

Chronobiology: Pulsatile Drug Delivery System - A Review

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Abstract

The mammalian circadian pacemaker resides in paired suprachiasmatic nuclei of hypothalamus and it influence a multitude of biological processes. The physiology and behavior of human body is influenced by circadian rhythm which is controlled by clock genes. Due to the advancement of chronobiology traditional way of drug delivery with constant way of releasing drug has become changed. The new era is focusing on delivering drug at right site, at right time and at right amount. Pulsatile drug delivery system is fulfilling all this requirements. The principal rationale of pulsatile drug delivery system is that it is best suited for those where zero order release is not required.

Keywords: Chronobiology, Circadian rhythm, Clock genes, Pulsatile drug delivery system

INTRODUCTION

Plants and animals are observed to show daily rhythms since long. From very early era it is noted that the leaves of certain trees opened during the day and closed at night showing a clear rhythmicity[1]. In 1729 the French astronomer Jean Jacques d' Ortois experimented on biological cycle. Since that time it has been proved that insects used photoperiodical informations for their sustainability with change in seasons. Biological rhythms are defined by different characteristics. The term 'Circadian' was coined by Franz Halberg from the latin term 'Circa' meaning about and 'dies' meaning days. Biological rhythm is a self sustaining oscillation. It is defined by its period, amplitude and phasing. The period is the duration of time required to complete a single cycle. A rhythm with a period close or equal to 24hrs is termed as 'Circadian'[2].

- Shorter period of rhythms are called as ultradian (more than 1 cycle per 24hr, e.g. electrical impulses of brain and heart, secretion of hormones)
- Cicadian (less than 1 cycle per 24hr, e.g. sleeping and waking pattern).
- longer ones called infradian ,e.g. Monthly menstruation

Ultradian, Circadian & Infradian rhythms coexist at all levels of biological organizations[3,4].

CIRCADIAN PHYSIOLOGY: IMPACT ON PHYSIOLOGICAL FUNCTIONS AND DISEASES

The mammalian circadian pacemaker reside in the suprachiasmatic nuclei (SCN) of brains hypothalamus and influences a multitude of biological processes such as sleep wake rhythm, hormone levels, secretion of digestive enzymes, intestinal peristalsis, bile and urine production etc. Like any timing system the circadian clock is made up of 3 components: An input pathway adjusting the time, a central oscillator generating the circadian signal and an output pathway manifesting circadian physiology and behavior. Light signals are perceived by photoreceptor cells

in the rating and transmitted to the neurons of SCN via retinohypothalamic tract (Fig.I). A great deal of research shows that the inherited period of human pacemaker clock is not precisely 24hrs. Infact it is closer to 25hrs. Clock genes are the genes that control the circadian rhythms in physiology and behavior. Three mammalian clock genes (Per1, Per2, Per3) and rhythmically expressed in SCN[5]. The timing of peaks and troughs of circadian rhythms is quite predictable from 1day to next in majority of people who adhere to a fairly regular sleep activity schedule. However the staging of 24hr rhythm in those who work in rotating shift schedules or follow variable rest activity is less predictable. The activity sleep routine determines when the peak and troughs of circadian rhythm occurs with reference to 24hrs scale. However the extent of individual benefit from circadian timed therapy can differ as a function of environmental, genetic and epigenetic factors. The result of numerous biological rhythm studies help to define the temporal organization of human being. Fig.II Shows the peak time of a no. of circadian rhythms with reference to the sleep activity cycle[6].

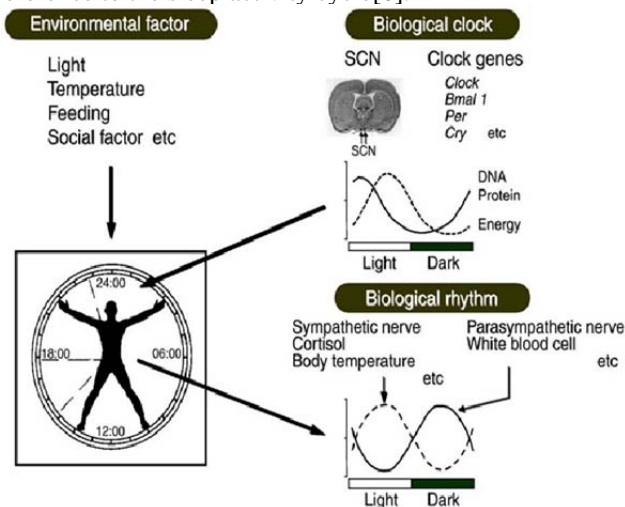


Fig.I: Schematic diagram of sleep wake cycle

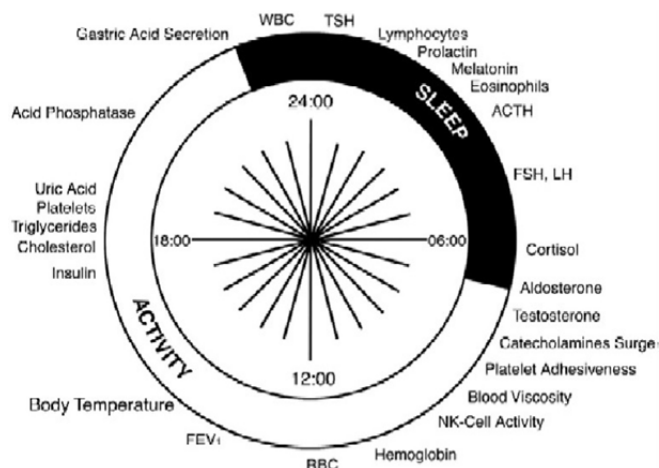


Fig. II: Picture showing peak time of biological activity

With the advancement of technology the emphasis of pharmaceutical galenic research has turned towards the development of more efficacious drug delivery system with existing molecules rather going for new drug discovery as because of inherent hurdles posed in drug discovery and development process. Traditionally drug discovery was meant for getting a simple chemical absorbed from the site of absorption. The second generation drug delivery goes for a continuous and constant rate of drug delivery system turned to be most successful for many years. This system turned to be most successful for many years. Still for many drugs use of this system is not suitable, particularly where drug is subjected to large metabolic degradation, less bioavailability due to first pass metabolism and drugs with short half life. In case of chronic treatment sustained release of drug produce adverse effects due to continuous exposure to body[7,8]. Hence the recent research is preferred to opt for dosage which provides concentration of drug at particular point of time only. Pulsatile drug delivery system is designed to meet that demand which releases the bioactive agent at a rhythm that ideally matches the biological requirement of the given disease therapy (Fig.III).

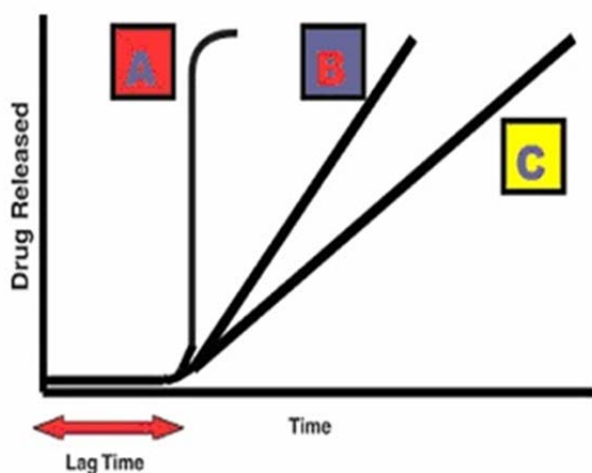


Fig.III: Release pattern of Pulsatile drug delivery system (A.Ideal sigmoidal release. B& C. Extended release after initial lag time)

ADVANTAGES AND DRAWBACKS OF PULSATILE DRUG DELIVERY SYSTEM

Advantages

- Predictability and reproducibility
- Drug targeting
- Improve bioavailability
- Reduces risk of local irritation
- No dose dumping
- Improve stability
- Improve patient comfort and compliance
- Achieve a unique release pattern

Drawbacks

- Lack of manufacturing reproducibility and efficacy
- number of process variables
- Multiple formulation steps
- Higher cost of production
- Need of advanced technology
- Skilled personal needed for manufacturing

METHODS FOR PULSATILE DRUG DELIVERY

Methodologies for the pulsatile drug delivery system can be broadly classified into four Classes[9, 15].

1. TIME CONTROLLED PULSATILE RELEASE SYSTEM

Time-dependent dosage forms are formulated to release drug after a predetermined lag time in a predictable manner. These systems are designed to release drug in pulses governed by the device fabrication and ideally, independent of the environment. The release mechanisms include bulk erosion, surface erosion, osmotic controlled erosion coating layer.

1.1. Delivery system with erodible barrier layers

In such systems the drug release is controlled by the dissolution or erosion of the outer coat which is applied on the core containing the drug. Time dependent release of the active ingredient can be obtained by optimizing the thickness of the outer coat.

1.2. Delivery system provided with rupturable coating layer

Most pulsatile delivery systems are reservoir devices coated with a rupturable polymeric layer. As media penetrates, drug is released from the core after rupturing of the surrounding polymer layer, due to pressure build-up within the system. The pressure required to rupture the coating layer can be achieved with swelling agents, gas-producing effervescent or by increased osmotic pressure. Water permeation and mechanical resistance of the outer membrane are key factors affecting the lag time.

1.3. Capsular systems with release controlling plug

A general architecture of such systems consist of an insoluble capsular body housing the drug, and a plug. The plug is removed after a predetermined lag time owing to swelling, erosion or dissolution. Pulsatile capsule was prepared by sealing the drug tablet and the buoyant material filler inside the impermeable capsule body with erodible plug. The drug delivery system showed typical floating and pulsatile release profile with a lag time

followed by a rapid release phase. The lag time prior to the pulsatile drug release is controlled by erosion, composition and weight of the plug. The buoyancy of the whole system depended on the bulk density of the dosage form.

2. INTERNAL STIMULI INDUCED PULSATILE RELEASE SYSTEM[16,17]

Responsive drug release of systems results from the stimuli-induced changes in the gels or in the micelles, which may deswell, swell, or erode in response to the respective stimuli. There has been much interest in the development of stimuli-sensitive delivery system that releases therapeutic agents in presence of specific enzyme or protein. In these systems there is release of the drug after stimulation by any biological factor like temperature or any other chemical stimuli.

2.1. Temperature – induced Pulsatile release

Temperature is the most triggering signal for a variety of triggered or pulsatile drug delivery systems. The use of temperature as a signal has been justified by the fact that the body temperature often deviates from the physiological temperature (37°C) in the presence of pathogens or pyrogens. This deviation sometimes can be a useful stimulus that activates the release of therapeutic agents from various temperature responsive drug delivery systems for disease accompanying fever. Thermal stimuli regulated pulsed drug release is established through the design of drug delivery device such as hydrogels and micelles.

2.2. Thermo-responsive hydrogel systems

The drug delivery systems that are responsive to temperature utilize various polymer properties, including the thermally reversible coil/globule transition of polymer molecules, swelling change of networks, glass transition and crystalline melting.

2.3. Chemical stimuli induced Pulsatile systems

In these systems the polymer undergoes swelling or deswelling phase in response of chemical reaction with membrane, alteration of pH and inflammation induce, release drug from polymer by swelling the polymer.

2.4. pH sensitive drug delivery system

pH-sensitive polymers are polyelectrolytes that bear in their structure weak acidic or basic groups that either accept or release protons in response to changes in environmental pH. In case of pH dependent system advantage has been taken of the fact that there exists different pH environment at different parts of the gastrointestinal tract. By selecting the pH dependent polymers drug release at specific location can be obtained. Examples of pH dependent polymers include cellulose acetate phthalate, polyacrylates, sodium carboxy methyl cellulose. These polymers are used as enteric coating materials so as to provide release of drug in the small intestine.

2.5. Inflammation-induced Pulsatile release

On receiving any physical or chemical stress, such as injury, fracture etc., inflammation take place at the injured sites. During inflammation, hydroxyl radicals are produced from these inflammation-responsive cells. When human beings receive physical or chemical stress, such as injury, broken bones, etc., inflammation reactions take place at the injured sites. At the inflammatory sites, inflammation-

responsive phagocytic cells, such as macrophages and polymorphonuclear cells play a role in the healing process of the injury. During inflammation, hydroxyl radicals (oh) are produced from these inflammation-responsive cells.

3. EXTERNALLY REGULATED PULSATILE RELEASE[18]

In this drug delivery are not self-operated, but instead required externally generated environmental changes to initiate drug delivery. These can include magnetic fields, ultrasound, electric field, light, and mechanical force.

3.1. Magnetic induces release

Magnetic carriers receive their magnetic response to a magnetic field from incorporated materials such as magnetite, iron, nickel, cobalt etc. For biomedical applications, magnetic carriers must be water-based, biocompatible, non-toxic and non-immunogenic

3.2. Ultrasound induces release

Highly toxic potent chemotherapeutic drugs like doxorubicin (dox) limits the therapeutic window in which they can be applied. This window can be expanded by controlling the drug delivery in both space and time such that non-targeted tissues are not adversely affected. Dox activity can be enhanced by ultrasound in one region, while in an adjacent region there is little or no effect of the drug.

3.3. Electric field induces release

Electrically responsive delivery systems are prepared from polyelectrolytes (polymers which contain relatively high concentration of ionisable groups along the backbone chain) and are thus, pH-responsive as well as electroresponsive. Under the influence of electric field, electro-responsive hydrogels generally deswell or bend, depending on the shape of the gel lies parallel to the electrodes whereas deswelling occurs when the hydrogel lies perpendicular to the electrodes.

3.4. Light induces release

Light-sensitive hydrogels have potential applications in developing optical switches, display units, and ophthalmic drug delivery devices. Since the light stimulus can be imposed instantly and delivered in specific amounts with high accuracy, light-sensitive hydrogels may possess special advantages over others. The capacity for instantaneous delivery of the sol-gel stimulus makes the development of light-sensitive hydrogels important for various applications in both engineering and biochemical fields.

4. MULTIPARTICULATE PULSATILE DRUG DELIVERY SYSTEM[19,20]

Recent trends indicate that multiparticulate drug delivery systems are especially suitable for achieving controlled or delayed release oral formulations with low risk of dose dumping, flexibility of blending to attain different release patterns as well as reproducible and short gastric residence time. The release of drug from microparticles depends on a variety of factors including the carrier used to form the microparticles and the amount of drug contained in them. Consequently, multiparticulate drug delivery systems provide tremendous opportunities for designing new controlled and delayed release oral formulations, thus

extending the frontier of future pharmaceutical development.

4.1. Reservoir systems with rupturable polymeric coatings

Most multiparticulate systems are reservoir devices coated with a rupturable polymeric layer. Upon water ingress, drug is released from the core after rupturing of the build-up within the system. The pressure necessary to rupture the coating can be achieved with swelling agents, gas-producing effervescent excipients or increased osmotic pressure. Water permeation and mechanical resistance of the outer membrane are major factors affecting the lag time.

4.2. Reservoir systems with soluble or eroding polymer coatings

Another class of reservoir-type multiparticulate pulsatile systems is based on soluble / erodible layers in place of rupturable coatings. The barrier dissolves or erodes after a specific lag time followed by burst release of drug from the reservoir core. In general, for this kind of systems, the lag time prior to drug release can be controlled by the thickness of the coating layer. However, since from these systems release mechanism is dissolution, a higher ratio of drug solubility relative to the dosing amount is essential for rapid release of drug after the lag period. Over the past two decades there has been a growing appreciation on the importance of circadian rhythms on GIT physiology and on disease states, together with the realization of the significance of time-of-day of the administration on resultant pharmacodynamics and pharmacokinetics parameters. The significance of these daylight variations has not been over looked from the drug-delivery perspective and pharmaceutical scientists have displayed considerable ingenuity in the development of time delayed drug delivery system to address emerging chronotherapeutic formulation.

CONCLUSION

Research in chronobiology has demonstrated the importance of biological rhythms in drug delivery. Since it seems that timing of drug delivery has significant effect on treatment success. So this can be concluded that pulsatile drug delivery system provides a solution for delivery of drugs for those disease conditions regulated by circadian rhythm .

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