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Chronotherapeutic Drug Delivery: A Way Forward to Treat Rhythm Guided Diseases

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Abstract

Chronopharmaceutical drug delivery includes the awareness of chronobiological and drug delivery systems to harmonize release of drug to match natural rhythms of the illness state. It refers to a regimen by which *in vivo* drug release time is matched with rhythms of ailment to optimize remedial outcome with added advantage of minimal side effects, low dose and more patient compliance. The rational of these systems are based on the fact that, optimal pharmacological effect may not be possible when plasma drug concentration is constant. When symptoms of diseases show circadian variations, the release of drugs should also vary with time. So, variations of disease state as well as plasma drug concentrations should be taken into thought in formulation proposed for the treatment of disease with sufficient dose correct time. Extensive reviews are available in public domain regarding the advantages, disadvantages, ideal characteristics and formal approaches to chronopharmaceutics. This article deals with the concepts, molecular basis and critical analysis of some retrospective research work done in this platform which may enable future researchers to formulate pharmaceutical delivery system to release the drug when it is mainly needed.

Keywords-Asthma, Chronopharmaceutical drug delivery system, Hypertension, Master biological clock

INTRODUCTION

The presence of circadian rhythms in human is been known since the time of Hippocrates. Around 400 B.C. Hippocrates understood the fact that sleeping during daytime is indication of disease and sleeplessness during night is indication of illness and suffering. The concept of circadian rhythm in flora was described by Jean-Jacques d'Ortous de Mairan in 18th century. The term circadian was first given by Franz Halberg in 1960s and he is considered as one of the architect of chronobiology and, during this time a large number of physiological functions and biological rhythms were described. Biological variations have now been reported for several processes and play a important role in clinical materialization of symptoms and diseases [1]. The word "chrono" fundamentally refers to the fact that every metabolic event undergoes rhythmic changes with time [2, 3]. Investigators have found that most of the living creatures are made up of rhythms with varying frequencies that can range from seconds to munities even to seasons also. Perhaps the most widely researched frequency is the circadian rhythm that approximates earth's 24-hour rotation around the sun [4]. With literatures and studies on chronobiology, investigators are now with the opinion that both sickness and therapy are affected by significant rhythmic changes that occurs within the human being [2]. Chronotherapeutics refers to the medical practice of harmonizing drug delivery to synchronize with body's circadian rhythm much more during disease states to generate maximum health benefit and minimum or no side effects [5]. As more and more research is done on this platform, it has become more apparent that the time a patient takes the medicine is actually more important than it was recognized in the past. The established method of giving drugs at evenly spaced time intervals throughout the dosage regimen, for maintaining constant drug concentration may get a blow as new research concludes that some drugs may act much better if their administration is matched with day-night patterns and biological rhythms [6]. In this article the authors retrospectively reviewed some of the research work carried in relation to chronotherapeutics drug delivery systems (CDDS).

MOLECULAR BASIS OF CIRCADIAN RHYTHMS

The master biological clock present in hypothalamus of brain called suprachiasmatic nuclei (SCN) directs cardian rhythms. Apart from the SCN, brain and peripheral tissue like liver also have circadian oscillators [7, 8]. With the environmental signals like sunrise and sunset the SCN is synchronized daily [9]. Depending on lighting conditions which SCN receives from the retina, it modulates secretion melatonin, a pineal gland hormone as well as and other peripheral clocks, and their outputs again modulate the SCN through feedback or feed-forward effects. Thus, in the body there is wide range of interacting clocks [10]. In all cells, the expression of gene changes rhythmically over 24 hours. Suprachiasmatic nuclei clock working machinery along with other subsidiary clocks in other parts of the body are depended on definite circadian genes such as CLOCK, Brain & Muscle ARNT-Like 1, and period circadian protein homolog 1. The studies on animal carried out till date has brought the investigators to its present thrilling position, because their findings suggested that ´clock genes´ are directing the circadian rhythms in all physiological processes [11].

CIRCADIAN TIME STRUCTURE

In late fifties Halberg and Stephens had coined the term circadian rhythm. Circadian rhythm governs all course of action of the body [12, http://www.medicinenet.com/script/main/art.asp?articlekey=551]. As the human physiology varies during 24 hour period so as medical conditions. The best way of explaining human circadian time structure is to represent the 24-h rhythms on a clock--like diagram as shown in Figure 1 [13, 14]. Figure represents time of a number of circadian rhythms with respect to typical routine of human beings dormancy at night time from around 10:30 p.m. to 6:30 a.m. and movement in the day time when the sun is out [14]. From the figure we can observe that, migraine headache is more prone to happen in early morning, allergic and infectious rhinitis which is also called hay fever is also worst in the morning hours, [3] same is the case of rheumatoid arthritis, while patients with osteoarthritis will feel the pain more in later hours of the day. The chances of cardiac events like acute myocardial infarction (MI), angina and others are more in the morning hours of day so as the case of thrombotic and hemorrhagic stroke. During the initial three to four hours ischemic events, chest pain, and ST-segment depression of angina are strongest. The events like pain, aggravation of peptic ulcer, gastric distress are most prone to happen in the late hours and dawn. During sleeping hours epilepsy seizures are mostly common, while it starts at night and the condition improves during the morning hours.

CONCEPT OF CHRONOPHARMACEUTICS

The relevance of chronobiology in delivery of pharmaceuticals is called Chronopharmaceutics. The study of biological rhythms and their response to metabolic functions of body is known as chronobiology. Till now three types mechanical rhythms are known in our body and they are: a) Circadian Rhythms b) Ultradian Rhythms c) Infradian Rhythms

(a) Circadian Rhythms

The term "circadian" is a combination of two Latin terms "circa" means "about" & "dies" means "day". The Oscillations in human body that completes within 24 hours are called circadian rhythms.

(b) Ultradian Rhythms

The Oscillations in human body that completes in less than 24 hours are called ultardian rhythms. (more than one cycle per day).

(c) Infradian Rhythms

The Oscillations in human body that takes more than 24 hours to complete are called infradian rhythms(less than one cycle per day) [17].

For formulation of chronotherapeutics drug delivery systems, systematic acquaintance of pathogenesis of ailment and role of circadian rhythm in its patho physiology is necessary. Thus these delivery systems are designed to target such diseases for which enough scientific background is available to justify their need for chronotherapeutics systems as compared to conventional drug delivery systems.

TARGETED DISEASES FOR CHRONOTHERAPY

Diseases that are justified by background studies about their indicative changes due to circadian rhythm are the one which are targeted by investigators for chronotherapy. The symptoms include bronchial asthma, myocardial infraction, rheumatic arthritis, cancer peptic ulcers, diabetes, etc. It is now a well known fact that variation in the severity and frequency of these diseases depends on the 24 h clock pattern of day-night. Increase of asthmatic attacks happens after midnight or in early morning when there is a limited lung function promoted by circadian changes at that time. Many of the common diseases also shows marked circadian variation during onset or exacerbation of symptoms [18].

Table 1: List of marketed Chronopharmaceutical drug delivery systems

Brand name	API	Chronopharmaceutical technology	Drug release mechanism
Cardizem LA	Diltiazem Hcl	CEFORM microsphere technology	Production of microspheres based on melt- spinning technology.
Uniphyll^{R}	Theophylline	CONTIN^{R}	Cellulose polymer and non polar solid aliphatic alcohols form complex which acts as antimatrix
Innopran^{R} XL	Propranolol Hcl	DIFFUCAPS	Rapid or sustained release formulation
Covera-HS^{R}	Verapamil	OROS	A laser drilled Pulsatile drug delivery which works on the principle of osmotic pump comprising a core drug reservoir covered by semi permeable membrane with osmotic agent in tablet dosage form.
Verelan^{R} PM	Verapamil	CODAS	Chronotherapeutical oral drug absorption system consisting of drug loaded beads that are coated with release-controlling polymer.
Innopran^{R} XL	Verapamil	DIFFUCAPS	Rapid/sustained release
Invega^{TM}	Paliperidone	OROS	A sustained release Osmotic formulation of anti schizophrenic drug
Moxatag^{TM}	Amoxicillin	PULSYS^{TM}	A novel double coating technology with a immediate release coat and a delayed release coating
Glizid-MR30	Gliclizide	Hydrophilic matrix technology	Swelling/diffusion/erosion
KAPIDEX^{TM}	Dexlansoprazole	DDR Technology	Dual drug release
Theirform	Diclofenac sodium	3DP	Immediate release/controlled release

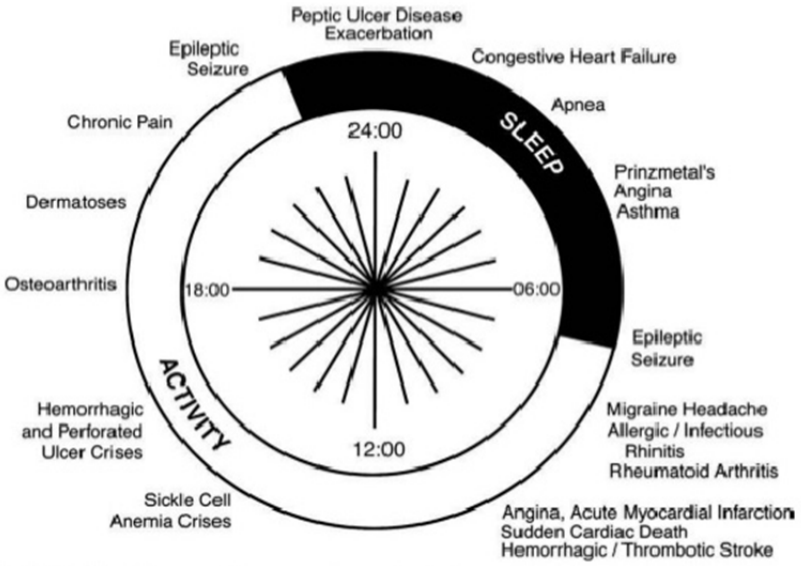

Figure 1:24 hrs clock timing, in human showing when symptoms or events of disease are worst [15-16].

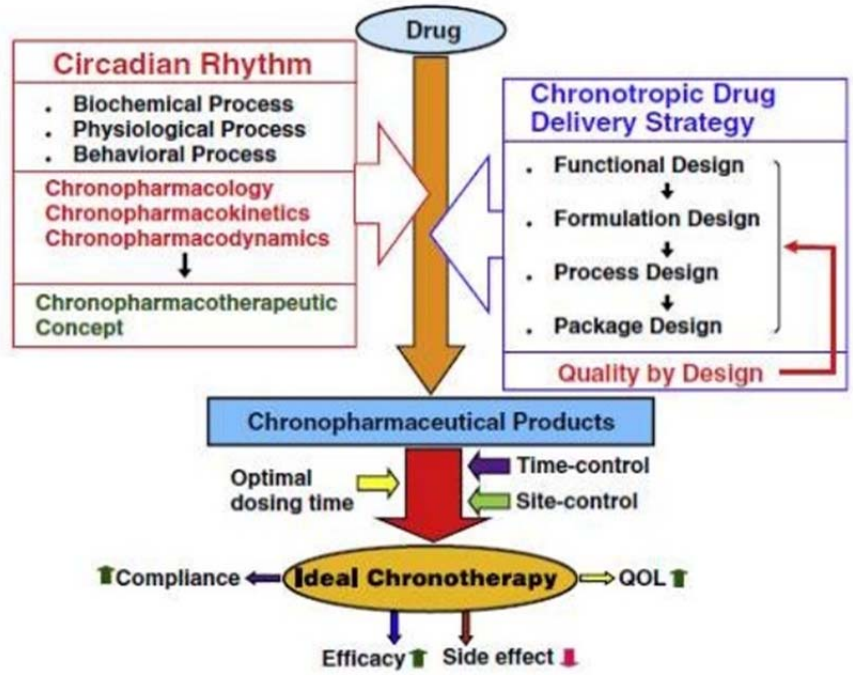

Figure 2: Approach to design new formulations in accord with circadian rhythm of body [19]

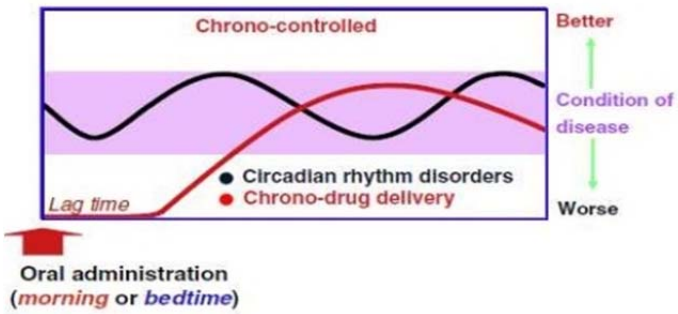

Figure 3: An ideal CDDS according to circadian rhythm disorders of the patients.

CASE STUDY OF FEW RESEARCHES ON CDDS PLATFORM

The approach to design drug delivery according to CDDS is based on the fact that, drug must be delivered when it is mostly needed i.e. the time when the chances of attack for the condition is more. The factors which need to be kept in mind while formulating the dosage form on CDDS platform is shown in figure 2. As from the figure it can be noted that a thorough knowledge about the diseases and its chronopharmacology will help to design the dosage which will deliver the drug when its mostly needed. Also to deliver the drug after a lag period, formulation parameters has to be designed accurately so that it can deliver the drug on its pre-calibrated time. A diagrammatic representation of such a delivery is shown in figure 3 which depicts a formulation which can deliver the drug after a lag time (red colour line) which more or less superimposes on the time when the attack is more prone to occur will show greater therapeutic results than marinating the drug concentration for the whole day by constant release mechanism. Taking this in account, a few research work is which is been carried out are exampled here.

Asthma is characterized by chronic obstructive lung disease with inflammation of lung and bronchopasm. In general the symptoms of asthma worsen during night with acute exacerbation being most common. Epidemiological studies also validate the fact that asthma attacks are more likely to happen during night in comparison to day with disturbance of sleep which occurs at least once weekly in approximately 75% of patients [20]. In this context, Shivakumar *et al.* worked on antiasthma drug theophylline to formulate pH-sensitive tablet in capsule dosage form intended to delay the release, by dissoluting the drug in colon to approximate the chronobiology of nocturnal asthma. The drug-loaded minitablets were coated by eudragit S-100 in different ratios using PVP K30 as binder. Scanning Electron Microscopy showed distinct continuous acrylic coat free from cracks or pores. *In vitro* dissolution studies performed using pH progression method showed that the release of drug from the coated minitablets depended on the coat weights applied and pH of the dissolution media. The invitro release of the drug from the minitablets s showed that coat weight of 10% weight gain was enough to impart an excellent gastro resistant property to the tablets for effective release of the drug at higher pH values that is in the intestine which may provide the necessary lag time for the actual need based release of the drug when it is mostly needed [21].

The attacks such as myocardial infraction, death due to impulsive heart attacks, stroke are reported to occur during the early hours than rest of the day. Domenic AM.D *et al*. carried clinical study taking in total four hundred thirty four patients having mild to moderate blood pressure that is hypertension. The study was done to check the antihypertensive efficacy of a propranolol chronotherapeutic formulation formulated for night time dosing (propranolol controlled release CR). The patients were divided in randomized fashion into either placebo or to 80, 120, 160 or 640 mg/d dose of propranolol. The average mean morning BP was similar in each treatment group at baseline was read to be 152/ 101mm Hg. After 56 days of treatment, the primary efficacy measurement, morning diastolic blood pressure, was considerably reduced from baseline in placebo (-6.98 mm Hg) to four different dosed propanolol groups ($p<0.001$). The decreases in diastolic BP was found to be in the range from 10.1 mm Hg in the 80 mg/d group of patients to 11.0 mm Hg in patients with dose of 120-mg/d and were significantly larger than placebo in the 120 mg/d, 160 mg/d, and 640 mg/d groups of patients ($p<0.05$). BP measured in the evening demonstrated related antihypertensive efficacy. All the formulations were well tolerated with minimum fatigue and dizziness being reported more in the placebo group. Researchers concluded that patients suffering with mild-to-moderate hypertension, propranolol CR when taken once around night time can provide effective and safe 24-hour control of BP. They also claimed it to be the first delayed-release β blocker specifically formulated for bedtime administration for providing optimum plasma drug concentration during the time when blood pressure rise is more common in accordance with circadian rhythm that is during the early hours in the morning. Since propranolol reduces hypertension by β-blocking action, therefore whether the formulations could specifically confers morning cardiovascular protection above and beyond that of conventional β-blocker formulations that could be administered on a bid. basis till today remains to be determined [22].

Rajyalakshmi K and Indira YM developed a series of gastro retentive matrix tablets of tramadol HCl for chronotherapeutic delivery for the treatment of night-time symptoms of arthritis with gum badam as carrier. Formulations were made using 30, 40 to 70% w/w of tablet of gum badam as carrier and then coated with eudragit S100 to provide enteric coating. The prepared tablets were then subjected to *invitro* dissolution analysis in a sequential manner in pH 1.2, pH 6.8 and pH 7.2 respectively for 2 h, 3 h and 19 h both in absence as well as presence of rat caecal content. The data was then fitted into release kinetics to evaluate the mechanism of drug release. It was also observed that presence of rat caecal content enhances the drug release in alkaline pH and as concentration of polymer increased, drug release was found to be retarded. X-ray studies confirmed that the tablet successfully reached colon without getting disintegrated in upper gastrointestinal tract. Based on the results, authors concluded that delivery of the drugs to the colon could be achieved using of gum badam as a carrier with eudragid S100 as coating material [23].

Compressed coated tablets containing nifedipine in tablet dosage form was prepared by Sawada *et al.* by dry coating using different polyethylene oxide-polyethylene glycol mixtures. As predicted the formulations showed a lag period before the drug release started, followed by sustained release up to 24 h. As the concentration of polyethylene oxide increased the lag time before the drug release started increased showing a direct relationship between the concentration of the coating medium and the initiation of drug release. This observation was used by the researchers for chronopharmaceutical delivery of nifedipine. *In vivo* studies were carried out on dogs where pharmacokinetics of two formulations having dissimilar *in*

vitro lag was compared with sustained-release (SR) tablet. The initiation of drug release and appearance in plasma was 0.7 ± 0.3 h for SR, 2.5 ± 1.2 h for one of the formulation, and 5.3 ± 1.0 h for the other. This observation in difference in initiation time of drug release was significant among the formulations that were in accordance with the *in vitro* data. Also, elevated plasma drug concentrations were observed at eight hours after administration of the one of the formulation than observed for the SR-tablet. These results indicated that the prepared formulations with a lag time before drug release can be potential candidate for chronopharmacotherapeutic drug delivery which can control the time and duration of drug release in comparison to available SR tablets in the market [24].

CONCLUSION

Drug delivery in accordance with biological clock provides a alternative to conventional formulations much more for the treatment of diseases which follows biological clock like asthma, ulcers, cancer etc. Since these delivery systems deliver the measured amount of drug at correct time and also sometimes at the targeted site, therefore, these systems are now taken up by many pharmaceutical industries and R & Ds for formulation development. Such new and more appropriate approaches for delivery of drug may lead to safe and efficient disease control in the near future. But obviously for translating these research data in to day to day clinical format, lot of progress has to be made to understand thoroughly the biological rhythm of human being.

Therefore, the knowledge of chronotherapeutics is not limited to pharmaceutical researchers only, but also to biologists, pharmacologists, scientists and clinicians so that there is better delivery of patient care.

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