REVIEW ARTICLE

Chronomodulated drug delivery system: A comprehensive review on the recent advances in a new sub-discipline of 'chronopharmaceutics'

Rohit Bisht

Siddhartha Institute of Pharmacy, Dehradun, Uttrakhand, India

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*

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 [Figure1].

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 supra-cervical 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].

Address for correspondence:
Mr. Rohit Bisht,
Lecturer, Siddhartha Institute of Pharmacy, Do Bachi,
Near I.T-Park, Sahastra Dhara Road, Dehradun,
Uttrakhand – 248 001, India.
E-mail: rohit_thakur1234@rediffmail.com

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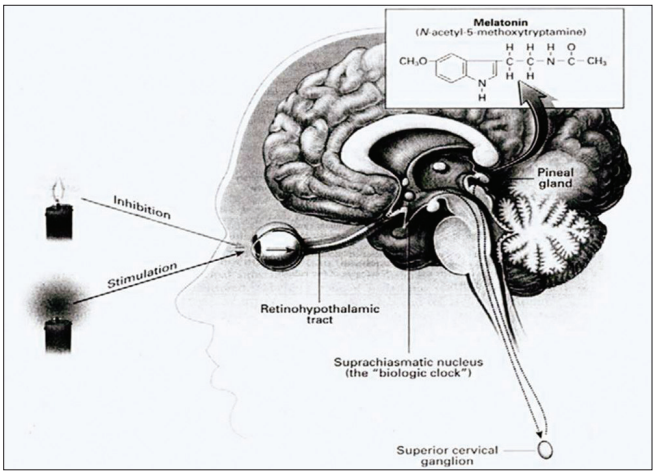

Figure 1: The suprachiasmatic nucleus controls circadian rhythms in response to hormonal variation in the body

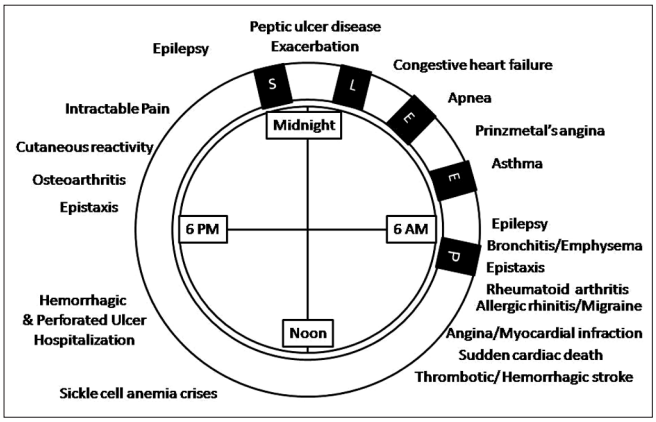

Figure 2: Time cycle when the diseases show their maximum effect

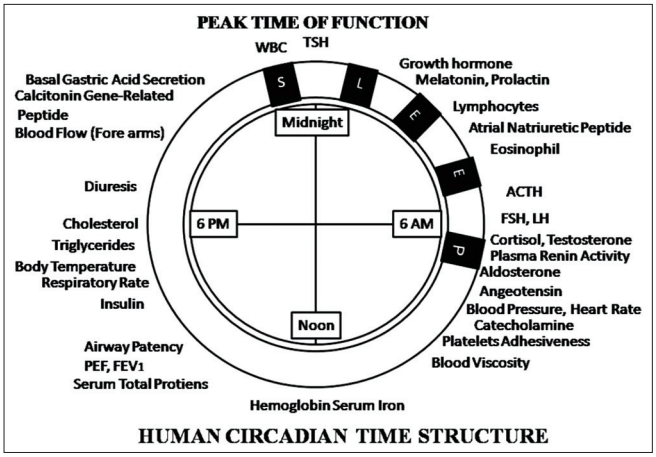

Figure 3: Human circadian time structure; shown is the approximate peak time of the circadian (24-hour) rhythms of selected biological variables in persons adhering to a normal routine of daytime activity (6 – 7 a.m. to 10 – 11 p.m.) alternating with night time sleep

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 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.[11] 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.[12,13] 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.[14-19]

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

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 6β-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

allergic 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 awakening.[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®[75] 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 nondispensable to a dispensable 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®). Pulsincap® 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 spheronization 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.[78] 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[84] 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.[85] The rate of release is independent of pH, posture, and food.

GeoClock® technology

The concept is designed on the basis of Geomatrix technology.[86] 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.[87] 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.[88] 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.[89] This technology is the basis of the TheriForm technology.[90]

TIMERx® technology

It is a hydrogel-based, controlled release device. This technology can provide from zero order to chronotherapeutic release.[91] 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.[92] The maximum plasma concentration of the drug (Tmax) varies upon the physiochemical modification of the parent compound.[93]

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.[94] 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.[95] To our knowledge

infusion pumps in the market that have been referred to as Chronomodulating for drug delivery application include, Melodie®,[96] programmable Synchromed®,[97] Panomat® V5 infusion,[98] and the Rhythmic®[99] 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.

REFERENCES

1. Halberg F, Stephens AN. Susceptibility to ouabain and physiologic circadian periodicity. Proc Minn Acad Sci 1959;27:139-43.
2. Albrecht U, Sun ZS, Eichele G, Lee CC. A differential response of two putative mammalian circadian regulators, mper1 and mper2, to light. Cell 1997;91:1055-64.
3. Tei H, Okamura H, Shigeyoshi Y, Fukuhara C, Ozawa K, Hirose M, *et al*. Circadian oscillation of a mammalian homologue of the Drosophila period gene. Nature 1997;389:512-6.
4. Takumi T, Taguchi K, Miyake S, Sakakida Y, Takashima N, Matsubara C, *et al*. A light independent oscillatory gene mPer3 in mouse SCN and OVLT. EMBO J 1998;17:4753-9.
5. Gekakis N, Staknis D, Nguyen HB, Davis FC, Wilsbacher LD, King DP, *et al*. Role of the CLOCK protein in the mammalian circadian mechanism. Science 1998;280:1564-9.
6. Ikeda M, Nomura M. cDNA cloning and tissue-specific expression of a novel basic helix–loop–helix/PAS protein (BMAL1) and identification of alternatively spliced variants with alternative translation initiation site usage. Biochem Biophys Res Commun 1997;233:258-64.
7. Sangoram AM, Saez L, Antoch MP, Gekakis N, Staknis D, Whiteley A, *et al*. Mammalian circadian autoregulatory loop: A timeless ortholog and mPER1 interact and negatively regulate CLOCKBMAL1- induced transcription. Neuron 1998;21:1101-13.
8. Okamura H, Miyake S, Sumi Y, Yamaguchi S, Yasui A, Muijtjens M, *et al*. Photic induction of mPer1 and mPer2 in Crydeficient mice lacking a biological clock. Science 1999;286:2531-4.
9. Lowrey PL, Shimomura K, Antoch MP, Yamazaks S, Zemenides PD, Ralph MR, *et al*. Positional systemic cloning and functional characterization of the mammalian circadian mutation tau. Science 2000;288:483-92.
10. Tei H, Okamura H, Shigey*oshi* Y, Fukuhara C, Ozawa K, Hirose M, *et al*. Circadian oscillation of a mammalian homologue of the *Drosophila* period gene. Nature 1997;389:512-6.
11. Bussemer T, Peppas NA, Bodmeier R. Evaluation of the swelling, hydration and rupturing properties of the swelling layer of a rupturable pulsatile drug delivery system. Eur J Pharm. Biopharm 2003;56:261-70.
12. Martin RJ, Banks-Schlegel S. Chronobiology of asthma. Am J Respir Crit Care Med 1998;158:1002-7.
13. Bruguerolle B, Labrecque G. Rhythmic pattern in pain and their chronotherapy. Adv Drug Deliv. Rev 2007;59:883-95.
14. Morta R, Jose L, Vila J. Design of new multiparticulate sysmem for potential site-specific and controlled drug delivery to the colonic region. J Contr Rel 1998;55:67-77.
15. Richard JM, Susan BS. Chronobiology of asthma. Am J Resp Crit Care Med. 1998;158:1002-7. Available from: http://www.atsjournals.org.[Last accessed on 2010 Dec 02].
16. Sangalli ME, Maroni A, Zema L, Busetti C, Giordano F, Gazzaniga A. *In vitro* and *in vivo* evaluation of an oral system for time and/or site-specific drug delivery. J Control Release 2001;73:103-10.
17. Mohamad A, Dashevsky A. pH-independent pulsatile drug delivery system based on hard gelatin capsules and coated with aqueous dispersion Aquacoat ECD. Eur J Pharm Biopharm 2006;64:173-9.
18. Gazzaniga A, Maroni A, Sangalli ME, Zema L. Time-controlled oral delivery systems for colon targeting. Exp Opin. Drug Deliv 2006;5:583-97.
19. Khan Z, Pillay V, Choonara YE, du Toit LC. Drug delivery technologies for chronotherapeutic applications. Pharm Dev Technol 2009;14:602-12.
20. Saigal N, Baboota S, Ahuja A, Ali J. Multiple pulse drug delivery systems: Setting a new paradigm for infectious disease therapy. Expert Opin Drug Deliv 2009;6:441-52.
21. Sawada T, Sako K, Yoshihara K, Nakamura K, Yokohama S, Hayashi M. Timed-release formulation to avoid drug–drug interaction between diltiazem and midazolam. J Pharm Sci 2003;92:790-7.
22. Stevens H, Chariot M, Arnold F, Lewis G. Sustained release pharmaceutical composition of diltiazem. U.S. patent 5112621, May 12, 1992.
23. Halberg F. Chronobiology. Annu Rev Physiol 1969;31:675-725.
24. Reinberg A, Halberg F. Circadian chronopharmacology. Annu Rev Pharmacol 1971;11:455-92.
25. Smolensky MH, Labrecque G. Chronotherapeutics. Pharm News 1997;4:10-6.
26. Ohdo S. Changes in toxicity and effectiveness with timing of drug administration. Implications for drug safety. Drug Safety 2003;26:999-1010.
27. Ohdo S. Chronopharmaceutics: Pharmaceutics focused on biological rhythm. Biol Pharm Bull 2010;33:159-67.
28. Ohdo S. Chronopharmacology focused on biological clock. Drug Metab Pharmacokinet 2007; 22:3-14.

29. Moore JG, Englert E Jr. Circadian rhythm of gastric acid secretion in man. Nature 1970;226:1261-2.
30. Bloom PB, Filion RD, Stunkard AJ, Fox S, Stellar E. Gastric and duodenal motility, food intake and hunger measured in man during a 24-h period. Am J Dig Dis 1970;15:719-25.
31. Belanger P, Bruguerolle B, Labrecque G. Rhythms in pharmacokinetics: Absorption, distribution, metabolism and excretion. In: Redfern PH, Lemmer B, editors. Physiology and Pharmacology of Biological Rhythms. Heidelberg: Springer-Verlag; 1997. p. 177-204.
32. Labrecque G, Belanger P. Biological rhythms in the absorption, distribution, metabolism and excretion of drugs. Pharmacol Ther 1991;52:95-107.
33. Reinberg A, Smolensky M. Circadian changes of drug disposition in man. Clin Pharmacokinet 1982;7:401-20.
34. Bruguerolle B. Chronopharmacokinetics: Current status. Clin Pharmacokinet 1998;35:83-94.
35. Labrecque G, Belanger P. Biological rhythms in the absorption, distribution, metabolism and excretion of drugs. Pharmacol Ther 1991;52:95-107.
36. Anderson NH, Devlin AM, Graham D, Morton JJ, Hamilton CA, Reid JL, *et al*. Telemetry for cardiovascular monitoring in a pharmacological study: New approaches to data analysis. Hypertension 1999;33:248-55.
37. Pleschka K, Heinrich A, Witte K, Lemmer B. Diurnal and seasonal changes in sympathetic signal transduction in cardiac ventricles of European hamsters. Am J Physiol 1996;270:304-9.
38. Bruguerolle B, Arnaud C, Levi F, Focan C, Touitou Y, Bouvenot G. Physiopathological alterations of alpha 1 acid glycoprotein temporal variations: Implications for chronopharmacology. In: Baumann P, C.B. Chronobiol Int 2008; 25(1):1-15
39. Feuers RJ, Scheving LE. Chronobiology of hepatic enzymes. Ann Rev Chronopharmacol 1988;4:209-54.
40. Belanger PM, Labrecque G. Temporal aspects of drug metabolism. In: Lemmer B, editor. Chronopharmacology: Cellular and Biochemical Interactions. Basel: Marcel Dekker; 1991. p. 15-34.
41. Ohno M, Yamaguchi I, Ito T, Saiki K, Yamamoto I, Azuma J. Physiopathological alterations of alpha 1 acid glycoprotein temporal variations: Implications for chronopharmacology. Circadian variation of the urinary 6 beta-hydroxycortisol to cortisol ratio that would reflect hepatic CYP3A activity. Eur J Clin Pharmacol 2000;55:861-5.
42. Cambar J, Cal JC, Tranchot J. Renal excretion: Rhythms in physiology and pathology. In: Touitou Y, Physiopathological alterations of alpha 1 acid glycoprotein temporal variations: Implications for chronopharmacology. Haus E, editors. Biological Rhythms in Clinical and Laboratory Medicine. Paris: Springer-Verlag; 1992. p. 470-82.
43. Detli L, Spring P. Diurnal variations in the elimination rate of sulphonamide in man. Helv Med Acta 1966;4:921-926.
44. Sydenham T. The Works of Thomas Sydenham. Translated from the Latin by Lathan RG, editor. Vol. 2. London, Sydenhm socity. 1850. p. 124.
45. Harris MD, Siegel LB, Alloway JA. Gout and hyperuricemia Am Fam Phys 1999;59:925-34.
46. Rigas B, Torosis J, McDougall CJ, Vener KJ, Spiro HM. The circadian rhythm of biliary colic. J Clin Gastroenterol 1990;12:409-14.
47. Moore JG, Halberg F. Circadian rhythm of gastric acid secretion in active duodenal ulcer: Chronobiological statistical characteristics and comparison of acid secretory and plasma gastrin patterns in healthy and post-vagotomy and pyloroplasty patients. Chronobiol Int 1987;4:101-10.
48. Cugini P, Di Palma L, Battisti P, Leone G, Materia E, Parenzi A, *et al*. circadian and infradian periodicity of some cardiovascular emergencies. Am J Cardiol. 1990;66:240-243.
49. Kroetz CO, Ein biologiescher 24-Studen-Rhythmus des Blutkreislaufs bei Gesundheit und bei Herzschivache zugleich ein Beitrag zur tageszeitlichen Haufung einiger akuter Kreislaufstorunge. Munch Med Wochenschr. 1940;87:314-7.
50. Turner-Warwick M. Epidemiology of nocturnal asthma. Am J Med 1998;85:6-8.
51. Bateman JR, Clark SW. Sudden death in asthma. Thorax 1979;34:40-4.
52. Kelmanson IA. Circadian variation of the frequency of sudden infant death syndrome and of sudden death from life-threatening conditions in infants. Chronobiologia 1991;18:181-6.
53. Reinberg AE, Gervais P, Levi F, Smolensky M, Del Cerro L, Ugolini C. Circadian and circannual rhythms of allergic rhinitis: An epidemiologic study involving chronobiologic methods. J Allergy Clin Immunol 1988;81:51-62.
54. Smolensky MH, Reinberg A, Labrecque G.Twenty-four hour pattern in symptom intensity of viral and allergic rhinitis: Treatment implications. J Allergy Clin Immunol 1995;95:1084-96.
55. Kowanko IC, Knapp MS, Pownall R, Swannell AJ. Domiciliary self measurement in rheumatoid arthritis and the demonstration of circadian rhythmicity. Ann Rheum Dis 1982;41:453-5.
56. Solomon GD. Circadian rhythms and migraine. Clevel Clin J Med 1992;59:326-9.
57. Dexter JD, Weizman ED. The relationship between nocturnal headaches to sleep stage patterns. Neurology 1970;20:513-8.
58. Rocco MB, Barry J, Campbell S, Nabel E, Cook EF, Goldman L, *et al,* Circadian variation of transient myocardial ischemia in patients with coronary artery disease. Circulation 1987;75:395-400.
59. Mulcahy D, Keegan J, Cunningham D, Quyyumi A, Crean P, Park A, *et al*, Circadian variation of total ischemic burden and its alteration with anti-anginal agents. Lancet 1998;2:755-9.
60. Behrens S, Ehlers C, Brüggemann T, Ziss W, Dissmann R, Galecka M, *et al*. Modification of the circadian pattern of ventricular tachyarrthythmias by beta-blocker therapy. Clin Cardiol1997;20:253-7.
61. Goldstein S, Zoble RG, Akiyama T, Cohen JD, Lancaster S, Liebson PR, *et al*, Relation of circadian ventricular ectopic activity to cardiac mortality CAST Investigators. Am J Cardiol 1996;78:881-5.
62. Venditti FJ Jr, John RM, Hull M, Tofler GH, Shahian DM, Martin DT. Circadian variation in defibrillation energy requirements. Circulation 1996;94:1607-12.
63. Cohen MC, Rohtla KM, Lavery CE, Muller JE, Mittleman MA. Meta analysis of the morning excess of acute myocardial infarction and sudden cardiac death. Am J Cardiol 1997;79:1512-6.
64. Elliott WJ. Circadian variation in the timing of stoke onset. A meta analysis. Stroke 1998;29:992-6.
65. Gallerani M, Manfredini R, Ricci L, Grandi E, Cappato R, Calò G. Sudden death from pulmonary thromboembolism: Chronobiological aspects. Eur Heart J 1992;6:305-23.
66. Gallerani M, Manfredini R, Fersini C. Chronoepidemiology in human disease. Ann Inst Super Sanita 1993;29:569-79.
67. Portaluppi F, Manfredini R, Fersini C. From a static to a dynamic concept of risk: The circadian epidemiology of cardiovascular risk. Chronobiol Int 1999;16:33-50.
68. Wehr TA. Circadian rhythm disturbances in depression and mania. In: Brown FM, Graeber RC, editors. Rhythmic Aspects of Behavior. New Jerey. Lawrence Erlbaum Ass; 1982. p. 399-428.
69. Bellamy N, Sothern RB, Campbell J. Rhythmic variations in pain perception in osteoarthritis of the knee. J Rheumatol 1990; 17:364-72.
70. Folkard S. Diurnal variation and individual differences in the perception of intractable pain. J Psychosom Res 1976;20:289-304.
71. Manfredini R, Gallerani M, Salmi R, Calò G, Pasin M, Bigoni M. Circadian variation in the time of onset of acute intestinal bleeding. J Emerg Med 1994;12:5-9.
72. Svanes C, Sothern RB, Sorbye H. Rhythmic patterns in incidence of peptic ulcer perforation over 5.5 decades in Norway. Chronobiol Int 1998;15:241-264.
73. Langdon-Down M, Brain WR. Time of day in relation to convulsion in epilepsy. Lancet 1929;12:1029-1032.
74. Baxil CW, Walczak TS. Effects of sleep and sleep stage on epileptic and nonepileptic seizures. Epilepsia 1997;38:56-62.
75. Ohdo S, Koyanagi S, Suyama H, Higuchi S, Aramaki H. Changing the dosing schedule minimizes the disruptive effects of interferon on clock function. Nat Med 2001;7:356-60.
76. Youan BC. Chronopharmaceutics: Gimmick or clinically relevant approach to drug delivery?. J Control Rel 2004;98:337-53.

77. Jao F, Wong P, Huynh H, McChesney K, Wat P. United States: Alza Corporation. 1992. p. 17.
78. Verma R, Sanjay G. Current status of drug delivery technologies and future directions. Pharm Technol 2001;25:1-14.
79. Leslie S. Euroceltique, SA, United States: 1982. p. 20.
80. Leslie S. The Contin delivery system: Dosing considerations. J Allergy Clin Immunol 1986;78:768-73.
81. Arkinstall WW. Review of the North American experience with evening administration of Uniphyl tablets, a once-daily theophylline preparation, in the treatment of nocturnal asthma. Am J Med 1988;85:60-3.
82. Percel P, Vishnupad K, Venkatesh GM. Timed pulsatile drug delivery systems. US Patent 6,627,223.
83. FDA. In: Electronic Orange Book. Washington, DC: Electronic Orange Book; 2003.
84. Youan BC. Overview of chronopharmaceutics. In: Youan BC, Editor. Chronopharmaceutics: Science and Technology for Biological Rhythm Guided Therapy and Prevention of Diseases. Hoboken, NJ: John Wiley and Sons, Inc; 2009.
85. Prisant LM, Devane JG, Butler J. A steady-state evaluation of the bioavailability of chronopharmaceutic oral drug absorption system verapamil PM after night time dosing versus immediate-acting verapamil dosed every 8 h. Am J Ther 2000;7:345-51.
86. Panoz D, Geoghegan E. Elan Corporation, United States, 1989. p. 49.
87. Conte U, Maggi L. Modulation of the dissolution profiles from Geomatrix® multilayer matrix tablets containing drugs of different solubility. Biomoterials 1996;17:889-96.
88. Katstra WE, Palazzolo RD, Rowe CW, Giritlioglu B, Teung P, *et al*, Oral dosage forms fabricated by three dimensional printing. J Control Release 2000;66:1-9.
89. Rowe CW, Katstra WE, Palazzolo RD, Giritlioglu B, Teung P, *et al*, Multimechanism oral dosage forms fabricated by three dimensional printing. J Control Release 2000;66:11-7.
90. Monkhouse D, Yoo J, Sherwood J, Cima M, Bornancini E. Therics. United States, 2003. p. 19.
91. Staniforth JN, Baichwal AR, TIMERx®: Novel polysaccharide composites for controlled/programmed release of drugs in the gastrointestinal tract. Expert Opin Drug Deliv 2005;2:587-95.
92. Horter D, Dressman JB. Influence of physicochemical properties on dissolution of drugs in the gastrointestinal tract. Adv Drug Deliv Rev 2001;46:75-87.
93. Mahey R, Bersot T. Drug therapy for hypercholesterolemia and dyslipidemia. In: Hardman J, Limbird L, Gilman A, editors. Goodman and Gilman's The Pharmacological Basis of Therapeutics. New York: McGraw-Hill; 2001.
94. Santini JT Jr, Cima MJ, Langer R. A controlled-release microchip. Nature 1999;397:335-8.
95. Santini JT Jr, Richards AC, Scheidt R, Cima MJ, Langer R. Microchips as controlled drug-delivery devices. Angew Chem Int Ed Engl 2000;39:2396-407.
96. Sershen S, West J. Implantable, polymeric systems for modulated drug delivery. Adv Drug Deliv 2002;54:1225-35.
97. Levi F, Zidani R, Misset JL. Randomised multicentre trial of chronotherapy with oxaliplatin, fluorouracil, and folinic acid in metastatic colorectal cancer. International Organization for Cancer Chronotherapy. Lancet 1997;350:681-6.
98. Remeling R, Hrushesky WJ. Circadian patterning of continuous floxuridine infusion reduces toxicity and allows higher dose intensity in patients with widespread cancer. J Clin Oncol 1989;7:1710-9.
99. Tzannis ST, Hrushesky WJ, Wood PA, Przybycien TM. Irreversible inactivation of interleukin 2 in a pump-based delivery environment. Proc Natl Acad Sci USA 1996;93:5460-5.

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