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A REVIEW ON CHRONOPHARMACEUTICAL DRUG DELIVERY SYSTEM TO SYNCHRONIZE WITH CIRCADIAN RHYTHM DISEASES

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ABSTRACT

It is secret that living beings, including plants, livestock, fungi and cyanobacteria, undergoes a biological and inner process called circadian rhythm that controls the sleep-wake period and repeats about every 24 hours. This cycle is coordinated by the suprachiasmatic nucleus and controls about all body features, including related to drug delivery systems. The major aim is it should match with the circadian clock of the body indicating that these drug delivery systems deliver the right dose at a specific time at a particular site in order to accomplish this different techniques, such as time-controlled, pulsed, and programmed drug delivery systems which have been created and widely studied leading to chrono pharmaceutical drug delivery so that synchronization of this drug implementation with circadian rhythms leads to enhanced disease management and a higher patient therapeutic outcome. This review article tries to explain the function of circadian rhythms in different diseases and their states such as asthma, cardiovascular disease, arthritis, and cancer in a concise way. It also discusses the different oral drug delivery techniques introduced and their results in chronotherapeutic disease therapy.

Keywords: Circadian rhythm, chronopharmaceutical drug delivery system, chronotherapeutic diseases, Pulsed drug delivery systems, Cardiovascular Diseases, Chronotherapy

INTRODUCTION

Daily rhythms have been noted in animals and plants since the early days. Alexander the Great's author and rosthenes noted in the fourth century BC that the leaves opened during the morning and closed at night demonstrating a definite rhythm. In 1729, the first known test on biological rhythms was performed by the French astronomer Jean Jacques d'Ortous deMairan **[1]**. It has been illustrated since then that Mammalian circadian pacemaker lies in CNS and affects many biological procedures, including the rhythm of sleep-wake. The circadian clock control homeostatic processes such as sleep and behaviour, concentrations of hormones, appetite, and other 24-hour body functions so a new theory called chronobiology. Generally, from the past studies the oral drug delivery route is generally preferred and most user-friendly and patient compliance, reproducible and efficient in vivo plasma levels. So, drug delivery systems have traditionally concentrated on sustainable drug production with the goal of minimizing drug concentration peaks and valleys in the body in order to modify drug effectiveness and decrease adverse effects. In the controlled release drug delivery systems, a decreased dosing frequency and enhanced patient compliance can be anticipated. However, increasing attention has recently been paid in the ground of modern drug treatment to the chronopharmaceutical delivery of drugs for which conventional controlled drug release systems with constant release are not optimal. It relates to delivering medicines in the right concentration to the right targeted tissues at the correct moment to satisfy biological rhythm determined requirements, such as changes in disease processes, symptom intensity and/or patient tolerance, in order to modify desired and minimize and prevent adverse effects. Besides this, biological rhythms have an effect not only on the function of physiology, but also on disease pathophysiology. The chronobiology and chronopharmacology representing the notion of chronotherapy as a tool to improve the effectiveness and safety of drug by delivering the dosage form for the different disease conditions such as hypertension, asthma, peptic ulcer, and cancer **[2-4]**.

BIOLOGICAL RHYTHMS:

A biological rhythm is an endogenous origin self-sustaining oscillation defined by period (length of time to complete a single cycle), level (rhythmic variation that oscillates in men and women), amplitude (measure of the magnitude of the predictable-in-time

variation), and phase (peak and trough values) characteristics **[5]**.

CIRCADIAN RHYTHM:

In many living organisms, such as cyanobacteria, plants, flies, rodents and humans, circadian rhythms have been shown to be biologically variable processes **[6]**. Generally, most body processes are not static but rather in an influx state so that when these dynamics happen within 24 hours, repeating cycle, they are called circadian rhythms and molecular clocks generate these rhythms within each cell consisting of 15 clock genes **[7]** and regulated by the master biological clock called suprachiasmatic nuclei (SCN) **[8]**. The daily changes in light intensity are significant of circadian cycle which controls a wide range of circadian rhythms in physiology, behavior. The circadian timing system (CTS) includes molecular, cellular, physiological and pacemaker components, and to coordinate body and cell functions which responsible for drug pharmacokinetics (PK) and drug metabolism over the 24h and circadian changes modulate phase I, II and III drug metabolism, detoxification and disposition processes at cell, tissue and whole organism levels resulting circadian timing system to determine optimal times of day or night when medications are best tolerated or most effective. Moreover, drugs can also alter the CTS so that chronotherapy integrates these CTS controls on biological functions into the design of circadian drug delivery patterns to optimize treatment effects. A major example is women's menstrual cyclic (duration 30days), heart rate and blood pressure (increase in early morning may disrupt oxygen supply and allowing thrombus to develop in morning causes myocardial ischemia **[6-10]**.

BENEFITS OF THESE TECHNOLOGIES [11]

- Once daily dose resembles multiple dosing by bursts release of drugs.
- Constant drug levels at the site of acti on and prevent fluctuations in the pea k valley.
- Reduced dose frequency, dose size, cost, drug resistance and tolerance, side effects increase patient compliance.
- Release rate independent of pH, food and minimal potential for dose dumping.
- Protection of mucosa against irritating drugs.

LIMITATIONS

- Multiple fabrication steps, require trained experts

- The uniformity of the coating is compulsory to ensure the predictability of the lag time.
- Rupture time depends on the polymer physicochemical characteristics.
- Drugs are expensive and raw materials are not accessible readily.
- Complicated technologies and equip ment used

APPROACHES FOR CHRONOPHARMACEUTICAL DRUG DELIVERY SYSTEMS:

CONTIN® technology:

Contin® technology requires controlled release because the formulation of a tablet contains aminophylline in a cellulosic polymer matrix. The desired in vivo release rate for a variety of drugs can be achieved by varying the amount of cellulose, the degree of cellulose hydration, the ratio of cellulose to higher aliphatic alcohol, or the water-soluble to water-insoluble cellulose ratio. Long-acting bronchodilators can be achieved in which Uniphyl evening administration demonstrates higher improvement of pulmonary function than the morning dose **[12, 13]**.

Chronotopic: Chronotopic technology is intended to achieve delayed or time-dependent colon release. Compress the tablet matrix by granulating the drug with excipients, then spray mixture of HPMC and PEG on to the core for time release (lag phase) and coating eudragit for delayed release. The variability of the gastric emptying phase, colon-specific release could be achieved. After oral consumption, the system is supposed to stay intact in the stomach and allows the system to react to p^H. Thus polymer becomes rubbery and makes permeable, dissolves and or erodes **[14]**.

Pulsincap®:

Pulsincap® technology comprising of a water-insoluble capsule containing the drug using a swelling hydrogel plug, the drug contents were sealed into the capsule body using polymers regulates the lag time by loading and enabling one or more minitablets, coated tablets, solutions or multiparticulates to be loaded into the capsule allows to interact with the fluid, it swells and delay the release, the plug pushes itself so that the capsule can be opened, and the drug can be quickly released **[15]**.

CEFORM®:

CEFORM® technology enables the manufacturing microspheres of pharmaceutical compounds that are used in a broad variety of dosage forms including tablets, capsules, suspensions, effervescent tablets and sachets. Diltiazem is formulated by melt spinning mechanism. The

microspheres acquired during this method are almost spherical (150-180 μm), allowing for coating with enteric polymer for controlled release **[16]**.

CODAS®:

Chronotherapeutic oral drug absorption scheme (CODAS®) provides delayed release according to circadian rhythms. It comprises of a core, multi-layered membrane loaded with drugs that consists of water-soluble which dissolves and diffuses the drug through the pores and water-insoluble (acts as a barrier) polymers. Verelan PM is delaying the release of verapamil for 4 to 5h after bedtime, where the maximum plasma concentration occur about 11h later **[17,18]**.

TIMERx®:

TIMERX® is a technology based on an agglomerated hydrophilic matrix with controlled release of drug. The matrix consists of locust bean gum and xanthan gum, when interact with aqueous environment form a tighter complex with a slowly eroding core from which the drug is released at a controlled rate for an extended period of time for 4h.Slofedipine XL and Cystrin CR are examples of controlled release and opioid analgesic oxymorphones **[19, 20]**.

DIFFUCAPS®:

DIFFUCAPS® is a technology which incorporating two drugs, verapamil HCL and propranolol HCL, as an extended release tablet in circadian release fashion with or without a predetermined lag time of 3-5 h depending on the physiological need helps in prediction of cardiovascular diseases. The active core is prepared by granulation and milling or by extrusion and spheronization comprising a drug and an inert particle, which is covered with an API-containing water-soluble polymer **[21]**.

OROS®:

The OROS® technology is used to design Covera-HS®, an anti-hypertensive. By utilizing the osmotic displacement process, the tablet is split into an active medication layer and a push compartment layer. The drug reservoir is surrounded by a semi-permeable membrane and formulated into a tablet. The drug diffuses through the orifice with rise in osmotic pressure and release the drug when contact with aqueous environment for longer periods of maintaining blood levels **[22, 23]**.

Geolock:

For continual drug release a multilayer method was suggested. The barrier layer (acts as modulating membrane which adjusts the core hydration mechanism and minimize drug release surface area) swells and

becomes a gel in the presence of the dissolution medium. The active core is exposed to the external setting after erosion, which helps to release drugs **[24]**.

Egalet:

Eaglet technology utilizes erosion it comprises of an impermeable shell with two lag plugs made up of biodegradable polymers and plasticizers which consist of the plug's matrix where the active drug is sandwiched. The matrix erodes when contact with gastrointestinal fluid and not diffuses until the release can be modulated by the length and structure of the plugs ensuring that the system follows the release of erosion control drugs. Using this technology, several opioid products are developed **[25]**.

Controlled release microchip:

The technique used is microfabrication technology which utilizes a silicon microchip to control the release. The active devices incorporate micrometre-sized pumps, valves and flow channels for the delivery of liquid solutions and their mechanism is based on the electrochemical dissolution of thin anode membranes covering solid, liquid or gel-filled micro reservoirs **[26]**.

Chronomodulating infusion pumps:

Melodie R programmable Synchromed R, Panomat R V5 infusion pumps (100) are modulators usually these are light weight pumps (300-500 g) for simple portability and accuracy in drug delivery. The clinical trial performed on patients with metastatic gastrointestinal malignancies compared with modulated three-drug regimen shows significant concurrent improvements in both tolerability and reaction rates **[27]**.

CIRCADIAN RHYTHMS IN OCCURRENCE AND SEVERITY OF DISEASE:

Cancer:

The timing of drug administration is based on circadian rhythms of susceptibility to cancer cells. ℓ-OHP was administered at 16:00 h to scirrhous gastric cancer patients causes in vitro cell lines apoptosis gastric cancer cells but circadian rhythm is not yet clarified and 5–FU + FA for 12 colorectal cancer patients in early morning three replied to chronotherapy and four reacted out of 10 patients with gastric cancer no kidney toxicity but nausea, vomiting was noted **[28]**.

Bronchial Asthma:

Bronchial asthma is a disease which causes enhanced and inflammation of airway hyperactivity (cough, dyspnea) between midnight and early morning so the night-time dosing avoids chronic inflammation. Methyl prednisolone (glucocorticoid) tablet minimize or eliminate chronic adrenocortical suppression. Dutimelan® reduces asthma

episodes, adverse effects and improves therapeutic efficiency and dosing differs with time and prevents bronchoconstriction **[29]**.

Cardiovascular diseases:

A cardiovascular diseases includes myocardial infarction, stroke and ischemia differs predictably occurs in early mornings. The blood pressure and heart rate are high during morning because of fibrinolytic activity is reduced in the morning which results in hypercoagulability of the blood. So, the chronotherapy of these diseases is to produce the drug during the early morning and lower during the mid night. Verapamil is an anti-hypertensive medicine which has a delay in release of about 4 to 5 hours after administration and then extended for18 hours **[30]**.

Hypercholesteremia:

The circadian rhythm takes place during synthesis of hepatic cholesterol. Cholesterol synthesis and levels of plasma mevalonate separate depending on the individual. HMG-CoA reductase and cholesterol-7α-hydroxylase circadian rhythms occur low in the day time, high in the evening at 12 p.m. peak so the evening dosing of HMG CoA reductase inhibitors is effective **[31]**.

Allergic rhinitis: The symptoms of allergic rhinitis are sneezing, nasal rhinorrhea (runny nose), nasal pruritus (itching), nasal congestion, wheezing, red itchy eyes, and stuffy nose which occur in the morning and less in the centre of the day because of nasal congestion and obstruction in the night. In the early phase of rhinitis reflects the release of chemical mediators such as histamine, prostaglandins, cysteinyl leukotrienes, cytokines, chemo tactic factors, protease enzymes, and TNF-α that evokes symptoms of sneezing, nasal itch, and rhinorrhea **[32]**.

Pain:

In patients with angina pectoris, myocardial infarction, migraine, rheumatoid arthritis, and toothache, morning pain is discovered and in patients with biliary colic disease intractable pain occurs morning or night. Rheumatoid arthritis shows highest morning pain and osteoarthritis has more pain in the evening hours **[33]**.

Diabetes:

Circadian rhythms of insulin are released in a pulsatile fashion. Insulin secretion is subjected by act on the B-cell and an inhibitory fashion. The failure of target cell resistance to insulin action and hyperglycaemia may be caused by the stress hormones, cortisol, epinephrine and growth hormone. The difference in daily maximum and a minimum insulin concentration in plasma considered as a secondary circadian rhythm. It is due to variable secondary early-

morning and late-afternoon insulin resistance **[34]**.

Duodenal Ulcer:

High evening acid secretion levels and low morning levels characterize the patterns of 24-hour gastric acidity in humans. Duodenal perforations showed the largest incidence in the afternoon, while gastric perforations showed a high peak close midnight and a secondary peak **[35]**.

Table 1: Spectrum of biological rhythm [5]

Period	Major rhythmic components
Short [τ <0.5 h]	0.1 s< τ <1s, τ ~min (Pulsatiles)
Intermediate [0.5 h< τ <6 days]	Ultradian (0.5 h< τ <20 h), Circadian (20 h < τ < 28 h) Infradian (28 h < τ < 6days)
Long [τ >6days]	Circaseptan (τ ~7days), Circamensual (τ ~30 days), Circannual (τ ~1 year)

Table 2: Circadian rhythmicity of various diseases [36]

Disease or syndrome	Circadian rhythmicity
Allergic rhinitis	Symptoms worse in early morning
Bronchial asthma	Exacerbations more common during the sleep period
Arthritis, rheumatoid	Symptoms are most intense upon awakening
Osteoarthritis	Symptoms worse in the middle/ latter portion of the day
Angina pectoris	Chest pain and ECG changes are more common during the early morning
Myocardial infraction	Incidence greatest in the early morning
Peptic ulcer disease	Symptoms worse after gastric emptying and in the early morning (sleep period)
Stroke	Incidence greatest in early morning
Acute coronary syndrome (AMI, uAP, sudden death)	Early morning
Subarachinoidal haemorrhage	Day time

Table 3: Examples of marketed products in the market [37, 38]

Active pharmaceutical ingredient (API)	Proprietary name dosage form	Proprietary chrono pharmaceutical technology	Manufacturers	Diseases
Theophylline	Uniphyl® extended release tablets	CONTIN®	Glen mark Generics Inc. USA	Asthma
Verapamil HCL	Verelan® PM, Covera HS	CODAS®, OROS®	Schwarz Pharma, Monheim, Germany, G.D. Searle(a division of Pfizer) N.Y, U.S.A.	Hypertension
Propranolol HCL	InnoPran® XL	DIFFUCAPS®	Glaxo smith Kline, USA	Hypertension
Tulobuterol	Hokunalin® tape	Transdermal chrono-delivery system	Maneho Co. Ltd. Japan	Asthma
Nifedipine	Procardia XL	PROCARDIA XL®	Pfizer Lbs. U.S Pharmaceuticals Group, New York	Hypertension

Table 4: List of patents in the field of chronotherapy [39-46]

Technology	Active agent	Type of formulation	Patent number
Time controlled drug delivery system	Sotalol HCL	Tablet in capsule	US 7048945
Pulsatile technology	Amphetamine, Diltiazem HCL	Multiple pulse amphetamine salt, Beads	US6605300, US6322819, US 5914134
Implantable electromagnetically driven device	Bethanidine	Implant	US4003379
Controlled release article with pulsatile release	Captopril	Multi-layered article	US5213808
Pulsatile drug delivery system	Ivermectin, Propranolol Nifedipine, Diltiazem	Bilayer tablet, Coated Tablet, Spherical particle	US4723958, US5229131, US5840329
Multiparticulate pulsatile drug delivery system	Diltiazem HCL	Pellets	US5508040
Pulsatile transdermal drug delivery system	Nitro glycerine	Transdermal device	US5312325
CODAS™	Glipizide	Coated tablet	US6500459

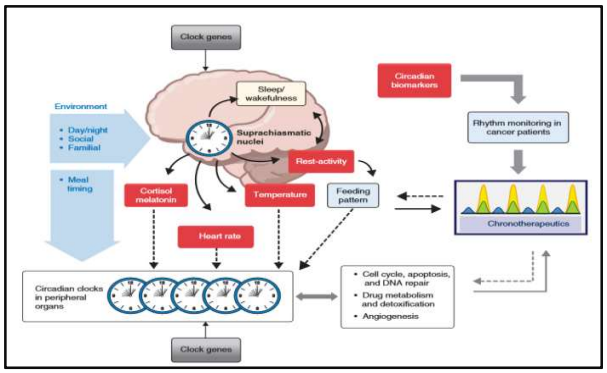

Figure 1: A comprehensive appraisal of the CTS for designing chronotherapy schedules

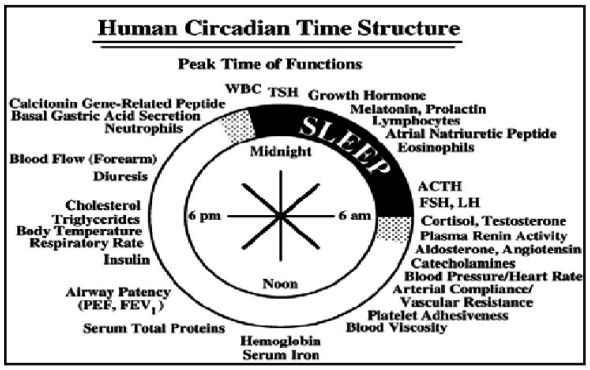

Figure 2: Human circadian time structure

CONCLUSION:

The article focuses primarily on promoting and educating the development and application of chronotherapeutics for improving the safety and efficacy. The significance of biological rhythm and circadian disease variations differ over time in drug treatment results in a special approach to drug delivery systems for these different techniques, time controlled, pulsed, triggered and programmed drug delivery systems have been developed to synchronize drug release with circadian rhythms (24hrs) of the disease states such as hypertension, asthma, duodenal ulcer, cancer. Finally, from this chronopharmaceutics will definitely enhance the result of patient outcome and optimize future disease management.

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