

Pulsatile release: A Novel Drug approach to drug delivery system

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Abstract- Pulsatile drug delivery systems (PDDS) are gaining importance as they deliver a drug at specific time as per the pathophysiological need of the disease, resulting in improved therapeutic efficacy as well as compliance. Diseases wherein PDDS are promising include asthma, peptic ulcer, cardiovascular diseases, arthritis, attention deficit syndrome in children, and hypercholesterolemia. These delivery systems can be classified into time controlled wherein the drug release is governed primarily by the delivery system; stimuli induced in which release is controlled by a stimuli, like the pH or enzymes present in the intestinal tract or enzymes present in the drug delivery system and externally regulated system where release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation. The current article focuses on the review of literature concerning the disease requiring PDDS, methodologies involved in the existing systems, recent update and product currently available in the market.

Index terms- Lag time, pulsatile release, multiple unit-systems, chronotherapy, regulatory aspect

PULSATILE DRUG DELIVERY SYSTEM

Now a days a lot of researchers implied that human biological processes are not constant they vary according time to time and repeated after a specific time. Recently much of drug delivery research has based upon constant drug release rate due to unable of delivering drug according to disease rhythmicity. Clinical studies show that efficacy of rhythmic

differences can be to a great extent and a strong determinant of when during a day most morbid and mortal event will occur. For the drugs constant release system is not suitable. Drugs not suitable for constant release are used in disease condition that exhibit rhythmic variation within a circadian cycle. For, drugs with decrease bioavailability due to first pass metabolism, gradual release of drug from constant release systems can result in greater degradation.

The researcher found lot of interest in pulsatile drug delivery system for its efficacy and advantages over other conventional dosage form. These systems are mainly appropriate for drugs that are metabolized to pharmacological active compounds, drugs which have long in vivo half-lives showing an inherently prolonged duration of action, drugs with very short in vivo half-life which require a prohibitively large amount of active ingredients in dosage form, drugs which are required in large doses for therapeutic effect and drugs which are required in very low dose. Additionally a delayed burst release can also be utilized for enhancing absorption, reducing side effects, increasing and decreasing dose.

Pulsatile drug delivery system is actually the release of drug with such a manner where drug is released very rapidly after a well-defined lag time or gap of time according to circadian rhythm of the body.

These situations therefore compel designing a delayed fast release systems.

The delivery of drug is based upon the quantity of drug is released from the dosage form within this lag time is negligible and after that all drug is released in burst manner. Among all the delivery, the oral controlled pulsatile drug delivery system represents the most popular form of controlled drug delivery system for the advantage of oral route of drug administration such system to maintain a plasma concentration of drugs within the therapeutic windows for longer number of pathological cases such as arthritis are mostly happening at morning.

Today, a vast amount of literature clearly documents that biological processes and functions are not constant, but highly variable in a predictable-in-time manner as expressed by prominent rhythms of various period.

Chronobiology is the study of biological rhythms and the mechanisms of biological timekeeping. Chronobiology is delivery systems which are developed to deliver drug respective to the circadian behavior of diseases in the body which are occurring after a specific time interval. The product follow a sigmoidal drug release profile are defined by the time period of no release (lag time) followed by a rapid and complete drug release. Thus drug can be delivered at right time, in right amount and at right site of action by use of such approach.

Pulsatile systems are achieving a lot of interest as they deliver the drug at the right site of action at the right time and in the right amount, thus providing spatial and temporal delivery and increasing patient compliance. These systems are designed based on the circadian rhythm of the body. However, there certain condition of drug which such a release pattern is not suitable. These are condition release of drug after lag time.

The release of drug from pulsatile dosage form indicate by the following diagram which shows the ideal sigmoidal release after a specific time interval in burst pattern in bulk to induce the therapeutic effect as required at that specific time.

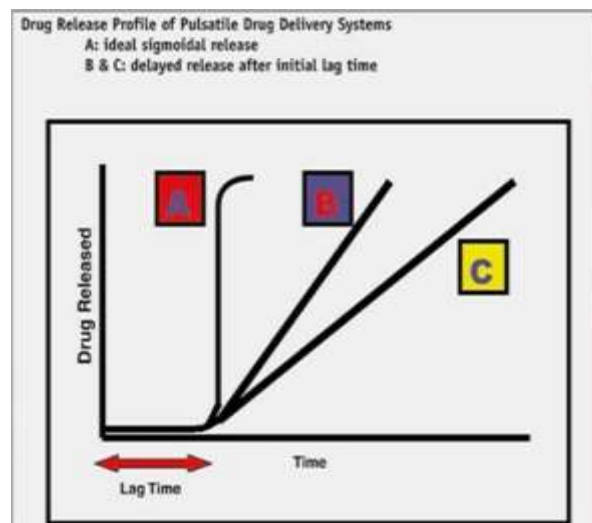


Fig. no 1.1:- Drug release profile of pulsatile drug delivery system

Chronobiology, Chronotherapeutics and Chronopharmaceutics:

Chronobiology is the science concerned with the biological mechanism of the disease according to a time structure. “chrono” pertains to time and “biology” pertains to the study, or science, of life.

The scientific studies of biological rhythms are clearly reveal that biological functions and process are the not over time. Some of the rhythms that is affect the bodies include:

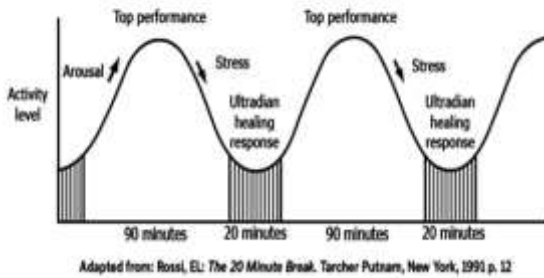
Ultradian:-In the 1950's, sleep researcher Nathaniel Kleitman discovered that the human body tends to move through 90-120 minute cycles. At night, these cycles correspond to the different stages of sleep (alertness, light, REM, deep, etc.). During the day, these cycles correspond to different levels of energy and alertness.

Kleitman referred to these cycles as the “basic rest-activity cycle”. Since then, others have called these cycles ultradian rhythms.

Oscillations of shorter duration are termed Ultradian Rhythms (more than one cycle per 24 hrs). 90 minutes sleep cycle (cycles shorter than a days)

FIGURE 2

THE ULTRADIAN PERFORMANCE RHYTHM



Circadian:-The term “circadian”, coined by Franz halberg, comes from the Latin circa, “around”, and diem of dies, “day”, meaning literally “approximately one day”. Our body appears to be genetically programmed to function on roughly a 24-hour cycle.

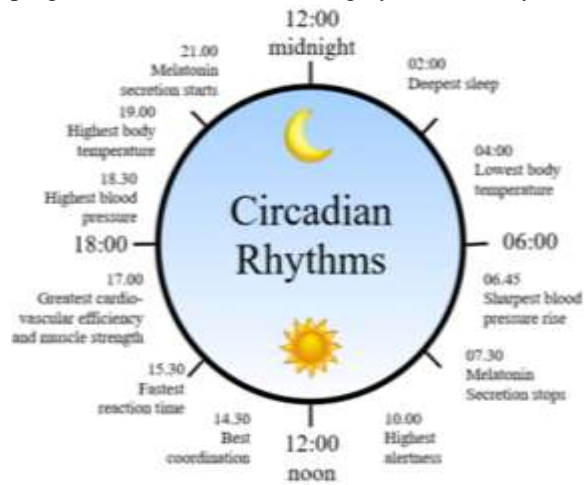


Fig. Circadian Rhythms of human body

Infradian:-In chronobiology an infradian rhythm is a rhythm with a period longer than the period of a circadian rhythm, i.e. with a frequency less than one cycle in 28 hours such as menstruation, breeding, tidal or seasonal rhythms. cycles longer than 24 hours (such as monthly menstruation),

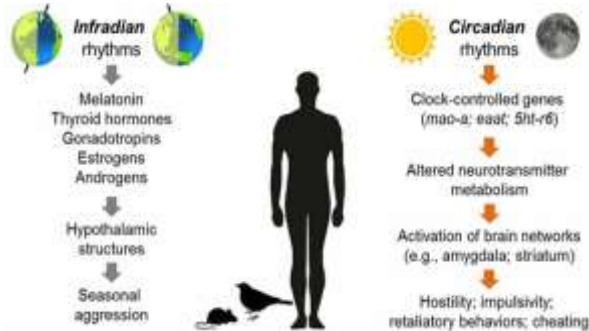


Fig. Infradian Rhythms

Seasonal:- seasonal are those who occur at particular season and symptoms are occurring only in that season. ex. a seasonal affective disorder (SAD) which is causes depression in a susceptible people during a winter for the short days.

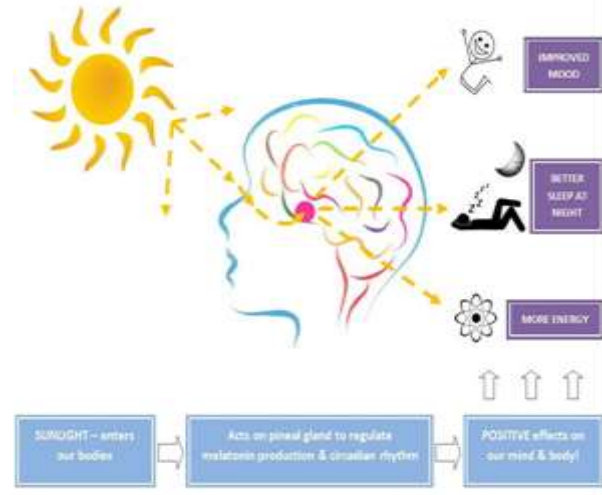


Fig. seasonal Rhythms

The Link between High Blood Pressure and Circadian Rhythm

The body’s regular clock also known as circadian rhythm, is occur oftenly the most important is the heart health because it is the mortal disease. The body continues the mechanism to regulate sleeping and feeding patterns core body temperature, brain wave activity, hormone production, glucose and insulin levels, cell regeneration, and many other biological activities. It is chiefly responsible for regulating two important hormones: melatonin and cortisol.

Melatonin is secreted by the pineal gland in the brain. Production into the bloodstream is stimulated by darkness and typically begins around 9pm, lasting about 12 hours.

Cortisol, also known as the “stress hormone” is produced by the adrenal glands. Because most bodily cells have cortisol receptors, it affects many different functions within the body. Cortisol can help control blood sugar levels, regulate metabolism, help reduce inflammation, and it has a controlling effect on salt and water balance which helps control blood pressure.

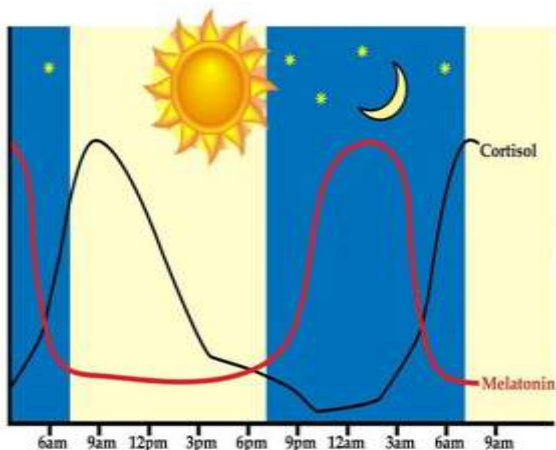


Fig. Melatonin and cortisol regulation throughout the day

Chronopharmacology:- Chronopharmacology is defined as the branch of pharmacology which deals with the study of manner and extent (amount) to which the pharmacokinetics and pharmacodynamics of medications are directly affected by endogenous biological rhythms.

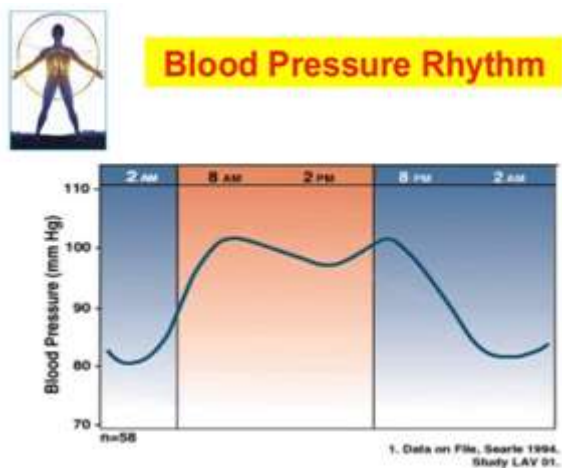


Fig. Blood Pressure Rhythm

Chronotherapy and Chronotherapeutics:-The goal in drug delivery research is to develop formulations that meet therapeutic needs relating to particular pathological conditions. Up to late 1980`s design of drug delivery systems governed by the homeostatic theory. This theory is based on the assumption of biological functions that display constancy over time. Research in chronopharmacological field has demonstrated the importance of biological rhythms in drug therapy.

Chronopharmaceutics (5):-Chronopharmaceutics is a branch of science and technology of dosage forms which deals to the design and evaluation of drug delivery systems that release a bioactive agent according to the chronotherapeutics need of body or disease condition. Chronopharmaceutical drug delivery system elevated to a new concept that is the ability to deliver the therapeutic agent to a patient in a staggered profile and should embody time controlled as well as site specific drug delivery systems regardless of the route of administration

Need for chronotropic DDS: 7

The conditions or the instances in which this system is required are:

When possible daily variations in pharmacokinetic may be responsible for time dependent variations in drug effects (e.g. some antimicrobial agents are more effective at a specific time of day).

When drugs have a narrow therapeutic range.

When symptoms of a disease are clearly circadian phase-dependent (e.g. Angina pectoris, myocardial infarction).

When drug plasma concentrations are well correlated to the therapeutic effect in case the latter is circadian phase-dependent.

When the drug has some serious adverse effects that can be avoided or minimized because they are related to time of administration.

1.4 Advantage of pulsatile drug delivery system: 9,10

- 1 Reduces dose of drug without decrease in therapeutic effects.
- 2 Decreases side effects.
- 3 Decreases drug interaction due to lower cytochrome P450 is enzymes.
- 4 Decreases food effect (change occurring in bioavailability of drug when given with food).
- 5 Improved compliance.
- 6 Chronotherapy, programmed delayed release provides optimal treatment of diseases.
- 7 Pulse release allows multiple dosing in a single dosage form.
- 8 Allows site specific release for local treatment of diseases.
- 9 Drug release is not affected by change in pH of the gastrointestinal tract.

Disadvantage of pulsatile drug delivery system:

- 1 Lack of manufacturing reproducibility and efficacy.
- 2 Homogeneity of the coated barrier is mandatory to assure the predictability of the lagtime.
- 3 Rupture time cannot be always adequately manipulated as it depends on the physicochemical properties of the polymer.
- 4 Pulsatile delivery drugs are costly, raw material is not easily available.
- 5 Dosage form design requires highly educated professionals.
- 6 Technologies employed and the equipment used is complicated incomplete release.

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