INTRODUCTION
The phrase “circadian rhythm” was first described by Halberg and Stephens in 1959.[1] The biological clock was since found to be represented by the suprachiasmatic nucleus (SCN), which creates biological rhythms under the control of clock genes such as PER1,[2,3] PER2,[2] PER3,[4] CLOCK,[5] BMAL1,[6] TIM,[7] CRY,[1] CRY2,[8] tau[9] and coordinate peripheral oscillators, for functions including cell proliferation and cellular metabolism. The cycle duration generated at the SCN is calibrated by the alternation of light / darkness, both directly and through melatonin secretion by the pineal body [Figure 1].

Period genes (PER) and the proteins produced by these genes generate circadian rhythms.[10] The transcription of PER is promoted by the CLOCK / BMAL1 complex, whose activation is inhibited by the PER1 / PER2 / PER3 / CRY1 / CRY2 / TIM complex. This giant complex acts as a negative auto-feedback system, which has an essential role in the generation of circadian oscillation. This biological clock generates signals of circadian rhythm, which are conducted to the suprachrinal sympathetic nucleus and the pineal body. The generated biological rhythms deal with the control of biological functions including those of the autonomic nerve system, endocrine system, and immune system, which are fundamental in homeostasis and in protection against various diseases [Figures 2 and 3].

Key words: Chronobiology, chronopharmacodynamics, circadian rhythm, drug delivery system, mechanism, pulsatile drug delivery, suprachiasmatic nuclei

Chromomodulated drug delivery system: A comprehensive review on the recent advances in a new sub-discipline of ‘chronopharmaceutics’

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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 therapeutic agent to a patient in a staggered profile. The mammalian circadian pacemaker resides in the paired suprachiasmatic nuclei and influences a multitude of biological processes, including the sleep–wake rhythm. Clock genes are the genes that control the circadian rhythms in physiology and behavior. Twenty-four hours rhythms are demonstrated for the function of physiology and the pathophysiology of diseases. The effectiveness and toxicity of many drugs vary depending on the dosing time. Such chronopharmacological phenomena are influenced by not only the pharmacodynamics, but also the pharmacokinetics of medications. The underlying mechanisms are associated with the 24-hour rhythms of biochemical, physiological, and behavioral processes under the control of the circadian clock. New technology for delivering medications precisely in a time-modulated fashion, by bedside or ambulatory pumps, is being developed to manage human diseases. From the point of view of pharmaceutics, the application of a biological rhythm to pharmacotherapy may be accomplished by the appropriate timing of conventionally formulated tablets and capsules, and a special drug delivery system, to synchronize the drug concentrations with the rhythms in the disease activity. Therefore, the present article gives an overview of the dosing time-dependent alterations in the therapeutic outcome and safety of the drug. The underlying mechanisms and usefulness are introduced from the point of view of chronopharmacology and chronotherapy.

Key words: Chronobiology, chronopharmacodynamics, circadian rhythm, drug delivery system, mechanism, pulsatile drug delivery, suprachiasmatic nuclei

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of a medication may depend on its administration time, in relation to the staging of circadian and other biological rhythms. On the other hand, the temporal (biological rhythm) structure of the human body may be altered by disease, leading to significant changes in the response to therapy. Although sustained and constant release systems have been developed, the biological systems are not so responsive to these release systems. In addition, sustained and controlled release devices are not applicable in some cases like the time-programmed administration of hormones and many drugs.

The pulsatile drug delivery system has fulfilled this requirement. Pulsatile drug release is a system where the drug is released suddenly after a well-defined lag time or time gap according to the circadian rhythm of disease states. No drug is released from the device within this lag time. This delivery system is suitable in cases where drugs including proteins and peptides undergo great metabolic degradation. In case of chronic treatment, the drug resistance may grow and an adverse effect may be seen. Here chances are less because the desired concentration of the drug at a certain time point is available. This method is good for drugs with extensive first pass metabolism and those targeted to specific sites in the intestinal tract. Therefore, by developing the pulsatile device for specific colonic delivery, the plasma peak is obtained at an optimal time, the number of doses per day can be reduced, it is with saturable first pass metabolism, and tolerance development can also be avoided.

ADVANTAGES AND DISADVANTAGES OF THE PULSATILE DRUG DELIVERY SYSTEM

Advantages
1. Predictable, reproducible, and short gastric residence time
2. Less inter- and intra-subject variability
3. Improves bioavailability
4. Reduced adverse effects and improved tolerability
5. Limited risk of local irritation
6. No risk of dose dumping
7. Flexibility in design
8. Ease of combining pellets with different compositions or release patterns
9. Improves stability
10. Improves patient comfort and compliance
11. Achieves a unique release pattern
12. Extends patent protection, globalizes the product, and overcomes competition

Disadvantages
1. Low drug loading
2. Proportionally higher need for excipients
3. Lack of manufacturing reproducibility and efficacy
4. Large number of process variables
5. Multiple formulation steps
6. Higher cost of production
7. Need of advanced technology
8. Trained / skilled personnel needed for manufacturing

Surprisingly not enough or very little consideration has yet to be given to a very important factor which may, by itself, represent a significant and often crucial determinant of therapeutic success: TIME. As all physiological functions oscillate rhythmically in time, the activity, toxicity, and kinetics

Figure 1: The suprachiasmatic nucleus controls circadian rhythms in response to hormonal variation in the body

Figure 2: Time cycle when the diseases show their maximum effect

Figure 3: Human circadian time structure; shown is the approximate peak time of the circadian (24-hour) rhythms of selected biological variables in persons adhering to a normal routine of daytime activity (6 – 7 a.m. to 10 – 11 p.m.) alternating with night time sleep
Circadian rhythms in gastrointestinal, liver, kidney, and other body processes and functions are of great importance for therapeutics, for example, in choosing when to administer medications, in relation to rhythm, influences their pharmacokinetics, effect-duration, efficacy, adverse effects, and beneficial outcomes.\[19\]

Besides chronotherapeutic applications, oral pulsatile delivery systems may offer a number of different advantages. When designed to yield repeated release profiles, they could accomplish multiple daily dosing regimens for those drugs that fail to be candidates for prolonged-release formulations, on account of a strong first-pass effect or pharmacological tolerance. Of late, multi-pulse delivery of antibiotics has also been described as a means of limiting the development of resistant bacterial strains thus possibly improving the outcome of infectious disease therapy.\[20\] Moreover, delayed-release dosage forms have been proposed to prevent the occurrence of detrimental drug–drug interactions, without modifying the administration schedule of combined medications, which could negatively affect patient compliance.\[21\] Stevens et al.,\[22\] have used extrusion / spheronization technology to produce a novel pellet formulation containing diltiazem that is coated with a mixed film coat comprising of ethylcellulose and Eudragit RS polymers. Although the ethylcellulose component acts as a diffusion barrier, retarding the release of diltiazem, the permeability of the Eudragit RS increases progressively. The overall effect is a sigmoidal release profile. The release profile of systems based on permeability changes depend strongly on the physicochemical properties of the drug and its interaction with the membrane. Therefore, with this system a pulsatile release profile may be obtained for some particular drug molecules in a specific formulation, but it cannot be generally applied to all drugs. This article reviews the current status and recent technologies available through a new sub-discipline chronopharmaceutics in a form of a chronomodulated drug delivery system.

INFLUENCE OF CIRCADIAN RHYTHMS ON PHARMACODYNAMICS AND PHARMACOKINETICS

Chronopharmacodynamics

Biological rhythms at the cellular and subcellular levels can give rise to significant dosing-time differences in the pharmacodynamics of medications that are unrelated to their pharmacokinetics.\[23\]-\[28\] This phenomenon is termed ‘chronesthesy’.

Drug absorption

Circadian changes in drug absorption have been demonstrated for several orally administered drugs, in humans. Gastric acid secretion and pH, motility, gastric emptying time, and gastrointestinal blood flow vary according to the time of the day.\[29\],\[30\] Such changes may contribute to the dosing time-dependent difference of drug absorption. For example, circadian changes of pH may induce circadian modifications of drug ionization according to its physicochemical properties. The dosing time-dependent difference of drug absorption is influenced by the physicochemical properties of a drug (lipophilicity or hydrophilicity).\[31\] The circadian changes in drug absorption are significant in lipophilic drugs, while such changes are not demonstrated for hydrophilic drugs.\[32\] Drug absorption by other than an oral route of administration is also influenced by biological rhythms.\[33\],\[34\]

Drug distribution

Circadian changes in biological fluids and tissues related to drug distribution are documented to vary according to the time of day.\[35\] Blood flow depends on several regulatory factors, including sympathetic and parasympathetic systems, in which activities are known to be circadian time-dependent with a predominant diurnal effect of the sympathetic system.\[36\] Thus, a diurnal increase and nocturnal decrease of blood flow and local tissular blood flows may explain a possible difference in drug distribution depending on the dosing time. Plasma proteins such as albumin or Alpha-1-glycoprotein acid have been documented to be circadian time-dependent.\[37\],\[38\]

Drug metabolism

Hepatic drug metabolism seems to depend on liver enzyme activity and / or hepatic blood flow. Both factors show a circadian time-dependent difference. Enzyme activities show a circadian time-dependent difference in many tissues such as brain, kidney, and liver.\[39\],\[40\] Several chronopharmacological studies have indirectly investigated the temporal variations in hepatic drug metabolism by evaluating the chronopharmacokinetics of drugs and their metabolites. Thus, conjugation, hydrolysis, and oxidation show a circadian time-dependent difference. For example, circadian variations in the urinary β-hydrocortisol to cortisol ratio in man show these in the cytochrome CYP3A activity.\[41\]

Drug elimination

Renal physiological functions such as glomerular filtration, renal blood flow, urinary pH, and tubular resorption show a circadian time-dependent difference with higher values during daytime.\[42\] These rhythmic variations in renal functions may contribute to a circadian-dependent change in drug urinary excretion. The rhythmicity in urinary pH modifies drug ionization and may explain that acidic drugs are excreted faster after an evening administration as demonstrated for sodium salicylate\[43\] and sulfasylazine.\[44\]

CIRCADIAN RHYTHMS IN OCCURRENCE AND SEVERITY OF DISEASE

The symptom intensity of many medical conditions and the occurrence of life-threatening medical emergencies exhibit rather precise timings. Gout,\[45\],\[46\] gallbladder,\[47\] and peptic ulcer attacks\[48\] are most frequent at night. Acute pulmonary edema,\[49\] congestive heart failure,\[50\] and asthma\[51\],\[52\] worsen nocturnally. Sudden infant death,\[47\] symptoms of

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alergic rhinitis,[53,54] and rheumatoid arthritis[55] are either most intense overnight or in the morning upon wakening. Migraine headache is typically triggered during rapid eyeball movement (REM) episodes during night time sleep or in the early morning hours after wakening.[56,57] Angina pectoris,[58,59] ventricular arrhythmia,[60,61] acute myocardial infarction,[62] sudden cardiac death,[63] stroke,[64,65] fatal pulmonary embolism, and hypertensive crises,[66] all are most frequent in the morning, as are other cardiovascular conditions.[67] Depression is most severe in the morning.[68] Symptoms of osteoarthritis worsen during the course of daily activity, being typically most intense in the late afternoon and evening.[69,70] Perforated and bleeding ulcer is reported to be most common in the afternoon.[71,72] Some seizure disorders are triggered during specific sleep stages and/or by transitions between sleep and wakefulness.[73,74]

**RECENTLY AVAILABLE DIFFERENT CHRONOPHARMACEUTICAL TECHNOLOGIES**

**OROS® technology**

Chronset™ is a proprietary OROS®[2][3] delivery system that reproducibly delivers a bolus drug dose, in a time- or site-specific manner, to the gastrointestinal tract.[76] It is nothing but an osmosis-based system. The active pharmaceutical is kept in a reservoir surrounded by a semipermeable membrane laser, drilled with a delivery orifice, and formulated into a tablet. There are two layers in this tablet comprising of one drug layer, and the other, a cosmetically active agent. Upon contact with the GI fluid this osmotic agent changes its characteristic from a nondispensible to a dispensible viscosity. As a result the active pharmaceutical 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.

**CEFORM® technology**

It produces uniformly sized and shaped microspheres of pharmaceutical compounds.[77] This approach is based on ‘melt-spinning,’ which means subjecting solid feedstock (i.e., biodegradable polymer / bioactive agent combinations) to a combination of temperature, thermal gradients, mechanical forces, and flow and flow rates, during processing. The microspheres obtained are almost perfectly spherical, having a diameter that is typically of 150 – 180μm, and they allow for high drug content. The microspheres can be used in a wide variety of dosage forms including tablets, capsules, suspensions, effervescent tablets, and sachets. The microspheres may be coated for controlled release with an enteric coating or may be combined into a fast / slow release combination. This technology has been actually used to develop CardizemR LA, a one-day diltiazem formulation like ChrDDS,[78]

**CONTINR 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 (semipermeable matrixes), which may be varied.[79] This technology has concretely enabled the development of tablet forms of sustained-release aminophylline, theophylline, morphine, and other drugs. The CONTINR technology provides for closer control over the amount of drug released to the bloodstream, and benefits patients in terms of reducing the number of doses they need to take every day, providing more effective control of their disease (particularly at night), and reducing unwanted side effects.[80,81]

**DIFFUCAPS® technology**

In the DIFFUCAPS® technology,[82] a unit dosage form, such as a capsule is used for delivering drugs into the body in a circadian release fashion. DIFFUCAPS®, is a multiparticulate technology by Reliant Pharmaceuticals LLC, for a chronotherapeutic delivery of a combination of two drugs, Verapamil HCl and Propanolol HCl, as an extended release tablet (Innopran®). Pulscincap® system is one of the most used pulsatile systems based on capsules. It was developed by R. P. Scherer International Corporation, Michigan, US. Diffucaps®, and comprises of one or more populations of drug-containing particles (beads, pellets, granules, etc.). Each bead population exhibits a pre-designed rapid or sustained release profile, with or without a predetermined lag time of 3 – 5 hours. The active core of the dosage form may comprise of an inert particle or an acidic or alkaline buffer crystal (e.g., cellulose ethers), which is coated with an API-containing film-forming formulation and preferably a water-soluble film forming composition (e.g., hydroxypropylmethylcellulose, polyvinylpyrrolidone) to form a water-soluble / dispersible particle. The active core may be prepared by granulating and milling and/or by extrusion and spherization of a polymer composition containing the API. Such a ChrDDS is designed to provide a plasma concentration time profile, which varies according to the physiological need during the day, that is, mimicking the circadian rhythm and severity / manifestation of a cardiovascular disease, predicted based on pharmacokinetic and pharmacodynamic considerations and in vitro / in vivo correlations. This technology has been used to formulate the first and recently FDA approved propranolol-containing ChrDDS (InnopranRXL) for the management of hypertension.[83]

**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.
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).

CODAS® technology
Chronotherapeutics Oral Drug Absorption System (CODAS) technology is a multiparticulate system designed for bedtime dosing. Here a nonenteric coating is applied on the drug-loaded beads to delay the release of the drug, up to five hours. Here release controlling contains a mixture of both water-soluble and water-insoluble polymers. When this dosage form comes in contact with the GI fluid, the water-soluble polymer gets dissolved slowly and pores are formed on the coating layer. Drug diffuses through these resulting pores. The water-insoluble polymer, acting as a barrier, maintains the controlled, fashion-like release of Verapamil. The rate of release is independent of pH, posture, and food.

GeoClock® technology
The concept is designed on the basis of Geomatrix technology. Initially a multilayer technology was recommended for constant drug release in this technology. The active core or hydrophilic matrix is coated partially on one or both bases. This partial coating adjusts the core hydration process and minimizes the surface area available for drug release. In the presence of the dissolution medium the barrier layer swells and becomes a gel. This gelling layer is not eroded, but acts as a modulating membrane to control the release process. The erodible surface is instead progressively removed by the dissolution medium. Upon erosion more of the planar surface(s) of the active core is exposed with increasing time to the outer environment, which helps drug release.

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. Active medicament 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.

Three-dimensional printing® (3DP) technology
Three-dimensional printing (3DP) is a novel technique used in the fabrication of complex oral dosage delivery pharmaceuticals, based on solid freeform fabrication methods. It is possible to engineer devices with complicated internal geometries, varying densities, diffusivities, and chemicals. Different types of complex oral drug delivery devices have been fabricated using the 3DP process: immediate-extended release tablets, pulse release, breakaway tablets, and dual pulsatory tablets. The enteric dual pulsatory tablets were constructed of one continuous enteric excipient phase into which diclofenac sodium was printed into two separated areas. These samples showed two pulses of release during in vitro with a lag time between the pulses of about four hours. This technology is the basis of the TheriForm technology.

TIMERx® technology
It is a hydrogel-based, controlled release device. This technology can provide from zero order to chronotherapeutic release. It can provide a different release kinetic by manipulating molecular interactions. Basically, this technology primarily combines xanthan 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.

Physicochemical modification of the API
Physicochemical properties like solubility, drug lipophilicity, partition coefficient, crystalline form, membrane permeability, melting point, and so on, of the API (active pharmaceutical ingredient), can be modified by introducing new substitution to the original structure, to achieve a chronopharmaceutical effect. The maximum plasma concentration of the drug (Tmax) varies upon the physicochemical modification of the parent compound.

Controlled-release microchip
The solid-state silicon microchip is an alternative microfabrication technique similar to micrometer scale pumps, valves, and flow channels, which delivers the active medicament in a pulsatile manner. It can provide controlled release of both single and multiple chemical substances according to the necessity. The release mechanism is based on the electrochemical dissolution of thin anode membranes covering the microreservoir filled with chemicals in solid, liquid, or gel form.

Chronomodulating infusion pumps
Externally and internally controlled systems across a range of technologies including pre-programmed systems, as well as systems that are sensitive to modulated enzymatic or hydrolytic degradation, pH, magnetic fields, ultrasound, electric fields, temperature, light, and mechanical stimulation, have been reviewed in detail elsewhere. To our knowledge
infusion pumps in the market that have been referred to as Chromonomulating for drug delivery application include, Melodie®, programmable Synchronized®, Panomat® V5 infusion,[8] and the Rhythmic® pumps. The portable pumps are usually characterized by a light weight (300 – 500 g) for easy portability and precision in drug delivery.

CONCLUSION AND PERSPECTIVES

Nowadays, pulsatile drug delivery is gaining popularity. The prime advantage in this drug delivery is that the drug is released when the necessity arises. As a result the chance of development of drug resistance, which is seen in conventional and sustained release formulations, can be reduced. Furthermore, some anticancer drugs are very toxic. These drugs cause serious problems in conventional and sustained release therapies. Now many FDA-approved chronotherapeutic drugs are available in the market. This therapy is mainly applicable where sustained action is not required and the drugs are toxic. Key point of development of this formulation is to find out the circadian rhythm, that is, a suitable indicator that will trigger the release of the drug from the device. Another point is the absence of suitable rhythmic biomaterial, which should be biodegradable, biocompatible, and reversibly responsive to specific biomarkers in a rhythmic manner. Regulation is another big question.

A significant amount of progress has been achieved in the field of pulsatile drug delivery systems that can effectively treat disease with non-constant dosing therapies, such as, diabetes. Products that are currently under development for commercialization are for the delivery of proteins, hormones, pain medications and other pharmaceutical compounds. The key considerations in the design of polymer-based pulsatile systems are the biocompatibility and the toxicity of the polymers used, response to external stimuli, the ability to maintain the desired levels of drugs in the serum, the shelf life and reproducibility. Besides, the body’s biological time structure must be counted and respected in the designing of the pulsatile drug delivery system for neuropeptides, hormones, cytokines or other agents that act upon the oscillating system. These considerations, coupled with the potential therapeutic benefits of pulsatile drug delivery systems, should ensure that the current high level of interest in this would extend well into the future and result in the betterment of the quality of life.

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