gum and 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 TIMERx gum matrix, which expands to form a gel and subsequently releases the active drug substance[5,20].

APPLICATIONS OFCHRONOPHARMACOLOGY 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.

Nocturnal asthma

The symptoms of nocturenal asthma more prevalent in night time .Some biological rhythms come about monthly or even annually, asthma changes fairly predictably on a circadian cycle or 24 hour. Even in normal, lung function differs between day and night. The activity of the lung exhibits a circadian rhythm with a maximum around 4 p.m. and a minimum around 4 a.m. In asthmatic patients, the intensity of variation in lung function is as much as 50% in a day. Bronchial reactivity generally follows the same circadian cycle in Asthmatic patients. It can be defined as any sleep-related Worsening of reversible airway disease. Shortness of breath or wheezing at night is symptoms generally shown. Nocturnal asthma is associated with critical symptoms and urgent need for proper medications[27].

Myocardial Infarction

Onset of myocardial infarction has been shown to be more frequent in the morning with 34% events occurring between 6 A.M. and noon. Acute cardiac arrest and transient myocardial ischemia shows an increased frequency in morning. The causes for these findings have been suggested to be release of catecholamines, cortisol, increase in the platelet aggregation and vascular tone[25].

Peptic ulcer disease

As the maximal acid secretion, peptic ulcer disease pain, perforation of ulcers are maximum at night time, H2 receptor blockers like ranitidine, famotidine are preferentially given at evening time. In the past time histamine (H2) antagonists were administered at regular intervals around the clock based on the basis of pharmacokinetic properties and circadian rhythm because maximal acid secretion, peptic ulcer disease ,pain and perforation of gastric and duodenal ulcers are more common at night administration of these drugs at bedtime is more effective. Nocturnal

administration of the peptic ulcer medicines is not only reduces the acid secretion more effectively but also promotes the ulcer healing and reduces ulcer recurrence[17].

Arthritis

The chronobiology, chronopharmacology and chronotherapeutics of pain have been extensively reviewed[21].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[6].Chronotherapy for all forms of arthritis uses standard treatment that includes the non-steroidal anti-inflammatory drugs and corticosteroids but in the treatment the dosages time are match with the rhythms of disease which are timed to ensuring that the highest blood levels of the drug coincide with peak pain[8].

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[6]. In cardiovascular disease capillary resistance and vascular reactivity are higher in the morning and decreases later in the day. Increased platelet aggregation and decreased fibrinolytic activity in the morning leads to relative hypercoagulability of the blood**.** Also BP is at its lowest during the sleep cycle and rises steeply during the early morning awakening period. These observations shows that myocardial ischemia, angina pectoris, acute myocardial infarction, congestive cardiac failure and sudden cardiac death are also unevenly distributed during the 24 h with greater expected events during the initial hours of the daily activity span, in the late afternoon or early evening[8]**.**

Hypertension

Hypertension,high blood pressure (HBP), is a long term medical condition in which the blood pressure in the arteries is persistently elevated .Heart rate and blood pressure will be high at the time we wake up in the morning i.e. A.M and it will begin to decrease in the afternoon and it reaches to the minimum at midnight. the dosage form of antihypertensive drug we can modulate according to the circadian pattern which release the drug during morning hours when the symptoms of hypertension are more prevalent[26].

Oral contraceptives

Female sex hormones exhibit monthly cycle and oral contraceptives are prescribed as per menstrual cycle[6].

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[6]. The antineoplastic drugs causes the cytotoxic effects on healthy and diseased tissues as the biological rhythms of both healthy and tumor cells influence the susceptibility of the normal and malignant cells to the cytotoxic agents[17].

Epilepsy

The circadian rhythm may also take a significant role in seizures of some types of epilepsy. The influence of the biological clock on seizure of some partial seizures has been found in some experimental animal models. The methodology for measurement of the circadian rhythm in humans is also investigated. Behavioral chronobiology provides the detection of probable new regulation processes concerning the central mechanisms of epilepsy. Because of this fact, the circadian psychophysiological patterns of epilepsy show dynamic biological systems which recommend some intermodulating endogenous processes between observation and seizure susceptibility. Furthermore, such chronobiologic studies applied to epileptic behaviour suggest the development of new heuristic aspects in the field of comparative psychophysiology[21].

Table 1: **Research work carried out on chronomodulated drug delivery system**

Sr no	Drug	Formulation	Disease
1.	Terbutaline sulphate	Pulsincap	Nocturnal asthma
2.	Salbutamol sulphate	Multiparticulatepulsinecap	Nocturnal asthma
3.	Salbutamol sulphate	Compression coated tablet	Nocturnal asthma
4.	Pravastatin sodium	Compression coated tablet	Hypercholesterolemia
5.	Simvastatin	Multiparticulatepulsinecap	Hypercholesterolemia
6.	Lornoxicam	Multiparticulatepulsinecap	Arthritis.
7.	Terbutaline sulphate	Multiparticulatepulsinecap	Nocturnal asthma
8.	Doxofylline	Compress coated pulsatile tablet	Nocturnal asthma
9.	Cilnidipine	Compress coated pulsatile Tablet	Hypertension
10.	Nifedipine	Compress coated pulsatile Tablet	Hypertension
11.	Theophylline and diltiazemhcl.	Multilayeredmultidisk oral tablet	Hypertension
12.	Montelukast sodium	Compress coated pulsatile tablet	Nocturnal asthma
13.	Valsartan	Compress coated pulsatile tablet	Blood pressure
14.	Montelukast sodium	Pelletisation compression	Nocturnal asthma
15.	Montelukast sodium	Tablets-filled-capsule	Nocturnal asthma

MARKETED SYSTEMS:

CODAS® (Chronotherapeutic Oral Drug Absorption System). The CODAS® technology is designed to allow a 4-5 h delay for onset following administration of drug. This delay in release is introduced by the level of release-a controlling polymer applied to the drug-loaded beads. Applying the CODAS® technology to Verapamil Hydrochloride, Verelan® PM complimented the

circadian pattern of hypertension and helped to minimize the risk of early morning cardiovascular events[1,16].Penwest Pharmaceuticals and Co., USA, considered to be top runner in drug delivery technologies with patented products such as TIMERx®, Geminex® and SyncroDoseTM The TIMERx oral drug delivery system achieves a variety of release profiles (First order, Zero order, BurstCR, etc.) for a wide range of drugs, accommodating even the most difficult actives. Alza Corporation uses OROS (Osmotic Release Oral Systems) drug delivery platform with marketed products such as Covera-HS® and Procardia XL®. Eurand Pharmaceuticals DIFFUCAPS® technology is a multiparticulate system that provides optimal release profiles for either single drugs or for a combination of drugs[15].More complex strategies can include the use of microchips in controlled release systems in order to obtain a determined release program. Hydrogels, namely stimuli-sensitive –hydrogels and temperature sensitive hydrogels have been reviewed as interesting drug delivery technology for chronopharmaceutics[1,28].

CONCLUSION

The chronotherapy of a medication may be accomplished by the appropriate timing of conventionally formulated tablets and capsules and the special drug delivery system to synchronize drug concentrations to rhythms in disease activity. Key point of development of this delivery system is to find out the circadian rhythm, that is, a suitable indicator that will trigger the release of the drug from the device. It can be concluded that oral chronotropic drugs help in various drug delivery problems such as extensive first pass metabolism, chronotropic 134 behavior of the diseases and nocturnal dosing thereby increasing the patient compliance and is the future of the drug delivery system. Different formulations have been developed based on chronopharmaceutical technologies for the effective management of the diseases which depends on circadian day night pattern of the body. chronomodulated drug delivery system developed by using different technologies for the treatment of diseases, as shown in Table 1.

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